

VOLUME 1
NEW SERIES

MARCH - APRIL
1972

NUMBER 2

ΧΗΜΙΚΑ ΧΡΟΝΙΚΑ
CHIMIKA CHRONIKA

**PUBLISHED BY
THE SCIENTIFIC COMMITTEE
OF THE GREEK CHEMISTS ASSOCIATION**

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Subscription rates: 300 drs per year: Hellas & Cyprus
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CHIMIKA CHRONIKA, *New Series*, **1**, 103-109 (1972)

Coordination Compounds of Co(II) and Ni(II) Part I. Magnetic and Spectral Properties of Complexes With Pyridine Dicarboxylic Acid

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(Received 10-7-71)

Complexes of Co(II) and Ni(II) with pyridine-2, 5-dicarboxylic acid have been isolated. Infrared and electronic spectral data have been taken and discussed in connection with their molecular structure. The magnetic susceptibility of these complexes has been measured at room temperature, although in the Ni(II) isocinchomeranate trihydrate the magnetic susceptibility has been measured over the temperature range 300-80°K. This complex obeys Curie or Curie-Weiss Law.

Introduction

In the present work the electronic and molecular structures of some complexes of isocinchomeronic acid (pyridine-2,5-dicarboxylic acid) with Co(II) and Ni(II) are studied. This work is relevant to our previous ones^{1,2} on complexes of Co(II), Ni(II) and lanthanides with various pyridine carboxylic acids. Similar work has been reported on Ag(II) and Cu(II).^{3,4,5} An X-ray single crystal analysis⁶ has been carried out on nickel(II) bis (pyridine-2-carboxylic acid) tetrahydrate. This analysis shows that the nickel atom has an octahedral arrangement consisting of two nitrogen atoms, two chelating oxygens and two aqueous oxygens, the related atoms of the two picolinic acid molecules being mutually trans.

Another three-dimensional X-ray analysis⁷ of Co(II) nicotinate tetrahydrate (nicotinic acid = pyridine-3-carboxylic acid) shows that the carboxylate groups are not coordinated to the central atom. This structure is best described as a nonclassical zwitterion, the charges formally residing on the cobalt and the oxygen atoms of each nicotinate moiety.

Lanthanide ions form complexes^{7a} with pyridine monocarboxylic and dicarboxylic acids. These complexes are stable, when the ligand behaves as a chelating agent.

Silver(II) dipicolinate tetrahydrate has been isolated.³ The monohydrate of this complex has been characterised by a single crystal X-ray analysis.^{8,9}

Analogous complexes of vanadium(IV) with dipicolinic acid have also been isolated.¹⁰

Experimental

The acid and the nitric salts of cobalt and nickel were commercially available (B.D.H. or Koch-Light).

Analyses. — Cobalt was determined spectrophotometrically and nickel gravimetrically through dimethylglyoxime complex formation. Carbon, hydrogen and nitrogen analyses were conducted in the microanalytical laboratory of the Reading University.

Physical Measurements. — Diffuse reflectance Spectra were measured on Unicam SP500 and 700 spectrophotometer. Magnetic susceptibility measurements were made on a Newport Instrument

Gouy balance system. (Tetrathiocyanatocobalt) mercury was used as calibrant, and diamagnetic corrections were estimated from Pascal's constants.

Preparation of Complexes. — Co(II) Bis (pyridine-2, 5-dicarboxylic acid) tetrahydrate and Ni(II) Bis (pyridine-2, 5-dicarboxylic acid) trihydrate.

The reaction mixture of M:Acid was 1:2.5. The reactants were mixed from hot solutions, the pH being around 3. The acid was neutralised before use with sodium hydroxide solution and then it was acidified with HNO_3 until pH about 3. The mixtures were allowed to reach room temperature and then they were cooled to 0°C . The precipitates were filtered, washed with water and then with alcohol and ether, and dried in vacuo over calcium chloride for 8h. The colour of the cobalt complex was orange-pink and of the corresponding nickel pale blue. Found for cobalt complex: C, 36.30; H, 3.50; N, 5.97; Co, 12.88%. Calc. for $\text{C}_{14}\text{H}_{16}\text{CoN}_2\text{O}_{12}$: C, 36.30; H, 3.49; N, 6.05; Co, 12.72%. Found for nickel complex: C, 38.17; H, 3.27; N, 6.32; Ni, 12.92%. Calc. for $\text{C}_{14}\text{H}_{14}\text{NiN}_2\text{O}_{11}$: C, 37.90; H, 3.17; N, 6.30; Ni, 13.19%.

The hydrates were heated under vacuo (ca. 10^{-2} mmHg) at 100°C for 7 hrs. The isolated complex of cobalt was violet and the nickel one green. Found for cobalt complex: C, 41.29; H, 2.40; N, 6.9; Co, 14.50%. Calc. for $\text{C}_{14}\text{H}_{10}\text{CoN}_2\text{O}_9$: C, 41.09; H, 2.46; N, 6.85; Co, 14.4%. Found for nickel complex: C, 38.91; H, 2.87; N, 6.48; Ni, 13.58%. Calc. for $\text{C}_{14}\text{H}_{12}\text{NiN}_2\text{O}_{10}$: C, 39.38; H, 2.83; N, 6.56; Ni, 13.75%.

When the dehydrated complexes were left under atmospheric conditions for one day they again absorbed water and the colours changed for cobalt to pale violet and for nickel to pale green. Found for cobalt complex: C, 37.90; H, 3.20; N, 6.31; Co, 13.30%. Calc. for $\text{C}_{14}\text{H}_{14}\text{CoN}_2\text{O}_{11}$: C, 37.76; H, 3.17; N, 6.29; Co, 13.24%. Found for nickel complex: C, 38.86; H, 2.85; N, 6.44; Ni, 13.54%. Calc. for $\text{C}_{14}\text{H}_{13}\text{NiN}_2\text{O}_{10.5}$: C, 38.57; H, 3.01; N, 6.43; Ni, 13.47%.

Results and Discussion

The isolated complexes are quite easy to prepare, bearing in mind to keep the volume of water as small as possible. Unfortunately, the insolubility of these complexes in suitable polar and non-polar solvents prevents the investigation of their conductivity, molecular weight and spectral properties in solution.

Table I shows the main peaks of the infrared spectra of these complexes. These spectra confirm the presence of free carboxylic acid groups, since the carbonyl stretching frequency of about 1700cm^{-1} of the free acid¹¹ is still present after the complex formation. On the other hand the presence of an asymmetric stretching frequency at a lower region (ca. 1650cm^{-1}) is strong evidence for a metal-carboxylic oxygen covalent bond. The other maxima of table I are assigned to $\nu(\text{C}=\text{C})$ or $\nu(\text{C}=\text{N})$ of the pyridine ring. The "dehydrates" do not show the characteristic frequency of $\nu(\text{O}-\text{H})$ which is shown as a broad weak band at ca. $2700\text{-}2500\text{cm}^{-1}$ in the free acid, although this band is also not clear in the corresponding hydrates. However, these hydrated complexes have lattices which are stabilized by different degrees of hydrogen-bonding between $-\text{COO}^-$, $-\text{COOH}$ and H_2O . Consequently, modification of the $\nu(\text{C}-\text{O})$ vibrations can arise from such strong bonds.

Magnetic and Spectral Studies. — The magnetic data of the isolated complexes are summarised in table III. From these values we deduce that the cobalt and nickel atoms are surrounded by a pseudo-octahedral field, although the values for cobalt complexes are somewhat lower than they should be in the case of an octahedral environment. The same comment should be made for the nickel complexes. In the case of trihydrated complex we have also investigated the temperature range magnetic properties. The complete temperature range data are given in table IV. This complex obeys the Curie or Curie-Weiss Law and has a θ value = + 9. With this value of θ we can certainly accept that the presence of antiferromagnetic exchange in this system is not significant.

The electronic spectral properties of the cobalt complexes (table II) are similar to those of $\text{Co}[\text{3-pyr}(\text{CO}_2)]_2 \cdot 4\text{H}_2\text{O}$, the structure of which has been previously established⁷ as a typical pseudo-octahedral arrangement. Because of that it is reasonable to conclude that octahedral coordination around the cobalt atom prevails in the complexes of the

TABLE I
I.r. spectra (1800-1500cm⁻¹) of Co(II) and Ni(II) complexes with
isocinchomeric acid in Nujol mulls

| Compound | Absorption maxima (cm ⁻¹) ^a | | | | | | |
|---------------------------------------|--|-----------|-----------|-----------|------------------|--------|--------|
| Isocinchomeric acid (2,5 -) | 1690s; * | 1625w; | 1600m; | 1575m; | 1560w,sh; 1535w; | | |
| Co(II) isocinchomeronate tetrahydrate | 1685s; | 1650vs; * | 1610vs; | 1585vs; | 1560s; | 1540m; | 1535w. |
| Ni(II) isocinchomeronate trihydrate | 1720s; | 1705s; | 1690vs; | 1670br; * | 1610vs; | 1580s; | 1560m. |
| Co(II) isocinchomeronate monohydrate | 1685m; | 1675s; * | 1655vs; * | 1610vs; | 1588vs; | 1560s; | 1540m. |
| Ni(II) isocinchomeronate dihydrate | 1745m; | 1680m; * | 1615br; | 1575m; | 1560w; | 1540w. | |
| Co(II) isocinchomeronate trihydrate | 1685s; | 1650s; * | 1610s; | 1585s; | 1560m; | 1540m; | 1535w. |
| Ni(II) isocinchomeronate 2.5 hydrate | 1720s; | 1705s; | 1690vs; | 1670br; * | 1610vs; | 1580s; | 1560m. |

a Bands marked * are assigned to vasym (COO).
s strong, m medium, ms medium strong, w weak, br broad, sh shoulder

present work. Likewise, the nickel complexes have similar electronic spectral properties and these are characteristic^{12,13} of an approximate octahedral arrangement around the metal ion. In the case of the isolated dehydrates we have to accept that gross structural changes occurred with the cobalt compound and the -COO⁻ groups participate in the first coordination sphere with the resulting formation of polymeric species. However, the electronic absorption spectra are similar to those for a pseudo-octahedral stereochemistry.

The octahedral arrangement which would be proposed for the isolated complexes is shown in figure 1. The remaining water molecules per formula unit are hydrogen-bonded within the lattice.

TABLE II

Diffuse reflectance spectra of Co(II) and Ni(II) complexes with isocinchomeric acid^a

| Compound | Absorption maxima (kK) | | | | | | |
|---------------------------------------|------------------------|------------|-------------|------------|-----------|--------|-------|
| Co(II) isocinchomeronate tetrahydrate | 45.2s, br; | 37.0s, br; | 30.6s, br; | 19.9sh; | 8.3s, br. | | |
| Ni(II) isocinchomeronate trihydrate | 44.9s; | 37.8s; | 31.8s; | 29.05sh; | 16.4s; | 15.4s; | 9.6s. |
| Co(II) isocinchomeronate monohydrate | 37.0s; | 35.3s, sh; | 31.3br; | 18.3br; | 8.5br. | | |
| Ni(II) isocinchomeronate dihydrate | 44.7s; | 37.2s; | 31.4s; | 29.2sh; | 16.9s; | 15.1s; | 9.4s. |
| Co(II) isocinchomeronate trihydrate | 45.5s; | 37.9s; | 29.3vs, br; | 20.3s, br; | 9.0s. | | |
| Ni(II) isocinchomeronate 2.5 hydrate | 44.9s; | 37.8s; | 31.8s; | 27.05sh; | 17.1s; | 15.4s; | 9.6s. |

a) MgO used as reference,

b) 1kK = 1000cm⁻¹

TABLE III

Summary of magnetic data at room temperature and the Weiss constant of some of the complexes studied

| Compound | μ_{eff} | T (°K) | Θ |
|---------------------------------------|--------------------|--------|----------|
| Co(II) isocinchomeronate tetrahydrate | 4.61 | | |
| Ni(II) isocinchomeronate trihydrate | 3.20 | 293.5 | +9 |
| Co(II) isocinchomeronate monohydrate | 4.51 | | |
| Ni(II) isocinchomeronate dihydrate | 3.28 | | |
| Co(II) isocinchomeronate trihydrate | 4.60 | | |
| Ni(II) isocinchomeronate 2.5 hydrate | 3.22 | | |

TABLE IV

Magnetic properties of Ni(II) isocinchomerionate trihydrate

| T (°K) | X'm × 10 ⁶ c.g.s.u. | μ _{eff} (B.M.) |
|--------|-----------------------------------|-------------------------|
| 303.2 | 4235 | 3.22 |
| 297.2 | 4385 | 3.24 |
| 287.2 | 4419 | 3.20 |
| 275.2 | 4603 | 3.196 |
| 263.2 | 4821 | 3.199 |
| 233.2 | 5420 | 3.193 |
| 203.2 | 6162 | 3.178 |
| 173.2 | 7169 | 3.165 |
| 143.2 | 8578 | 3.148 |
| 113.2 | 10674 | 3.122 |
| 79.2 | 13465 | 2.933 |

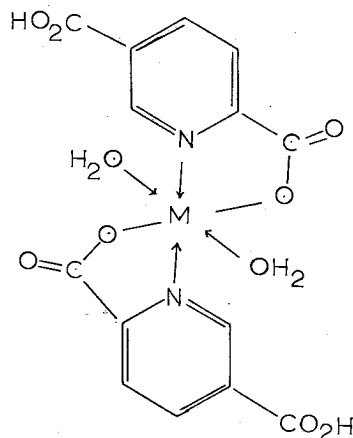


Fig. 1. The proposed structure of the isolated complexes.

Acknowledgment

I thank the Greek Ministry of Coordination for the award of a grant and Professor G.W.A. Fowles in whose department some measurements were taken.

ΠΕΡΙΛΗΨΙΣ

Ένώσεις συντάξεως του Co(II) και Ni(II). Μέρος I. Μαγνητικά και Φασματοσκοπικά ιδιότητες των συμπλόκων μετά δικαρβονικού όξέος της πυριδίνης.

Είς την παρούσαν εργασία άπεμονώθησαν αί σύμπλοκοι ενώσεις του κοβαλτίου (II) και νικελίου (II) μετά του περιφερειακού ύποκαταστάτου πυριδινο-2,5-δικαρβοξυλικού όξέος είς ύδατικά διαλύματα. Η αναλογία μεταξύ μετάλλου-ύποκαταστάτου ήτο 1:2, ενώ ό αριθμός των μορίων του ύδατος έποίκιλεν αναλόγως των συνθηκών. Ούτω, κατά την θέρμανσιν των ένυδατωμένων συμπλόκων ένώσεων είς τούς 100°C άπεμακρύνθη μέρος του ύδατος, τό όποίον έπανεκτήθη έν μέρει κατά την παραμονήν αύτων είς άτμοσφαιρικάς συνθήκας.

Αί σύμπλοκοι αὔται ἐνώσεις παρασκευάζονται εὐκόλως εἰς καλὴν ἀπόδοσιν, ἐφ' ὅσον χρησιμοποιοῦνται μικροὶ ὄγκοι ὕδατος. Αἱ ἐνώσεις αὐταὶ εἶναι ἀδιάλυτοι εἰς πολικά καὶ μὴ πολικά διαλυτικά μέσα, πρᾶγμα τὸ ὁποῖον ἐμποδίζει τὴν περαιτέρω διερεῦνησιν τῆς ἀγωγιμότητός των. τὸν προσδιορισμὸν τοῦ μοριακοῦ θάρους καὶ τὰς φασματικὰς ιδιότητάς των ἐν διαλύματι.

Ἐκ μετρήσεων τῶν υπερύθρων φασμάτων εὐρέθη, ὅτι ὑπάρχει ἐλευθέρα καρβοξυλομάς εἰς τὰς ἀπομονωθείσας ἐνώσεις, πρᾶγμα τὸ ὁποῖον ἀποτελεῖ ἰσχυρὰν ἐνδειξιν ὅτι ἐκ τῶν δύο καρβοξυλομάδων τοῦ μορίου τοῦ πυριδινο-2,5-δικαρβοξυλικοῦ ὀξέος μόνον ἡ μία εἶναι συνδεδεμένη μετὰ τοῦ μετάλλου.

Ἐκ τῶν μετρήσεων τῆς μαγνητικῆς ἐπιδεικτικότητος ἐφάνη, ὅτι μᾶλλον πρόκειται περὶ ἐνώσεων, ἢ κατασκευὴ τῶν ὁποίων στηρίζεται εἰς ὀκταεδρικὴν δομὴν ἀκόμη δὲ καὶ εἰς τὴν περίπτωσιν τοῦ $\text{Co}[2,5-\text{pyr}(\text{CO}_2)_2]_2 \cdot \text{H}_2\text{O}$, ὅπου πιστεύεται ὅτι, παρὰ τὴν ἐπιφερομένην ἀλλαγὴν ἔναντι τῆς τετραενυδατωμένης μορφῆς, ἡ ἔνωσις αὕτη ἐμφανίζει μία ψευδο-ὀκταεδρικὴν δομὴν μὲ συμμετοχὴν περισσοτέρων $-\text{COO}^-$ ομάδων. Τὰ ἀνωτέρω ὑποστηρίζονται ἐπιπροσθέτως καὶ ὑπὸ τῶν ἠλεκτρονιακῶν φασμάτων, ἔνθα ἐμφανίζονται χαρακτηριστικαὶ ἀπορροφήσεις τῆς ὀκταεδρικῆς δομῆς.

Εἰς τὸ σχῆμα (1) προτείνεται ἡ δομὴ τῶν ἀνωτέρω ἐνώσεων. Τυχὸν ἐπιπρόσθετος ποσότης ὕδατος συνδέεται ἐντὸς τοῦ κρυστάλλου διὰ δεσμῶν ὕδρογόνου.

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L'hydrolyse alcaline du phénobarbital

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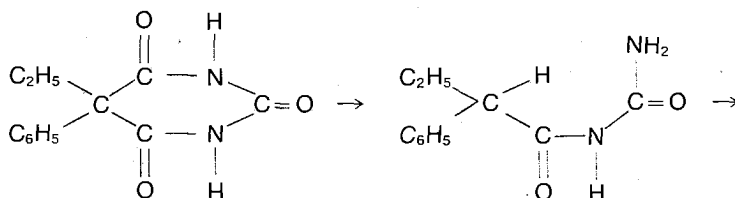
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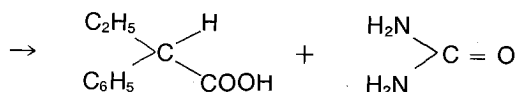
Une solution 6% de phénobarbital-2-¹⁴C a été chauffée à 80°C pendant 24 h. Le résidu a été dissous dans le CHCl₃. La phase aqueuse a été extraite aussi au CHCl₃. Une chromatographie sur papier dans le système alcool-n-amylique saturé par un tampon borate à pH 10 a démontré la présence du bicarbonate de sodium, de l'urée et de l'éthyl-phényl-acétyl-urée. Dans le cas du phénobarbital-5-¹⁴C nous avons signalé la présence du bicarbonate, de l'éthyl-phényl-acétyl-urée et de l'acide éthyl-phényl acétique. L'hydrolyse a été complète. Une simple dissolution du phénobarbital-5-¹⁴C dans 0,45N NaOH suivie d'une chromatographie a démontré la présence du bicarbonate, du phénobarbital, de l'acide éthyl-phényl-acétique et de l'éthyl-phényl-acétyl-urée. Le degré de décomposition était de l'ordre de 4% après 3 minutes et de 5,5% au bout d'une heure.

A solution of Phenobarbitone-2-¹⁴C sodium is heated for 24 hours at 80°C. The residue is taken up in CHCl₃ and the aqueous phase extracted by CHCl₃. Paper chromatography of the two phases in n-amyl alcohol saturated by a borate buffer of pH 10 system showed the presence of bicarbonate, urea and ethyl-phenyl-acetyl-urea. Under the same conditions phenobarbitone-5-¹⁴C yielded bicarbonate, ethyl-phenyl-acetyl-urea and ethyl-phenyl-acetic acid. The hydrolysis of the two kinds of phenobarbitone was considered to be a complete one. Simple dissolution of phenobarbitone-5-¹⁴C in a 0.45N NaOH, followed by paper chromatography in iso-amyl alcohol/ammonia/ethylene glycol system (V/V/V 85/15/5) yielded bicarbonate, phenobarbitone, ethyl-phenyl-acetic acid and ethyl-phenyl-acetyl-urea. The rate of hydrolysis was found to be 4% in 3 minutes time and 5.5% in the first hour.

Introduction

On sait que l'hydrolyse alcaline du phénobarbital provoque l'ouverture du cycle barbiturique (Kapadia et al.⁵ 1959, Benakis et al.² 1963). Les produits de cette hydrolyse sont: l'éthyl-phényl-acétyl-urée, l'acide éthyl-phényl-acétique et l'urée.





Dans ce travail nous étudions les conditions expérimentales de cette hydrolyse et nous discutons ses conséquences sur la détermination du phénobarbital dans des produits biologiques.

Matériel — Méthodes — Techniques

Nous avons utilisé du phénobarbital marqué soit en position 2 soit en position 5 du cycle barbiturique. Le phénobarbital-2-¹⁴C avait une activité spécifique de l'ordre de 15,2 mCi/mM et une pureté radiochimique, contrôlée par chromatographie sur papier, de l'ordre de 99,5%.

En ce qui concerne le phénobarbital-5-¹⁴C l'activité spécifique était de l'ordre de 17,57 μ Ci/mM et une chromatographie sur papier n'a démontré que l'existence du phénobarbital.

La phényl-éthyl-acétyl-urée est obtenue (M.P. Gold)⁴ par condensation du chlorure de l'acide éthyl-phényl-acétique avec l'urée en présence d'antipyrine.

L'acide éthyl-phényl-acétique est synthétisé à partir du benzonitrile (P. Gold⁴ 1958) par transformation en ethyl-benzonitrile. Ce dernier, par saponification, donne l'acide.

L'urée-¹⁴C employée avait une activité spécifique de 6,86 mCi/mM.

Pour l'hydrolyse complète du phénobarbital nous avons suivi les conditions expérimentales décrites par Kapadia. Une solution 6% de phénobarbital sodique a été placée dans une ampoule et chauffée à 80°C pendant 24 heures au moins au bain d'huile. Après cela l'ampoule a été cassée et le résidu déposé a été dissous dans le chloroforme. Ensuite la phase aqueuse a été extraite au chloroforme. Ainsi nous avons deux phases, une phase chloroformique et une phase aqueuse. La chromatographie a été faite sur papier Watman No. 1 dans les systèmes: alcool n-amylique saturé par un tampon borate à pH 10 et alcool isoamylique, ammoniac et éthylène glycol (85/15/5 V/V/V).

La radioactivité sur chromatogramme a été mesurée par un compteur sans fenêtre à courant gazeux (Benakis 1962¹) et chaque secteur évalué quantitativement par mesure directe en scintillation liquide (Beckman LS 200B) avec le mélange scintillant ESLA: naphtalène 80g, PPO 4g, POPOP 50 mg dans un litre de xylène, dioxane et éthanol (V/V/V 5/5/3). Le rendement est de l'ordre de 87%.

Des spectres ultra-violets de différents produits étudiés ont été réalisés au moyen du spectrophotomètre Beckman DB dans les conditions suivantes: a) phénobarbital, dans une solution 0,45N NaOH, concentration 25 μ g/ml, b) acide éthyl-phényl-acétique dans une solution 0,45N NaOH, concentration 0,5 μ g/ml.

Résultats

A. Hydrolyse complète

L'hydrolyse alcaline du phénobarbital suivie d'une chromatographie sur papier de deux phases dans le système alcool amylique saturé par un tampon borate à pH 10 nous a donné, après enregistrement des chromatogrammes, les résultats suivants:

a) Phénobarbital-2-¹⁴C, phase aqueuse: un pic sur spot qui correspond au bicarbonate de sodium, un pic à la place de l'urée et un pic à la place de l'éthyl-phényl-acétyl-urée.

b) Phénobarbital-2-¹⁴C, phase chloroformique: un pic qui correspond à l'urée et le pic de l'éthyl-phényl-acétyl-urée.

c) Phénobarbital-5-¹⁴C, phase aqueuse: un pic sur spot qui correspond au bicarbonate de sodium et le pic de l'acide éthyl-phényl-acétique.

d) Phénobarbital-5-¹⁴C, phase chloroformique: le pic de l'éthyl-phényl-acétyl-urée et le pic de l'acide éthyl-phényl-acétique.

Dans aucun cas nous n'avons observé de pic qui corresponde au produit inchangé; l'hydrolyse est donc complète dans ces conditions d'expérience.

B. Hydrolyse en fonction du temps.

Dans ce cas-là nous avons employé du phénobarbital-5-¹⁴C, car son hydrolyse donne de l'acide éthyl-phényl-acétique marqué, produit interférant dans le dosage du phénobarbital, comme nous aurons l'occasion d'y revenir.

Pour cela une certaine quantité de phénobarbital a été dissoute dans 0,45N NaOH. Après 3, 15, 30, 60 minutes nous avons neutralisé la solution. Ensuite nous avons procédé à une chromatographie sur papier dans le système alcool isoamylique, ammoniac, éthylène glycol. Dans ce système les R_f du phénobarbital, de l'acide éthyl-phényl-acétique et de l'éthyl-phényl-acétyl-urée sont 0,38, 0,43, et 0,95 respectivement. Au contraire le bicarbonate de sodium reste sur spot.

L'enregistrement de la radioactivité des chromatogrammes a démontré la présence, dans les quatre cas, du bicarbonate de sodium, du phénobarbital, de l'éthyl-phényl-acétyl-urée et de l'acide éthyl-phényl-acétique. Chacun des secteurs radioactifs des chromatogrammes a été découpé et mis dans 20ml de la solution scintillante ESLA, pour mesurer quantitativement la radioactivité; les résultats, exprimés en %, sont exposés dans le tableau suivant.

TABLEAU I
Pourcentage de produits d'hydrolyse en fonction du temps

| Temps min. | 3 | 15 | 30 | 60 |
|-----------------------------|-------|-------|-------|-------|
| Bicarbonate de sodium | 0,2% | 0,2% | 0,2% | 0,5% |
| Phénobarbital | 96,2% | 96,0% | 95,5% | 94,6% |
| Acide éthyl-phényl-acétique | 2,8% | 2,4% | 2,3% | 1,8% |
| Ethyl-phényl-acétyl-urée | 0,8% | 1,4% | 2,0% | 3,1% |

La figure 1 donne l'enregistrement de la radioactivité du chromatogramme de 60 minutes; nous y remarquons l'existence de quatre pics distincts.

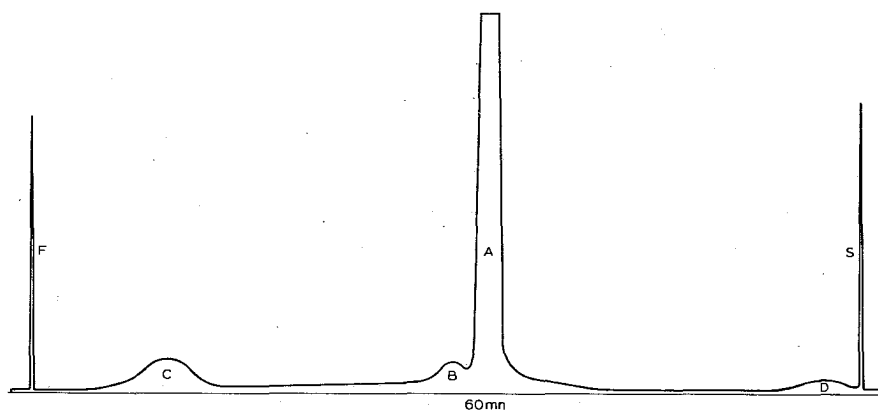


Fig. 1: Radiochromatogramme des produits d'hydrolyse après 60 minutes. A) Phénobarbital. B) Acide éthyl-phényl-acétique. C) Ethyl-phényl-acétyl-urée. D) Bicarbonate de sodium.

C. *Interférence de l'acide éthyl-phényl-acétique dans le dosage du phénobarbital.*

L'enregistrement des spectres UV du phénobarbital et de l'acide éthyl-phényl-acétique (fig. 2) dans une solution de 0,45N NaOH a démontré l'existence d'un maximum

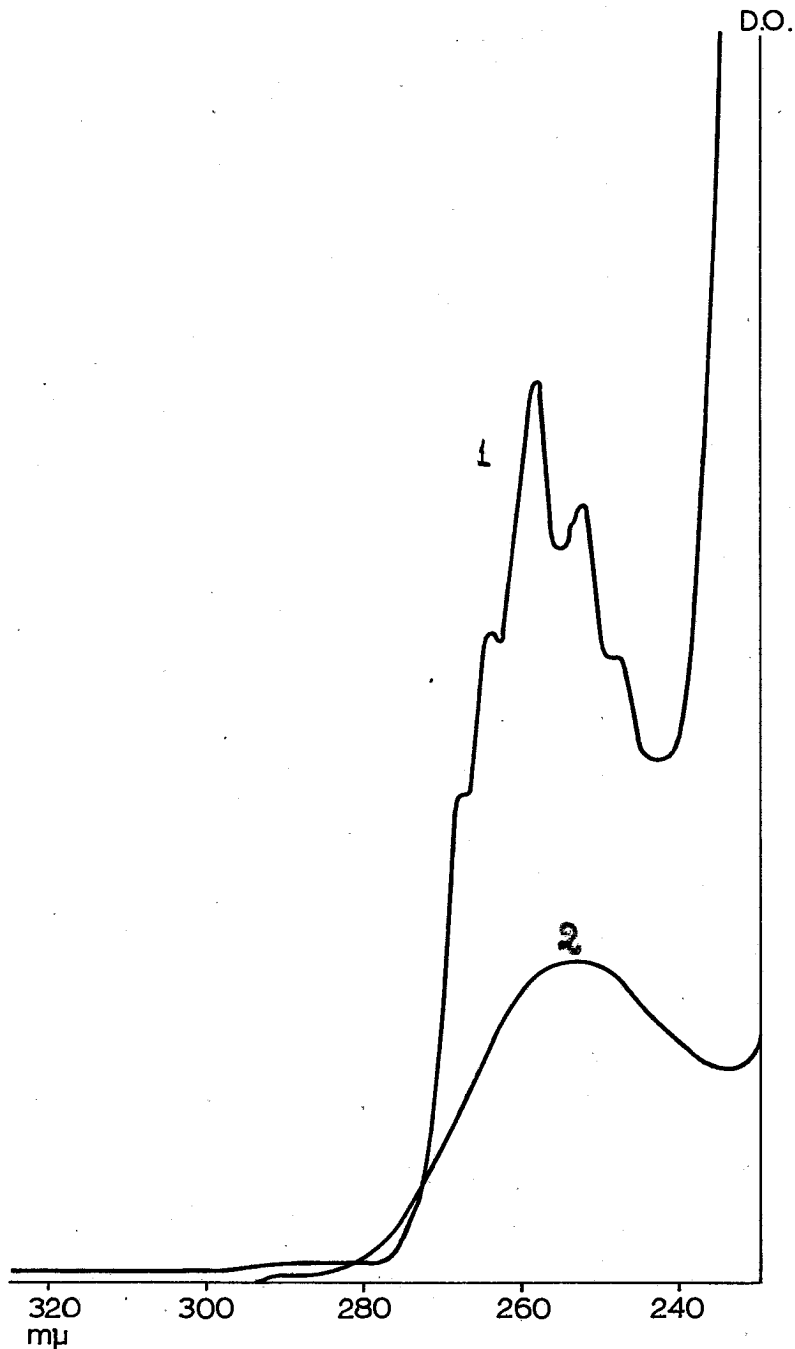


Fig. 2: Spectres UV du phénobarbital (1) et de l'acide éthyl-phényl-acétique (2).

à 254 nm (acide) et à 258 nm (phénobarbital). La fig. 3 donne les courbes d'étalonnage de ces deux produits à 260 nm et 258 nm (cas de l'acide). Cette longueur d'onde de 260 nm est choisie par tous les chercheurs pour le dosage du phénobarbital par spectrophotométrie (Broughton 1959³). L'acide éthyl-phényl-acétique peut intervenir lors du dosage du barbiturique à 260 nm. Nous constatons toutefois que la pente de la courbe d'étalonnage du phénobarbital est considérablement plus élevée que celle de l'acide éthyl-phényl-acétique.

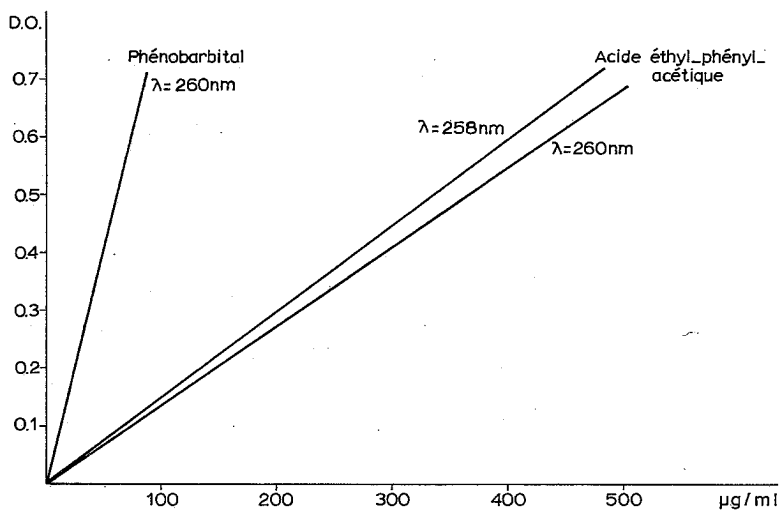


Fig. 3: Courbe d'étalonnage aux UV du phénobarbital et de l'acide éthyl-phényl-acétique.

Discussion

L'hydrolyse complète de phénobarbital a été déjà étudiée par Kapadia.⁵ Au contraire, Broughton et al.³ ont constaté une dégradation de 32% quand on chauffe au bain-marie une solution alcaline de phénobarbital pendant 15 min. Le pourcentage de cette dégradation sert à l'identification des barbituriques étant donné que leurs spectres UV sont identiques, chose qui ne permet que le dosage global des barbituriques dans un mélange inconnu.

Les deux chercheurs précités ont travaillé avec du phénobarbital non marqué et ils ont employé des méthodes classiques dont la sensibilité est inférieure à celle de la mesure de la radioactivité. L'étude d'une hydrolyse sous conditions modérées est alors difficilement réalisable, comme p.ex. la simple dissolution du produit dans 0,45N NaOH.

Dans nos expériences nous avons utilisé du phénobarbital marqué et nous avons pu dépasser ainsi les difficultés mentionnées. Nous avons alors constaté qu'une dissolution du phénobarbital provoque une décomposition déjà après trois min.

En ce qui concerne les produits de dégradation nos résultats s'accordent avec ceux des autres. Dans le cas du phénobarbital-5-¹⁴C nous n'avons pas signalé l'existence de l'urée et cela à cause de la position du marquage (position 5 du cycle). Au contraire, en travaillant avec du phénobarbital-2-¹⁴C nous avons trouvé ce produit de l'hydrolyse.

Comme nous l'avons déjà signalé, le dosage spectrophotométrique du phénobarbital ainsi que des autres barbituriques se fait à 260 nm dans une solution de 0,45N NaOH. Au cours de cette détermination le phénobarbital subit une décomposition de l'ordre de

4% déjà après trois minutes. En tenant compte de la pente de la courbe d'étalonnage et de l'interférence de l'acide éthyl-phényl-acétique provenant de cette décomposition dans le dosage du phénobarbital nous constatons qu'une légère décomposition de phénobarbital provoque une diminution notable de la densité optique à 260 nm. L'acide éthyl-phényl-acétique provoque une augmentation de la densité optique beaucoup plus faible que la diminution provoquée par l'hydrolyse du phénobarbital. Ainsi nous avons une source d'erreurs qui, dans certains cas, peut devenir importante comme p.ex. le cas des liaisons protéiniques des barbituriques et la détermination du phénobarbital dans des milieux biologiques.

ΠΕΡΙΛΗΨΙΣ

Ἀλκαλικὴ ὑδρόλυσις τῆς φαινοβαρβιτάλης.

Διάλυμα τοῦ μετὰ νατρίου ἄλατος τῆς φαινοβαρβιτάλης-2-¹⁴C θερμαίνεται ἐπὶ 24 ὥρας εἰς τοὺς 80°C. Τὸ στερεὸν ὑπόλειμμα διαλύεται εἰς CHCl₃ καὶ ἡ ὑδατικὴ φάσις ἐκχυλίζεται ὁμοίως διὰ CHCl₃. Χρωματογραφία χάρτου τῶν δύο φάσεων εἰς τὸ σύστημα κ-ἀμυλικὴ ἀλκοόλη κορεσθεῖσα διὰ ρυθμιστικοῦ διαλύματος βορικοῦ ὀξέος, KCl καὶ NaOH pH 10, ἔδειξε τὴν παρουσίαν διττανθρακικοῦ νατρίου, οὐρίας, αἰθυλ-φαινυλ-ακετυλ-ουρίας. Ὑπὸ τὰς αὐτὰς συνθήκας ἡ ὑδρόλυσις τῆς φαινοβαρβιτάλης-5-¹⁴C ἔδωσεν ὡς προϊόντα διττανθρακικὸν νάτριον, αἰθυλ-φαινυλ-ακετυλ-ουρίαν, αἰθυλ-φαινυλ-οξικὸν ὄξύ. Ἡ ὑδρόλυσις ἦτο πλήρης. Ἀπλῆ διάλυσις τῆς φαινοβαρβιτάλης-5-¹⁴C εἰς 0,45N NaOH καὶ μετὰ χρωματογραφίαν εἰς τὸ σύστημα ἰσοαμυλικὴ ἀλκοόλη-ἄμμωνία-αἰθυλενογλυκόλη (V/V 85/15/5) ἔδειξε τὴν παρουσίαν διττανθρακικοῦ νατρίου, φαινοβαρβιτάλης, αἰθυλ-φαινυλ-οξικοῦ ὀξέος καὶ αἰθυλ-φαινυλ-ακετυλ-ουρίας. Ὁ βαθμὸς ὑδρολύσεως ἦτο 4% μετὰ 3 λεπτὰ καὶ 5,5% εἰς τὸ τέλος τῆς πρώτης ὥρας.

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A Study of the Luminol-Fluorescence Decay

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(Received 30-11-71)

The fluorescence decay of Luminol and of 3-aminophthalic acid, studied with the aid of a nanosecond-pulse spectral source are reported as functions of pH. The decay times thus obtained are in the order of 7 and 5.5. nanoseconds at the pH of maximum emission. The spectral shifts of Luminol absorption and fluorescence as a function of pH are also reported. The results of the fluorescence decay measurements are verified by comparison with the results obtained by a new technique employing ultra-fast detection means. The possibility of energy transfer in the Luminol light reaction from the excited 3-aminophthalic anion produced, back to unreacted Luminol is also discussed.

Introduction

Measurement of the lifetime of the lowest electronically excited state is a very important factor in the study of luminescence processes. De-excitation followed by light emission usually obeys the function:

$$I = I_0 e^{-\frac{t}{\tau}} \quad (1)$$

where I is the luminescence intensity at time t , I_0 the luminescence intensity at $t=0$ (end of excitation) and τ the luminescence decay time defined as the time required for the luminescence intensity to fall to the I_0/e level. When luminescence is the sole path of de-excitation the decay is exponential and the lifetime τ equals the "natural lifetime" τ_0 giving rise to a quantum yield (Q) equal to 1 according to the equation:

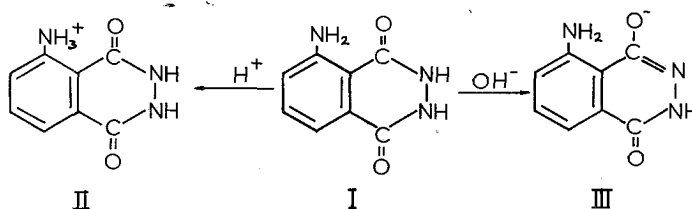
$$\tau = \tau_0 Q \quad (2)$$

In the event, however, of radiationless transitions leading to luminescence quenching as for example in the case of collisional quenching, the lifetime measured is smaller than the "natural lifetime" giving rise to quantum yields lower than 1 as is usually the case. Measurement, therefore, of luminescence lifetimes can give information regarding quantum yields, radiationless transitions and especially of energy transfer between unlike species.^{1,2,3} As fluorescence decay times of organic molecules usually lie in the region of a few nanoseconds (1 nsec. = 10^{-9} sec.), rather complicated instrumentation is necessary for the study of this phenomenon and means such as fluorescence depolarization, phase fluorimetry⁴ and Kerr cells,¹ flash lamps,^{5,6,7} electron beams⁸ etc., have been employed in such studies.

In studying chemiluminescence, it is a well accepted fact that the chemiluminescence emission spectrum of a light-reaction is identical with the photoluminescence (fluorescence or phosphorescence depending on the multiplicity of the excited state involved) spectrum of the emitting species under similar conditions.^{9,10} It follows, there-

fore, that study of the chemiluminescence of a system must be accompanied by a study of the fluorescence of the chemiluminescent compound and of the light-reaction products.

Luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) (I) until recently the most highly chemiluminescent compound known has been extensively studied¹¹⁻¹⁹ but due to the complexity of the problem arising from the low quantum yields involved, the reaction mechanism remains obscure and even the identification of 3-aminophthalate anion as the emitting species is being questioned.



The study of the Luminol fluorescence decay as well as of 3-aminophthalic acid was therefore undertaken and is described in the present work with the hope that a little more light might be shed on the chemiluminescent reaction and on the quenching processes involved.

Results and Discussion

Fluorescence decay was studied in the present work by two methods, both employing a nanosecond-flash source. Our results obtained by the first method, a modification of the one reported by Chen et al.,³ were verified by a second method proposed by ourselves and described in the next section. Both methods were tested with compounds of known fluorescence decay prior to their employment in the study of the Luminol and 3-aminophthalic acid fluorescence with good and consistent results. (The error in both methods is not greater than 10%. Although deviations were never greater than 0.3 ns., the decay times reported here are the mean values of three measurements.)

With an observed maximum radiative lifetime of 7 nanoseconds for Luminol and 5.5 nanoseconds for 3-aminophthalic acid and taking into account the maximum fluorescence quantum yields reported²⁰ for these two compounds as 0.55 and 0.08 at the same pH values, the natural (mean radiative) lifetimes could be calculated from equation (2) as 12 and 70 nanoseconds respectively. The rate of fluorescence can be calculated from the relationship:

$$K_F = \frac{1}{\tau_0} \quad (3)$$

Substituting the values 12 and 70 nanoseconds for τ_0 one arrives to $K_F(\text{Luminol}) = 8.3 \times 10^7 \text{ sec}^{-1}$ and $K_F(\text{Aminophthalic acid}) = 1.4 \times 10^7 \text{ sec}^{-1}$.

The pH dependence of the observed decay times is shown in Fig. 1 for Luminol and 3-aminophthalic acid. The curves are roughly similar to those published earlier on the pH dependence of the fluorescence intensity.^{14,20} The neutral Luminol molecule (I) exhibits, as expected, the longest lifetimes the dependence of which on the pH in the region 3 to 9 is much less pronounced than the dependence of fluorescence intensity on pH in the same region. It should also be noted that maximum decay time is found at pH 6 while maximum fluorescence intensity is reported by a number of authors at a pH of about 4.8.^{14,20,21,22} It should be pointed out, however, that the curve of Fig. 1 reported here, represents a truer image of the Luminol fluorescence as being less dependent on absorption and emission spectral characteristics. Another important aspect of the curve of Fig. 1 is the peak at pH 0.75: This implies the fact that protonated Luminol

(II) is an entirely different fluorescent species. This is in agreement with Fig. 2 which shows the emission-maximum shift as a function of pH. A dramatic change is also observed at this low pH region. Something similar is observed in the case of the absorption maxima. Until a pH of 1.5 is reached, there is only one absorption maximum about 290 nm. It is at this pH value that the second absorption maximum in the region of 340 nm appears which increases in intensity on ascending the pH scale. The decay of 3-aminophthalic acid on the other hand is almost independent of pH in the region 4 to 11, indicating that if the Luminol chemiluminescence maximum quantum yield appears at a pH of

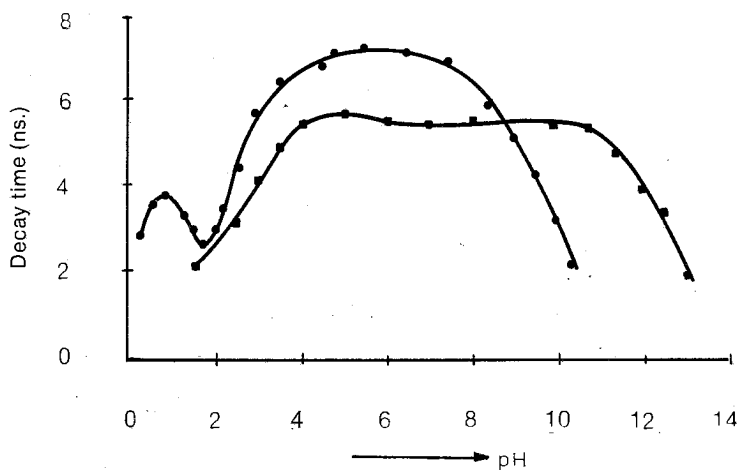


Fig. 1. Fluorescence decay of Luminol (—●—) and of 3-aminophthalic acid (—■—) as a function of pH.

about 11 this must be due to some aspect of the Luminol oxidation reaction mechanism and not to the emission characteristics of the excited species.

The Luminol as well as the 3-aminophthalic acid fluorescent decay was found to be independent of concentration in the range $5 \times 10^{-2} - 10^{-5}$ M. This in itself indicates a complete absence of concentration quenching. As chemiluminescence quantum yields have also been shown²⁰ to be independent of concentration and as the decay of the fluorescent pulse in our experiments could be easily superimposed on the exponential decay produced by the computer,³ the assumption that 3-aminophthalate is the emitting species (irrespective of emission wavelength)¹⁸ in the Luminol light reaction is further supported. Indeed, all evidence points towards absence of energy transfer from 3-aminophthalate back to unreacted Luminol.

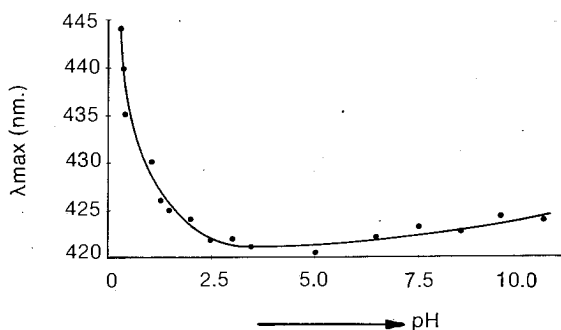


Fig. 2. Fluorescence-maximum shift as a function of pH.

Experimental

(i) Measurement of fluorescence decay. Method employing decay-time computer.

A T.R.W. model 31A Nanosecond Spectral Source was employed for exciting our samples, in combination with a deuterium quartz lamp generating a near-continuum in the spectral region 200-350 nm. Short pulses of light were thus obtained with a risetime and a falltime of 1.6nsec., a duration of approximately 4nsec., and a repetition rate of 2 kc. The light pulses were passed through a quartz relay lens assembly, an iris and a monochromator employing a Balzers' R-UV 255 nm. interference filter and were focussed on the sample contained in a quartz cell. The fluorescence pulses thus generated were passed at right angles through a Jena GG 400 Cut-filter cutting all light below 400 nm., then through a second relay lens assembly and were focussed on the photocathode of an R.C.A. 931A photomultiplier tube. This was connected to a Tektronix 555 dual beam oscilloscope with 1A1 units displaying the fluorescence pulse shape and feeding data to a T.R.W. 32A decay time computer. To obtain the excitation pulse shape, the sample cylindrical cuvette was removed from the sample compartment and was replaced by a similar cuvette covered with metallic silver forming a first surface mirror. The cut-filter was also removed as the light pulse displayed was in the U.V. region. With the oscilloscope set at "Upper beam — Channel A" (50 Ohm termination) and a time base 20 nsec./cm., and with the aid of the iris, a pulse height of 2.2 cm. was produced on the oscilloscope screen; a computer simulated light-pulse was then superimposed on the excitation pulse (Lower-beam, Channel B, time-base 200nsec./cm.), the computer keeping the pulse

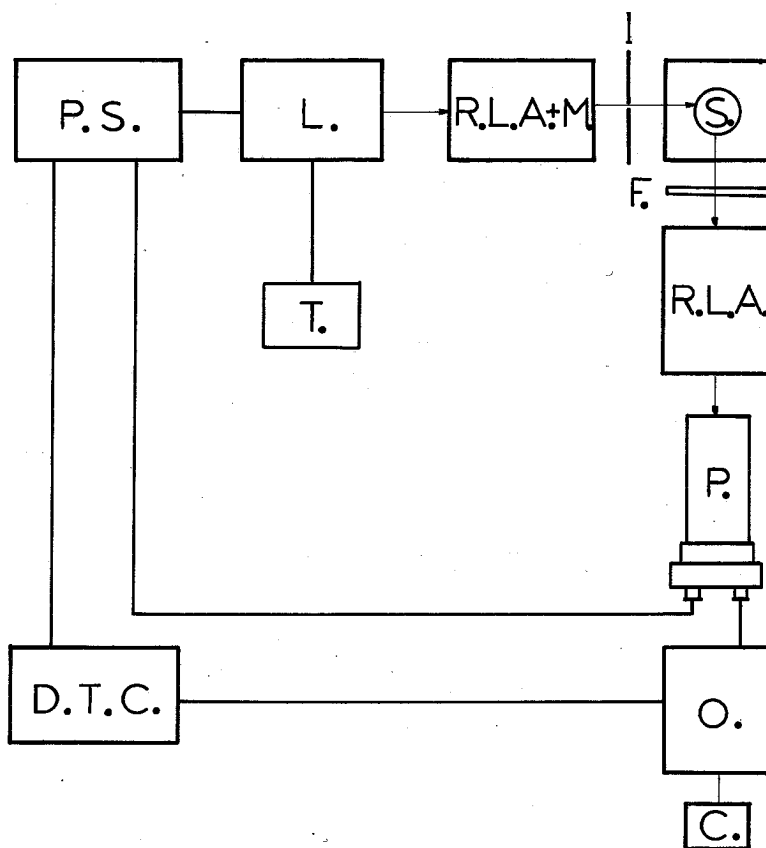
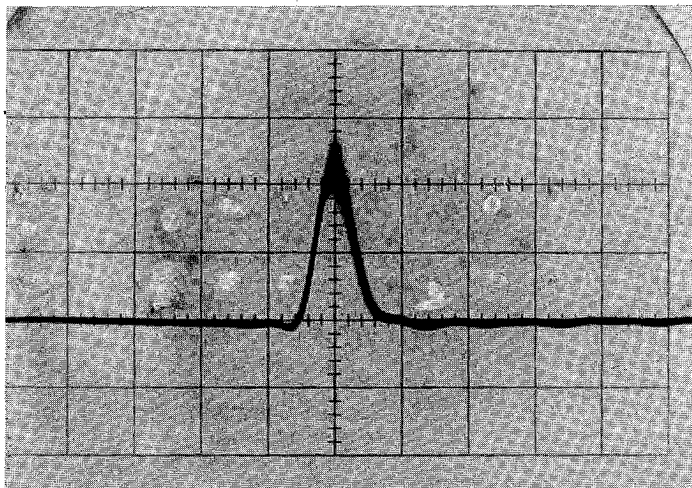
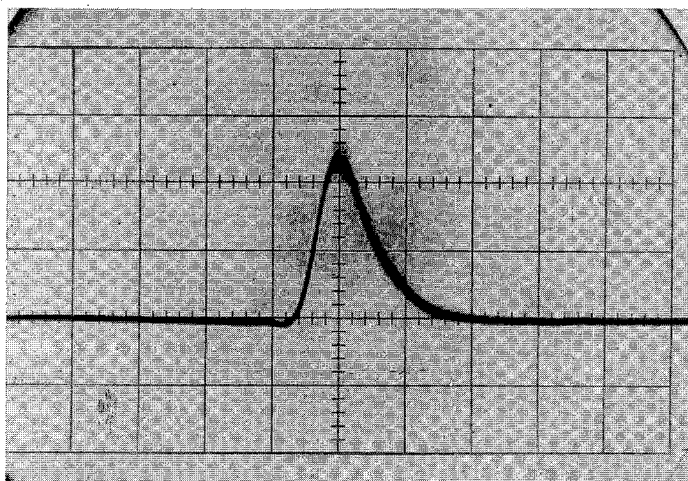


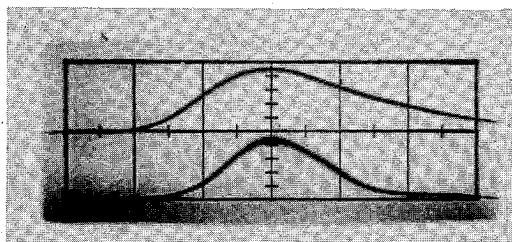
Fig. 3. Block diagram of the apparatus employed in the measurement of decay times with Decay Time Computer. P.S., Power Supply; L., Lamp; R.L.A., Relay Lens Assembly; I., Iris; S., Sample; F., Filter; M., Monochromator; P., Photomultiplier; O., Oscilloscope; C., Camera; D.T.C., Decay Time Computer; T., Trigger.



Photograph 1. Computer simulated pulse superimposed on the fluorescence-excitation pulse.



Photograph 2. Computer simulated pulse superimposed on the fluorescence-emission pulse.



Photograph 3. Excitation and fluorescence pulses. Time base 5nsec. per division.
Luminol 0.0001 M., pH 9.5. Calculated decay time 5nsec.

height and shape in its memory. Photograph 1 shows the excitation pulse with the simulated computer pulse superimposed. The sample cuvette and the cut-filter were then inserted and with the oscilloscope set at "Upper beam-Channel A" the fluorescence pulse was displayed. The computer-simulated light pulse was then guided to "Lower beam-Channel A" of the oscilloscope and was modified in shape and height to match the fluorescence pulse: the decay time was then obtained directly from the computer. Photograph 2 shows the computer simulated pulse superimposed on the fluorescence decay pulse.

The block diagram of the experimental assembly is shown in Fig. 3.

(ii) *Measurement of fluorescence decay. Method without decay time computer.*

The mirror-cuvette was placed in front of the deuterium quartz lamp and was illuminated with light pulses (λ_{max} 252 nm., isolated with the aid of a Balzers R-UV 252 nm. interference filter) at a repetition rate of 1Kc. The reflected light pulses were viewed with a Philips 56AVP photomultiplier (S11-type photocathode) operating at 2150 Volts, the circuitry of the photomultiplier's base being equipped with a suitable divider giving anode pulse risetimes as low as 2nsec. The photomultiplier was connected to a Tektronix 519 high speed oscilloscope (time-base 5nsec./cm) equipped with a polaroid camera with the aid of which the exciting light pulse shape displayed on the screen was photographed. The mirror cuvette was then replaced by the sample cuvette and a suitable combination of filters was inserted between the sample cuvette and the photomultiplier tube allowing passage of light with λ_{max} 430 nm. and the fluorescence pulse shape was also photographed. By suitable enlarging of the photographs and by measuring the fluorescence decay starting from a point on the decay curve at which the excitation pulse was virtually ended; the fluorescence life-time could be measured with good accuracy. The excitation and fluorescence pulses are shown in Photograph 3.

The block diagram of the experimental assembly is shown in Fig. 4.

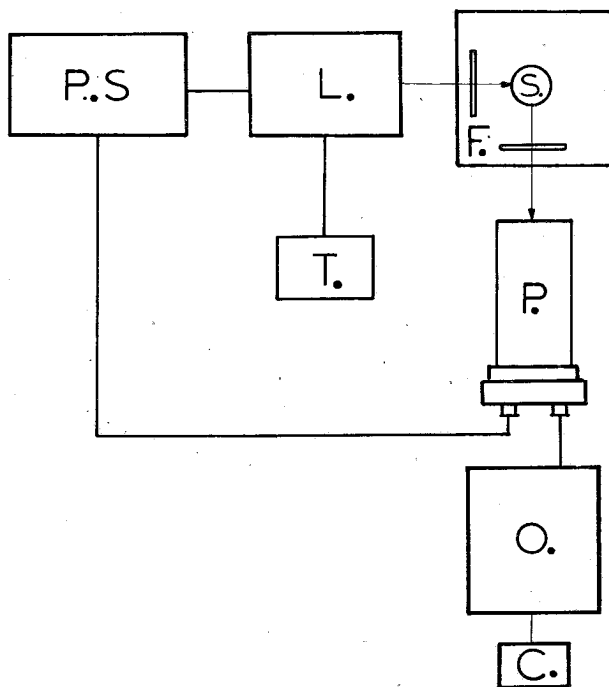


Fig. 4. Block diagram of the apparatus employed in the measurement of decay times, without decay time computer. P.S., Power Supply; L., Lamp; F., Filter; S., Sample; P., Photomultiplier; O., Oscilloscope; C., Camera; T., Trigger.

(iii) *Decay times as a function of pH.*

The solutions employed were aqueous alkaline 10^{-4} M Luminol solutions in which the pH was varied by the addition of small amounts of hydrochloric acid. The pH was measured just prior to the measurement of the decay time; this technique was also employed with 3-aminophthalic acid and the results are shown in Fig. 1.

(iv) *Decay times as a function of concentration.*

These were measured employing aqueous Luminol solutions (pH 5) in the concentration range $5 \times 10^{-1} - 10^{-5}$ M. None of the above-described techniques could be employed at lower concentrations due to the low fluorescence intensities involved.

(v) *Absorption and emission as a function of pH.*

This was measured with the aid of a Cary 14 spectrophotometer and the position of the maxima for the various pH values was tabulated. It should be noted that a peak at 340 nm. appears at pH 1.5 and keeps increasing in intensity on ascending the pH scale.

The fluorescence maxima were obtained employing a Perkin-Elmer 203 Fluorescence Spectrophotometer and are uncorrected (excitation λ_{\max} 365 nm.). The emission maximum shift as a function of pH is shown in Fig. 2.

Acknowledgements

The authors wish to thank Mr. B. Papadopoulos for running the fluorescence spectra reported here.

Thanks are also extended to Mrs. E. Sekeri-Papazoglou for her assistance in the above-described experiments.

ΠΕΡΙΛΗΨΙΣ

Μελέτη της άποσβέσεως φθορισμού της Λουμινόλης.

Οί χρόνοι άποσβέσεως (1/e) του φθορισμού της Λουμινόλης και του 3-άμινοφθαλικού όξέος έμελετήθησαν με την βοήθειαν φασματικής πηγής παλμών της τάξεως νανοδευτερόλεπτου ως συναρτήσεις του pH. Οί μέγιστοι χρόνοι άποσβέσεως είναι 7 και 5.5 νανοδευτερόλεπτα αντίστοιχως. Παραλλήλως περιγράφονται αι μετατοπίσεις των μεγίστων άπορροφήσεως και έκπομπής συναρτήσεις του pH. Τα άποτελέσματα των μετρήσεων των χρόνων άποσβέσεως έπαληθεύονται διά συγκρίσεως με άποτελέσματα ληφθέντα διά νέας, εις την άνα χείρας έργασίαν προτεινομένης και περιγραφομένης μεθόδου, εις την όποιαν χρησιμοποιούνται ύπερ-ταχεία μέσα άνιχνεύσεως άποφευγομένης της χρησιμοποιήσεως ύπολογιστού. Συζητείται επίσης ή δυνατότης μεταφοράς ένεργείας κατά την χημιφωταυγή αντίδρασιν της Λουμινόλης, από τό προκύπτον διεγερμένον άμινοφθαλικόν άνιόν εις μη αντίδρασαντα μόρια Λουμινόλης.

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A Circular Dichroism Band at 300 nm observed in the High Coordination Number Complexes of L-Threonine with Copper (II) in Aqueous Solutions

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(Received 21-12-71)

The cupric L-threonine complexes having a high ligand to metal ratio, show a positive circular dichroism band at 300 nm. Cupric complexes of L-alanine, L-valine and L-serine do not show a corresponding band by increasing the concentration of the ionic form of L-amino acid in aqueous solutions. This band is probably due to a $n(s, p) \rightarrow \sigma^* x_2-y_2$ charge transfer transition from the ligand to the metal ion.

Introduction

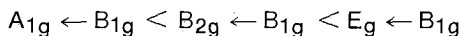
Two predominant Cotton effects were observed in the visible Circular Dichroism spectrum of most bis (L-amino acids) Cu (II) chelates. One is located in the region 720-710 nm, which always exhibits a positive sign and another in the region 620-590 nm.

The latter Cotton effect has in the majority of cases a negative sign and is more intense than the former.^{1,2}

In the $3d^9$ cupric system under D_{4h} symmetry the following sequence has been accepted for the d orbitals:³



In this system there are three one electron transitions with the following order of increasing energy:



As the symmetry is reduced either to C_{2h} or to C_2 splitting of the $E_g \leftarrow B_{1g}$ transition occurs.

The transition $A_{1g} \leftarrow B_{1g}$ is magnetic dipole forbidden but both $B_{2g} \leftarrow B_{1g}$ and $E_g \leftarrow B_{1g}$ are magnetic dipole allowed under the D_{4h} point group.

The bis (L-amino acids) Cu (II) chelates belong to the C_2 point group. The discussion of the spectroscopic properties of bis (L-amino acids) Cu (II) chelates using arguments based on the D_{4h} symmetry, which is parent for the C_2 , is a rigorous approximation. In this respect we can assign to the 720-710 nm C.D. band the $A_{1g} \leftarrow B_{1g}$ transition character and the 620-590 nm band the $B_{2g} \leftarrow B_{1g}$.

There are several cases where a third C.D. band has been observed in the region 570 to 460 nm which is probably due to the degenerate $E_g \leftarrow B_{1g}$ transition.²

This transition exhibits either a positive or a negative sign. A positive sign of this band can be correlated with an apical chelation to the Cu (II).²

The ultraviolet spectrum of the cupric complexes of amino acids consists of two C.D. bands. One is located in the longer wave length region from 260 nm to 240 nm and another in the shorter wave length from 225 nm to 215 nm.

The 260 to 240 nm band has an intense absorption accompanied by a negative sign and is due to a charge transfer transition from the ligand to the cupric ion. The 225 to 215 nm band has in the majority of cases a positive sign and originates from a $\pi \rightarrow \pi^*$ transition of the ligand.⁴

The $n \rightarrow \pi^*$ C.D. band of the carbonylic transition of the amino acid ligand of the cupric complexes which ought to be found at the vicinity of 220 to 240 nm with a negative sign, in accordance with the octant rule, is not observed. This C.D. band probably is lost in the region of the negative charge transfer C.D. band at 240-260 nm.

Results

The present paper reports the effects caused upon increasing the ligand concentration in respect to Cu (II), of some bis (L-amino acid) Cu (II) chelates on the visible and the near ultraviolet C.D. bands. The complexes of L-alanine, L-valine, L-serine and L-threonine were examined. All ligands were in the anionized form.

Addition of up to 24 times as much anionic amino acid ligand as Cu (II), gave no significant change in the visible and near ultraviolet absorption or C.D. spectra compared to the 2:1 cupric complexes of L-alanine and L-valine (table I).

TABLE I
Circular Dichroism and Absorption in the Visible and
Near Ultraviolet of Some Complexes of Amino Acids with Cu (II)

| L-Amino Acid | moles of aa | | C.D. λ max. [nm], $\Delta\epsilon$ max. | Absorption λ max. [nm], ϵ max. |
|--------------|------------------|------------|--|--|
| | gr. atom Cu (II) | | | |
| Alanine | 2 | 622, -0.09 | 577, -0.08 sh | 619,57 |
| » | 3 | 610, -0.10 | | 618,58 |
| » | 24 | 610, -0.09 | | 628,59 |
| Valine | 2 | 592, -0.35 | | 622,57 |
| » | 3 | 582, -0.41 | | 617,60 |
| » | 24 | 594, -0.38 | | 622,59 |
| Serine | 2 | 627, -0.19 | | 624,51 |
| » | 3 | 610, -0.25 | | 625,51 |
| » | 24 | 580, -0.22 | | 629,57 |
| Threonine | 2 | 595, -0.26 | | 614,53 |
| » | 3 | 592, -0.30 | 305, +0.25 (+0.08)** | 621,55 305,50* |
| » | 4 | 586, -0.38 | 300, +0.38 (+0.09) | 621,55 |
| » | 12 | 578, -0.31 | 300, +0.70 (+0.06) | 616,54 |
| » | 16 | 578, -0.35 | 300, +0.85 (+0.05) | 616,60 |
| » | 18 | 576, -0.35 | 300, +0.93 (+0.04) | 616,58 |
| » | 24 | 578, -0.33 | 300, +1.03 (+0.04) | 616,60 |
| » | 30 | 570, -0.30 | 300, +1.08 (+0.04) | 613,52 |

sh = shoulder, ** no peak or shoulder, ϵ was read from the absorption curve, ** values of $\Delta\epsilon$ max in parenthesis are based on ligand concentration.

In the cases of L-serine and L-threonine a slight shift to shorter wave length of the visible C.D. band is observed by increasing the ratio of moles of amino acid per gr. atom of Cu (II). This shift probably indicates more nitrogen environment around the cupric ion.

Only in the case of L-threonine complex a dramatic change in the near ultraviolet C.D. spectrum is observed, where on increasing the ligand to metal ratio above two from three up to thirty a positive C.D. band appears at 305-300 nm as shown in figure 1.

The intensity of the C.D. band increases according to the diagram in figure 2 with increasing ratio of ligand to the metal ion.

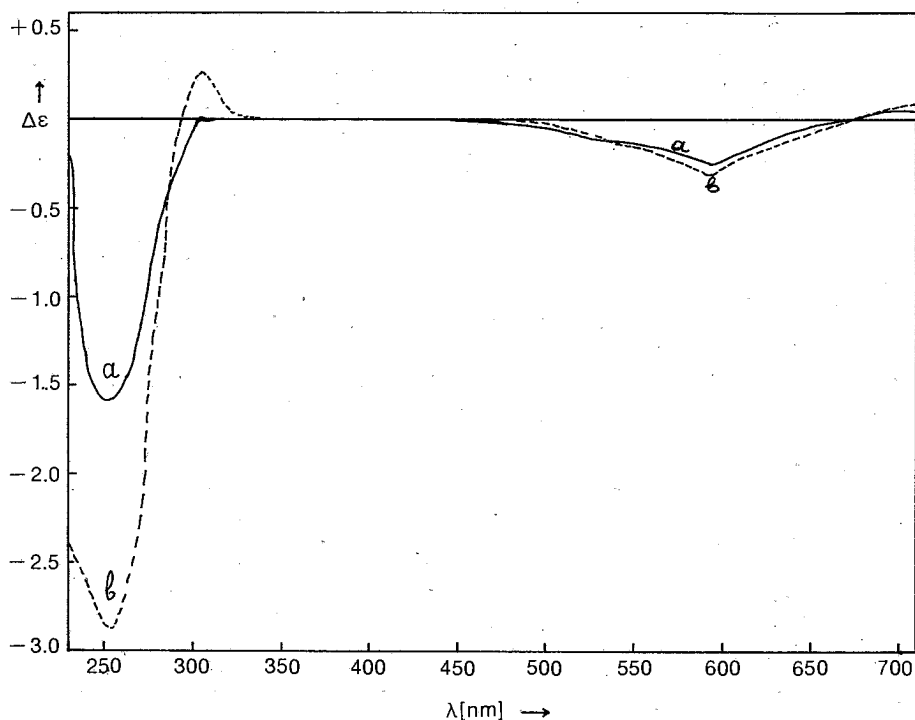


Fig. 1: Circular Dichroism in the visible and near Ultraviolet of the (a) bis (L-threonato) Cu (II) and (b) tris (L-threonato) Cu (II) complexes.

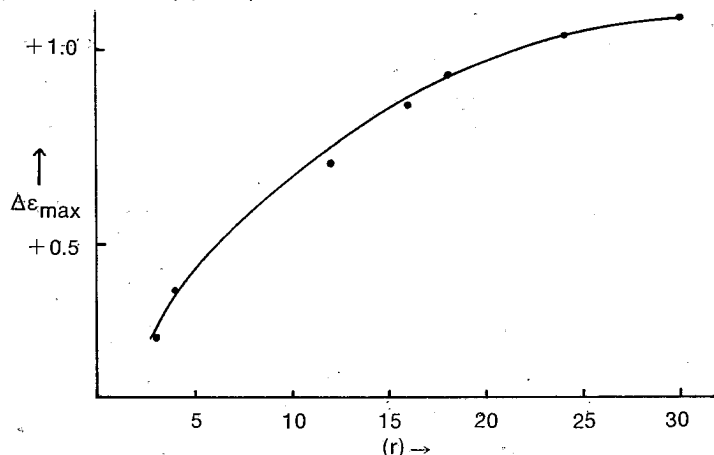


Fig. 2: Variation of the $\Delta\epsilon_{\max}$ of the 300 nm C.D. band with the ratio (r) of the moles of aa. per gr. atom Cu (II).

The absorption spectrum at room temperature of the aqueous solutions of high ligand to metal ratio complexes of L-threonine with Cu (II) does not show a corresponding band or shoulder at 300 nm. A value $\epsilon = 50$ was read from the absorption spectrum of $[\text{Cu}(\text{L-threo})_3]^{1-}$ complex at 305 nm. The value of ϵ increases considerably from 315 nm until the maximum value ϵ ca. 12×10^3 is reached at 255 nm; this absorption band can be correlated to the charge transfer transition at 260 nm of the bis (amino acids) Cu (II) complexes.

Discussion

When ligands are approaching the cupric ion in the bis (L-amino acids) Cu (II) complex along the z molecular axis the resulting high coordination number complexes may well be represented by the structure indicated in figure 2, in which water molecules are replaced from the apical positions.

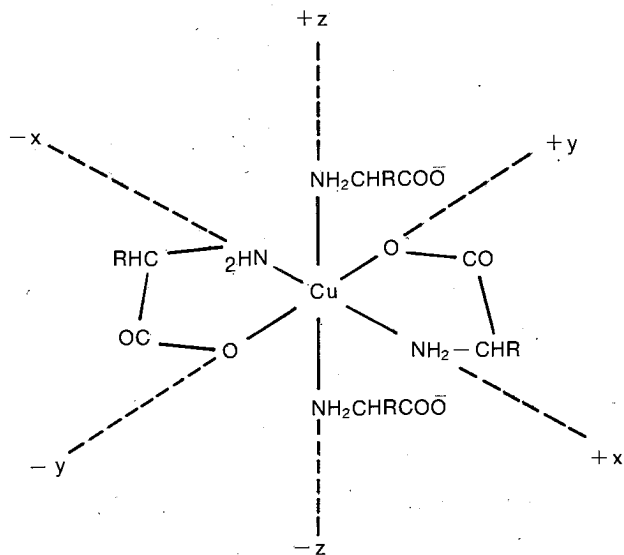


Fig. 3: Schematic representation of the high coordination number complexes of the amino acids with Cu (II).

Graddon and Munday⁵ have demonstrated that high coordination number complexes of amino acids with Cu (II), of the same structure as in figure 2, cannot be formed in solution when the ligand is possessing strongly non-polar and large R groups. In the case of L-valine and L-alanine the high coordination number complexes are not formed because these amino acids possess strongly non-polar R radicals. L-serine and L-threonine can predominately give high coordination number complexes owing to their polar alcoholate groups.

In the high coordination number amino acid cupric complexes the d_{xz} and d_{yz} orbitals of the cupric ion are shifted to the higher energies. Consequently the transition from $d_{x^2-y^2}$ to either d_{xz} or d_{yz} orbitals already split under the C_2 symmetry is forced to be displaced towards higher energies. If the 300 nm C.D. band was a ligand field band caused by a $E_g \leftarrow B_{1g}$ transition which usually occurs at the region from 570 to 460 nm, a shift of 160 nm is very unreasonable.

Table I shows that the $\Delta\epsilon_{\text{max}}$ increases with the ligand to metal ratio if $\Delta\epsilon_{\text{max}}$ is calculated based on the Cu (II) concentration. On the contrary if $\Delta\epsilon_{\text{max}}$ is calculated

based on the ligand concentration $\Delta\epsilon_{\max}$ reaches a maximum value when the ligand to metal ratio becomes four and then decreases slightly. This result indicates that the 300 nm C.D. band is rather a ligand transition.

Another possibility for the band is to be a $n \rightarrow \pi^*$ transition of the carbonyl group of the ligand. L-threonine in acid, neutral and alkaline solutions does not show a C.D. band at the neighborhood of 300 nm. The $n \rightarrow \pi^*$ transition of the L-threonine carbonyl is located at 208-223 nm.⁶ Considerable shifts of the $n \rightarrow \pi^*$ transition C.D. bands of the amino acids after complexation with Cu(II) and Ni(II) have not been observed.⁴ Therefore the above assignment is ruled out.

A charge transfer nature of the 300 nm C.D. band seems more likely. The reason why this C.D. band is observable only in the case of L-threonine complexes can be ascribed to the two asymmetric carbon atoms of L-threonine causing a stronger perturbation to the chromophoric center. L-serine possesses only one asymmetric carbon atom exhibiting weaker perturbations. Charge transfer bands of the cupric-amino acid system are due to the transitions $n(s, p) \rightarrow \sigma^* x^2-y^2$. A large number of such transitions could be optically active and we tentatively propose that the 300 nm C.D. band is one of them.

The investigation of the 300 nm C.D. band may be useful for the in vitro identification of the mixed complex L-histidine-Cu-L-threonine. This complex is stable when either of its components is in high ratio in respect to Cu(II). L-histidine-Cu-L-threonine was identified in the human serum.⁷

Experimental

Amino acids were obtained from Cyclo Chem. Co. chromatographically pure. Copper (II) chloride and carbonate free sodium hydroxide aqueous solutions were standardized by the usual procedures. Weighed amounts of ligands were mixed with appropriate volume of the copper (II) chloride solution. The resulting solutions were adjusted by calculated equivalent amounts of sodium hydroxide solution to convert all amino acid ligand in the anionized form.

The absorption spectra were measured on a Cary 14 spectrophotometer and C.D. spectra on a Durrum-Jasco ORD/UV5 recording spectropolarimeter with a C.D. attachment. All experiments were performed at 22-24°.

The optical density of the solutions used for C.D. measurements was varied from 1 to 1.5. Distilled water was used as reference material in the cells for obtaining the C.D. spectra. Calibrations of the intensity scale of the C.D. instrument were performed using as reference material d-10-camphor sulfonic acid in concentration 1mg/ml in water solution and 1 cm cell. $\Delta\epsilon$ was measured as a difference in molar absorptivity between the left and right circularly polarized light based on cupric ion concentration. The extinction coefficient (ϵ) was also calculated based on Cu(II) concentration.

The experimental part of the present work was carried out at the Chemistry Department of the University of Virginia.

ΠΕΡΙΛΗΨΙΣ

Περί μιᾶς ταινίας στροφικού διχρωϊσμοῦ εἰς 300 nm, παρατηρουμένης εἰς ὑδατικά διαλύματα συμπλόκων ὑψηλοῦ ἀριθμοῦ μοριακῆς ἐντάξεως τῆς L-θρεονίνης μετὰ Cu (II).

Ὅταν εἰς τὰ ὑδατικά διαλύματα τοῦ συμπλόκου δις (L-θρεονικοῦ) Cu (II) αὐξηθῆ ἡ συγκέντρωσις τῆς ἀνιονικῆς μορφῆς τῆς L-θρεονίνης εἰς τρόπον ὥστε ὁ λόγος τῶν moles τῆς L-θρεονίνης ὡς πρὸς τὰ gr. atoms τοῦ Cu (II) νὰ εἶναι 3 ἕως 30, παρατηρεῖται θετικὴ ταινία στροφικοῦ διχρωϊσμοῦ εἰς τὰ 305-300 nm μὴ παρατηρουμένη εἰς τὸ σύμπλοκον τοῦ δις (L-θρεονικοῦ) Cu (II). Ἐξετάσθησαν ὁμοίως τὰ ἀντίστοιχα σύμπλοκα τῆς L-ἀλανίνης, L-βαλίνης καὶ L-σερίνης. Εἰς οὐδὲν ἐξ αὐτῶν παρατηρήθη ἀνάλογος ταινία, δι' αὐξήσεως τῆς συγκεντρώσεως τῆς ἀνιονικῆς μορφῆς τοῦ L-ἀμινοξέος ἐν ὑδατικῷ διαλύματι. Πιθανῶς ἡ ταινία εἰς τὰ 305-300 nm νὰ ὀφείλεται εἰς μίαν ἐκ τῶν ὀπτικῶν ἐνεργῶν $n(s, p) \rightarrow \sigma^* x^2-y^2$ ἠλεκτρονικῶν μεταπτώσεων ἐκ μεταφορᾶς φορτίου ἐκ τῆς ἀνιονικῆς L-θρεονίνης πρὸς τὸ κατιόν Cu (II).

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Über einige Grenzflächenreaktionen zur Bildung von polymeren Catenaverbindungen

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(Received 10-1-72)

Mit Hilfe einiger orientierender Grenzflächenreaktionen ist es möglich zwei ringförmige Moleküle hoher Gliederzahl in der Form von polymeren Catenaverbindungen miteinander zu verketten. Die Bildung von ringförmigen Polymeren wird in Gegenwart eines Polyoxacyclans bzw. eines Cyclosiloxans mit circa 60 Gliedern, an den Grenzflächen von H_2O , Hg und von Wasserschichten, die an NaCl adsorbiert sind, vorgenommen. Die spektroskopische Untersuchung der Reaktionsprodukte liefert Beweise für die Bildung der polymeren Catenaverbindungen.

It is possible by the aid of the orienting action of interfaces to link two high-membered ringmolecules to form chains of polymeric catena compounds. The formation of ringpolymers in the presence of polyoxacyclane or cyclosiloxan with 60 members at the surface of H_2O , Hg and water layers adsorbed on NaCl leads to the linked ring molecules. The spectroscopic investigation of the reaction products proves the formation of polymeric catena compounds.

In der vorliegenden Publikation soll über die Ergebnisse einer über mehrere Jahre sich erstreckenden Untersuchung berichtet werden, welche die Synthese von polymeren Catenaverbindungen durch Kondensations- bzw. Polymerisationsreaktionen an Grenzflächen zum Gegenstand hat.

Catenane sind Verbindungen, welche mindestens aus zwei Ringmolekülen A und B bestehen die miteinander verketten sind ohne durch eine chemische Bindung verbunden zu sein (Abb. 1).

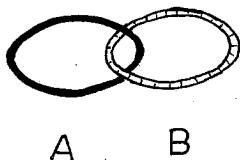


Abb. 1.

Niedermolekulare Catenaverbindungen, bis zu drei Ringmolekülen sind durch E. Wasserman^{1, 9, 10, 11} sowie von A. Lüttringhaus G. Schill und Mitarbeiter² durch gezielte Synthese dargestellt worden.

Vor mehreren Jahren hat der eine von uns (G.K.) im chemischen Kolloquium der Universität Freiburg i.Br. den Vorschlag gemacht polymere Catenaverbindungen d.h. Verbindungen bei welchen eine grosse Zahl zweier Ringssysteme A und B zu einer langen Kette zusammengefügt sind (Abb. 2) dadurch zu synthetisieren, dass man an einer Grenzfläche eine Kondensations — bzw. Polymerisationsreaktion die zu Ringmolekülen führen

kann in Gegenwart einer Ringverbindung mit grosser Gliederzahl vornimmt. Die orientierende Wirkung der Grenzfläche auf polare Moleküle sollte dazu verwendet werden um eine Einfädung langgestreckter Moleküle durch grosse ringförmige Moleküle zu erleichtern und zu erreichen.

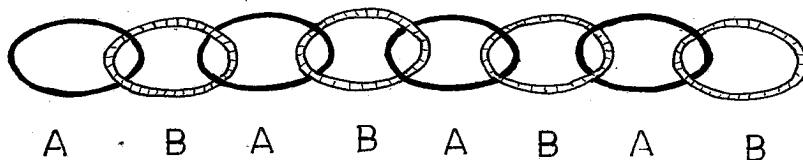


Abb. 2.

Schon die ersten Versuche, die im Physikalisch-Chemischen Institut der Universität Freiburg i.Br. ausgeführt und welche durch die Deutsche Forschungsgemeinschaft unterstützt wurden (1965-1967), brachten deutliche Hinweise auf die Verwirklichung einer solchen Einfädung von linearen Polymeren durch ringförmige Moleküle, die zur Bildung von Polycatenanen führte. Die Versuche wurden im Physikalisch-Chemischen Laboratorium der National Research Foundation in Athen fortgesetzt und die ersten Ergebnisse sind in zwei Publikationen^{3,4)} mitgeteilt worden.

Im Laufe der Jahre wurde eine sehr grosse Zahl von Versuchen ausgeführt, wobei drei verschiedene Arbeitsweisen, mit dem gemeinsamen Merkmal von Kondensationsreaktionen an Grenzflächen, angewandt wurden. Wir wollen im Folgenden vier typische Versuche beschreiben.

Versuch I. Ein rechteckiger Trog aus Plexiglas von 1,5 cm Tiefe und 2700 cm² Fläche wird mit reinem, destilliertem Wasser derart gefüllt, dass die Wasseroberfläche etwas über den Rand des Gefässes ragt. Sie wird von den geringen Spuren von Verunreinigungen durch "Fegen" mit Barrieren aus feingeschliffenen Plexiglasstäben befreit. Auf dieser Wasserfläche wird durch Verdampfen einer ätherischen Lösung der berechneten Menge von Hexadecan-1-16-dicarbonsäure (Thapsiasäure) und der Ringverbindung "Crown-60" im Molverhältnisse 1:1, durch Spreiten ein monomolekularer Film gebildet. Die "Crown 60"-Ringverbindung ist ein 60-gliedriger Ring des Dibenzopolyäthoxacyclans (Abb. 3).

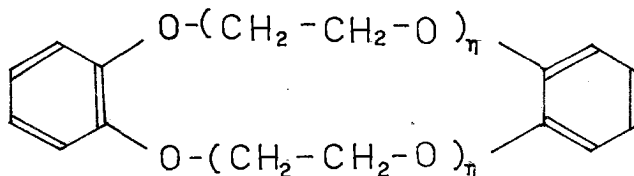


Abb. 3

welcher nach dem Verfahren von Pedersen⁵ aus Brenzkatechin und Dichloropolyoxyäthylen hergestellt wurde. Das für die Herstellung der letzten Verbindung benutzte Polyoxyäthylenglycol hat ein mittleres Molekulargewicht von 400, so dass das resultierende Dibenzopolyäthoxacyclan eine Mischung von Ringpolymeren mit variierendem n ist, dessen Mittelwert einem "Crown 60" d.h. einem 60-gliedrigen Ring der obigen Konstitutionsformel entspricht.

Der Äther, wie alle verwendeten Lösungsmittel sind einer sorgfältigen Reinigung unterworfen worden. Sie müssen fettfrei sein und dürfen keinen Rückstand hinterlassen. Dieser Reinheitsgrad wird so geprüft, dass ein ml des Äthers auf der Wasseroberfläche der Langmuir-Waage zur Verdampfung gebracht wird und durch Zusammenrücken der

Barrieren der entstehende Oberflächenseitendruck gemessen wird. Das Lösungsmittel darf bei einer Kompression von 700 auf 38 cm² nicht mehr als 20 Dyn/cm Oberflächenseitendruck zeigen.

Auf die Wasseroberfläche wird, bei variierender Kompression, eine ätherische Lösung des 1,12-Diaminododecans aufgebracht. Nach Verdampfen des Äthers wird der aus einer Mischung von Thapsiasäure, "Crown 60" und Diaminododecan bestehende Oberflächenfilm mit Hilfe eines feinen Luftstrahles aus einer Glaskapillare, durch die entstehende Wellenbewegung, durchgerührt, bis die Salzbildung beendet ist.

Der langsam sich bildende Oberflächenfilm, der an sich nicht sichtbar ist wird mehrmals durch Verschiebung der Barrieren komprimiert bzw. dilatiert. Nach Verlauf

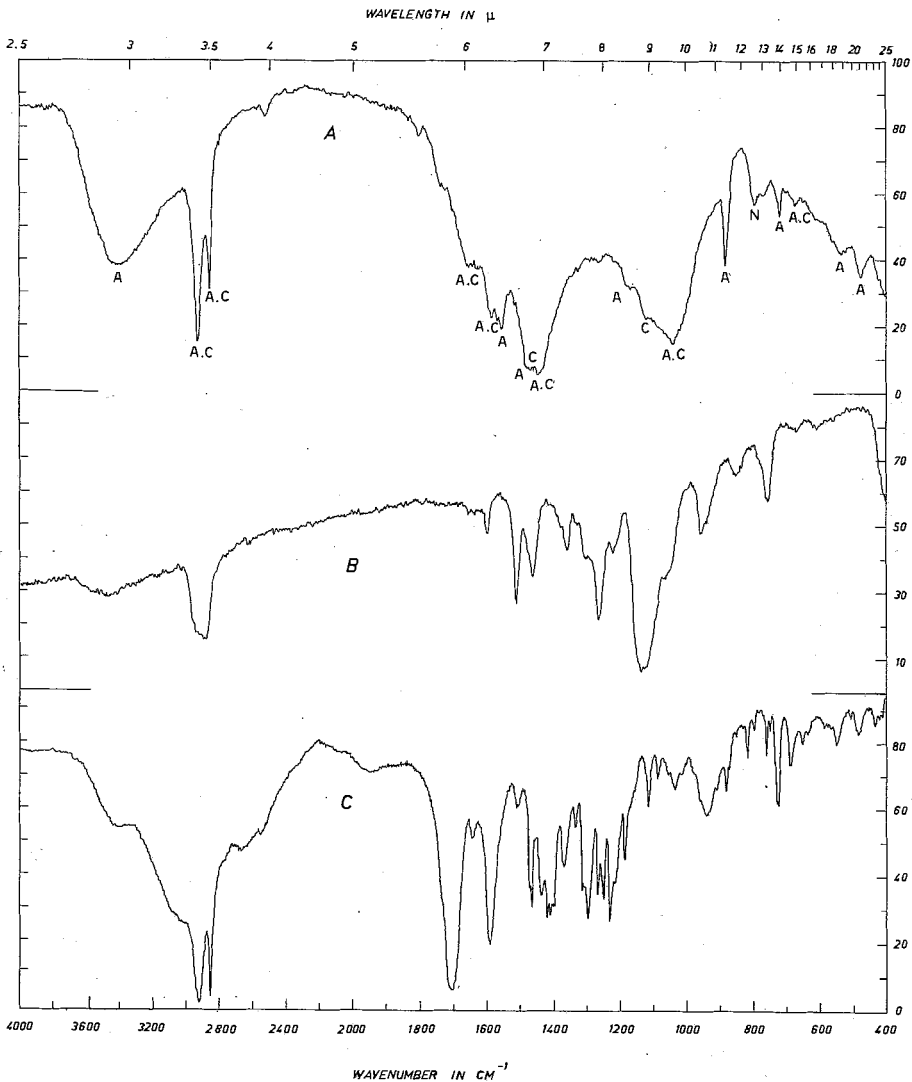


Abb. 4. IR-Spektren: (A) Reaktionsprodukt von Thapsiasäure und 1-12 Diaminododecan in Gegenwart von "Crown 60". (B) "Crown 60" und (C) Salz aus Thapsiasäure und 1-12-Diaminododecan.

von ca. 10-20 Min. wird der gebildete Oberflächenfilm durch Zusammenrücken der Barrieren bis auf 1 cm Abstand zusammengepresst, und daraufhin das nunmehr sichtbare Oberflächenprodukt mit einem Porzellanspatel zusammengefeigt und gesammelt. Die nach dieser Arbeitsweise erhaltenen Mengen von 30-40 einzelnen Versuchen wurden vereinigt (20-35 mg) und nach dem Trocknen im Mikro-Soxhlet mit CCl_4 erschöpfend extrahiert. Der Rückstand wurde IR-spektroskopisch mit den Ausgangsverbindungen verglichen.

Aus Abb. 4 ist zu ersehen, dass das erhaltene Spektrum (A) sowohl Banden des Diammoniumdodecans der Thapsiasäure (C) als auch Banden der Ringverbindung Crown-60 (B) enthält. Man beobachtet aber darüberhinaus, wie auch aus der Zusammenstellung der Tabelle 1 hervorgeht, dass die Lage der Crown-60 Banden und des Thapsates gegenüber der Verbindungen in reinem Zustand schwach verschoben sind, und zwar um $5\text{-}50\text{ cm}^{-1}$ in beiden Richtungen.

Im Falle einer grösseren Bandenanhäufung ist es oft schwierig zu beurteilen, ob eine verschobene Bande der höher-oder der niedriger liegenden Frequenz angehört. Wo die Form der Bande kein Hinweis dafür liefert entscheiden wir uns für die wellenzahlmässig am nächsten liegende Bande.

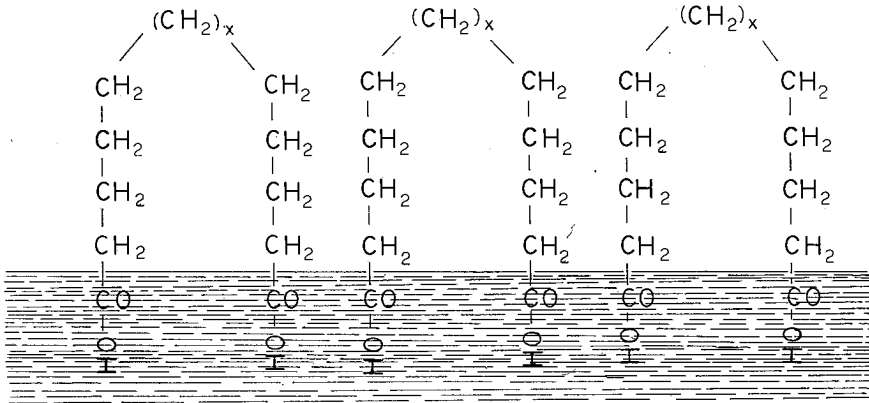
Wir betrachten die Tatsache der Verschiebung der Banden, welche den Verschiebungen der Einschlussverbindungen gleichen, als eine Indikation für die Einfädung des gebildeten polymeren Ammoniumthapsates durch die Crown-60 Verbindung.

Der *Bildungsmechanismus* der polymeren Catenane nach der vorgeschlagenen Oberflächenmethode ist mutmasslich der folgende: Durch Spreitung der Dicarbonsäure auf der Wasseroberfläche bildet sich ein monomolekularer Film bei welchem die Dicarbonsäuremoleküle die in Abb. 5a angegebene Orientierung zur Wasseroberfläche aufweisen.

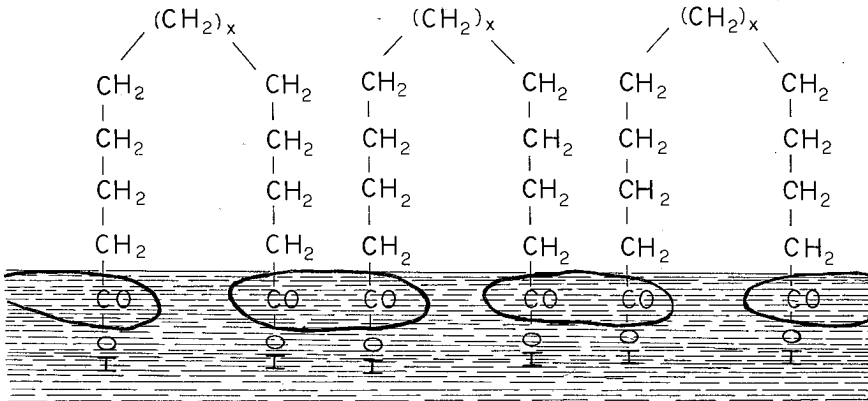
TABELLE I

| Reakt. Produkt | Lage der IR-Banden | | | | Verschiebungen gegenüber der reinen Substanz in cm^{-1} | |
|----------------|--------------------|--------------|----------|--------------|--|------|
| | Crown-60 | Amm. Thapsat | Crown-60 | Amm. Thapsat | | |
| 475 | — | 486 | — | — | — | — 9 |
| 535 | — | 550 | — | — | — | — 15 |
| 670 | — | 655 | — | — | — | + 15 |
| — | — | 690 | — | — | — | — |
| 718 | 754 | 725 | — | -36 | — | - 7 |
| 792 | — | 800 | — | — | — | - 8 |
| 879 | 851 | 881 | — | +28 | — | - 2 |
| — | 936 | — | — | — | — | — |
| — | 955 | — | — | — | — | — |
| 1040 | 1060 | 1035 | — | -20 | — | + 5 |
| 1117 | 1132 | 1118 | — | -15 | — | - 1 |
| 1165 | 1220 | 1188 | — | — | — | -23 |
| — | 1260 | — | — | — | — | — |
| 1440 | — | 1440 | — | — | — | 0,0 |
| 1460 | 1460 | 1468 | — | 0,0 | — | - 8 |
| 1550 | 1510 | — | — | +40 | — | — |
| 1563 | — | — | — | — | — | — |
| 1580 | 1600 | 1591 | — | -20 | — | -11 |
| 1620 | — | — | — | — | — | — |
| 1650 | — | 1647 | — | — | — | + 3 |
| 2860 | 2880 | 2855 | — | -20 | — | + 5 |
| 2935 | 2920 | 2920 | — | +15 | — | +15 |
| 3420 | 3470 | 3420 | — | -50 | — | 0,0 |

Die hydrophilen COOH-Gruppen tauchen ins Wasser ein, während die hydrophoben CH₂-Gruppen zur Luft hinausragen. Der Abstand der Carboxylgruppen kann durch die Kompression bzw. Dilatation des Filmes mit Hilfe der beweglichen Oberflächenbarrieren beliebig variiert werden. Der hochgliedrige Ring "Crown-60", welcher als kapillaraktive Verbindung sich ebenfalls an der Oberfläche anhäuft, verteilt sich zwischen den Dicarbonsäuremolekülen (Abb. 5b). Die grosse Flexibilität dieses Ringes wird durch die Abhängigkeit des Spreitungsdruckes eines Oberflächenfilmes von der ihm zur Verfügung stehenden Fläche demonstriert. Die π-F Kurve zeigt mehrere Stufen deren Auftreten und Bedeutung bei Hochpolymeren bereits in einer früheren Arbeit diskutiert worden ist.^{6,8}



a



b

Abb. 5

Bei einer solchen Einstellung der beiden Molekülarten zueinander besteht, rein statistisch, eine gewisse Wahrscheinlichkeit für eine Einfädung der Dicarbonsäure, welche einen halben noch offenen Ring formiert, durch den grossen Ring. Eine der vielen Möglichkeiten ist in Abb. 5b für den eindimensionalen Fall dargestellt worden. Diese gegenseitige Orientierung kann im folgenden Schritt durch die Zugabe des 1,12-Diamino-

dodecans, fixiert werden, indem es zu einer Ammoniumsalzbildung kommt, unter Ring-schliessung an den Carboxylgruppen. Hierbei entstehen die polymeren Catenane. Das Reaktionsprodukt wird zusammengefügt und gesammelt.

Eine der wahrscheinlichen Formeln für das obengennante Catenan wird in Abb. 6 wiedergegeben.

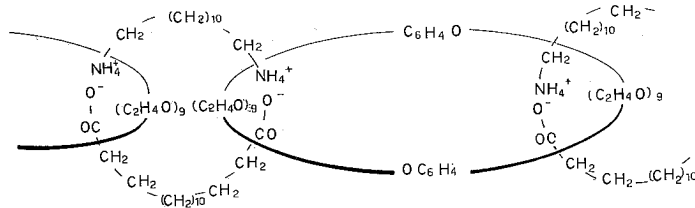


Abb. 6

Der beschriebene Bildungsmechanismus kann sich auch bei den folgenden Versuchen II bis IV einstellen, bei welchen die Reaktionen entweder sich an einer sich ständig erneuernden Hg-Oberfläche oder an einer Wasserschicht die an NaCl adhärirt ist und die sich ebenfalls immer wieder erneuert, abspielen.

Versuch II. In diesem Versuch haben wir durch einen experimentellen Kunstgriff die grosse Zahl (30-40) der einzelnen Spreitungen und Fegungen an dem Längmuirschen Trog vom Oberflächenversuch I zu einem einzigen vereinigt. Zu diesem Zwecke wurde eine H₂O-Oberfläche von 1300 cm² in einem kleinen Raum dadurch geschaffen, dass 2 g NaCl der spezifischen Oberfläche 650 cm²/g in einem Exsiccator einer Wasserdampf-atmosphäre ausgesetzt wurden bis 73 mg Wasser aufgenommen worden sind. Aus obigen Daten errechnet sich, dass eine Wasserschicht von der Dicke von 2500 Å sich auf der NaCl-Oberfläche bildet. In 15 ml einer Mischung von Äther und Chloroform wurden 143 mg Thapsiasäure und 325 mg "Crown-60" gelöst. Sie wurden in einem Rundkolben zu der obigen Menge des behandelten NaCl hinzugegeben und unter Evakuierung kräftig geschüttelt. Die beiden Substanzen spreiten sich beim vollkommenen Entfernen des Lösungsmittels auf der am NaCl adhärirenden Wasserschicht. Zu diesem Adsorbat wurden dann 105 mg. Trimethylhexamethylendiisocyanat (Abb. 7) gelöst in

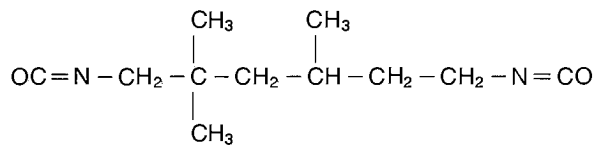


Abb. 7

CHCl₃, hinzugegeben und die Mischung bei 50° unter zeitweiligem Evakuieren kräftig geschüttelt. Nach Beendigung der Anlagerungsreaktion wurde, zur Aufarbeitung, das Reaktionsprodukt-NaCl-adsorbat mit Wasser behandelt und das nach Auflösen des NaCl zurückbleibende Öl solange mit Wasser ausgewaschen bis das Waschwasser keine NaCl-Reaktion mehr zeigte. Das Öl wurde alsdann mit CHCl₃ und daraufhin mit heissem CCl₄ behandelt, sodass insgesamt 4 einzelne Lösungsfractionen gewonnen wurden. Das IR-Spektrum der nach dem Verdampfen des CCl₄ zurückbleibenden öligen Produkte wurde zwischen NaCl-Plättchen aufgenommen.

Es muss sogleich hervorgehoben werden, dass die IR-Spektren sowohl dieser Fraktionen als auch des unlöslichen Rückstandes aneinander gleich sind. Sie bestehen aus den Banden der Ringverbindung "Crown-60" und den Banden des Polyamidoanhydrites mit nur kleinen Lageverschiebungen (Abb. 8) die in Tabelle II zusammengestellt sind. Das Intensitätsverhältnis der Banden des "Crown 60" zu den Anhydritbanden variiert bei den einzelnen Lösungsfractionen zwischen 1,05 und 1,60.

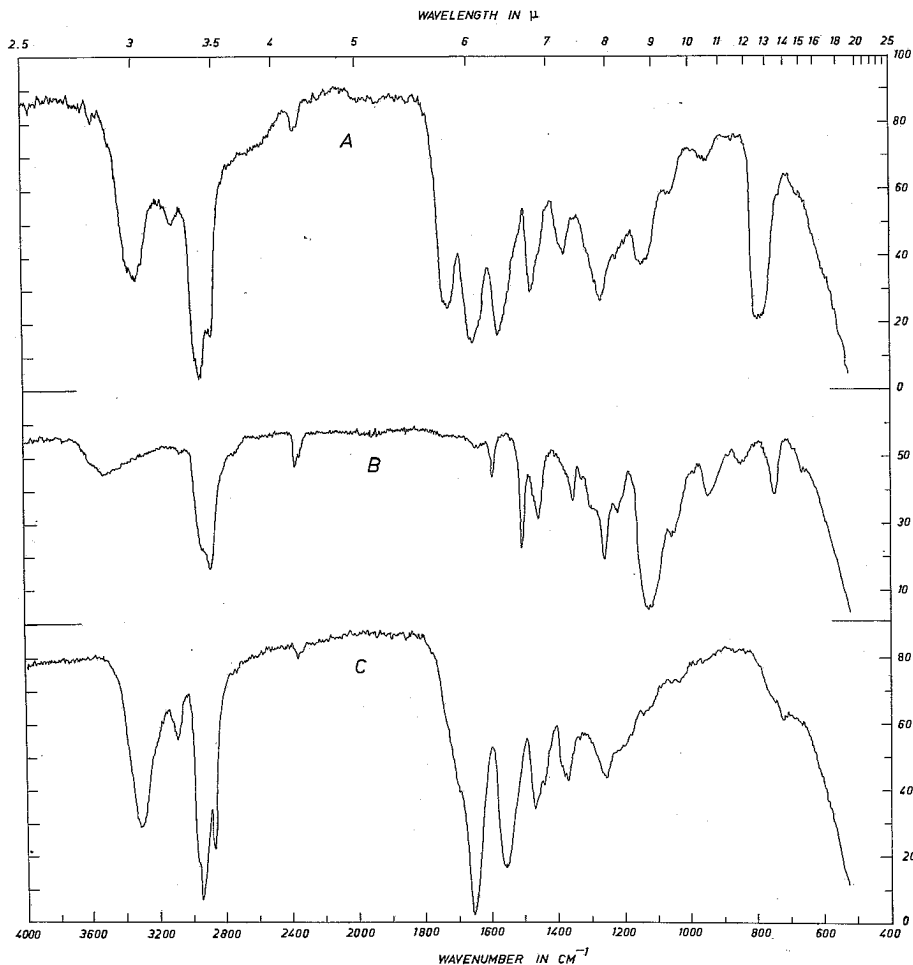


Abb. 8. IR-Spektren: (A) Reaktionsprodukt von Thapsiasäure und Trimethylhexamethylendiisocyanat in Gegenwart von "Crown 60". (B) "Crown 60". (C) Polyamidoanhydrit aus Thapsiasäure und Trimethylhexamethylendiisocyanat.

Die Molekulargewichte der einzelnen Lösungsfraktionen wurden nach der kryoskopischen Methode mit C_6H_6 als Lösungsmittel bestimmt und zwischen 1780 und 4980 gefunden. Wenn man das Verhältniss der Bandenintensität des "Crown 60" zu den des Anhydrites der einzelnen Fraktionen gegen das Molekulargewicht derselben aufträgt, so erhält man die in Abb. 9 dargestellte Kurve. Es ist möglich durch Extrapolation auf den Quotienten Null das Molekulargewicht des Anhydrites, aus welchem die Catena-Verbindung aufgebaut ist, zu bestimmen. Man findet den Wert 1494, welcher sehr nahe neben dem Molekulargewicht eines trimeren Amidoanhydrites von 1488, liegt.

Mit steigendem Molekulargewicht wird die Löslichkeit in den zur Kryoskopie benutzten Lösungsmitteln immer kleiner und damit parallel fällt die Genauigkeit der Bestimmung. Der prozentual grösste Anteil der gebildeten Reaktionsprodukte entzieht sich, wegen Schwerlöslichkeit, der osmotischen Molekulargewichtsbestimmung. Das IR-Spektrum dieser Produkte besteht jedoch, wie bereits auseinandergesetzt, aus den Banden des Polyamidoanhydrites und der "Crown 60" Verbindung.

Wir haben die Lösungsfraktionen einer absteigenden papierchromatischen Reinigung

unterworfen. Wir benutzten Whatman Filterpapier No. 1 und als Elutionsmittel eine wasser-gesättigte Mischung von CHCl_3 und Benzol 1:1. Wir beobachteten die Formierung eines einheitlichen Wanderfleckes mit $R_f = 0,84$ der im UV-Licht weisslich fluoreszierte. Durch Vereinigung von 6 solchen Papierchromatogrammen, Extraktion der gewanderten Flecke mit CCl_4 im Soxhlet, und Verdampfung des CCl_4 , wurde eine ölige Substanz erhalten, deren IR-Spektrum die "Crown 60" Banden in starker und die Polyamidoanhydridbanden in schwächerer Intensität enthielt. Wenn man bedenkt, dass das reine "Crown 60" unter genau den gleichen papierchromatographischen Bedingungen ein $R_f = 0$ zeigt d.h. überhaupt nicht wandert, so muss man aus dem Ergebnis der papierchromatographischen Versuche schliessen, dass die Wanderflecke die beiden Ringbestandteile, Polyamidoanhydrid und "Crown-60", in gegenseitiger Verkettung miteinander enthalten. Eine der wahrscheinlichen Arten der Verkettung zur Bildung des erwähnten Catenanes wird in Abb. 10 wiedergegeben.

TABELLE II

| Reakt. Produkt | Lage der IR-Banden in cm^{-1} | | | |
|----------------|--|--------------------|--|--------------------|
| | Crown-60 | Poly-amidoanhydrit | Verschiebungen gegenüber der reinen Substanz in cm^{-1} | |
| | | | Crown-60 | Poly-amidoanhydrit |
| 674 | 670 | — | + 4 | — |
| 726 | 750 | 726 | -24 | 0,0 |
| — | 850 | — | — | — |
| 945 | 950 | — | - 5 | — |
| 1050-65 | 1060 | — | — | — |
| 1135 | 1125 | 1145 | +10 | -10 |
| 1218 | 1221 | — | - 3 | — |
| 1255 | — | 1256 | — | - 1 |
| 1263 | 1260 | — | + 3 | — |
| 1372 | 1355 | 1370 | +17 | + 2 |
| 1472 | 1458 | 1440 | +14 | +32 |
| — | — | 1468 | — | — |
| 1565 | 1596 | 1558 | -31 | + 7 |
| 1650 | — | 1650 | — | 0,0 |
| 1722 | — | — | — | — |
| 2870 | 2880 | 2865 | -10 | + 5 |
| 2940 | 2935 | 2940 | + 5 | 0,0 |
| 3100 | — | 3090 | — | +10 |
| 3280 | — | — | — | — |
| 3320 | — | 3300 | — | +20 |
| 3360 | — | — | — | — |
| — | 3520 | — | — | — |

Versuch III. In diesem Versuch wird die Bildung eines Polyurethanes in Gegenwart des Ringmoleküls "Crown-60" auf einer Quecksilberoberfläche vorgenommen. Eine konzentrierte Lösung von 1, 14-Tetradecandiol $\text{HO}-(\text{CH}_2)_{14}-\text{OH}$ und der "Crown-60" Ringverbindung wurden in einem dickwandigen Rundkolben mit circa 20 g Quecksilber kräftig geschüttelt. Das Quecksilber verteilt sich ausserordentlich fein unter Bildung sehr kleiner Tropfen. Aus deren Grösse und der Menge des benutzten Quecksilbers errechnet sich die Gesamtoberfläche des Hg zu 3000 bis 4000 cm^2 . Zu dieser Mischung wurde das flüssige Trimethylhexamethylendiisocyanat im Molverhältnis 2:1 zum verwendeten Diol

hinzugegeben und die Mischung bei 80° stark geschüttelt. Es findet eine Anlagerung des Diols an das Isocyanat statt, welche sowohl zu linearen (I) als auch zu cyclischen Polyurethanen (II) führen kann (Abb. 11).

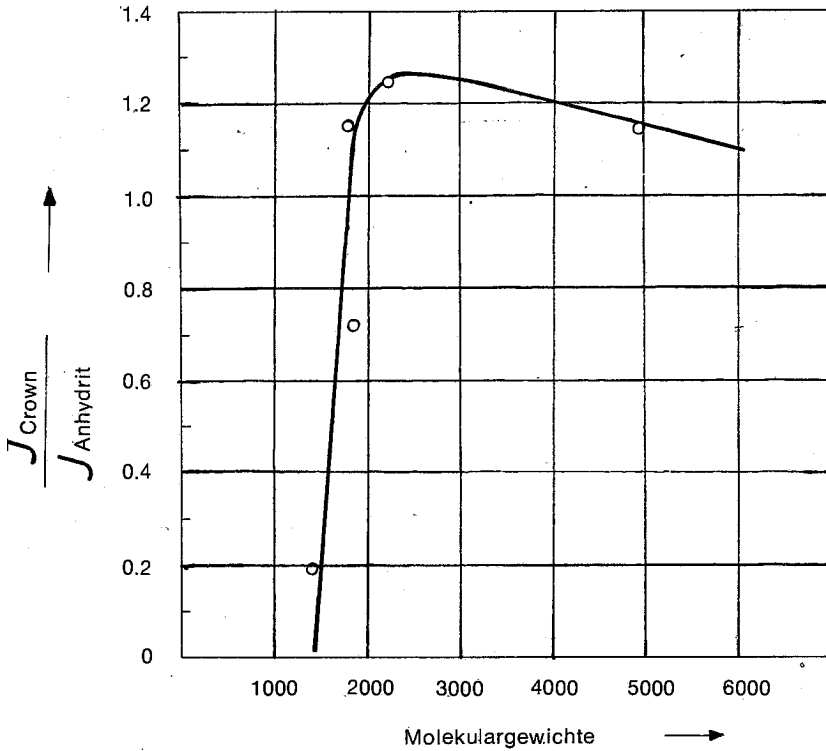


Abb. 9. Abhängigkeit des Molekulargewichtes eines polymeren Catenanes von der Menge des eingefädelt "Crown 60".

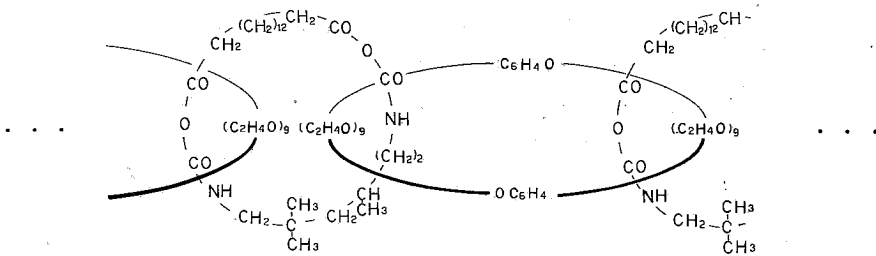


Abb. 10

Letztere Reaktion wird, wegen der orientierten Adsorption des polaren Diols, vorzugsweise an der Grenzfläche der Hg Tropfen stattfinden. Da nun die Bildung der cyclischen Urethane in Gegenwart des Grossringes "Crown-60" erfolgt, besteht, wie bei der Besprechung des Reaktionsmechanismus dargelegt wurde, eine gewisse Wahrscheinlichkeit für eine Einfädung der entstehenden Polymere durch die vorgebildeten "Crown-60" Ringe, was zur Bildung von verketteten Ringen führt. Eine der wahrscheinlichen Formen der Verkettung wird in Abb. 12 wiedergegeben. Nach 4-stündigem Schütteln kommt es zur Bildung eines festen Produktes, welches mit sehr feinen Hg-Tropfen durchsetzt ist

Zur Aufarbeitung wurde zunächst das Hg nach Möglichkeit mechanisch entfernt.

Durch Erhitzen auf 250° im Hochvacuum wurde eine bessere wenn auch nicht vollständige Entfernung des Hg erreicht. Das Produkt wurde dann unter gleichzeitigem Zentrifugieren mit CCl₄ behandelt. Es ergaben sich zwei Anteile, ein in CCl₄ löslicher und ein unlöslicher. Vom unlöslichen Produkt wurde nach der KBr-Methode das IR-Spektrum aufgenommen. Es zeigt (Abb. 13) sowohl die Banden des Polyurethans als auch die Banden

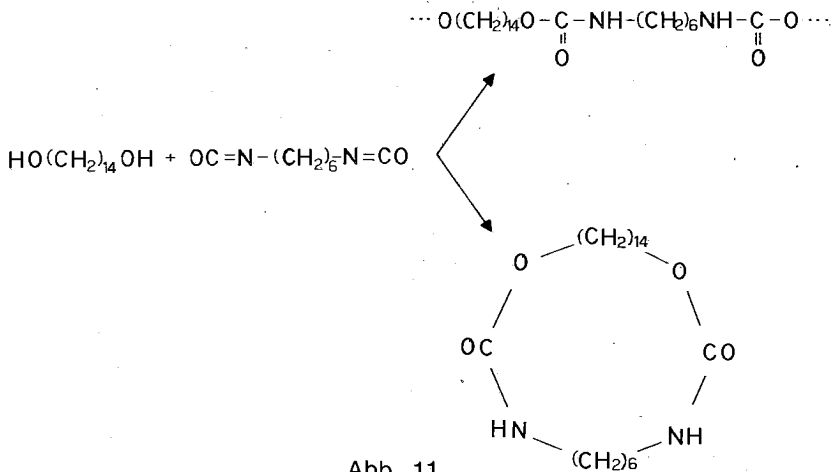


Abb. 11

der "Crown-60" Verbindung. Die genaue Ablesung der Bandenlage ergibt auch hier, dass die Wellenzahlen gegenüber der reinen Bestandteile, Polyurethan und "Crown-60", sowohl nach höheren als auch nach tieferen Frequenzen schwach verschoben sind. In Tabelle III sind diese Verschiebungen zusammengestellt. Sie reichen von +50 cm⁻¹ bis -15 cm⁻¹.

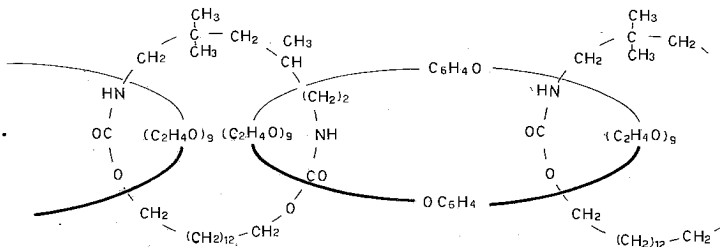


Abb. 12

Versuch IV. In diesem Versuch sind die Bedingungen des Hg-Versuchs III angewandt worden. Als Reaktionsteilnehmer wurden jedoch Hexadecan-1-16-dicarbonsäure (Thapsiasäure) und Trimethylhexamethylen-diisocyanat gewählt, die wir an der Hg-Grenzfläche in Gegenwart eines hochgliedrigen Cyclosiloxanringes der Konstitutionsformel (Abb. 14) miteinander reagieren ließen. Das Cyclosiloxan wurde nach der Vorschrift von W. Padnote and D.F. Wilcock⁷ durch Hydrolyse des Dimethyldichlorosilans und nachheriger cyclischer Polymerisation mit Schwefelsäure hergestellt. Sowohl das IR als auch das NMR-Spektrum der Präparate zeigen die Abwesenheit von OH-Gruppen und bestehen nur aus den IR-Banden eines Cyclosiloxans (vergleiche Irsco, Infrared Structural Correlation Tables and Data Cards Table 9). Das NMR-Spektrum besteht aus einem einzigen Protonen-Peak der CH₃-Gruppe.

TABELLE III

| Reakt. Produkt | Lage der IR-Banden in cm^{-1} | | Verschiebungen gegenüber der reinen Substanz in cm^{-1} | |
|----------------|--|-------------|--|-------------|
| | Crown-60 | Polyurethan | Crown-60 | Polyurethan |
| — | 610 | — | — | — |
| 670 | 670 | 670 | 0,0 | 0,0 |
| 752 | 755 | 725 | - 3 | + 27 |
| 785 | — | 782 | — | + 3 |
| 850 | 850 | — | 0,0 | — |
| — | 935 | — | — | — |
| 950 | 955 | — | - 5 | — |
| — | — | 1005 | — | — |
| 1055 | 1060 | 1047 | - 5 | + 8 |
| — | — | 1103 | — | — |
| — | 1120 | — | — | — |
| 1125 | 1131 | 1145 | - 6 | - 20 |
| — | 1220 | — | — | — |
| 1260 | 1260 | 1265 | 0,0 | - 5 |
| — | 1305 | — | — | — |
| 1355 | 1357 | 1370 | - 2 | - 15 |
| 1385 | — | 1385 | — | 0,0 |
| 1462 | 1460 | 1470 | + 2 | - 8 |
| 1510 | 1510 | — | 0,0 | — |
| 1545 | — | 1545 | — | 0,0 |
| — | 1598 | — | — | — |
| 1655 | — | — | — | — |
| 1722 | — | 1695 | — | + 27 |
| 2865 | 2880 | 2855 | - 15 | + 10 |
| 2935 | 2920 | 2925 | + 15 | + 10 |
| 2970 | — | 2980 | — | - 10 |
| 3390 | — | 3340 | — | + 50 |
| — | 3460 | — | — | — |

Man beobachtet, dass das IR-Spektrum des Cyclopolysiloxans nachdem es mit Wasserspuren gesättigt worden ist, im Bereich zwischen 1300 cm^{-1} und 1800 cm^{-1} die Feinstruktur der Wasserbanden zeigt (Abb. 15). Diese verschwinden nicht durch gewöhnliches Trocknen des Siloxans im Exsiccator sondern erst durch Erhitzen im Hochvakuum auf 200° . Wir glauben, dass es sich hier um im Inneren des Cyclopolysiloxanringes fest eingeschlossene Wassermoleküle handelt, welche auch andere Wirkungen auf die Schwingungen des Ringmoleküls ausüben. So stellt man fest, dass die Intensität der Cyclopolysiloxanbande bei 700 cm^{-1} gegenüber der des wasserfreien Präparates stark abgenommen hat. Will man nach Kriegsmann¹² die Bande 700 cm^{-1} der symmetrischen Si-O-Si-Schwingung zuschreiben, so erscheint plausibel, dass durch den Einbau von Fremdmolekülen in den Siloxanring diese Atmungsschwingungen des Ringes eine Behinderung der Schwingungsamplitude und somit eine Intensitätsabnahme erfährt.

Ähnliche Effekte beobachtet man auch bei der Einfädung des Siloxanringes durch andere Ringsysteme wie bei der Besprechung der IR-Spektren der entsprechenden Catenane geschildert wird.

Für die Catena-Synthese wurden Cyclosiloxanpolymerisate des mittleren Molekulargewichtes 2350 benutzt. Sie entsprechen einem 63-gliedrigen Polysiloxanring. Das nach der Arbeitsweise des Versuchs III erhaltene Reaktionsprodukt wurde mit Benzol gründlich ausgekocht und der ungelöste Rückstand zur Trennung von eingeschlossenem Hg,

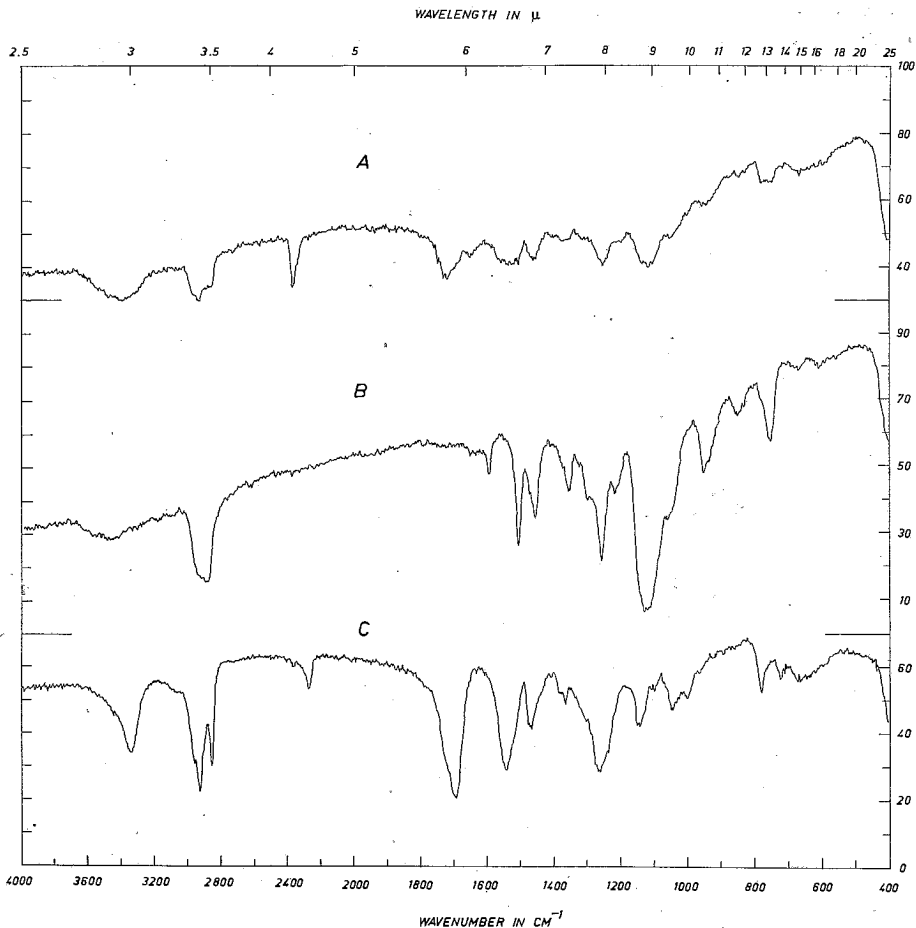


Abb. 13. IR-Spektren: (A) Reaktionsprodukt aus 1-14 Tetradecandiol und Trimethylhexamethylendiisocyanat in Gegenwart von "Crown 60". (B) "Crown 60". (C) Polyuerethan aus Tetradecandiol und Trimethylhexamethylendiisocyanat.

in Tetramethylharnstoff gelöst. Nach Entfernung des Lösungsmittels wurde das IR-Spektrum nach der KBr Methode aufgenommen. Wie aus Abb. 16 zu entnehmen ist besteht das IR-Spektrum des Reaktionsproduktes A aus der Summe der Banden des reinen Siloxanringes B und der Banden des Polyamidoanhydrites C. Man beobachtet (Tabelle IV) neben kleinen Lageverschiebungen Änderungen im Intensitätsverhältnis der Banden. Ähnlich wie beim Einbau von Wassermolekülen findet, auch hier, bei der Einfädung des Siloxanringes durch einen anderen Ring, eine Intensitätsabnahme der symmetrischen ν Si-O bei 700 cm^{-1} statt.

Eine der wahrscheinlichen Arten der zu erwartenden Verkettung wird in Abb. 17 wiedergegeben.

Das NMR-Spektrum wurde in Hexamethylphosphoramid mit Cyclohexan als Bezugs-substanz ermittelt. Es wurde ein starker Siloxanpeak beobachtet, welcher jedoch gegenüber dem reinen Cyclopolysiloxan um 210 Hz nach kleinerem H_0 verschoben ist. Die Verschiebung rührt nicht von der Gegenwart des Hexamethylphosphoramides her.

wie ein Blindversuch bestätigt. Auch eine Zugabe von reinem Polysiloxan zum Röhrchen mit der Catenaverbindung in Hexamethylphosphoramid liess den Peak des zugesetzten reinen Siloxans 210 Hz rechts von dem der Catena erscheinen.

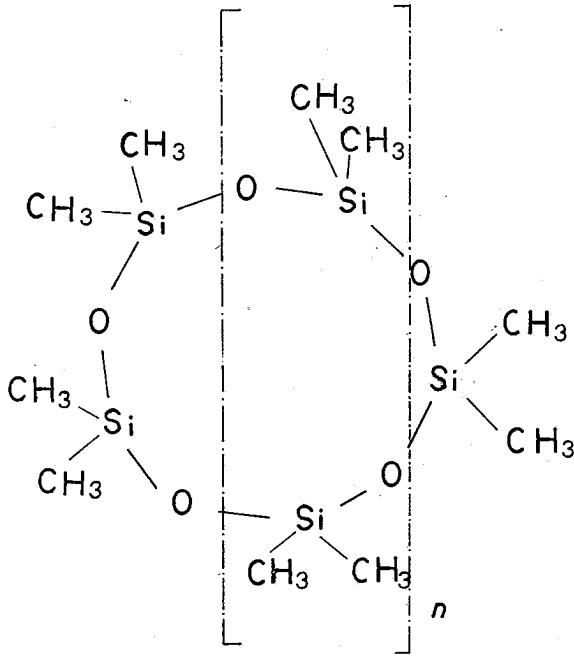


Abb. 14

TABELLE IV

| Reakt. produkt | Lage der IR-Banden in cm^{-1} | | Verschiebungen gegenüber der reinen Substanz in cm^{-1} | |
|----------------|--|--------------------|--|--------------------|
| | Siloxan | Poly-amidoanhydrit | Siloxan | Poly-amidoanhydrit |
| 725 | 705 | 725 | +20 | 0,0 |
| 805 | 805 | — | 0 | — |
| 875 | 870 | — | + 5 | — |
| 1025 | 1025 | — | 0 | — |
| 1102 | 1110 | — | - 8 | — |
| 1268 | 1268 | 1255 | 0 | — |
| 1372 | — | 1370 | — | + 2 |
| 1415 | 1415 | — | 0,0 | — |
| 1440 | — | 1440 | 0,0 | 0,0 |
| 1473 | — | 1468 | — | + 5 |
| 1562 | — | 1558 | — | + 4 |
| 1645 | — | 1655 | — | -10 |
| 1705 | — | — | — | — |
| 2859 | — | 2865 | — | - 6 |
| 2930 | 2910 | 2940 | +20 | -10 |
| 2970 | 2970 | — | 0,0 | 0,0 |
| 3097 | — | 3096 | — | +10 |
| 3340 | — | 3300 | — | +40 |

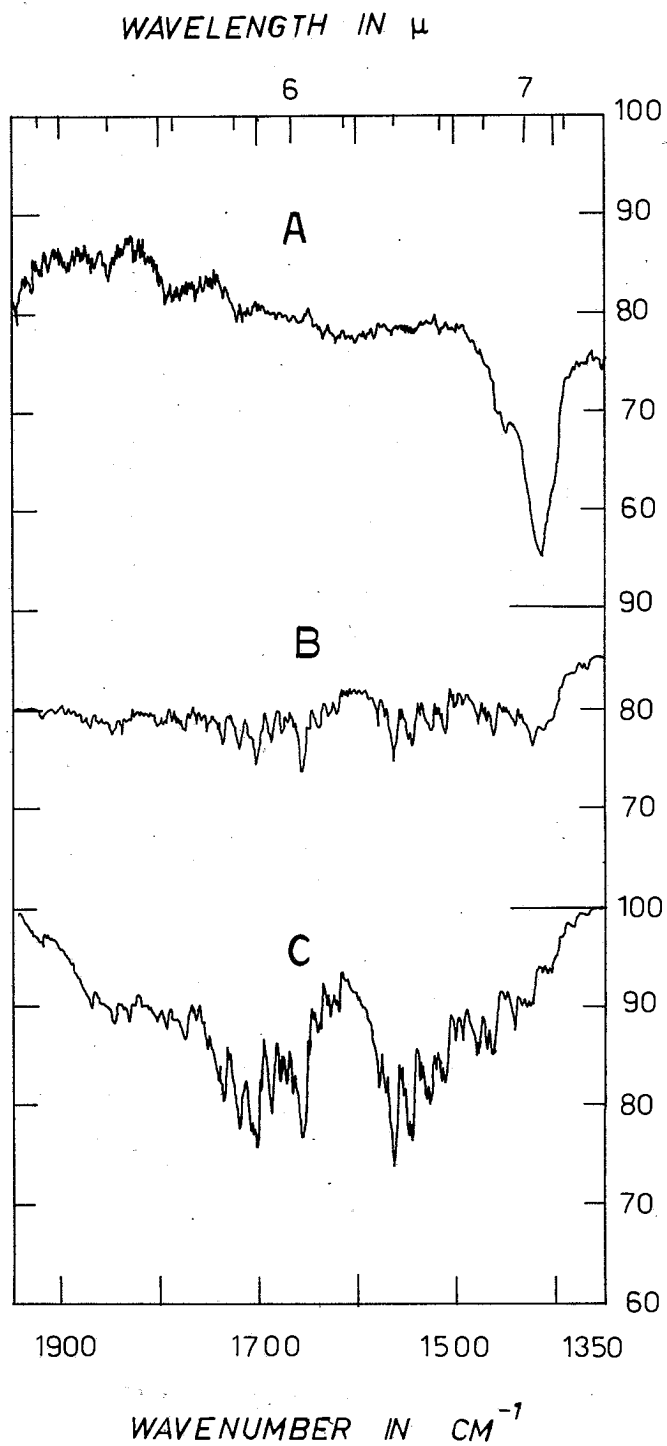


Abb. 15. IR-Spektrum von: (A) wasserfreiem Polysiloxan
 (B) wassergesättigtem Polysiloxan
 (C) wasser zwischen Antimonsulfidplättchen.

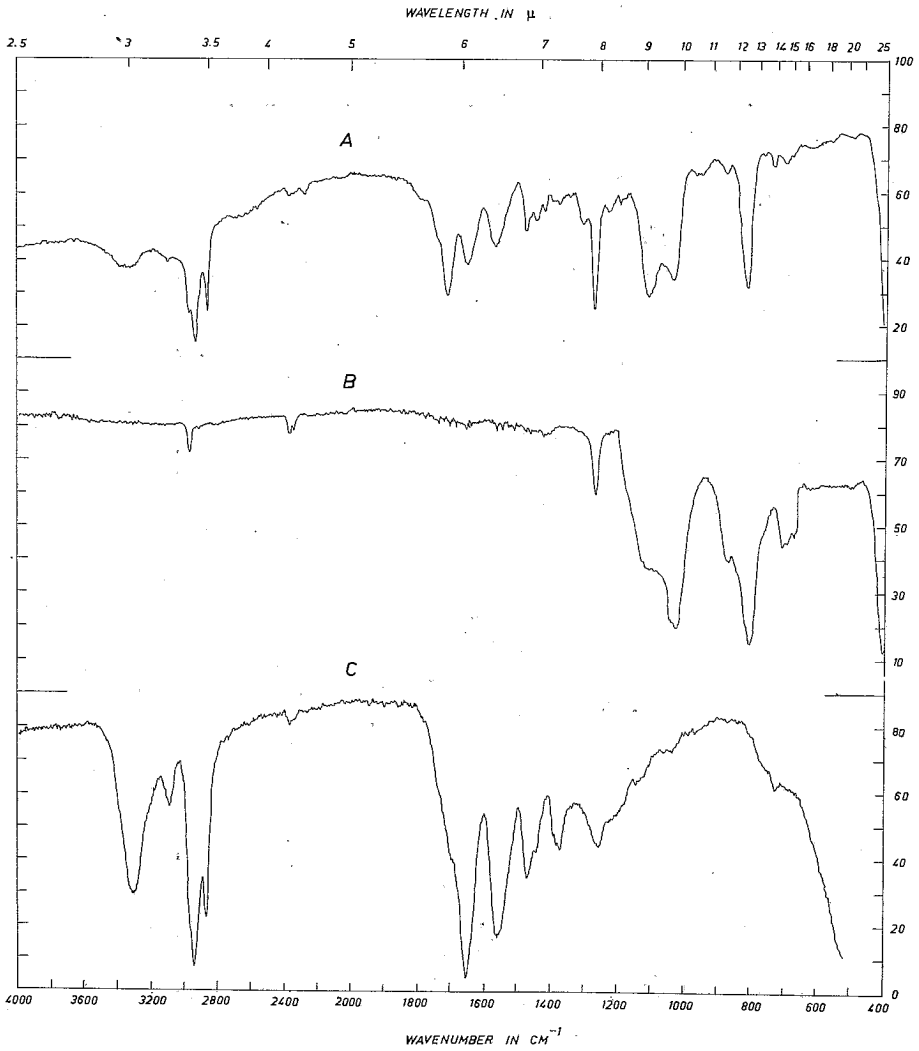


Abb. 16. IR-Spektren: (A) Reaktionsprodukt von Thapsiasäure und Trimethylhexamethylen-diisocyanat in Gegenwart von Polycyclosiloxan. (B) Polycyclosiloxan. (C) Polyamidoanhydrit aus Thapsiasäure und Trimethylhexamethylen-diisocyanat.

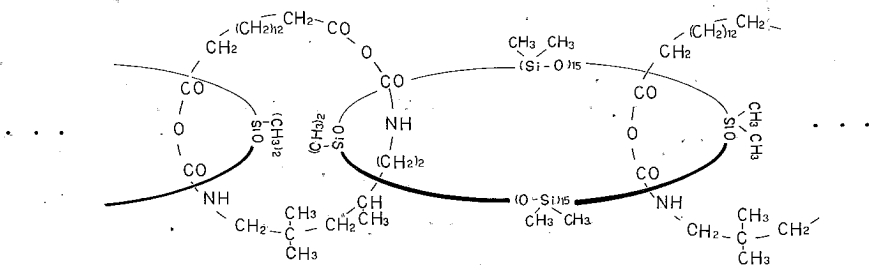


Abb. 17

Diskussion der Ergebnisse.

Das Ziel der vorliegenden Untersuchung ist zunächst zu beweisen, dass nach den vorgeschlagenen Grenzflächenreaktionen eine Verkettung zweier Ringmoleküle ohne chemische Bindung zwischen ihnen stattgefunden hat. Hierbei lassen wir zunächst die Frage offen in welcher Weise diese Verkettung (eventuelle Bildung von Rotaxanen) vorliegt. Aus der beschriebenen Versuchsreihe lässt sich mit Sicherheit der Schluss ziehen, dass bei den angeführten Grenzflächenpolykondensationen in Gegenwart eines grossen Ringmoleküls eine Einfädung desselben unter Bildung von verketteten Ringen stattfindet. Als Beweise für die Bildung von Polycatenanen nach den beschriebenen Arbeitsweisen können folgende Tatsachen angesehen werden:

1) Die IR-Spektren der erhaltenen Produkte bestehen aus der Summe der Spektren der einzelnen Komponenten. Dieses beweist, dass keine chemische Reaktion zwischen den beiden Ringkomponenten stattgefunden hat.

2) Das Intensitätsverhältnis der Banden der zwei verketteten Ringmoleküle bleibt bei jedem Produkt, trotz Behandlung desselben mit den verschiedenartigsten Lösungsmitteln (ausser den üblichen, mit Tetramethylharnstoff, Dimethylformamid, Hexamethylphosphoramid u.s.w.) unverändert, obwohl die eine der reinen Komponenten in diesen Lösungsmitteln löslich sind.

Das Intensitätsverhältnis der Banden der Komponenten erfährt bei der Bildung der Catenane eine mehr oder minder grosse Veränderung, welche in manchen Fällen so gross sein kann, dass eine Bande fast die Intensität Null aufweist d.h. verschwindet. Andererseits erscheinen in den Catenanen neue IR-Banden, welche in den konstituierenden Ringen nicht vorkommen.

3) Eine papierchromatische Reinigung vermag die erhaltenen Produkte nicht in die beiden Ringkomponenten zu trennen. Die unter 2 und 3 angeführten Tatsachen beweisen dass keine Molekülverbindung im üblichen Sinne zwischen den Ring-Komponenten vorliegt.

4) Es bestehen Lageverschiebungen der IR-Banden der Ringe ($4-50\text{ cm}^{-1}$) aus welchen die Catena konstituiert sind, gegenüber der Bandenlage der reinen Ringsubstanzen. Diese Verschiebungen entsprechen der Grössenordnung nach van der Waals' schen Kräften, erfolgen in beiden Richtungen und gleichen denen bei Einschlussverbindungen beobachteten.

5) Produkte verschiedenen Molekulargewichtes weisen daselbe IR-Spektrum auf, mit Verschiedenheiten allein im Verhältnis der Bandenintensität der Ringkomponenten aus welchen sie konstituiert sind.

Wir möchten der Deutschen Forschungsgemeinschaft auch an dieser Stelle für die Sachbeihilfe danken, welche sie uns in den Jahren 1965-1967 gewährt hat. Die früheren Versuche bildeten die erste Grundlage für diese Untersuchung.

Der Firma VEBA CHEMIE AG möchten wir bestens danken für die kostenlose Überlassung von Isocyanat Präparaten (Isophorondiisocyanat und Trimethylhexamethylendiisocyanat).

ΠΕΡΙΛΗΨΙΣ

Σύνθεσις πολυμερών κατενανίων τη βοηθεία μεσεπιφανειακών τινών αντιδράσεων.

Διὰ τῆς παρούσης πειραματικῆς ἐργασίας δεικνύεται, ὅτι εἶναι δυνατόν νὰ συνδέσῃ τις δύο δακτυλίους μὲ μέγαν ἀριθμὸν μελῶν κατὰ τρόπον κρικωτῶν - καδενοειδῶς - ἀνευ χημικοῦ δεσμοῦ μεταξύ αὐτῶν, χρησιμοποιῶν τὴν προσανατολιστικὴν δράσιν μεσεπιφανειῶν. Ἡ σύνθεσις αὕτη ἐπιτυγχάνεται, ὅταν εἰς ὕδατικὴν ἐπιφάνειαν ἢ εἰς ἐπιφάνειαν ὑδραργύρου ἢ εἰς ἐπιφανειακὰ στοιβάδα ὕδατος προσροφημέναν ἐπὶ NaCl λάθῃ χώραν ἢ σύνθεσις ἐνὸς δακτυλίου A παρουσία ἐνὸς δευτέρου, προκατασκευασμένου δακτυλίου B. Διὰ τῆς διερευνήσεως τῶν IR- καὶ NMR- φασμά-

των τῶν προϊόντων τῆς ἀντιδράσεως καθίσταται πρόδηλον, ὅτι οἱ δύο δακτύλιοι Α καὶ Β εἶναι συνδεδεμένοι μεταξύ των κατὰ τρόπον κρικωτόν, σχηματίζοντες μακρὰν ἄλυσιν. Προσδιορίσθησαν τὰ μοριακὰ βάρη τῶν συνθετικῶν αὐτῶν ἀλύσεων, αἵτινες ἀφ' ἑτέρου ὑπεβλήθησαν εἰς καθαρισμόν δι' ἐκχυλίσεων καὶ χρωματογραφικῆς ἐπεξεργασίας.

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Beckmann Rearrangement of Testosterone Oximes

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The preparation of oximes of testosterone acetate (II), (III) and their acetate derivatives are described. The resolution of syn- and anti-isomers was effected by column chromatography and their structure was determined by spectral data. Boron fluoride and thionyl chloride have been used for the rearrangement.

The increased interest in azasteroids is due to the interesting pharmacological properties of steroid alkaloids. Convenient methods for the introduction of nitrogen into the steroid molecule are the Beckmann and Schmidt rearrangements. Beckmann rearrangement of α , β -unsaturated ketoximes may give lactams A or B depending on the stereochemistry of the starting oxime.

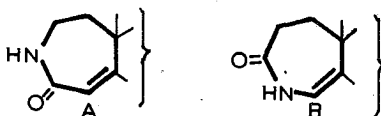


Figure 1

The product of that rearrangement is usually derived from the syn-isomer while the anti-isomer does not undergo the rearrangement.

Testosterone-17-acetate was converted to the two 3-ketoximes (II, III) by heating with excess hydroxylamine hydrochloride in a mixture of pyridine-ethanol.

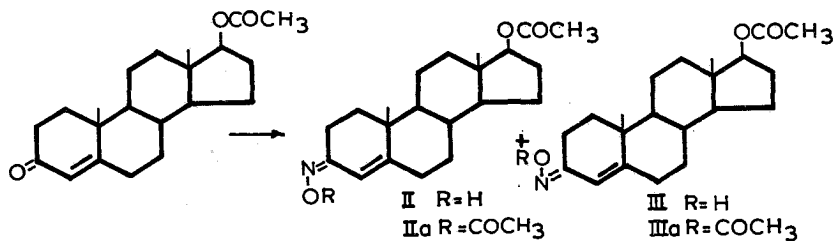


Figure 2

The resolution of syn- and anti-isomers was effected by column chromatography on silica gel eluting with a mixture of benzene-ethylacetate. The assignment of syn- and anti-configurations was made from the chemical shifts of the olefinic proton.^{1,2} The NMR spectrum of syn-testosterone oxime showed a downfield shift, relative to the anti- of 40Hz for the vinyl proton and 2.5 Hz for the 19-CH₃ protons.

The anti-isomer showed stronger ultraviolet absorption.

Infrared spectra showed for syn-ketoxime 3500 (OH), 1725, 1260 cm^{-1} (C=O) and for anti 3275 (OH), 1750, 1240 cm^{-1} (C=O).

Attempts were made to isomerise syn- to anti- and anti- to syn- by ultraviolet irradiation (low pressure mercury lamp) or by heating in dioxane. In both cases each isomer was converted into an equilibrium mixture. The oximes (II) and (III) were acetylated with an excess of pyridine-acetic anhydride at room temperature to produce the acetate derivatives (IIa) and (IIIa).

When boron fluoride was used as catalyst for the Beckmann rearrangement of ketoxime acetates of D-ring it was found that lactam (A) and exocyclic unsaturated nitrile³ (B) were formed.

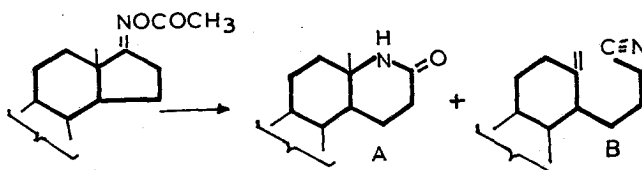


Figure III

In the present investigation it was found that boron fluoride converted the mixture of oxime acetates (IIa) (IIIa) to the lactam (IV) in low yield and to the ketoximes (II) and (III), which have been separated by column chromatography.

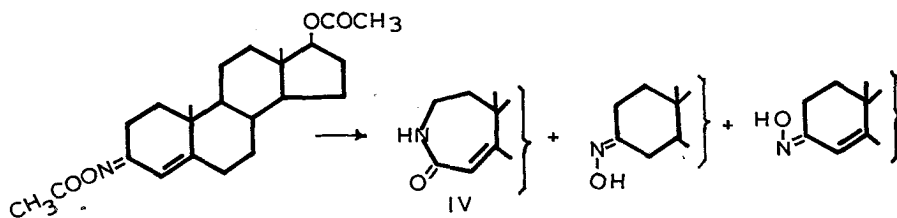


Figure IV

The boron fluoride catalyst has been used for Beckmann rearrangement of aromatic ketoximes.⁴ It has been postulated that BF_3 first attacks the nitrogen of the oxime (immonium complex) A, which then rearranges to the oxonium complex (B) and yields immonium cation for the rearrangement.

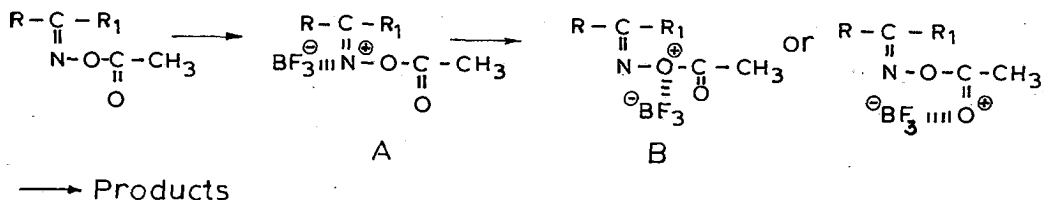


Figure V

The oxonium complex from the oxime acetate should have greater tendency to rearrange.^{5,6}

When thionyl chloride was used as catalyst² for the rearrangement of α, β -unsaturated ketoximes mixture, then lactam (IV) was obtained in 50% yield.

Experimental

All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained in KBr on a Perkin-Elmer IR-337 spectrometer. Ultraviolet spectra were measured in ethanol solution on a Cary Model 11 instrument, whereas NMR spectra were run in deuteriochloroform on a Varian Associates A-60 instrument with tetramethylsilane as an internal standard.

Testosterone Acetate Oximes (II), (III)

Testosterone-17-acetate (6.3 g) was dissolved in a mixture of 25 ml ethanol and 25 ml pyridine. 5.5 g of hydroxylamine hydrochloride was added to this solution and the mixture was heated under reflux for 2 hours. The solution was poured into ice-water, and the resulting precipitate was collected by filtration, washed with water and dried, to yield 6.8 g of mixture (II) and (III) m.p. 185-190°.

The product mixture (6.5 g) was chromatographed on a column of silica gel (200 g) prepared with chloroform. Elution with benzene-ethylacetate (5:1) yielded (III) (3.5 g). Crystallization from methanol-chloroform gave a m.p. 204-205°; Rf, 0.33 (Benzene-ethylacetate) (17:3).

$$[\alpha]_D^{20} + 142^\circ (c, 1.3 \text{ CHCl}_3)$$

ν_{max} 3275 (OH), 1750, 1240 (C=O), 1650 cm^{-1} (C=C)

λ_{max} 241 m μ (ϵ , 21,300).

NMR. 18-CH₃, 9.18, 19-CH₃, 8.93, 17-Ac, 7.97, 17-H

(triplet) 5.4, vinyl proton 4.22 τ .

Analysis Calcd. for C₂₁H₃₁NO₃: C 73.04; H 8.98; N 4.05

Found: C 72.90; H 8.70; N 4.02

Further elution of the column with benzene-ethylacetate (3:1) yielded the syn-isomer (II) (1 g). Crystallization from benzene-hexane gave m.p. 186-188°; Rf, 0.3 [α]_D²⁰ + 220° (c, 1.1. CHCl₃).

ν_{max} 3500 (OH), 1725, 1260 (C=O), 1650 (C=C), 1620 cm^{-1} (C=N)

λ_{max} 243 (ϵ , 16500)

NMR. 18-CH₃, 9.18, 19-CH₃, 8.9, 17 Ac, 7.98, 17-H

(triplet) 5.4 vinyl proton 3.54 τ .

Analysis Calcd. for C₂₁H₃₁NO₃: C 73.04; H 8.98; N 4.05

Found: C 72.84; H 8.69; N 4.14

Acetylation of (II) and (III)

Reacting compound (II) (255 mg) in excess acetic anhydride and pyridine, at room temperature for 9 hours gave syn-testosterone oxime diacetate IIa (270 mg) m.p. 102-104°.

Analysis Calcd. for C₂₃H₃₃NO₄: N 3.6

Found: N 3.5.

ν_{max} 1780 (N-OAc), 1750 (Ac), 1645 (C=C), 1605 cm^{-1} (C=N).

Using the same procedures as for compound (II) anti-testosterone acetate oxime (III) was obtained in 95% yield m.p. 144-146°.

λ_{max} 1780 (N-OAc), 1745 (Ac), 1645 (C=C), 1600 cm^{-1} (C=N).

NMR. 18-CH₃, 9.17, 19-CH₃, 8.94, 17-Ac, 7.89, N-OAc, 7.87

17-H, 5.4 (Vinyllic proton) 4.3 τ .

Analysis Calcd. for C₂₃H₃₃NO₄: N 3.6.

Found: N 3.45.

3-Aza-17 β -hydroxy-A-homo-4a-androsten-4-one (IV)

A. With boron fluoride etherate.

A mixture of syn- and anti-testosterone oxime diacetate (1.760 g) was dissolved in purified dioxane (25 ml). To this solution was added 10 ml of purified boron fluoride etherate. After heating at 90° for 3 hours, the solution was poured into ice-water. The mixture was extracted with chloroform, the organic layer washed twice with water, dried and evaporated under vacuum, to yield solid material which on t.l.c. gave three spots. This residue was chromatographed with 60 g silica

gel. Elution with benzene ethylacetate (9:1) 200 ml gave a solid (900 mg), which had m.p. 198-201°, identical by infrared and NMR spectra to (III). Further elution with benzene: ethylacetate (7:3) 200 ml gave 150 mg of syn-isomer (II) contaminated with a small amount of anti (III). Finally the column was washed with chloroform: methanol (9:1) 200 ml to give 3-Aza-17β-acetoxy-A-homo-4α-androsten-4-one (300 mg). Crystallization once from acetone-hexane gave m.p. 239-241°.

ν_{\max} 3300, 3200 (NH), 1750, 1250 (CH₃CO), -1680, 1615 cm⁻¹ (NHCO).
NMR. 18-CH₃, 9.28, 19-CH₃, 8.87, 17-H, 5.4
(triplet) vinyl proton 4.3 τ.

This compound was hydrolysed with 4N lithium hydroxide in methanol to 3-Aza-17β-hydroxy-A-homo-4α-androsten-4-one (IV) m.p. 281-284° (ethanol). (Lit² m.p. 288-291°).

ν_{\max} 3300-3200 (OH, NH), 1670, 1625 cm⁻¹ (NHCO)
 λ_{\max} 221 μm (ε = 17000).

B. With thionyl chloride.

A mixture (7,5 g) of syn- and anti-testosterone-17-acetate oxime (II and III) was dissolved in 180 ml of purified dioxane. The mixture was cooled to about 10°, and while the mixture was stirred continuously, 7,5 ml of purified thionyl chloride was added dropwise. The mixture was kept at room temperature and stirred for one hour and was then poured into a solution of 2N potassium bicarbonate and extracted with chloroform. The organic layer, having been washed with water, dried over sodium sulfate and having had the solvent removed under reduced pressure, gave a mixture of products. These products were separated by column chromatography, using the procedures described in method A to give the oximes and 3-Aza-17β-acetoxy-A-homo-4α-androsten-4-one, which after hydrolysis by the known procedures gave lactam (IV) in 50% yield, m.p. 287-290° (ethanol), identical by infrared and ultraviolet to the lactam prepared by the method A.

Attempted isomerization of syn-ketoxime (II) to the corresponding anti (III)

A. Syn-ketoxime (0.1 g) was refluxed in 10ml of pure dioxane for 12 hours. Evaporation of the solvent yielded a mixture of syn- and anti-isomers.

B. Syn-ketoxime (0.1 g) was dissolved in 10 ml of pure dioxane and irradiated with ultraviolet low pressure mercury lamp for 12 hours. Evaporation of the solvent gave the two isomeric ketoximes.

ΠΕΡΙΛΗΨΙΣ

Μετάθεσις κατὰ Beckmann τῶν ὀξειμῶν τῆς τεστοστερόνης.

Ἡ ἀντίδρασις ὕδροξυλαμίνης μετὰ τῆς 17-ἀκετυλοτεστοστερόνης παρέσχε δύο στερεοϊσομερεῖς ὀξίμας, αἱ ὁποῖαι διεχωρίσθησαν χρωματογραφικῶς καὶ ἐλήφθησαν εἰς ἀναλογίαν βάρους 1:3 (σύν-: ἀντι-). Τῇ βοήθειᾳ πυρηνικοῦ μαγνητικοῦ συντονισμοῦ, ὑπερύθρου καὶ ὑπεριώδους φάσματος καθωρίσθησαν αἱ δύο γεωμετρικῶς ἰσομερεῖς ἐνώσεις. Κατὰ τὴν μελέτην μεταθέσεως κατὰ Beckmann μίγματος ἀκετυλιωμένων ὀξειμῶν μετ' αἰθερικοῦ διαλύματος τριφθοριούχου βορίου, ἐλάβωμεν παραλλήλως μὲ τὴν λακτάμην τὴν προκύπτουσαν ἐκ τῆς συν- ὀξίμας καὶ τὰς δύο μὴ ἀκετυλιωμένας ὀξίμας. Εἰς ἰκανοποιητικὴν ἀπόδοσιν ἐλάβωμεν τὴν λακτάμην, ὅταν ἐχρησιμοποιήθη θειουλοχλωρίδιον ὡς καταλύτης διὰ τὴν μετάθεσιν.

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Eine bequeme synthese von Pyridonen aus Acetondicarbonsäurediäthylester und Alkylisocyanaten

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(Received 28-1-72)

Im Gegensatz zu dem aromatische Isocyanaten, die mit Acetondicarbonsäurediäthylester N-Aryl-pyridonen liefern, die aliphatische Isocyanaten reagieren wahrscheinlich zum offenkettige Produkten von N-Alkylamiden des Acetontricarbonsäure-diäthylesters. Bei der Behandlung dieser Verbindungen mit POCl_3 findet eine Cyclisierung zum N-Alkyl-4,6-dihydroxy-2-pyridonen statt.

In contrast to Arylisocyanates which react readily with diethyl acetonedicarboxylate to afford N-Aryl-pyridones, aliphatic Isocyanates failed to produce the corresponding cyclic derivatives. However, the postulated intermediate product, 1-(N-alkylamido)-1, 1'-diethyl acetone-tricarboxylate, cyclise, by the action of phosphorus oxychloride to give N-Alkyl-pyridones in high yield.

Es ist von Michael¹ bekannt, daß sich Phenylisocyanat an aktivierte Methylengruppen in Gegenwart von Natrium zu addieren vermag. So läßt sich u.a. Phenylisocyanat an Malonester unter Bildung des Methantricarbonsäurediäthylesteranilids^{2,3} anlagern, welches beim Erhitzen auf etwa 210°C in einer komplizierten Reaktionsfolge zum 2,4-Dioxo-3,3-bis-(carboxanilido)-1,2,3,4-tetrahydrochinolin³ reagiert. Eine Umsetzung des Natriumsalzes von Acetondicarbonsäurediäthylester mit Phenylisocyanat führt gleich nach dem Ansäuern mit verd. HCl bei Zimmertemperatur zu einem cyclischen Produkt das 4,6-Dihydroxy-1-phenyl-2-pyridon⁴ (85% d. Th.).

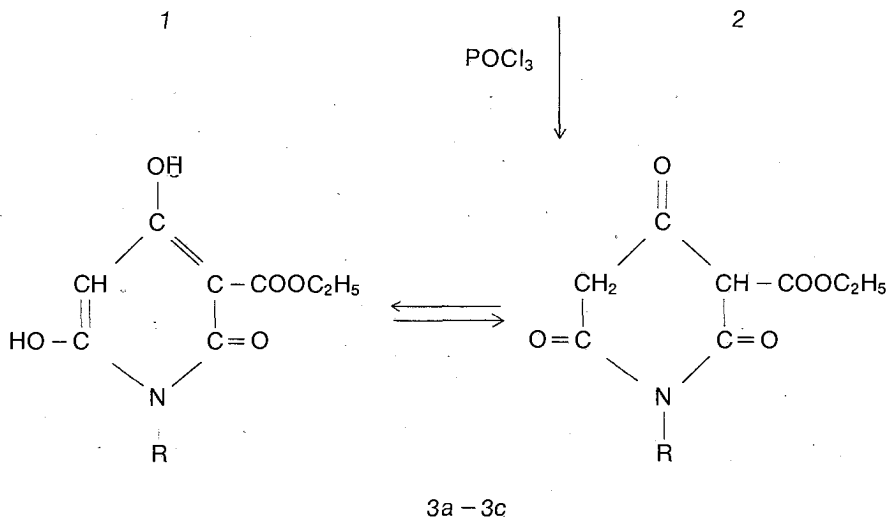
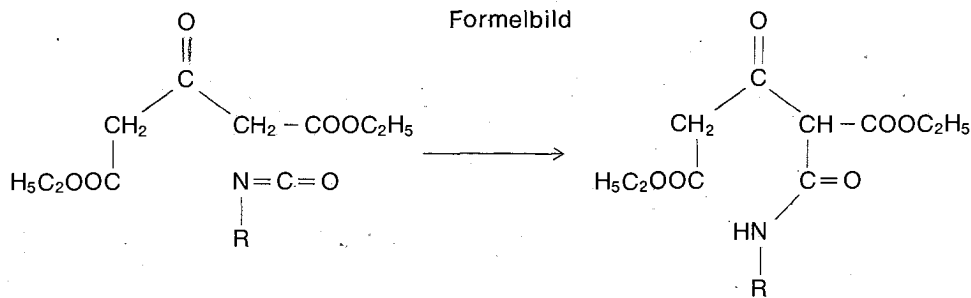
Da wir uns interessierten N-Alkyl substituierte 4,6-Dihydroxy-2-pyridonen herzustellen, versuchten wir auf dem gleichen Weg, wie bei den aromatische Isocyanaten,⁴ diese zu synthetisieren.

Setzt man nun in Analogie zu den oben erwähnten Versuchen das Natriumsalz des Acetondicarbonsäurediäthylesters 1 mit Alkylisocyanaten (Allylisocyanat, Cyclohexylisocyanat, Hexamethylendiisocyanat u.a.) um, so stellt man fest, daß nach dem Ansäuern des Umsetzungsproduktes keine Cyclisierung statt findet, sondern erhält man ölartige Produkte die einem offenkettigen Charakter aufweisen.

Es kann also mit große Wahrscheinlichkeit angenommen werden, daß intermediär Acetontricarbonsäurediäthylesteralkylamide 2 entstehen die durch zugabe von Säuren nicht zum cyclisieren vermögen, wie es bei dem aromatischen Isocyanaten bzw. Isothiocyanaten beobachtet wurde.

Behandelt man dagegen die ölartigen Verbindungen 2 mit POCl_3 in der Hitze, so kondensieren sie sich durch Eliminierung eines Mols Äthanol zu N-alkyl-4,6-dihydroxy-2-pyridonen in guten Ausbeuten.

Alle auf dieser weise hergestellte Verbindungen, sind Lauge löslich und mit HCl wieder ausfällbar. Die auftretende intensiv rote bis violett FeCl_3 -Reaktion entspricht einem phenolischen Charakter der Verbindungen.



3a. R = -CH₂-CH=CH₂

3b. R = -C₆H₁₁

3c. R = -(CH₂)₆-NC₈H₈O₅

Beschreibung der Versuche

Allgemeine Vorschrift zur Darstellung der Verbindungen 3a-3c

Zu 2,3g metall. Na in 130 ml abs. Äther gibt man 20,2g Acetondicarbonsäurediäthylester und erhitzt 4 Stdn. zum Sieden. Nach 5 Stdn. fügt man die entsprechende Molmenge des Alkylisocyanats hinzu und erwärmt nochmals 2 Stdn. zum Sieden. Danach wird das Reaktionsgemisch in Wasser gegossen und nach dem Ansäuern mit verd. HCl die äther. Schicht abgetrennt und mit Na₂SO₄ getrocknet. Nach Abdunsten des Äthers, wird das erhaltene Ölprodukt mit 4 ml POCl₃ auf 80-90°C eine Stdn. unter dem Rückfluß erhitzt. Nach dem Erkalten, wird das Reaktionsgemisch in Eiswasser gegossen mit Wasser und danach mit Natriumbicarbonatlösung gewaschen und schließlich aus Methanol, bzw. Äthanol umkristallisiert.

1. 4,6-Dihydroxy-2-oxo-1-allyl-1,2-dihydro-pyridin-3-carbonsäureäthylester (3a).
Ausb. 62%, Schmp. 178-179°.

C₁₁H₁₃NO₅ (239) Ber. C 55,23 H 5,48 N 5,85
Gef. C 54,98 H 5,40 N 5,85

2. 4,6-Dihydroxy-2-oxo-1-cyclohexyl-1,2-dihydro-pyridin-3-carbonsäureäthylester (3b).
Ausb. 70%, Schmp. 168-170°.

$C_{14}H_{19}NO_5$ (281) Ber. C 59,78 H 6,81 N 4,98
Gef. C 59,47 H 6,95 N 4,57

3. 1,1'-Hexamethylen-bis-(4,6-dihydroxy-2-oxo-1,2-dihydro-pyridin-3-carbonsäureäthylester) (3c).

Ausb. 65%, Schmp. 150-151°.

$C_{22}H_{28}N_2O_{10}$ (480) Ber. C 55,0 H 5,81 N 5,83
Gef. C 54,74 H 5,52 N 5,37

Die IR-Spektren von 3a-3c zeigen Charakteristische assoziierte OH Schwingungen bei 3000-2900 K, ihr Estergruppe absorbiert bei 1735 K und schließlich die Carbonylbanden dieser Verbindungen liegen fast alle bei 1650 K.

Der Nationalen Griechischen Forschungsstiftung bin ich für die Förderung der Arbeit, Herrn Prof. D. Theodoropoulos für wertvolle Diskussionen zu großem Dank verpflichtet.

ΠΕΡΙΛΗΨΙΣ

Εύχερης σύνθεσις πυριδονών εκ του άκετονοδικαρβοξυδιαιθυλεστερος και άλκυλοϊσοκυανικών έστερων.

Έν αντιθέσει προς τους άρυλο-ισοκυανικούς έστερας, οι όποιοι μετά του άκετονοδικαρβοξυδιαιθυλεστερος δίδουν 4,6-διϋδροξυ-1-φαινυλο-2-πυριδόνας, αι άλειφατικοι ισοκυανικοι ένωσεις παρέχουν, προφανώς, μη κυκλικά παράγωγα, ήτοι Ν-άλκυλαμίδια του άκετονοτρικαρβονικού διαιθυλεστερος. Κυκλοποιήσις των τελευταίων τούτων προς Ν-άλκυλοπυριδόνας δύναται να επιτευχθῆ, ως διεπιστώθη, τη επίδράσει δεξυχλωριούχου φωσφόρου. Τα IR-φάσματα των, ούτω, ληφθέντων προϊόντων (3a-3c) παρουσιάζουν χαρακτηριστική άπορρόφησην της καρβονυλομάδος εις 1650 cm^{-1} , της έστερικής ομάδος εις 1735 cm^{-1} και του συνεζευγμένου -OH εις 3000-2900 cm^{-1} .

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Racemisation by the Azide Method. The Synthesis of Cbzo-L-Valyl-L-Tyrosyl-L-Isoleucine Methyl Ester

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A model condensation of Cbzo-L-Valyl-L-Tyr.N₃ with Ileu.OCH₃ in the presence or absence of triethylamine revealed that coupling, in the presence of base, proceeded with distinct racemisation (table 1).

During the synthesis of the histidine²-angiotensin II analog, which has been found inactive in the dog, but it possessed about 10 units/mg of oxytocic activity on the isolated rat uterus,¹ a distinct difference was found in optical rotation values of peptide intermediates, when coupling was effected by the azide method in the presence or absence of triethylamine.

TABLE I
Cbzo-Val-Tyr-Ileu.OCH₃^a

| Fraction | yield % | M.p., °C | [α] _D ^b | R _f ^c | R _f ^d |
|----------|---------|-----------|-------------------------------|-----------------------------|-----------------------------|
| A | 70 | 208 – 210 | – 12.74 | 0.86 | 0.75 |
| B | 12 | 178 – 188 | – 3.23 | 0.86 | 0.75 |
| C | 10 | 156 – 162 | – 0.89 | 0.86 | 0.75 |

^a Absolute methanol (20ml/gr) was used for purification of crude product. Fractions B and C were isolated by gradual concentration of mother-liquor of A.

^b as 2% solution in DMF (dimethylformamide).

^c *n*-Butanol-acetic acid-water (10:1:3).

^d dioxane-water (5:5).

Characteristically, when the condensation of fragments for the formation of the Tyr-Ileu peptide bond was effected *via* the azide method, the octapeptide, Cbzo-(β-benzyl)-L-Asp.-im.benzyl-L-His-L-Val-L-Tyr-L-Ileu-im.benzyl-L-His-L-Pro-L-Phe.OCH₃, exhibited [α]_D²⁹ – 38° value, against [α]_D²⁹ – 43.2° (0.5% MeOH) in the absence of triethylamine. In order to investigate the tendency of the Tyr residue to racemise, under the experimental conditions used, a model condensation of Cbzo-L-Val-L-Tyr.N₃ with free isoleucine methyl ester, and its hydrochloride neutralised by triethylamine, was chosen. It should be mentioned in this connection, that the optical homogeneity of Cbzo-L-Val-L-Tyr-L-Ileu.OCH₃ is well established.²

The ester, Cbzo-L-Val-L-Tyr.OCH₃, was prepared by the carbodiimide method,³ m.p. 153°, [α]_D²⁰ + 13° (c, 4.8% in pyridine), Ref.⁴ m.p. 156, [α]_D²⁵ + 10.5 (c, 4.9% in pyridine) and converted to its hydrazide, m.p. 239-241°, [α]_D²⁰ – 13° in accord with literature.⁴

The azide was prepared from the hydrazide, Cbzo-L-Val-L-Tyr.NHNH₂, in acetic acid-hydrochloric acid (3 equiv.) adding sodium nitrite at -10°. It was then precipitated with cold water, filtered quickly, washed with diluted sodium bicarbonate, water and dried for 2 hrs, at -5°, over P₂O₅.

The azide, thus prepared, was divided in two portions, one used for coupling with Ileu.OCH₃ ester and the other with its hydrochloride in DMF containing one equiv. of triethylamine.

In the absence of triethylamine the obtained Cbzo-L-Val-L-Tyr-L-Ileu.OCH₃ ester in 85% yield m.p. 213-215°, $[\alpha]_D^{20} - 13.98^\circ$ (c,2% in DMF), was identical with that reported for the all L-Isomer² after recrystallization from methanol. The mother-liquor upon concentration deposited a small fraction (4% yield), m.p. 199-201°, $[\alpha]_D^{20} - 1.0^\circ$ (c,2% in DMF). In the presence of base, the fractions, summarized in table I, were isolated.

All the isolated fractions were found homogeneous according to paper chromatography in two solvent systems. Furthermore, upon complete hydrolysis by acid they gave the expected amino acids in equal amounts and the microanalytical values confirmed their composition as Cbzo-Val-Tyr-Ileu.OCH₃.

As the Cbzo-L-Val-D-Tyr-L-Ileu.OCH₃ has an $[\alpha]_D^{22} + 11.3^\circ$ value,² it became apparent that coupling of Cbzo-L-Valyl-L-Tyr.N₃ with Ileu.OCH₃ proceeded with partial racemisation. These findings are cited as supporting evidence that racemisation should not always be excluded, even by the azide method.^{5,6}

Acknowledgments

We thank Miss. M. Liakopoulou and Mr. Ch. Platsoukas for technical assistance. The National Hellenic Research Foundation is thanked for a grant in partial support of this research.

ΠΕΡΙΛΗΨΙΣ

Ρακεμίωσις διὰ τῆς μεθόδου τῶν ἀζιδίων. Ἡ σύνθεσις τοῦ μεθυλεστέρου τῆς καρβοβενζοξυ-L-βαλυλο-L-τυροσυνου-L-ισολευκίνης.

Κατὰ τὴν σύνθεσιν τοῦ ὁρμονικοῦ ἀναλόγου τῆς ἀγγειοτενσίνης, ἰστιδινο²-ἀγγειοτενσίνη II, διεπιστώθη διαφορά εἰς τὴν ὀπτικήν στροφικὴν ἰκανότητα ἐνδιαμέσων τινῶν παραγῶγων κατὰ τὸν σχηματισμὸν πεπτιδικῶν δεσμῶν διὰ τῆς χρήσεως τῆς μεθόδου τῶν ἀζιδίων παρουσία τριαιθυλαμίνης. Δεδομένου ὅτι ἡ μέθοδος αὕτη θεωρεῖται ἡ ἀσφαλεστέρα διὰ τὴν ἀποφυγὴν ρακεμίωσεως ἐμελετήθη, ἐν εἴδει προτύπου ἀντιδράσεως, ἡ σύζευξις τῆς Cbzo-L-val-L-tyr N₃ μετὰ τοῦ ἐλευθέρου μεθυλεστέρου τῆς L-ισολευκίνης καὶ τοῦ ὕδροχλωρικοῦ αὐτῆς ἄλατος, παρουσία τριαιθυλαμίνης. Διεπιστώθη, παρουσία μὲν βάσεως, σημαντικὴ ρακεμίωσις (πίναξ 1), ἀπουσία δὲ βάσεως ἀπεμονώθη προϊόν ὀπτικῶς καθαρὸν κατὰ 85%, εἰς ἐλαχίστην δὲ ποσότητα (4%) ρακεμιωθὲν τοιοῦτον. Τὰ ἀποτελέσματα ταῦτα συνηγοροῦν ὑπὲρ τῆς ἀπόψεως, ὅτι ὁ κίνδυνος ρακεμίωσεως δὲν δύναται πάντοτε νὰ ἀποφευχθῆ, ἔστω καὶ διὰ τῆς μεθόδου τῶν ἀζιδίων.

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Spectroscopic Study of a Wax Isolated from *Alkanna tinctoria* Tausch.

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(Received 18-2-72)

A wax has been isolated from *Alkanna tinctoria* Tausch. and its spectral properties have been examined, with particular emphasis on mass spectra. An approximate composition of the wax, which is mainly a mixture of eight esters with 42-50 C atoms, is proposed.

The dried shoots with their leaves and flowers of *Alkanna tinctoria* Tausch.¹ are commercially available in Greece and they are still used in some instances for the preparation of an ointment which is believed to have healing properties against wounds, burns, etc.² No active compound has been isolated from this plant so far, except for the well known naphthoquinone alkannine.^{3a}

For some time, an effort has been undertaken in this laboratory to isolate other constituents of the plant which might present some pharmacological activity. The first such constituent is the wax reported in this paper. This is proved to be a mixture of at least eight esters containing 42-50 C atoms of an even number. Their components are six acids with 18-28 C atoms and four alcohols with 22-28 C atoms, all even-numbered. It is not possible to find out the exact qualitative and quantitative compositions of the wax from the data obtained. Nevertheless, an approximate composition may be worked out, based mainly on mass spectral data.

Experimental

Isolation of the wax. Dried and pulverised shoots with their leaves and flowers of the plant (100 g) were extracted with petroleum ether (b.p. 30-40°) in a Soxhlet apparatus for 120 hours. A dark red residue (3g) remained upon evaporation of the solvent and it was chromatographed on a silica gel column, using benzene as solvent and eluent. The first eluates were contaminated with some red pigment and they were rechromatographed under the same conditions, affording a colourless microcrystalline compound (400 mg), m.p. 73-77°. This could be recrystallised from several solvents but m.p.'s were never sharp, ranging from 73-80°. Elemental analysis: C 80.80% and H 14.28% (mean value of four determinations).

Hydrolysis. The substance (50 mg) was dissolved in isopropanol (15 ml) containing its sodium salt (10 mg) and the mixture was refluxed for 24 hours. Upon cooling colourless crystals were obtained (20 mg), m.p. 60-70°, characterised as a mixture of alcohols. The filtrate, after removal of the alcohols, was acidified and a precipitate was collected (26 mg), m. p. 55-66°, characterised as a mixture of acids. Identification of the hydrolysis products was effected through their mass spectra.

Instruments. The IR spectrum was obtained with a Perkin-Elmer spectrophotometer, type 257. The NMR spectra were taken with Varian spectrometers, types A-60A and HA-100. The mass spectra were recorded with an AEI MS9 mass spectrometer.

Spectra and their interpretation

UV spectrum. A cyclohexane solution of the substance shows only end-absorption until about 215 nm.

IR spectrum. This was taken in KBr disc and had absorptions at 1725 and 1175 cm^{-1} , suggesting a carbonyl group and a C-O-C group, respectively, and at 2910, 2840, 1460 and 720 cm^{-1} , i.e. the typical stretching, C-H deformations and CH_2 rocking vibration frequencies of saturated carbon chains.

NMR spectrum. This spectrum when taken with an instrument of 60 MHz shows an unresolved singlet at 8.7 τ (in CDCl_3) while with an instrument of 100 MHz two triplets appear centered at 6.0 and 7.8 τ and the unresolved singlet is shifted a little to 8.8 τ (in benzene- d_6 ; approximate ratio of areas 1:1:40). The difference between these spectra is due to the enhanced sensitivity of the 100 MHz spectrometer.

The above spectral data make it possible to draw some conclusions about the nature of the isolated substance. Simple structures of carbonyl compounds are excluded because of the lack of absorption in the UV spectrum. Also, the lack of characteristic absorptions in the IR spectrum rules out the presence of COOH and OH groups and unsaturated bonds as well. Therefore, since acid anhydrides are not encountered in nature, the probable structures of the compound are confined to an ester or a lactone. The lactonic structure is rejected after alkaline hydrolysis, upon which two products are obtained and proved to be acids and alcohols by mass spectrometry. The structure of an ester is in agreement with all spectral data: the carbonyl IR frequency is only slightly lower to that expected for an ester (1750-1735 cm^{-1}), while the triplet at 6.0 τ in the NMR spectrum corresponds to a CH_2 group adjacent to oxygen and the triplet at 7.8 τ to a CH_2 group near the carbonyl carbon. Finally, the NMR spectrum suggests that the carbon chain is straight, since branched chains would have altered the unresolved singlet at 8.8 τ .

It is evident from the ratio of areas in the NMR spectrum that the compound is of relatively high molecular weight. This is confirmed by elemental analysis, where an approximate empirical formula of $(\text{C}_{23}\text{H}_{45}\text{O})^n$ is calculated; since two atoms of oxygen must be present per molecule for an ester a molecular formula of $\text{C}_{46}\text{H}_{90}\text{O}_2$ is suggested.

The broad range of melting points in the original sample and its hydrolysis products suggest that they are not chemically pure. Indeed, most natural waxes are mixtures of various esters. Therefore, in order to gain a further insight into the composition of the wax, the mass spectra and that of the hydrolysis products were recorded and are discussed below in some detail.

Mass spectra. Because of changes in the wax composition upon recrystallisation mass spectra were taken from material purified only chromatographically. The hydrolysis products were also not further purified. Their mass spectra are presented in Table I.

TABLE I

The Mass Spectra of Esters, Alcohols and Acids.^a

| | |
|--------------|---|
| 1. Esters. | m/e 788 (trace), 760 (trace), 732 (20), 704 (45), 676 (47), 648 (52), 620 (30), 437 (1), 409 (1), 397 (22), 396 (8), 392 (6), 381 (3), 379 (76), 369 (76), 368 (20), 364 (21), 353 (4), 351 (7), 341 (66), 340 (16), 336 (32), 323 (1), 313 (95), 312 (10), 308 (1), 295 (2), 285 (100), 284 (20), 267 (10), 257 (20), 239 (6), 225 (4), 211 (4), etc. ^b |
| 2. Alcohols. | m/e 392 (2), 364 (55), 350 (14), 336 (100), 322 (6), 308 (39), 294 (5), 280 (6), 267-266-265-264, 253-252-251-250, etc. ^c |
| 3. Acids. | 424 (1), 396 (4), 368 (10), 353 (2), 340 (7), 325 (7), 312 (8), 297 (4), 284 (8), 269 (7), 241 (2), 185 (2), 60 (100). |

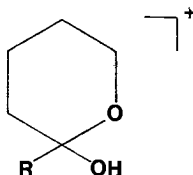
^a Samples were introduced into the mass spectrometer by direct insertion (esters at 170°, alcohols at 100°, acids at 230°) and the spectra were run under normal conditions (ionisation energy 70 eV). All ions of relative abundance > 10% are included, together with other ions of special interest.

Figures in brackets are relative abundances to the base peak (100).

b Ions of lower values are hydrocarbon units and they are omitted.

c This pattern is continued down to the lowest values.

1. *Esters.* The mass spectra of waxes have not been studied systematically. The only pertinent studies are those of certain esters derived from medium-chain acids with long-chain alcohols, RCOOR' .⁴ Their characteristics, apart from the molecular ion, are: base peak corresponding to RCOOH_2^+ and significant ions due to $[\text{RCOOH}]^+$, $[\text{R}'\text{-O-CO}]^+$ and $[\text{R}'\text{-1H}]^+$. Two more ions of low relative abundance are also observed: one of the type $[\text{R}'\text{-O-C(OH)=CH}_2]^+$, resulting from 2,3-cleavage of the acid chain with rearrangement of one H atom and one of the cyclic structure shown below, resulting from 4,5-cleavage of the alcohol chain with rearrangement of one H atom.



From Table I it can be seen that in the region m/e 600-800 there are seven ions differing by 28 mass units. These are evidently seven distinct molecular ions, since it is not possible to visualise any conceivable way of fragmentation of the higher mass ion leading to the others; their relative abundance also rules out such a possibility. Therefore, there are seven molecular ions corresponding to seven sets of esters with 42-54 C atoms, all of an even number. The esters with 52 and 54 C atoms are of minimal intensity (traces only) and, as they do not give any detectable fragments, will be omitted from further discussion. From the relative abundances of the remaining five molecular ions it is feasible to make an approximate calculation of the contribution of each set of esters to the wax composition. This is effected by assuming that relative abundance is proportional to actual concentration and that volatility of the esters is of the same order.* The results appear in Table II.

TABLE II

Ratios of Esters, Alcohols and Acids Calculated from Relative Abundances (RA) of Their Mass Spectra

| Esters | m/e (RA) | Ratio | Alcohols | m/e (RA) ^a | Ratio | Acids | m/e (RA) | Ratio |
|---|------------|-------|--------------------------------------|-------------------------|-------|--|------------|-------|
| $\text{C}_{42}\text{H}_{84}\text{O}_2$ | 620 (30) | 1.5 | $\text{C}_{22}\text{H}_{46}\text{O}$ | 308 (39) | 2.0 | $\text{C}_{18}\text{H}_{36}\text{O}_2$ | 284 (8) | 2.1 |
| $\text{C}_{44}\text{H}_{88}\text{O}_2$ | 648 (52) | 2.7 | $\text{C}_{24}\text{H}_{50}\text{O}$ | 336 (100) | 5.1 | $\text{C}_{20}\text{H}_{40}\text{O}_2$ | 312 (8) | 2.1 |
| $\text{C}_{46}\text{H}_{92}\text{O}_2$ | 676 (47) | 2.4 | $\text{C}_{26}\text{H}_{54}\text{O}$ | 364 (55) | 2.8 | $\text{C}_{22}\text{H}_{44}\text{O}_2$ | 340 (7) | 1.8 |
| $\text{C}_{48}\text{H}_{96}\text{O}_2$ | 704 (45) | 2.3 | $\text{C}_{28}\text{H}_{58}\text{O}$ | 392 (2) | 0.1 | $\text{C}_{24}\text{H}_{48}\text{O}_2$ | 368 (10) | 2.6 |
| $\text{C}_{50}\text{H}_{100}\text{O}_2$ | 732 (20) | 1.0 | | | | $\text{C}_{26}\text{H}_{52}\text{O}_2$ | 396 (4) | 1.0 |
| | | | | | | $\text{C}_{28}\text{H}_{56}\text{O}_2$ | 424 (1) | 0.3 |

^a Calculations in alcohols are based on the olefin fragment.

* Based on melting points, since boiling points are not known. Melting points of certain esters: $\text{C}_{15}\text{H}_{31}\text{CO}_2\text{C}_{30}\text{H}_{61}$ 79°, $\text{C}_{25}\text{H}_{51}\text{CO}_2\text{C}_{26}\text{H}_{53}$ 81°, etc. ^{3b}

Careful examination of Table I reveals the existence of several series of ions differing by 28 mass units. The following series are observed:

Series A: 397, 369, 341, 313 and 285.

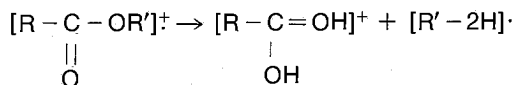
Series B: 396, 368, 340, 312 and 284.

Series C: 392, 364, 336 and 308.

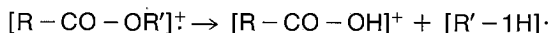
Series D: 379, 351, 323, 295 and 267.

Series E: 437, 409, 381 and 353.

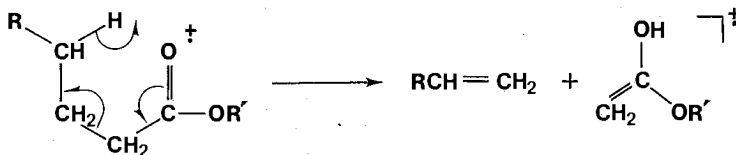
Ions of series A are of the highest relative abundance and correspond to protonated acids resulting from R'-O cleavage, accompanied by rearrangement of two H atoms



Ions of series B correspond formally to acids but they may come either from R'-O cleavage of esters accompanied by rearrangement of one H atom

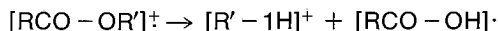


or from a McLafferty rearrangement:



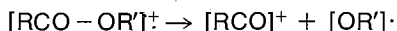
Both types of ions have been previously observed: the former in various ethyl esters,^{5a} the latter in methyl and long-chained alkyl esters.^{5b} Ions $[\text{RCOOH}]^{\dagger}$ and $[\text{CH}_2=\text{C}(\text{OH})\text{OR}']^{\dagger}$ will have identical masses if R and R' differ by one methylene group; but since the alcohols contain 22-28 C atoms (Table II) they would have produced ions of the latter type with m/e ranging from 452 to 368. The observed ions have m/e values between 396 and 284, so by necessity they must come from the acids, which contain 18-26 C atoms (Table II).

Ions of series C are olefins derived also from R'-O cleavage with one H atom rearrangement but with formation of a non-charged acid

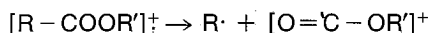


The same ions are observed in the spectra of alcohols.

The ions of series D are of low relative abundance and they may be attributed to either R⁺ or RCO⁺. In the case of methyl esters the former are usually of negligible abundance, while formation of the latter is energetically more favourable.^{5c} High resolution measurements showed that acylium ions are actually formed, arising from cleavage of the CO-O bond

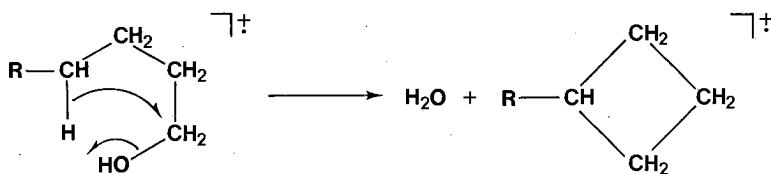


The ions of series E are of the lowest relative abundance and they also may correspond to two structures, $[\text{OR}']^{\dagger}$ and $[\text{O}=\text{C}-\text{OR}']^{\dagger}$, both of which have been observed in various esters.^{5c} It is concluded, however, that the latter explains better the ions of this series, because the fragment 437 with an alcoxy structure would have come from an alcohol with 30 C atoms, which is not found in the hydrolysis products. Simple α -cleavage occurs also in this case



Apart from the above described ions there exist groups of three peaks spaced 14 mass units apart, i.e. differing by one methylene group, and each having as the most abundant species the C_nH_{2n+1} ion. These groups of ions occur with gradually increasing abundance as the fragment weight decreases and are probably formed from acylium ions by ejection of CO. Such hydrocarbon ions are typical of straight-chain compounds and they have not any diagnostic value.^{5d} They are omitted from Table I.

2. *Alcohols.* The main characteristic of long-chain alcohols is the lack of a molecular ion; their base peak is an "olefin" formed (non-thermally) by way of a 1,4-elimination of water through a six-membered intermediate.⁶ This "olefin" may have a cyclic structure as shown below^{6a} or it may be a true olefin, resulting either from hydrogen migration concerted with loss of water or through isomerisation of the cyclic hydrocarbon^{6b}



Such ions are observed in the mass spectra of the alcohols obtained from hydrolysis of the wax and they have m/e values of 308, 336, 364 and 392, corresponding to alcohols with 22, 24, 26 and 28 C atoms. Since volatility of these alcohols is very similar,^{7a} an approximate ratio of them may be calculated, as in the case of the esters (Table II).

Ions corresponding to loss of 1,2 and 3 H atoms, usually observed in lower alcohols, are absent. All other ions are hydrocarbon units, as above.

3. *Acids.* The mass spectra of acids show six molecular ions at m/e 424, 396, 368, 340, 312 and 284, corresponding to acids with 28, 26, 24, 22, 20 and 18 C atoms. The volatility of these acids, judged from their melting points which range from 70-90°,^{7b} is not comparable as previously and their ratio in Table II is of limited accuracy.

Other ions appear at m/e 353, 325, 297, 269, 241 and 185 and they belong to the general structural unit $[(CH_2)_nCOOH]^+$. Such ions are formed from both long-chain normal acids and their methyl esters by several possible mechanisms.^{5e}

All other ions are hydrocarbon fragments, with the exception of m/e 60 which corresponds to $[CH_2=C(OH)OH]^+$ and is due to a McLafferty rearrangement.^{5e}

Conclusion

The mass spectra of acids and alcohols are very similar to those of analogous compounds previously studied. This is also the case with the esters, with the difference that ions of cyclic structure are not observed.

From the mass spectra of the esters it is not possible to differentiate among isomeric esters, even under high resolution. Random combination of all the acids and alcohols present leads to a total of seventeen esters with 42-50 C atoms. Those with an alcohol of equal or lower number of C atoms from the acid may be not present at all, since there is always a tendency in nature for a fatty acid to become esterified with an alcohol of a higher C atom number.^{7c} Also, since alcohol $C_{26}H_{57}OH$ is present in a very small quantity, its esters, four in all possible, must be present virtually in traces. Therefore, the most probable qualitative composition of the wax is

| | | | |
|------------------------|-------------------------------|-----|-------------------------------|
| Esters with 42 C atoms | $C_{17}H_{35}COOC_{24}H_{49}$ | and | $C_{19}H_{39}COOC_{22}H_{45}$ |
| Esters with 44 C atoms | $C_{17}H_{35}COOC_{26}H_{53}$ | and | $C_{19}H_{39}COOC_{24}H_{49}$ |
| Esters with 46 C atoms | $C_{19}H_{39}COOC_{26}H_{53}$ | and | $C_{21}H_{43}COOC_{24}H_{49}$ |
| Esters with 48 C atoms | $C_{21}H_{43}COOC_{26}H_{53}$ | | |
| Esters with 50 C atoms | $C_{23}H_{47}COOC_{26}H_{53}$ | | |

Acknowledgment

I wish to thank Professor R.G. Cooks, now of Purdue University, who when in Cambridge University recorded the mass spectra and the 100 MHz NMR spectrum and helped in their interpretation.

ΠΕΡΙΛΗΨΙΣ

Φασματοσκοπική μελέτη ενός κηρού άπομονωθέντος εκ του φυτού
Alkanna tinctoria Tausch.

Το φυτόν *Alkanna tinctoria Tausch.* ενδέχεται να παρουσιάζη θεραπευτική ενέργειαν. Διά τουτο ανέληφθη μία προσπάθεια άπομόνωσης εξ αύτου συστατικών πιθανώς φαρμακολογικώς δραστικῶν. Εἰς τὴν παροῦσαν ἔργασίαν περιγράφεται ἡ άπομόνωσις ενός κηροῦ, τοῦ ὁποίου μελετῶνται αἱ φασματοσκοπικαὶ ιδιότητες μεῖς ἰδιαιτέραν ἔμφασιν εἰς τὰ φάσματα μαζῶν.

Φάσματα μαζῶν κηρῶν λαμβάνονται ἐνταῦθα διὰ πρώτην φοράν καὶ εὐρίσκειται ὅτι ὁμοιάζουν βασικῶς μεῖς ἄλλους μελετηθέντας ἐστέρας μέσων ὀξέων μεῖς ἀνωτάτας ἀλκοόλας.

Ἡ σύνθεσις τοῦ κηροῦ δὲν εἶναι δυνατὸν νὰ ἐξευρεθῇ ἑπακριβῶς μεῖς μόνον τὰ φασματοσκοπικὰ δεδομένα, μεῖς θάσιν ὅμως τὰ φάσματα μαζῶν ὑπολογίζεται μία κατὰ προσέγγισιν ποιοτικὴ σύστασις τοῦ μίγματος τῶν ἐστέρων, ἐκ τῶν ὁποίων ἀποτελεῖται ὁ κηρός. Οὕτω τὰ ἐπὶ μέρους συστατικά του εἶναι ἕξ κεκορεσμένα μονοκαρβονικὰ ὀξέα μεῖς 18-28 ἄτομα ἄνθρακος καὶ τέσσαρες κεκορεσμένοι μονοσθενεῖς ἀλκοόλοι μεῖς 22-28 ἄτομα ἄνθρακος, ἅπαντα εὐθείας ἀλύσεως καὶ ἄρτιου ἀριθμοῦ ἀτόμων ἄνθρακος. Ἐν καὶ ὁ συνδυασμὸς ὄλων τῶν ὀξέων μεῖς ὅλας τὰς ἀλκοόλας δίδει συνολικῶς δεκαεπτὰ πιθανοὺς τύπους ἐστέρων, συνάγεται ὅτι βασικῶς μόνον ὀκτῶ ἐξ αὐτῶν εἶναι τὰ κύρια συστατικά τοῦ κηροῦ.

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Synthèse de Quelques Nouveaux Acides Hydroxamiques

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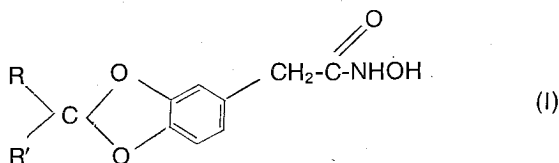
(Received 3-3-72)

En vue d'étudier éventuellement le comportement pharmacologique, les auteurs ont préparé un certain nombre d'acides hydroxamiques nouveaux, de formule générale (I). Ces acides, dérivés de l'acide dialcoylméthylènedioxy-3, 4-phénylacétique, sont préparés par une série de réactions en partant de la pyrocatechine. La liaison dialcoylméthylènedioxy étant particulièrement fragile en milieu acide minéral, des méthodes respectant cette fragilité sont utilisées, pour éviter la rupture de cette liaison. Plus spécialement, la synthèse des acétophénonnes correspondantes s'effectue à l'aide de fluorure de bore, et non par la méthode classique de Friedel-Craft. De même, l'estérification des acides phénylacétiques correspondants se fait par le diazométhane.

In this paper the synthesis of new hydroxamic acids of the general formula (I) is reported. These compounds are to be tested as antipyretics and antirheumatics. These acids are derivatives of the 3,4-dialkylmethylene-dioxyphenyl-acetic acid and are prepared by the following reaction series: pyrocatechol reacts with different ketones in the presence of phosphorus pentoxide to give dialkylmethylene-dioxybenzene (a), which combines with acetic anhydride in the presence of borontrifluoride to give the corresponding acetophenones (b). The latter undergo the Willgerdt reaction and are transformed by the intermediate morpholides (c) to the substituted phenylacetic acids (d), which are esterified with diazomethane (e). The esters thus obtained are converted with satisfactory yields by the action of hydroxylamine, to the hydroxamic acids (f), solid crystalline compounds.

On a préparé récemment^{4,5} certains acides hydroxamiques, dérivés de l'acide phénylacétique, pour lesquels on a reconnu une activité analgésique et anti-inflammatoire, comparable à celle de l'aspirine. L'étude pharmacologique de ces substances a montré, que ces composés étaient en plus doués de propriétés tranquillisantes et même hypocholestérolémiantes, sans, toutefois, présenter une grande toxicité.

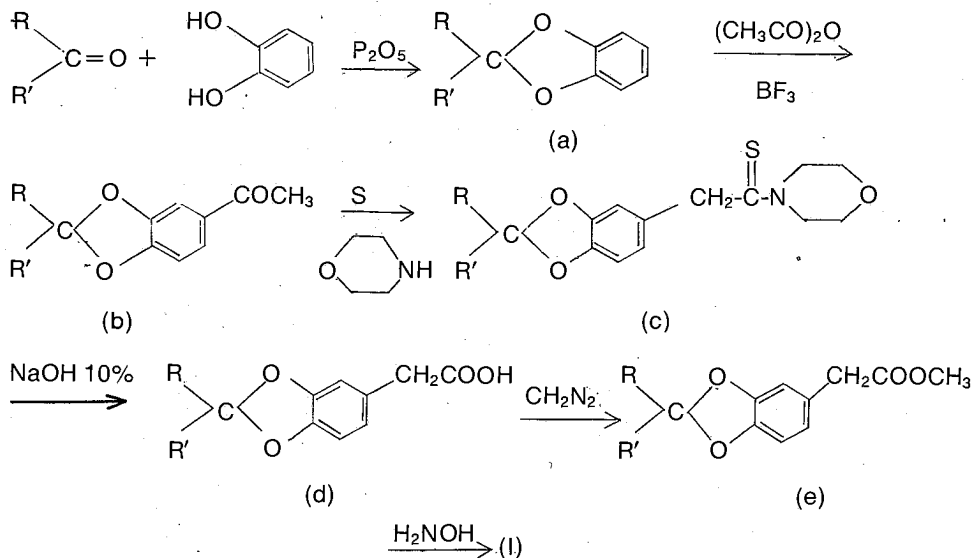
Ces observations nous ont incités à préparer un certain nombre d'acides hydroxamiques, de formule générale (I), présentant deux fonctions phénols en position ortho, étherifiées sous forme de dialcoylméthylènedioxy, en vue d'étudier leur activité pharmacologique.

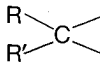


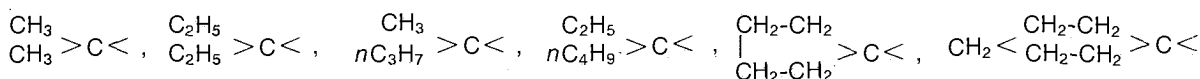
Dans cette formule R et R' peuvent être identiques ou différents et représenter un radical alcoyle inférieur, comme méthyle, éthyle, n-propyle, n-butyle ou former avec l'atome de carbone adjacent un radical cycloalcoyle, comme cyclopentyle ou cyclohexyle.

Pour la synthèse des produits en question, ont été employés comme matières premières, les éthers méthyléniques disubstitués du pyrocatechol (a), qui ont été obtenus avec de bons rendements, suivant le procédé décrit par Böeseken et Sloof,¹ soit, par action de la cétone appropriée sur le pyrocatechol, en présence d'anhydride phosphorique. Les éthers ainsi obtenus, ont été transformés en méthylènedioxy-3, 4-acétophénonés substitués (b), par action de trifluorure de bore en présence d'anhydride acétique, selon le procédé rapporté par J. Hoch et G. Tsatsas.² L'application de la réaction Willgerodt, comme celle-ci est décrite en détail par E. Schwenk et E. Bloch,³ sur les dérivés de l'acétophénone (b) a donné les acides méthylènedioxy-3, 4-phénylacétiques substitués (d), sous forme solide ou huileuse, en passant par l'intermédiaire des morpholides correspondants (c), qui, eux aussi, ont été isolés sous forme tantôt solide, tantôt huileuse. Les morpholides (c) et les acides (d) obtenus sous forme d'huile épaisse ont été employés bruts pour l'étape suivante. Les acides phénylacétiques (d) ont été ensuite estérifiés à l'aide d'une solution étherée de diazométhane, ce qui a fourni les esters (e) avec un bon rendement. Il a aussi été essayé l'estérification par transformation des acides à leurs sels d'argent et action sur ces derniers de l'iodure de méthyle, mais, le procédé ne donnant pas de rendements satisfaisants, la méthode a été abandonnée. En ce qui concerne les autres procédés classiques d'estérification, ils sont à éviter, étant donné la sensibilité des fonctions étherées aux acides minéraux. Les esters (e) ainsi obtenus ont été finalement transformés en acides hydroxamiques correspondants par action de l'hydroxylamine, comme il est décrit par Buu-Hoi, C. Gillet et al.^{4 5}

Les diverses étapes de la synthèse ci-avant peuvent être représentées par la série de réactions suivantes:



Dans les produits de formule (I) préparés, ainsi que les divers intermédiaires de leur synthèse, le radical R  représente:



Partie Expérimentale

Dans le présent article seulement la partie chimique a été rapportée. L'étude pharmacologique fera l'objet d'un mémoire dans une revue spécialisée.

1) Ethers méthyléniques du pyrocatechol disubstitués (a)

Obtenus selon Böeseken et Sloof,¹ ils sont tous rapportés dans la littérature, sauf l'éthyl-*n*-butyl-méthylène dioxy-1, 2-benzène, qui a été préparé suivant le même procédé avec un rendement de 35%. Eb₁₂mm = 121°C.

Analyse: Calc. % pour C₁₃H₁₈O₂ C 75,7 H 8,8
Tr. % 75,4 8,9

2) Méthylènedioxy-3, 4-acétophénones disubstituées (b)

Les acétophénones utilisées ont été obtenues selon J. Hoch et G. Tsatsas,² avec de bons rendements. Il faut noter qu'en opérant avec des quantités d'éthers ne dépassant pas les 30 g à la fois, on obtient, dans la plupart de cas, une amélioration nette des rendements. Les auteurs précités décrivent les acétophénones (b) préparées, sauf les deux produits suivants, qui sont des composés nouveaux:

Méthyl-*n*-propyl-méthylènedioxy-3, 4-acétophénone. Eb₁₂mm = 162-164°C.

Analyse: Calc.% pour C₁₃H₁₆O₃ C 70,9 H 7,3
Tr. % 70,5 7,6

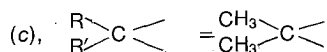
Ethyl-*n*-butyl-méthylènedioxy-3, 4-acétophénone. Eb₁₂mm = 173-176°C.

2,4-Dinitrophénylhydrazone F = 148-150°C (cap.)

Analyse: Calc.% pour C₁₅H₂₀O₃ C 72,5 H 8,1
Tr. % 72,7 8,2

3) Méthylènedioxy-3, 4-phénylthioacétomorpholides disubstitués (c).

Diméthyl-méthylènedioxy-3, 4-phénylthioacétomorpholide³



Un mélange de 24 g de diméthyl-méthylènedioxy-3, 4-acétophénone, 4 g de soufre et 12 g de morpholine est chauffé au bain d'huile, pendant 8h, à 135-140°C. Le mélange de la réaction est ensuite versé sur de la glace pilée et extrait à l'éther. Les extraits éthers sont séchés sur le sulfate de sodium anhydre, traités au noir décolorant et évaporés à sec. Le résidu, recristallisé dans le méthanol, donne 18 g de morpholide, qui fond à 105-106°C (cap.) Rend. 57%.

Analyse: Calc. % pour C₁₅H₁₉NO₃S C 61,4 H 6,5 N 4,8
Tr. % 61,6 6,3 4,5

Suivant le procédé qui vient d'être décrit, ont été préparés les morpholides suivants:

— Diéthyl-méthylènedioxy-3, 4-phénylthioacétomorpholide

F = 60-62°C (cap.) Rend. 45%

Analyse: Calc. % pour C₁₇H₂₃NO₃S C 63,5 H 7,2 N 4,4
Tr. % 63,2 7,4 4,6

— Méthyl-*n*-propyl-méthylènedioxy-3, 4-phénylthioacétomorpholide

Huile épaisse. Rend. 76% (en produit brut).

— Ethyl-*n*-butyl-méthylènedioxy-3, 4-phénylthioacétomorpholide

Huile épaisse. Rend. 44% (en produit brut).

— Cyclopentyl-méthylènedioxy-3, 4-phénylthioacétomorpholide
F = 85-86°C (cap.). Rend. 33%

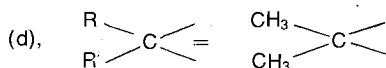
| | | | |
|---|--------|-------|-------|
| Analyse: Calc. % pour C ₁₇ H ₂₁ NO ₃ S | C 63,9 | H 6,6 | N 4,4 |
| Tr. % | 63,5 | 6,7 | 4,6 |

— Cyclohexyl-méthylènedioxy-3, 4-phénylthioacétomorpholide
F = 135-136°C (cap.). Rend. 50%

| | | | |
|---|--------|-------|-------|
| Analyse: Calc. % pour C ₁₈ H ₂₃ NO ₃ S | C 64,8 | H 6,9 | N 4,2 |
| Tr. % | 64,4 | 6,7 | 4,3 |

4) Acides méthylènedioxy-3, 4-phénylacétiques (d)

Acide diméthyl-méthylènedioxy-3, 4-phénylacétique.³



17g de diméthyl-méthylènedioxy-3, 4-phénylthioacétomorpholide et la solution de 26g d'hydroxyde de sodium dans 350 ml d'éthanol, sont chauffés au bain-marie pendant 14 h, puis l'alcool est éliminé par distillation, et le résidu est additionné d'eau et acidifié avec précaution à l'aide d'acide acétique. Le mélange est extrait à l'éther et les extraits étherés sont lavés à l'eau, séchés et évaporés à sec. Le résidu, recristallisé dans l'éther de pétrole, fournit 11g d'acide, qui fond à 72-73°C (cap.). Rend. 78%.

| | | |
|--|---------|-------|
| Analyse: Calc. % pour C ₁₁ H ₁₂ O ₄ | C 63,45 | H 5,8 |
| Tr. % | 63,1 | 5,4 |

En opérant comme il vient d'être décrit on obtient les acides méthylènedioxy-3, 4-phénylacétiques suivants:

— Acide diéthyl-méthylènedioxy-3, 4-phénylacétique
Huile épaisse. Rend. 93% (en produit brut).

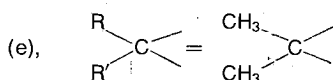
— Acide méthyl-*n*-propyl-méthylènedioxy-3, 4-phénylacétique
Huile épaisse. Rend. 66% (en produit brut).

— Acide éthyl-*n*-butyl-méthylènedioxy-3, 4-phénylacétique
Huile épaisse. Rend. 60% (en produit brut).

— Acide cyclopentyl-méthylènedioxy-3, 4-phénylacétique
F = 80-82°C (cap.). Rend. 84%.
Analyse: Calc. % pour C₁₃H₁₄O₄ C 66,6 H 6,0
Tr. % 66,2 6,2

— Acide cyclohexyl-méthylènedioxy-3, 4-phénylacétique
F = 83-84°C (cap.). Rend. 45%.
Analyse: Calc. % pour C₁₄H₁₆O₄ C 67,7 H 6,5
Tr. % 67,9 6,2

5) Esters méthylènedioxy-3, 4-phénylacétiques disubstitués (e) Diméthyl-méthylènedioxy-3, 4-phénylacétate de méthyle



Une solution étherée de diazométhane contenant environ 3 g de ce réactif⁵ est additionnée de 7,5 g d'acide diméthyl-méthylènedioxy-3, 4-phénylacétique, ajoutés par petites portions et à la température ambiante. Le mélange est abandonné à la glacière pendant 12 h, puis l'éther est éva-

poré sous pression réduite, en chauffant très légèrement sur bain-marie de sorte que l'élimination de l'éther aie lieu à la température ambiante. Le résidu (8,5g) est employé tel quel pour l'étape suivante:

Analyse: Calc. % pour C₁₂H₁₄O₄ C 64,9 H 6,4
Tr. % 64,5 6,0

D'une façon identique à celle décrite ci-avant, ont été obtenus les esters suivants:

— Diéthyl-méthylènedioxy-3, 4-phénylacétate de méthyle

Analyse: Calc. % pour C₁₄H₁₈O₄ C 67,2 H 7,3
Tr. % 67,4 7,6

— Méthyl-*n*-propyl-méthylènedioxy-3, 4-phénylacétate de méthyle

Analyse: Calc. % pour C₁₄H₁₈O₄ C 67,2 H 7,3
Tr. % 66,9 7,0

— Ethyl-*n*-butyl-méthylènedioxy-3, 4-phénylacétate de méthyle

Analyse: Calc. % pour C₁₆H₂₂O₄ C 69,0 H 8,0
Tr. % 68,9 8,0

— Cyclopentyl-méthylènedioxy-3, 4-phénylacétate de méthyle

Analyse: Calc. % pour C₁₄H₁₆O₄ C 67,7 H 6,5
Tr. % 68,1 6,5

— Cyclohexyl-méthylènedioxy-3, 4-phénylacétate de méthyle

Analyse: Calc. % pour C₁₅H₁₈O₄ C 68,8 H 6,9
Tr. % 69,0 7,1

6) Acides méthylènedioxy-3, 4-phénylméthylène-hydroxamiques disubstitués (I)^{4,5}

Acide diméthyl-méthylènedioxy-3, 4-phénylméthylène-hydroxamique

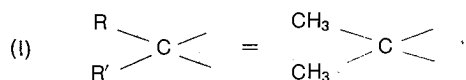
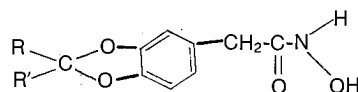


TABLEAU I
Acides hydroxamiques



| T | $\begin{array}{c} R \\ \diagdown \\ C \\ \diagup \\ R' \end{array}$ | Formule brute | F°C (cap.) | Rend.* | Calc. % | | | Tr. % | | |
|------|--|---|------------|--------|---------|-----|-----|-------|-----|-----|
| | | | | | C | H | N | C | H | N |
| 2400 | $\begin{array}{c} CH_3 \\ \diagdown \\ C \\ \diagup \\ CH_3 \end{array}$ | C ₁₁ H ₁₃ NO ₄ | 136 - 137 | 57% | 59,2 | 5,8 | 6,3 | 59,2 | 6,1 | 6,5 |
| 2411 | $\begin{array}{c} C_2H_5 \\ \diagdown \\ C \\ \diagup \\ C_2H_5 \end{array}$ | C ₁₃ H ₁₇ NO ₄ | 116 - 117 | 45% | 62,1 | 6,8 | 5,6 | 62,4 | 6,6 | 5,4 |
| 2412 | $\begin{array}{c} CH_3 \\ \diagdown \\ C \\ \diagup \\ nC_3H_7 \end{array}$ | C ₁₃ H ₁₇ NO ₄ | 87 - 88 | 37% | 62,1 | 6,8 | 5,6 | 62,4 | 7,1 | 5,4 |
| 2413 | $\begin{array}{c} C_2H_5 \\ \diagdown \\ C \\ \diagup \\ nC_4H_9 \end{array}$ | C ₁₅ H ₂₁ NO ₄ | 114 - 115 | 70% | 64,5 | 7,6 | 5,0 | 64,1 | 7,4 | 4,9 |
| 2414 | $\begin{array}{c} CH_2-CH_2 \\ \diagdown \\ C \\ \diagup \\ CH_2-CH_2 \end{array}$ | C ₁₃ H ₁₅ NO ₄ | 108 - 110 | 54% | 62,6 | 6,1 | 5,6 | 63,0 | 5,9 | 5,5 |
| 2415 | $\begin{array}{c} CH_2-CH_2 \\ \diagdown \\ C \\ \diagup \\ CH_2-CH_2 \end{array}$ | C ₁₄ H ₁₇ NO ₄ | 97 - 98 | 52% | 63,9 | 6,5 | 5,3 | 63,6 | 6,6 | 5,1 |

* Calculé sur l'ester de l'étape précédente et après recristallisation.

La solution de 1,16g de chlorhydrate d'hydroxylamine dans 17ml de méthanol absolu est additionnée d'une solution de 0,83g de sodium dans 25ml de méthanol et le chlorure de sodium, qui précipite, est filtré. 3,7g de diméthyl-méthylènedioxy-3, 4-phénylacétate de méthyle sont ajoutés au filtrat et le mélange est chauffé au reflux pendant 1 h. Après refroidissement, acidification à l'aide d'acide chlorhydrique à 10% et dilution à l'eau, un produit précipite, qui, essoré, lavé à l'eau et recristallisé dans le mélange acétone-éther de pétrole, fournit 2,1g de l'acide hydroxamique désiré, $F = 136-137^{\circ}\text{C}$ (cap.).

D'une façon identique ont été préparés tous les acides hydroxamiques de cette série, dont les analyses et constantes sont rassemblées au tableau (I).

ΠΕΡΙΛΗΨΙΣ

Σύνθεσις νέων τινῶν ὑδροξαμικῶν ὀξέων.

Πρὸς τὸν σκοπὸν ὅπως μελετηθοῦν αἱ φαρμακολογικαὶ αὐτῶν ιδιότητες, ἰδιαίτερος αἱ ἀντιπυρετικαὶ καὶ ἀντιρρευματικαὶ τοιαῦται, παρασκευάζονται, εἰς τὴν παροῦσαν μελέτην, νέα ὑδροξαμικὰ ὀξέα τοῦ γενικοῦ τύπου (I). Τὰ ὀξέα ταῦτα, παράγωγα τοῦ 3, 4-διαλκυλομεθυλενο-διοξυφαινυλοξικοῦ ὀξέος παρασκευάζονται διὰ τῆς κάτωθι σειρᾶς ἀντιδράσεων: ἡ πυροκατεχίνη ἀντιδρᾷ μετὰ διαφόρων κετονῶν παρούσῃ πεντοξειδίου τοῦ φωσφόρου πρὸς διαλκυλομεθυλενο-διοξυβενζόλια (α) τὰ ὅποια ἐνοῦνται μετ' ὀξικοῦ ἀνυδρίτου παρουσίᾳ τριφθοριούχου βορίου πρὸς τὰς ἀντιστοίχους ἀκετοφαινόνας (β). Αἱ τελευταῖαι αὗται ὑφίστανται τὴν ἀντίδρασιν Willgerodt καὶ μετατρέπονται διὰ τῶν ἐνδιαμέσων μορφολιδίων (c) εἰς τὰ ὑποκατεστημένα φαινυλοξικά ὀξέα (d), τὰ ὅποια ἐστεροποιοῦνται διὰ τοῦ διαζωμεθανίου (e). Οἱ ληφθέντες ἐστέρες, τῇ ἐπιδράσει ὑδροξυλαμίνης, μετατρέπονται εἰς τὰ ὑδροξαμικὰ ὀξέα (I), σώματα στερεά, καλῶς κρυσταλλούμενα, ληφθέντα, γενικῶς, μὲ ἱκανοποιητικὰς ἀποδόσεις.

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Domain Structure in Single Crystals of GeTe and Ge_{1-x}Sn_xTe

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(Received 22-2-72)

Single crystals of GeTe and its alloys with Sn grown by a vapor transport method possess a twin structure, as revealed by optical and electronic microscopic methods, with the coherent twin plane being the (100) plane. The twins become more regular as the Sn content increases.

Introduction

Germanium telluride and its alloys with tin (Ge_{1-x}Sn_xTe) at high temperatures have a cubic NaCl-type structure, which upon cooling is transformed at a temperature which depends on x to a face-centered rhombohedral structure. This transformation, according to Bierly et al,¹ occurs through an elongation of the face-centered cell along the [111] direction, with a simultaneous relative displacement of the Ge-Te layers, so that the crystal is no longer centrosymmetric and it belongs to the group R3m(C_{3v}⁵).^{2,3} Under these conditions the crystal should develop a dipole moment and behave as a ferroelectric material. The ferroelectric behaviour has been established through neutron diffraction experiments associated with phonon interactions^{4,5} and by measurements of light scattering as a function of temperature on single crystalline α -GeTe,⁶ but it is masked by the free electron concentration, since GeTe is a narrow band semiconductor. According to Megaw,⁷ who describes ferroelectricity mainly from the crystallographic aspect of the problem, it is always possible for a ferroelectric crystal to contain domains (twins). Recently¹³ it has been established that such a twin structure was evident in the case of thin epitaxial films of GeTe and its alloys with Sn grown by vacuum evaporation under appropriate conditions. Therefore, we felt justified in extending these observations to bulk single crystals.

Experimental

Crystal Growth

The reported ways of growing large GeTe and Ge_{1-x}Sn_xTe single crystals are either a modified Czochralski technique in which liquid encapsulation is combined with a substantial neutral-gas overpressure to eliminate vaporization during growth^{8,9} or a Bridgman technique.¹⁰ In our case a vapor growth technique was used with a silica ampoule of tubular cross section about 8 mm diameter and 50 mm long, tapered to a point at the one end. The source material used was powdered GeTe of 5N purity, and, in the case of Ge_{1-x}Sn_xTe single crystal growth, GeTe powder was mixed with the appropriate proportions of SnTe of the same purity. After the ampoule was loaded it was evacuated to a vacuum of 1×10^{-6} Torr or lower and sealed. The ampoule was placed in a horizontal resistance furnace with a temperature profile from a maximum of 850°C near the load to a minimum of 720°C at the tip. The transport time was approximately 96 hours. At the end of this time almost

the entire charge was transferred to the far end. The single crystal grew at the tip with a direction of growth close to the [111] direction (fig. 1). With this method we obtained single crystals up to 6 mm in length and 8 mm in diameter. After the required time of transport the ampoules were cooled slowly (at a rate of 7°C/hr).

Since no transport material was used the crystals may be considered relatively free of impurities and suitable for electrical measurements. Electrical measurements performed on GeTe crystals using a modified a.c. Van Der Pauw method gave the following values for a typical sample; resistivity 2.055×10^{-3} Ohm. cm, Hall mobility $296 \text{ cm}^2/\text{Volts}$ from which the computed carrier p concentration was of the order $2.1 \times 10^{19} \text{ cm}^{-3}$.

Preparation of Specimens

In order to examine the samples it was necessary to develop a suitable etchant since none has been reported for GeTe/SnTe.¹⁰ Such an etchant was found by using an aqueous KOH or NaOH solution. Thus after orientation by back-reflection Laue techniques the samples were lapped. The damaged layer caused by cutting and lapping was removed by etching with a 0.4N KOH solution for about 5 minutes, after which the samples were rinsed with distilled water. Usually patterns of lines and zones were seen on the surface of the specimens (fig. 2a). A perfect shiny surface was obtained by a jet electropolishing technique, using a sodium hydroxide solution (N/10) as electrolyte.

The same technique was used for preparing specimens for electron microscope studies. It was found that the current density is rather critical in order to obtain a polished surface and it must be held constant at the high value of 5A/cm^2 . Below this value instead of electropolishing, an etched surface is obtained. The thickness was controlled by the colour of the transmitted light, the jet acting as a condensing light guide.¹¹

Observations with Reflected Light

The existence of twin patterns in chemical etched GeTe or $\text{Ge}_{1-x}\text{Sn}_x\text{Te}$ specimens has been reported previously by Bierly et al.¹ but he did not study the structure of these twins.

Germanium telluride at room temperature has a f.c.r. symmetry, the optical axis coinciding with the [111] direction. Since GeTe is opaque the indicatrix will be complex resulting from the intersection of two ellipsoids.¹² This permits optical examination of the expected domain structure.

When an electropolished surface of single crystal GeTe or $\text{Ge}_{1-x}\text{Sn}_x\text{Te}$ is observed in reflected light between crossed polarisers, patterns can be seen that show a twin structure, the twins following the [100] and [010] directions. Bright and dark domains alternate at a given extinction position when the analyser is rotated through a very small angle either side from the crossed position. Greatest contrast with normal incident light is observed when the [100] and [010] directions coincide with the directions of the polariser and analyser in crossed position. In pure GeTe (fig. 2b) the length of these twins is rather short and their shape irregular. The length increases progressively and a more regular pattern is obtained by increasing the Sn content of the crystals. Figure 2a shows a surface of a crystal of composition $(\text{GeTe})_{0.6}(\text{SnTe})_{0.4}$ where a rectangular pattern of the twins is evident with the directions stated above. The regular pattern in the Sn rich alloys may be due to the fact that the strain during the transformation from the cubic structure of the rhombohedral one is less.

Electron Microscope Observation

The electron microscope offers the attractive possibility of increased resolution as compared with the optical microscope and of simultaneous diffraction experiments. Figure 3 is an example of the type of bright field image which can be obtained in rhombohedral GeTe thin specimen where the incident beam is perpendicular to the (001) surface of the sample.

The twins in the micrograph have sharp boundaries along [100] direction, the contrast is clearly diffraction contrast as can be concluded from tilting experiments. The boundaries were found to disappear when the image is formed by the reflection from the atomic plane common to the domains. The splitting of the diffraction spots is normal to the twin boundary (inset fig. 3).

The absence of Kikuchi lines is consistent with the high density of defects. Observations normal to the (111) plane revealed a rather complicated structure due to the fact that the twin planes in this case are inclined with respect to the plane of observation.

Results and Discussion

The existence of twins all through the observed area is a result of the transformation from the cubic to rhombohedral structure by the elongation of the unit cell along the [111] direction (the angle of the axis is 88.6°). In the case when the coherent twin plane is the (100) or (110) the orientation of the structure on both sides of the twin plane forms a very small angle, about 5°.

The effect of this twin structure upon the electron diffraction pattern arising from an area that covers two domains, is to split the spots in two components. The difference between the corresponding \bar{g} vectors is very small and normal to the twin plane. Thus in the case of twin {100} type we have

$$|\Delta\bar{g}| = \frac{2\left(\frac{\pi}{2} - \alpha\right)}{a} (k+l)$$

where, α is the rhombohedral angle, a the lattice constant, and h, k, l are the crystallographic indices as has been confirmed in detail by Stoemenos and Vincent.¹³ When the twin planes are perpendicular to the surface of the sample the fringes disappear, while a splitting of the diffraction spots is expected with the direction of splitting normal to the twin plane, the $\Delta\bar{g}$ vector being parallel to the surface.¹⁴ The observations in GeTe single crystals show that this is actually the case, the twin plane being of the (100) type (fig. 3). In all the samples examined here we noticed the absence of (110) twin planes, which were observed in the case of thin films grown by evaporation.¹³

In view of the above results, one could expect a pronounced effect of the twin structure upon the electrical properties of these materials. Thus Lewis working on polycrystalline GeTe¹⁵ concluded that the transport properties of these materials could be interpreted by postulating the existence of extra vacancies, which are the result of the distortion of the lattice from the cubic symmetry. Since intersecting (100) and (010) twins do not even form a twin boundary, it is reasonable to expect that a large number of vacancies result at incoherent boundaries, e.g. at the intersection of (100) and (010) twins, although further investigation of the electrical properties on well developed crystals is needed to draw any definite conclusions.

Acknowledgments

The authors would like to acknowledge helpful and stimulating discussions with Dr. A. Howie and to thank Mr. O. Valasiades for making the electrical measurements.

ΠΕΡΙΛΗΨΙΣ

Διδυμιαί εις μονοκρυστάλλους GeTe και Ge_{1-x}Sn_xTe

Μονοκρυστάλλοι GeTe και κραμάτων αυτού με Sn ανεπτύχθησαν διά της μεθόδου της μεταφοράς, άνευ μεταφορέως. Ήλεκτρικαί μετρήσεις γενόμεναί διά μεθόδου, αναλόγου της του Van Der Pauw, έναλλασσομένου ρεύματος, έδειξαν ότι οι ούτω αναπτυχθέντες μονοκρυστάλλοι παρουσιάζουν ίκανοποιητικήν τελειότητα. Παρατηρήσεις διά πολωτικού και ήλεκτρονικού μικροσκοπίου καταδεικνύουν την ύπαρξιν κανονικών διδυμιών. Αί διδυμιαί αύται καθίστανται κανονικώτεροι όσον ή περιεκτικότης των κραμάτων αύξάνεται εις κασσίτερον. Διαγράμματα περιθλάσεως ήλεκτρονίων παρουσιάζουν διάσπασιν κηλίδων, χαρακτηριστικών διδυμιών, καταδεικνύουν δέ ότι τὸ ἐπίπεδον διδυμίας είναι τὸ (100).

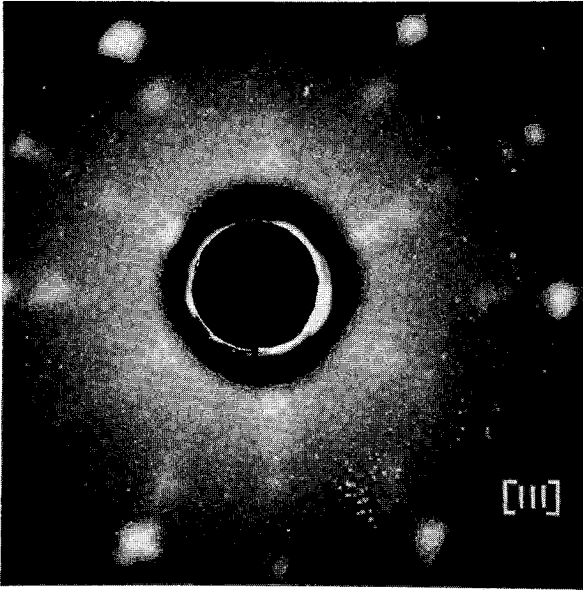


Fig. 1. Back reflection diffraction pattern of GeTe. The broadening of spots is due to rhombohedral structure and the twinning.

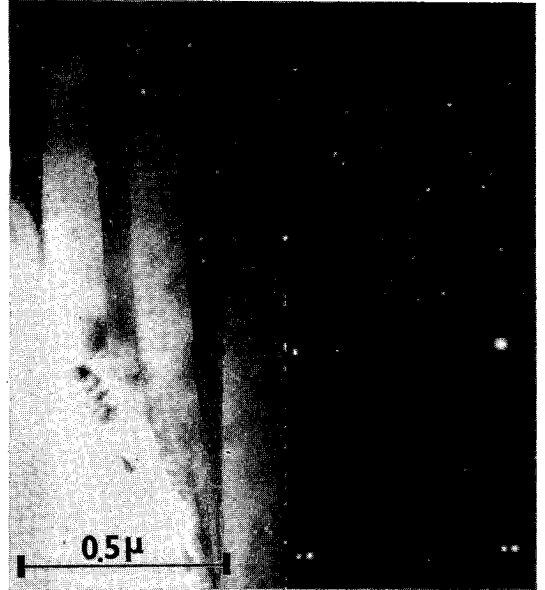
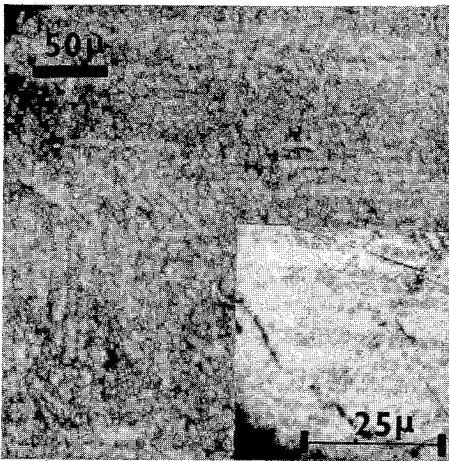
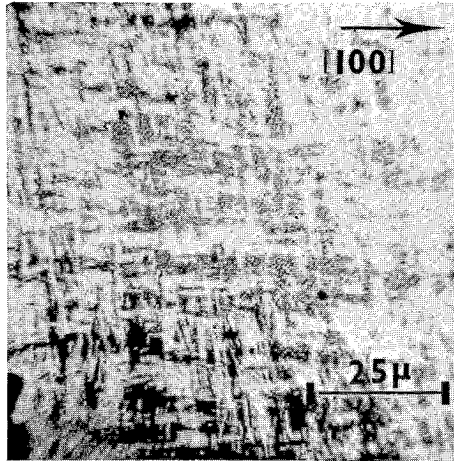


Fig. 3. Transmission electron micrograph and the related diffraction pattern of a (001) face of GeTe showing the presence of twins. The splitting of the diffraction spots is normal to twin boundary.



(a)



(b)

Fig. 2. (001) crystal face under normally incident reflected light:

(a) $(\text{GeTe})_{0.6}(\text{SnTe})_{0.4}$ etched with NaOH.

The inset is the same face electropolished, viewed with crossed polarisers. The twin structure is evident in both cases.

(b) GeTe viewed with crossed polarisers.

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TABLE OF CONTENTS

| | Page |
|---|------|
| Aug. Anagnostopoulos: <i>Coordination Compounds of Co(II) and Ni(II). Part I. Magnetic and Spectral Properties of Complexes with Pyridine Dicarboxylic Acid</i> | 103 |
| Ch. T. Plessas: <i>L'Hydrolyse Alcaline du Phénobarbital</i> | 109 |
| J. Nikokavouras and G. Vassilopoulos: <i>A Study of the LuminoI-Fluorescence Decay</i> | 115 |
| John M. Tsangaris: <i>A Circular Dichroism Band at 300 nm Observed in the High Coordination Number Complexes of L-Threonine with Copper (II) in Aqueous Solutions</i> | 124 |
| Georg Karagounis, Johanna Pandi-Agathokli und E. Kondaraki: <i>Über einige Grenzflächenreaktionen zur Bildung von polymeren Catenaverbindungen</i> | 130 |
| P. Catsoulacos: <i>Beckmann Rearrangement of Testosterone Oximes</i> | 147 |
| A. Metallidis: <i>Eine bequeme Synthese von Pyridonen aus Acetondicarbonsäurediäthylester und Alkylisocyanaten</i> | 151 |
| A. Metallidis and D. Theodoropoulos: <i>Racemisation by the Azide Method. The Synthesis of CbzO-L-Valyl-L-Tyrosyl-L-Isoleucine Methyl Ester</i> | 154 |
| A.G. Varvoglis: <i>Spectroscopic Study of a Wax Isolated from Alkanna Tinctoria Tausch</i> | 156 |
| G. Tsatsas et Mme A. Papadaki-Valiraki: <i>Synthèse de Quelques Nouveaux Acides Hydroxamiques</i> | 162 |
| J. Stoemenos and N. Economou: <i>Domain Structure in Single Crystals of GeTe and Ge_{1-x}Sn_xTe</i> | 168 |

ΕΝΩΣΙΣ ΕΛΛΗΝΩΝ ΧΗΜΙΚΩΝ

ΝΟΜΙΚΟΝ ΠΡΟΣΩΠΟΝ ΔΗΜΟΣΙΟΥ ΔΙΚΑΙΟΥ Ν. 6129

ΟΔΟΣ ΚΑΝΙΓΓΟΣ 27 - ΤΗΛ. 621.524, 629.266

ΑΘΗΝΑΙ - Τ. 147

Έν Αθήναις τῆ 12ῃ Ἰουνίου 1972

Ἀριθ. Πρωτ. 404

Π ρ ό ς

τούς ἐκ τῶν μελῶν τῆς Ἐνώσεως Ἑλλήνων Χημικῶν μὴ ἐγγραφέντας εἰς τὸ νέον Περιοδικόν

Κύριε Συνάδελφε,

Τὸ Διοικ. Συμβούλιον τῆς ἡμετέρας Ἐνώσεως διὰ τῆς ὑπ' ἀριθ. 229/31.3.1972 ἐγκυκλίου του πρὸς ἅπαντα τὰ μέλη αὐτῆς, εἰς ἐκτέλεσιν τῆς σχετικῆς ἀποφάσεως τῆς Γεν. Συνελεύσεως τῆς 5.3.1972, ἐζήτησε τὰς δηλώσεις ἐκείνων οἵτινες ἐπιθυμοῦν ὅπως ἐγγραφοῦν συνδρομηταὶ τῆς Νέας Σειρᾶς τῶν «Χημικῶν Χρονικῶν». Ἡ ἀνταπόκρισις τῶν συναδελφῶν, εἰς τὴν τοιαύτην παράκλησιν τῆς Διοικήσεως, ὑπῆρξεν λίαν ἱκανοποιητικὴ. Διότι μεγάλος ἀριθμὸς αὐτῶν — πολὺ μεγαλύτερος τοῦ προβλεφθέντος — ἐσπευσε νὰ δηλώσῃ ὅτι ἐπιθυμεῖ νὰ λαμβάνῃ καὶ τὴν νέαν αὐτὴν ἔκδοσιν ἐπὶ καταβολῇ τῆς προσθέτου μικρᾶς συνδρομῆς τῶν δραχμῶν 120 ἐτησίως.

Τὸ διὰ τὴν νέαν αὐτὴν προσπάθειαν ἐπιδειχθὲν ζῶηρόν ἐνδιαφέρον, λίαν τιμητικὸν διὰ τὸν κλάδον ἀλλὰ καὶ δι' ἡμᾶς τοὺς ἐν τῇ Διοικήσει, μᾶς ὑποχρεώνει νὰ ἀναθεωρήσωμεν τὰς ἀρχικὰς ἀποφάσεις μας. Ὡς γνωστὸν ἀπεστείλαμεν τὸ 1ον τεῦχος τῆς σειρᾶς αὐτῆς, εἰς ἅπαντας τοὺς συναδέλφους, ἵνα τὸ μελετήσουν καὶ ἐκτιμήσουν τὴν ἀναληφθεῖσαν προσπάθειαν, μὲ τὴν δήλωσιν ὅτι τὸ 2ον θὰ σταλῇ πλέον εἰς ἐκείνους μόνον, οἵτινες ἐν τῷ μεταξύ θὰ ἐγγραφοῦν συνδρομηταὶ τῆς. Ἡ ἐπιδειχθεῖσα ὁμως προθυμία μᾶς ὀδηγεῖ ἤδη εἰς τὴν σκέψιν ὅτι πιθανῶς νὰ ὑπάρχουν καὶ πολλοὶ ἄλλοι οἵτινες ἐνῶ ἐπίσης προτίθενται νὰ γίνουν συνδρομηταὶ ἠμέλησαν νὰ μᾶς ἀποστείλουν τὴν σχετικὴν δήλωσιν.

Κατόπιν τούτου τὸ Διοικ. Συμβούλιον ἐν τῇ ἐπιθυμίᾳ ὅπως παράσχη μίαν ἀκόμη εὐκαιρίαν, ἔλαβε τὴν ἀπόφασιν ὅπως ἀποστείλῃ καὶ τὸ μόνον ἐκδοθὲν 2ον τεῦχος, τόσον εἰς τοὺς ἤδη ἐγγραφέντας συνδρομητὰς ὅσον καὶ εἰς τοὺς ἄλλους, τοὺς μὴ εἰσέτι δηλώσαντας, διὰ τοὺς τελευταίους ὁμως ἐπὶ ἐπιστροφῇ. Καὶ παρακαλεῖ αὐτούς, ἐὰν μὲν προτίθενται νὰ γίνουν συνδρομηταὶ καὶ τοῦ νέου περιοδικοῦ ὅπως ἀποκόψουν καὶ ἐπιστρέψουν συμπληρωμένην τὴν ἀποστελλομένην δήλωσιν περὶ ἐγγραφῆς των, κατὰ τὰ γινώστά, καὶ κρατήσουν καὶ τὸ ἀνὰ χεῖρας 2ον τεῦχος, ἐὰν δὲ δὲν ἐπιθυμοῦν τοῦτο νὰ μᾶς τὸ ἐπιστρέψουν διὰ τοῦ ταχυδρομείου. Ἐπίσης, ἐὰν δὲν τοὺς εἶναι χρήσιμον, νὰ ἐπιστρέψουν καὶ τὸ εἰς χεῖρας των 1ον τεῦχος.

Εἰς τὰς σκέψεις αὐτὰς ὠδηγήθημεν καὶ ἐκ τοῦ γεγονότος ὅτι ἡ ἐπανεκδοσις τῶν πρώτων τευχῶν θὰ εἶναι διὰ πολλοὺς λόγους εἰς τὸ μέλλον ἀνέφικτος. Ἐπομένως θὰ καταστῇ ἀδύνατος ἡ ἱκανοποίησις μεταγενεστέρας αἰτήσεως, περὶ ἀναδρομικῆς ἐγγραφῆς καὶ ἐξασφαλίσεως τῶν πρώτων ἐκδοθέντων τευχῶν εἰς τοὺς σήμερον ἀμελήσαντας ἢ διστάσαντας, ὡς πρὸς τὸ σκόπιμον τῆς ἐγγραφῆς των.

Μετὰ συναδελφικῶν χαιρετισμῶν

Διὰ τὸ Διοικητικὸν Συμβούλιον

Ὁ Πρόεδρος

Δρ Ι.Ω. Δ. ΚΑΝΔΗΛΗΣ

Π Ρ Ο Σ
ΤΗΝ ΕΝΩΣΙΝ ΕΛΛΗΝΩΝ
ΧΗΜΙΚΩΝ

Δ Η Λ Ω Σ Ι Σ

Ἐπώνυμον

Ὄνομα

Ὄνομα Πατρός ἢ Συζύγου

Δ/νσις κατοικίας (Πόλις - ὁδὸς - τομεύς)
.....

Δ/νσις ἐργασίας

Τηλ. οἰκίας

Ἐν τῆ 1972

Ἔχω τὴν τιμὴν νὰ γνωρίσω εἰς ὑμᾶς διὰ τῆς παρούσης δηλώσεώς μου ὅτι ἐπιθυμῶ ὅπως μὲ ἐγγράφητε ὡς συνδρομητὴν τῆς «Νέας Σειρᾶς τῶν Χημικῶν Χρονικῶν», τὰ τεύχη τῆς ὁποίας παρακαλῶ ὅπως μοῦ ἀποστέλλονται ἐφ' ἐξῆς εἰς τὴν παραπεύρως διεύθυνσιν τῆς οἰκίας μου. Τὴν διὰ τὴν ἔκδοσιν αὐτὴν ἐκ δραχμῶν 120 συνδρομὴν τοῦ ἔτους 1972, ἐπιφυλάσσομαι ν' ἀποστείλω.*

Μετὰ τιμῆς

* Ἐν περιπτώσει παραλλήλου ἀποστολῆς τῆς ἐκ δραχμῶν 120 συνδρομῆς δέον νὰ σημειωθῇ ὁ τρόπος τοῦ ἐμβάσματος.