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TRICYCLIC HYDANTOINS AND THIOHYDANTOINS OF PHENYLALANINE

E.C. WEIR,[1] I. NIOPAS[2] and G.A. SMAIL[1]

1. *Department of Pharmacy, University of Strathclyde, Glasgow, G1 1XW, U.K.*
2. *Department of Pharmacy, Aristotle University of Thessaloniki, 540 06, Greece.*

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SUMMARY

The cyclisation of phenylalanine with formaldehyde gave 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. The reaction of the ethyl ester of this amino acid with isocyanates and isothiocyanates afforded a series of 1,3-dioxo-5H-10,10a-dihydroimidazo[1,5-b]isoquinolines (isoquinoline hydantoins) and 1-oxo-3-thio-5H-10,10a-dihydroimidazo[1,5-b]isoquinolines (isoquinoline thiohydantoins).

The reaction of the ethyl 2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate with propylamine gave the expected N-propyl isoquinoline hydantoin.

A series of 1,2,3,4-tetrahydroisoquinoline-3-carboxamides was derived through the intermediacy of the N-carboxyanhydride, was reacted with chloroformates and the obtained 2-alkoxycarbonyl derivatives cyclised to give the desired isoquinoline hydantoins.

The ^{1}H NMR spectral characteristics of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives are tabulated and interpreted.

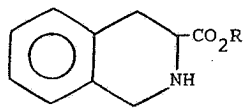
Key words: Isoquinoline hydantoins, isoquinoline thiohydantoins, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives, synthesis.

INTRODUCTION

In an earlier paper[1] we reported that the cyclisation of phenylalanine with formaldehyde gives the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *1a*, and subsequently the treatment of its ethyl ester *1b* with isocyanates affords the tricyclic isoquinoline hydantoins *2a-2e*.

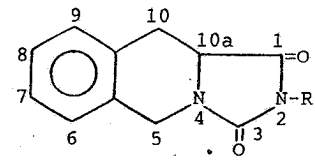
We now wish to report the syntheses of some new tricyclic isoquinoline hydantoins *2f - 2k* and thiohydantoins *3a - 3e* by the treatment of *1b* with alkyl and aryl isocyanates and isothiocyanates.

Although this reaction proceeds smoothly and in good yields as a general route to the preparation of the isoquinoline hydantoins *2*, it is limited by the commercial availability of the appropriate isocyanates and by the risk of toxicity associated with their preparation.



1

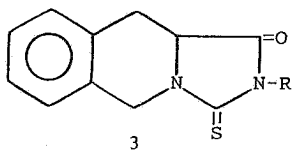
1a, R=H
1b, R=Et



2

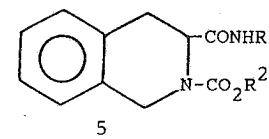
2a, R=H
2b, R=Me
2c, R=Et
2d, R=Pr
2e, R=Ph
2f, R=Pr^{i}
2g*, R=Pr
2h, R=Bu
2i, R=Allyl
2j, R=Cyclohexyl
2k, R=p-C_6H_4Cl

* L-isomer



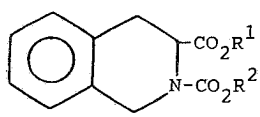
3

3a, R=Me
3b, R=Et
3c, R=Allyl
3d, R=Cyclohexyl
3e, R=Ph



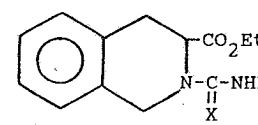
5

5a, R^1=Pr^{i}, R^2=Et
5b, R^1=Cyclohexyl, R^2=Et
5c, R^1=Me, R^2=Bz
5d, R^1=Bu^{i}, R^2=Bz
5e, R^1=Bu^{s}, R^2=Bz



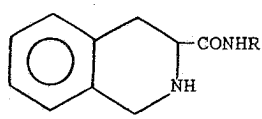
4

4a, R^1=R^2=Et
4b, R^1=Et, R^2=Bz
4c, R^1=H, R^2=Bz



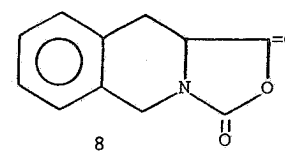
6

6a, R=Alkyl or aryl, X=O
6b, R=Alkyl or aryl, X=S



7

7a, R=H
7b, R=Me
7c, R=Et
7d, R=Pr
7e, R=Pr^{i}
7f, R=Bu
7g, R=Bu^{i}
7h, R=Bu^{s}
7i, R=Bu^{t}
7j, R=Cyclohexyl
7k, R=Ph



8

Two alternative and potentially more versatile general routes for the preparation of the desired hydantoins *2* were therefore investigated, a) reaction of the ethyl 2-alkoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylates *4a*, *4b* with primary amines and b) cyclisation of the 2-alkoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamides *5* under basic conditions.

RESULTS AND DISCUSSION

The Pictet-Spengler reaction of phenylalanine with formaldehyde provided the cyclised amino acid *1a* [2] which was esterified to give the ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate *1b*. This material was subsequently converted to the desired isoquinoline hydantoins *2f-2k* through the intermediacy of the hydantoates *6a* on treatment with selected isocyanates. The hydantoins *2* showed the characteristic[3, 4] strong absorption bands at approximately 1760 and 1710 cm^{-1} supporting the cyclised structure.

The treatment of *1b* with alkyl and aryl isothiocyanates under similar conditions gave the corresponding thiohydantoins *3a-3e*; the intermediate thiohydantoates *6b* could not be isolated.[5] In the mass spectra the molecular ion (M^+) of hydantoins *2* and thiohydantoins *3* was usually appeared as the base peak.

Reaction of N-alkoxycarbonyl derivatives of α-amino acid esters with primary amines or ammonia was found to afford 3-substituted hydantoins.[6] By analogy, treatment of ethyl 2-alkoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylates *4a* and *4b* with a variety of alkyl and arylamines was considered to offer a promising route to the desired hydantoins *2*. The 2-alkoxycarbonyl derivatives *4a*, *4b* were prepared by treating *1b* with ethyl and benzyl chloroformates; subsequently the product *4a* reacted at 200°C under pressure (25 kg/cm^2) with propylamine to give the propyl isoquinoline hydantoin *2d* but in low yield. Refluxing *4a* or *4b* with cyclohexylamine or propylamine failled to give the desired hydantoins *2*.

Another useful method of preparation of hydantoins is through cyclisation of N-alkoxycarbonyl amides of α-amino acids.[7, 8] The first step in this method involved the synthesis of a series of N-substituted amides of type *7*. The reaction of the ester *1b* with various primary amines by the method of De Feo and Strickler[9] was unsuccessful. The amides *7a-7k* were prepared from the reaction of N-carboxyanhydride *8* with primary amines. N-Carboxyanhydrides of amino acids have been shown[10] to provide a convenient route to the corresponding secondary amides on treatment

with primary amines. The N-carboxyanhydride *8* was prepared starting from the acid *1a* which reacted with benzyl chloroformate to give the 2-benzyloxycarbonyl derivative *4c*; the benzyloxycarbonyl group was found to induce[11] the formation of the N-carboxyanhydride. Subsequently treatment of *4c* with phosphorous pentachloride gave the crude product *8* which exhibited characteristic carbonyl bands at 1875, 1840 and 1780 cm^{-1}. The amides *7* reacted further with ethyl and benzyl chloroformates to give the 2-alkoxycarbonyl derivatives *5* which on treatment with ethanolic potassium hydroxide cyclised to the desired tricyclic isoquinoline hydantoins *2* in satisfactory yields.

^{1}H NMR Study of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives

The C-1 and C-3 protons (C-5 and C-10a protons of the tricyclic derivatives *2*, *3* and *8*) in the ^{1}H NMR spectra of the compounds prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *1a* showed marked variation in chemical shift (Table I).

Table I: Aproximate chemical shift values (δ) for the C-1* and C-3* protons in different derivatives of 1a.

Compound	C-1 (C-5)	C-3 (C-10a)
1b	4.08 s	3.70 dd
2	4.20-5.20 ABq	4.00-4.20 dd
3	4.45-5.75 ABq	3.85-4.40 dd
4	4.70 d, J=3 Hz	4.80-5.30 m
5	4.65 s	4.60-5.00 m
7	4.00 s	3.40-3.80 dd
8	4.34-5.16 ABq	4.34 dd

*Equivalent to C-5 and C-10a protons of the tricyclic derivatives 2, 3 and 8.

In both the ethyl ester *1b*[1] and the corresponding amides *7* the C-3 methine proton appeared as a double of doublets reflecting coupling to the non-equivalent C-4 methylene protons and upfield from the C-1 methylene protons which gave a singlet. The N-alkoxycarbonyl derivatives *4* and *5* showed a downfield shift for the C-3 methine proton which may be attributed to the deshielding by the N-alkoxycarbonyl group. In the tricyclic derivatives *2*, *3* and *8* the C-5 methylene protons appeared as an AB quartet (J=17 Hz); the conformational rigidity imposed by the tricyclic ring system renders the two protons non-equivalent and therefore geminal coupling is observed. The C-10a methine proton of these compounds appeared as a double of doublets (J=6 and 13 Hz) due to the coupling with the non-equivalent C-10 methylene protons which appeared as a double of quartets (AB protons of an ABX system). Coupling was also observed between the N-adjacent protons of the N-substituent and the proton on the nitrogen atom in the amides *7*. The small value of the coupling constant (J=3 Hz) which was observed for the C-1 methylene protons of the 2-alkoxycarbonyl derivatives *4a*, *4b* and *4c* may be interpreted by long range coupling with the C-3 proton.[12]

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and IR spectra were recorded on a Perkin-Elmer 197 instrument using KCl pellets or neat films.

The ^{1}H NMR spectra were obtained with a Perkin-Elmer R32 (90 MHz) spectrometer and chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Mass spectra were run on an AEI MS 902 double focussing, high resolution spectrometer.

Microanalyses were performed by the Microanalytical Laboratory, Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow.

General Procedure for Preparation of Hydantoins 2 from Isocyanates. The cyclisation of phenylalanine* with formaldehyde and hydrochloric acid gave the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *1a* which was converted to the ester *1b* [2] on treatment with a saturated ethanolic HCl

* DL-isomer.

solution. The ester *1b* was dissolved in dry and cold (0°C) chloroform and treated with the appropriate isocyanate to give the intermediate hydantoate *6a* which was refluxed with hydrochloric acid and acetone[1] to give the desired isoquinoline hydantoins *2* (Tables II and III).

Preparation of Thiohydantoins 3. A solution of the appropriate isothiocyanate in dry chloroform was added dropwise to an equimolar solution of the ester *1b* in dry chloroform cooled to 0°C, and protected with a drying tube ($CaCl_2$). The mixture was stirred for half hour at 0°C and for a further half hour at room temperature. The solvent was removed under reduced pressure to give a solid residue. Recrystallisation from a suitable solvent afforded the desired isoquinoline thiohydantoin (Tables II and III).

Ethyl 2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 4a. Ethyl cloroformate (1.62 g, 15 mmol) in chloroform (10 ml) was added slowly with constant stirring to a mixture of *1b* (2.05 g, 10 mmol) in chloroform (150 ml) and 10% aqueous sodium carbonate. After 2 hours the organic layer was separated, washed with 2M hydrochloric acid and water and dried (Na_2SO_4). Removal of the chloroform gave the product *4a* (2.34 g, 84%) as a colourless oil which was used without further purification. $\nu_{max.}$(film) 1740 (CO) and 1710 (CO) cm^{-1}; δ ($CDCl_3$) 1.00-1.50 (6H, two overlapping triplets, $CO_2CH_2\underline{Me}$); 3.24 (2H, d, J=4.5 Hz, 4-H); 3.93-4.46 (4H, two overlapping quarters, $CO_2C\underline{H}_2Me$); 4.72 (2H, d, J=3 Hz, 1-H); 4.83-5.33 (1H, m, 3-H); 7.22 (4H, s, Ar.). R_f (methanol) 0.53.

Ethyl 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, 4b. Benzyl chloroformate (1.87 g, 11 mmol) was added dropwise with constant stirring to a suspension of *1b* (2.05 g, 10 mmol) in 2M aqueous sodium bicarbonate (20 ml). After 1 hour the precipitate which formed was collected by filtration and washed with water. Recrystallisation from aqueous ethanol gave the product *4b* (2.05 g, 60.5%), m.p. 88-9°C (cor.) (Found: C, 70.8; H, 6.3; N, 3.8%. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.3; N 4.1%); $\nu_{max.}$ 1740 (CO) and 1690 (CO) cm^{-1}; δ ($CDCl_3$) 1.05 (3H, t, $CO_2CH_2\underline{Me}$); 3.22 (2H, d, 4-H); 3.80-4.30 (2H, q, $CO_2C\underline{H}_2Me$); 4.75 (2H, d, J=3 Hz, 1-H); 4.80-5.20 (1H, m, 3-H); 5.27 (2H, s, $CO_2C\underline{H}_2Ph$); 7.22 (4H, s, Ar.); 7.41 (5H, s, Ph). R_f (methanol-ethyl acetate-water, 4:1:1) 0.77.

Table II: Analytical data for the hydantoins 2f-2k and the thiohydantoins 3a-3e.

Compound (Formula)	Yield (%)	Solvent	M.P. (°C)	(M^+)	Found (%)/Required C	H	N
2f	88.5	Aqueous EtOH	97*	244	68.6	6.65	11.7
($C_{14}H_{16}N_2O_2$)					(68.8	6.6	11.5)
2g**	69	Aqueous EtOH	67-69	244	68.8	6.7	11.6
($C_{14}H_{16}N_2O_2$)					(68.8	6.6	11.5)
2h	75	Aqueous EtOH	63*	258	70.05	6.95	11.1
($C_{15}H_{18}N_2O_2$)					(69.8	7.0	10.8)
2i	14.5	Aqueous EtOH	104	242	69.2	5.85	11.7
($C_{14}H_{14}N_2O_2$)					(69.4	5.8	11.6)
2j	69.5	EtOH	121*	284	71.9	7.1	10.3
($C_{17}H_{20}N_2O_2$)					(71.8	7.0	9.9)
2k	89	Chloroform-Ether	204-206	314 (^{37}Cl)	65.5	4.0	8.8
($C_{17}H_{13}ClN_2O_2$)				312 (^{35}Cl)	(65.3	4.2	9.0)
3a	79	Acetone	175-176*	232	61.9	5.1	11.9
($C_{12}H_{12}N_2OS$)					(62.1	5.2	12.1)
3b	60	EtOH	125-126	246	63.0	5.8	11.4
($C_{13}H_{14}N_2OS$)					(63.4	5.7	11.4)
3c	66.5	EtOH	86-87	258	65.3	5.6	11.1
($C_{14}H_{14}N_2OS$)					(65.1	5.4	10.9)
3d	40.5	EtOH-Acetone	175-176	300	68.2	6.8	9.3
($C_{17}H_{20}N_2OS$)					(68.0	6.7	9.3)
3e	86.5	Acetone	214-215	294	69.2	4.8	9.5
($C_{17}H_{14}N_2OS$)					(69.4	4.8	9.5)

*Cor., **L-Propyl hydantoin 2g, $[\alpha]_D^{20}$ = -191.9° (C 1.0, EtOH

2-Propyl-1,3-dioxo-5H-10,10a-dihydroimidazo 1,5-b isoquinoline, 2d.

A mixture of *4a* (3.58 g, 13 mmol), a 35% ethanolic solution of propylamine (3.4 ml, 20 mmol), absolute ethanol (8 ml) and two pieces of sodium was placed in the steel cylinder of a Roth autoclave and heated at 200°C (which gave a pressure of 25 kg/cm²) for 7 hours. The reaction was cooled and the solvent was removed under reduced pressure to give a dark brown residue

Table III: Chemical shift values (δ) of hydantoins 2f-2k and thiohydantoins 3a-3e.

Compound Substituent (R)	C-5[a]	C-10a[b]	C-10[c]	Ar	Other Protons
2f Pr^i	4.25-5.22	3.80-4.32	2.83-3.23	7.29 s	1.46 (d, $NCH\underline{Me}_2$); the signal for $NC\underline{H}Me_2$ is obscurred by 10a-H).
2g Pr	4.28-5.24	3.86-4.25	2.80-3.24	7.27 s	0.92 (t, $NCH_2CH_2\underline{Me}$); 3.58 (t, $NC\underline{H}_2Et$); 1.4-1.9 (m, $NCH_2C\underline{H}_2Me$).
2h Bu	4.25-5.21	3.96-4.23	2.80-3.20	7.25 s	0.96 (t, $NCH_2CH_2CH_2\underline{Me}$); 3.59 (t, $NC\underline{H}_2CH_2CH_2Me$); 1.15-1.80 (m, $NCH_2C\underline{H}_2$-$C\underline{H}_2Me$).
2i Allyl	4.00-6.00[d]		2.60-3.60	7.28 s	
2j Cyclohexyl	4.24-5.19	3.88-4.16	2.74-3.46	7.26 s	1.04-2.20 (m, cyclohexyl methylene protons); the signal for the cyclohexyl methine proton is obscurred bt 10a-H.
2k p-Chlorophenyl	4.33-5.30	4.11-4.40	2.90-3.30	7.30 s	7.48 (s, Ar.).
3a Me	4.46-5.65	3.90-4.40	2.60-3.40	7.30 s	3.33 (s, $M\underline{Me}$).
3b Et	4.43-5.68	3.80-4.44	2.30-3.27	7.29 s	1.29 (t, $NCH_2\underline{Me}$); the signal for $NC\underline{H}_2Me$ is obscurred by 10a-H.
3c Allyl	4.09-5.66[d]		2.80-3.28	7.30 s	
3d Cyclohexyl	4.48-5.70	3.86-4.26	2.75-3.23	7.31 s	1.05-2.40 (m, cyclohexyl methylene protons); the signal for the cyclohexyl methine proton is obscurred by 10a-H.
3e Ph	4.54-5.80	4.20-4.50	2.90-3.40	7.33 s	7.50 (s, Ar.).

[a]AB quartet (J=17 Hz), [b]double of doublets, [c]double of quartets, [d]complex multiplet for 5-H, 10a-H and allylic protons.

which dissolved in chloroform (100 ml), washed with dilute hydrochloric acid and dried (Na_2SO_4). Removal of the chloroform and recrystallisation from aqueous ethanol gave the product *2d* (0.08 g, 2.5%), m.p. 112°C (lit.,[1] 113-114°C).

2-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 4c. Benzyl chloroformate (5.61 g, 33 mmol) was added portionwise and under stirring to a suspension of the acid *1a* (5.31 g, 30 mmol) in 2M aqueous sodium bicarbonate (60 ml). After 2 hours the solution was extracted once with ether (50 ml), the aqueous layer was neutralised (PH~6) with 5M hydrochloric acid, extracted with chloroform (3X25 ml) and the chloroformic extracts dried (Na_2SO_4). Removal of the solvent gave the product *4c* (6.2 g, 66.5%) as a viscous oil which was used without further purification. $\nu_{max.}$ (film), 1740 (CO) and 1710 (CO) cm^{-1}; δ ($CDCl_3$) 3.17 (2H, d, J=4.5 Hz, 4-H); 4.65 (2H, d, J=3 Hz, 1-H); 5.10 (1H, m, 3-H); 5.18 (2H, s, $CO_2\underline{CH}_2Ph$); 7.12 (4H, s, Ar.); 7.33 (5H, s, Ph); 11.96 (1H, s, exchanged with D_2O, $CO_2\underline{H}$).

1,3-Dioxo-5H-10,10a-dihydro-oxazolo[3,4-b]isoquinoline, 8. To a solution of *4c* (10.8 g, 35 mmol) in dry chloroform (50 ml) phosphorous pentachloride (12 g) was added portionwise. The reaction mixture was cooled in an ice bath and shaken periodically for 1 hour. The excess of phosphorous pentachloride was removed by filtration and the filtrate was evaporated to give a yellow residue which washed with dry petroleum ether (b.p. 40-60°C) and gave the N-carboxyanhydride *8* (4.83 g, 69%), m.p. 158°C (cor.) (Found: C, 65.0; H, 4.4; N, 6.9%. $C_{11}H_9NO_3$ requires C, 64.6; H, 4.4; N, 6.6%); $\nu_{max.}$ 1875 and 1840 (CO), 1780 (CO) cm^{-1}; δ ($CDCl_3$) 3.19 (2H, m, 10-H); 4.34 (1H, dd, 10a-H); 4.34-5.16 (2H, AB quartet, J=17 Hz, 5-H); 7.30 (4H, s, Ar.).

General Procedure for the Preparation of 1,2,3,4-Tetrahydroisoquinoline-3-carboxamides, 7. The appropriate amine (freshly distilled, 2 mol excess) was added dropwise to a solution of the N-carboxyanhydride *8* in dry chloroform. The reaction was stirred for 2 hours and protected from moisture with a drying tube ($CaCl_2$). Evaporation of the cloroform gave a residue which was treated with ethereal HCl to give the corresponding amide *7* as the hydrochloride salt (Tables IV and V).

Preparation of N-Cyclohexyl-2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide, 5b. A solution of ethyl chloroformate (0.54 g, 5 mmol)

in chloroform was added dropwise and with constant stirring to a cooled (0°C) mixture of the amide *7j* (1.03 g, 4 mmol), chloroform (30 ml) and 10% aqueous sodium carbonate (30 ml). The stirring was continued for 2 hours, the organic layer washed successively with hydrochloric acid and water and dried (Na_2SO_4). Evaporation of the chloroform gave an oil which was triturated with petroleum ether (b.p. 40-60°C) to give the product *5b* (0.79 g, 60%), m.p. 148°C (cor.) (Found: C, 68.5; H, 7.8; N, 8.4%. $C_{19}H_{26}N_2O_3$ requires C, 69.1; H, 7.9; N, 8.5%); $\nu_{max.}$ 3260 (NH), 1690 (CO), 1650 (CO) and 1550 (NH) cm^{-1}; δ ($CDCl_3$) 1.29 (3H, t, $CO_2CH_2\underline{Me}$); 0.60-1.90 (10H, m, cyclohexyl methylene protons); 3.20 (2H, t, 4-H); 3.37-3.80 (1H, m, cyclohexyl methine proton); 4.07-4.42 (2H, q, $CO_2\underline{CH_2}Me$); 4.62-4.90 (3H, s, 1-H and m, 3-H); 5.40-5.87 (1H, br s, exchanged with D_2O, NH); 7.27 (4H, s, Ar.).

N-Isopropyl-2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide, 5a. By the same procedure treatment of *7e* (2 g, 9 mmol) with ethyl chloroformate (1.2 g, 11 mmol) gave the product *5a* (1.77 g, 66%), m.p. 110-111°C (cor., from ethyl acetate-petroleum ether b.p. 40-60°C), $\nu_{max.}$ 3330 (NH), 1690 (CO), 1650 (CO) and 1540 (NH) cm^{-1}; δ ($CDCl_3$) 0.76-1.19 (6H, d, $NHCH\underline{Me}_2$); 1.29 (3H, t, $CO_2CH_2\underline{Me}$); 3.22 (2H, t, 4-H); 3.70-4.10 (1H, m, $NHC\underline{H}Me_2$); 4.10-4.46 (2H, q, $CO_2\underline{CH_2}Me$); 4.56-4.90 (3H, m, 3-H and s, 1-H); 5.50-5.90 (1H, br s, NH); 7.26 (4H, s, Ar.).

N-s-Butyl-2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide, 5e. To a mixture of *7h* (2.09 g, 9 mmol) in chloroform (50 ml) and 2M aqueous sodium bicarbonate (30 ml) benzyl chloroformate (1.68 g, 10 mmol) was added dropwise and with constant stirring. After 2 hours the chloroformic layer washed with dilute hydrochloric acid (2X15 ml), water (15 ml) and dried (Na_2SO_4). Evaporation to dryness gave a yellow residue which on trituration with petroleum ether (b.p. 40-60°C) gave the product *5e* (2.02 g, 61%), m.p. 99-100°C (from EtOH-petroleum ether b.p. 40-60°C) (Found: C, 72.7; H, 7.1; N, 7.3%. $C_{22}H_{26}N_2O_3$ requires C, 72.1; H, 7.1; N, 7.65%); $\nu_{max.}$ 3300 (NH), 1700 (CO), 1640 (CO) and 1540 (NH) cm^{-1}; δ ($CDCl_3$) 0.20-1.35 (8H, m, $NHCH(\underline{Me})C\underline{H_2}\underline{Me}$); 3.05-3.30 (2H, t, 4-H); 3.50-3.90 (1H, m, $NHC\underline{H}(Me)CH_2Me$); 4.65 (2H, s, 1-H); 4.70-4.97 (1H, m, 3-H); 5.25 (2H, s, $CO_2\underline{CH_2}Ph$); 7.25 (4H, s, Ar.); 7.40 (5H, s, Ph).

Table IV: Analytical data for the 1,2,3,4-tetrahydroisoquinoline-3-carboxamides, 7 (hydrochloride salts).

Compound (Formula)	Yield (%)	Solvent	M.P. (°C)	Found (%)/Required C	H	N
7a ($C_{10}H_{13}ClN_2O$)	58.5	Aqueous EtOH-Ether-Acetone	268*	56.3 (56.5	6.2 6.1	13.4 13.2)
7b ($C_{11}H_{15}ClN_2O$)	35.5	Aqueous EtOH-Ether	263-265	58.4 (58.3	6.7 6.6	12.3 12.4)
7c ($C_{12}H_{17}ClN_2O$)	36.5	EtOH-Ether	230-233	60.05 (59.9	6.9 7.1	11.0 11.6)
7d ($C_{13}H_{19}ClN_2O$)	53	EtOH-Ether	210-212	61.2 (61.3	7.6 7.5	10.7 11.0)
7e ($C_{13}H_{19}ClN_2O$)	66	EtOH-Ether	227-229	61.35 (61.3	7.5 7.5	11.0 11.0)
7f ($C_{14}H_{21}ClN_2O$)	47	EtOH-Ether	187-188	62.5 (62.6	7.8 7.8	10.5 10.4)
7g ($C_{14}H_{21}ClN_2O$)	27	EtOH-Ether	226-228	62.5 (62.6	7.8 7.8	10.5 10.4)
7h ($C_{14}H_{21}ClN_2O$)	48	EtOH-Ether	221-223	62.6 (62.6	7.8 7.8	10.6 10.4)
7i ($C_{14}H_{21}ClN_2O$)	57	EtOH-Ether	260-263	62.5 (62.6	7.9 7.8	11.05 10.4)
7j ($C_{16}H_{23}ClN_2O$)	29	EtOH-Ether	209-211	64.8 (65.2	8.15 7.8	9.6 9.5)
7k ($C_{16}H_{17}ClN_2O$)	35	EtOH-Ether	238-241	66.5 (66.65	6.0 5.9	9.8 9.7)

*Decomp.

N-Isobutyl-2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide, 5d. By the same procedure treatment of *7g* (1.2 g, 5 mmol) with benzyl chloroformate (0.97 g, 5.5 mmol) gave the product *5d* (0.72 g, 38%), m.p. 118-119°C (cor., from aqueous ethanol) (Found: C, 72.3; H, 7.2; N, 7.7%. $C_{22}H_{26}N_2O_3$ requires C, 72.1; H, 7.1; N, 7.65%. $\nu_{max.}$ 3330 (NH), 1690 (CO), 1640 (CO) and 1530 (NH) cm^{-1}; δ ($CDCl_3$) 0.62 (6H, d, $NHCH_2CH\underline{Me}_2$);

Table V: Chemical shift values (δ) of 1,2,3,4-tetrahydroisoquinoline-3-carboxamides 7.

Compound Subst. (R)	Solv.	C-1	C-3	C-4	Ar	Other Protons
7a H	D_2O[a]	4.54 s	b	3.20-3.48 m	7.22 s	
7b Me	$CDCl_3$	4.04 s	3.46-3.72 dd	3.00-3.17 m	7.20 s	2.83 (d, J=5 Hz, the signal collapsed on a singlet on addition of D_2O, NHMe).
7c Et	D_2O[a]	4.54 s	4.20-4.40 dd	3.10-3.50 m	7.42 s	1.17 (t, $NHCH_2\underline{Me}$); 3.1-3.5 (m, $NHC\underline{H}_2Me$).
7d Pr	CD_3OD	4.50 s	4.18-4.38 dd	3.10-3.44 m	7.33 s	0.95 (t, $NHCH_2CH_2\underline{Me}$); 1.28-1.78 (m, $NHCH_2-C\underline{H}_2Me$); 3.10-3.44 (m, $NHC\underline{H}_2CH_2Me$).
7e Pr^i	$CDCl_3$	4.04 s	2.70-3.70[c]	2.70[c]	7.33 s	1.09-1.25 (d, $NHCH-\underline{Me}_2$); 2.70-3.70 (m, $NHC\underline{H}Me_2$).
7f Bu	$CDCl_3$	4.02 s	2.71-3.70[c]	2.70[c]	7.19 s	0.92 (t, $NH(CH_2)_3\underline{Me}$); 1.10-1.65 (m, $NHCH_2-C\underline{H}_2C\underline{H}_2Me$); 2.71-3.70 (m, $NHC\underline{H}_2Pr$).
7g Bu^i	$CDCl_3$	4.03 s	3.46-3.75 dd	3.00-3.30 m	7.19 s	0.91 (d, $NHCH_2CH\underline{Me}_2$); 1.2-1.6 (m, $NHCH_2C\underline{H}-Me_2$); 2.00 (br s, $N\underline{H}$); 3.08 (m, $NHC\underline{H}_2Pr^i$).
7h Bu^s	$CDCl_3$	4.04 s	3.40-3.75 dd	2.98-3.14 m	7.16 s	0.90 (t, $NHCH(Me)-CH_2\underline{Me}$); 1.45 (d, $NHCH(\underline{Me})CH_2Me$); 1.34-1.68 (m, $NHCH-(Me)C\underline{H}_2Me$); 1.88 (br s, $N\underline{H}$).
7i Bu^t	D_2O[a]	4.55 s	4.30-4.47 dd	3.24-3.42 m	7.44 s	1.40 (s, $NC\underline{Me}_3$).
7j Cyclohexyl	$CDCl_3$	4.00 s	3.42-3.68 dd	2.70-3.16 m	7.18 s	0.9-2.1 (m, cyclohexyl methylene protons); 1.9 (br s, $N\underline{H}$); 3.6-3.9 (m, cyclohexyl methine proton).

[a]Spectra of the hydrochloride salts, [b]the signal is obscurred by D_2O, [c]broad multiplet.

1.20-1.80 (1H, m, $NHCH_2C\underline{H}Me_2$); 2.85-3.32 (4H, m, 4-H and $NHC\underline{H}_2CHMe_2$); 4.66 (2H, s, 1-H); 4.75-5.00 (1H, m, 3-H); 5.26 (2H, s, $CO_2C\underline{H}_2Ph$); 7.25 (4H, s, Ar.); 7.42 (5H, s, Ph).

N-Methyl-2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide, 5c. Phosphorous pentachloride (2.5 g, 12 mmol) was added under constant stirring to a suspension of the acid *4c* (3.85 g, 12 mmol) in anhydrous ether (50 ml) at 0°C. The reaction was stirred for 2 hours, the excess of phosphorous pentachloride was removed by filtration and to the filtrate a 33% ethanolic solution of methylamine (3.35 ml, 36 mmol) was added. The methylamine hydrochloride which formed was separated by filtration and the ethereal filtrate washed with dilute hydrochloric acid (3X10 ml). Evaporation to dryness gave a yellow oil which on trituration with anhydrous ether gave the product *5c* (0.55 g, 14%), m.p. 127°C (cor.); $\nu_{max.}$ 3400 (NH), 1700 (CO), 1660 (CO) and 1570 (NH) cm^{-1}, δ ($CDCl_3$) 2.60 (3H, d, J=5 Hz, the signal collapsed to a singlet on addition of D_2O, NH$\underline{Me}$); 3.20 (2H, t, 4-H); 4.64 (2H, s, 1-H); 4.57-4.95 (1H, m, 3-H); 5.23 (2H, s, $CO_2C\underline{H}_2Ph$); 5.78-6.28 (1H, br s, exchanged with D_2O, N$\underline{H}$Me); 7.22 (4H, s, Ar.); 7.39 (5H, s, Ph).

Preparation of 2-Cyclohexyl Isoquinoline Hydantoin, 2j. The amide *5b* (0.66 g, 2 mmol) was heated with 4% ethanolic potassium hydroxide (15 ml) to give a clear solution which was left at room temperature for 12 hours. Acidification with ethanolic HCl, removal of potassium chloride which formed by filtration and evaporation to dryness gave the product *2j* (0.22 g, 39%), m.p. 120°C (cor., from aqueous ethanol) (Tables II and III).

Preparation of 2-Methyl Isoquinoline Hydantoin, 2b. Treatment of *5c* (0.4 g, 1.2 mmol) with 4% ethanolic potassium hydroxide (10 ml) by the same procedure gave the product *2b* (0.09 g, 34%), m.p. 128°C (cor., from EtOH) (lit.,[1] 128-129°C).

ΠΕΡΙΛΗΨΗ

ΤΡΙΚΥΚΛΙΚΕΣ ΥΔΑΝΤΟΙΝΕΣ ΚΑΙ ΘΕΙΟΥΔΑΝΤΟΙΝΕΣ ΑΠΟ ΦΑΙΝΥΛΑΛΑΝΙΝΗ

E.C. WEIR, I. NIOPAS, G.A. SMAIL

Κυκλοποίηση της φαινυλαλανίνης με φορμαλδεΰδη και υδροχλωρικό οξύ έδωσε το 1,2,3,4-τετραϋδροϊσοκινολινο-3-καρβοξυλικό οξύ *1a* που μετατράπηκε στον αιθυλεστέρα του *1b* κατεργαζόμενο μ' ένα κεκορεσμένο αιθανολικό διάλυμα HCl. Αντίδραση του 1,2,3,4-τετραϋδροϊσοκινολινο-3-καρβοξυλικού αιθυλεστέρα *1b* με ισοκυανικά και ισοθειοκυανικά παράγωγα έδωσε μια σειρά από 2-υποκατεστημένες 1,3-διοξο-5H-10,10a-διυδροϊμιδαζο[1,5-b]ισοκινολίνες (τρικυκλικές ισοκινολινοϋδαντοΐνες), *2* και 1-οξο-3-θειο-5H-10,10a-διυδροϊμιδαζο[1,5-b]ισοκινολίνες (τρικυκλικές ισοκινολινοθειοϋδαντοΐνες), *3*.

Αντίδραση του εστέρα *1b* με χλωροφορμικό αιθυλεστέρα ή βενζυλεστέρα έδωσε τα αντίστοιχα 2-αλκοξυκαρβονυλο παράγωγα *4a* και *4b*. Κατεργασία του *4a* στο αυτόκαυστο με προπυλαμίνη έδωσε την επιθυμητή N-προπυλοϋδαντοΐνη *2*, αλλά σε μικρή απόδοση.

Αντίδραση του οξέος *1a* με χλωροφορμικό βενζυλεστέρα έδωσε το 2-βενζυλοξυκαρβονυλο παράγωγο *4c* που στη συνέχεια κατεργάστηκε με πενταχλωριούχο φωσφόρο και έδωσε σαν τελικό απομονώσιμο προϊόν τον N-καρβοξυανυδρίτη, *8*. Περαιτέρω κατεργασία του ανυδρίτη *8* με αμίνες έδωσε μια σειρά από 1,2,3,4-τετραϋδροϊσοκινολινο-3-καρβοξαμίδια *7* τα οποία αντιδρώντας με χλωροφορμικό αιθυλεστέρα ή βενζυλεστέρα έδωσαν τα 2-αλκοξυκαρβονυλο παράγωγα *5*. Κυκλοποίηση των *5b* και *5c*, σε βασικό περιβάλλον, έδωσε τις αντίστοιχες τρικυκλικές υδαντοΐνες *2j* και *2b*, προσφέροντας έτσι έναν εναλλακτικό τρόπο για την παρασκευή τους.

Τα ^{1}H NMR φασματοσκοπικά δεδομένα των παραγώγων του 1,2,3,4-τετραϋδροϊσοκινολινο-3-καρβοξυλικού οξέος *1a* δίδονται σε πίνακες και ερμηνεύονται.

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DÉRIVÉS AMINÉS OXABICYCLIQUES

G. FYTAS, G. B. FOSCOLOS, A. VYZAS et S. GAROUFALIAS

Laboratoire de Pharmacie Chimique
Université d' Athènes, 104 rue Solonos, 106 80 Athènes, GRÈCE

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RÉSUMÉ

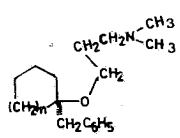
Nous décrivons la synthèse des γ-benzyl-α-(diméthylaminométhyl)-γ-lactones bicycliques 2 et de leurs analogues tétrahydrofuranniques 3 . La synthèse des aminolactones 2 comprend la benzylation des cycloalcanones sous forme d'énamine, la réaction de Reformatskii, lactonisation, carboxylation et enfin la réaction de Mannich. La transformation des aminolactones 2 en dérivés tétrahydrofuranniques 3 est réalisée avec ouverture réductive du cycle et recyclisation.

Key-words : Bicyclic aminolactones and tetrahydrofurans - Synthesis and stereochemistry.

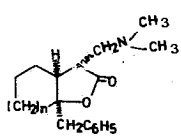
INTRODUCTION

Il est connu que les dialkylamino-3, propyléthers des benzyl-1, cycloalcanols 1 présentent une activité antiparkinsonienne, anticonvulsivante et vasodilatatrice.[1-4]

Dans le présent mémoire on décrit la synthèse des dérivés aminés bicycliques des formules générales 2 et 3 qui présentent une analogie structurale avec les produits 1 . En effet dans la molécule des dérivés 2 et 3 est contenu le squelette des composés 1 à la différence que la partie dialkylaminopropoxy présente une rigidité stéréochimique.



1



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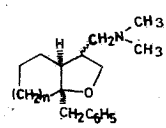

3

PARTIE THÉORIQUE

La voie de synthèse des dérivés 2 et 3 est donnée dans le Schéma 1 . Ainsi, comme matières premières nous avons utilisé les cycloalcanones 4 qui, sous forme d'énamines avec la pyrrolidine[5], sont transformées aux benzyl-2, cycloalcanones correspondantes 5 . Les cétones 5 réagissent à leur tour selon Reformatskii[6-8] et fournissent les hydroxyesters 6 . La saponification de ces derniers conduit aux hydroxyacides correspondants 7 . Par action de l'acide sulfurique concentré les hydroxyacides 7 subissent une transposition intramoléculaire[8-10] en γ-lactones bicycliques 8 .

Les γ-lactones 8 et par conséquent les dérivés 2 et 3 doivent posséder une cis-configuration de leurs deux noyaux (Schéma 2). Ce point de vue est basé à une plus grande stabilité thermodynamique des cis-lactones bicycliques par rapport aux trans-lactones correspondantes.

Ainsi les cis-lactones se forment de préférence durant la

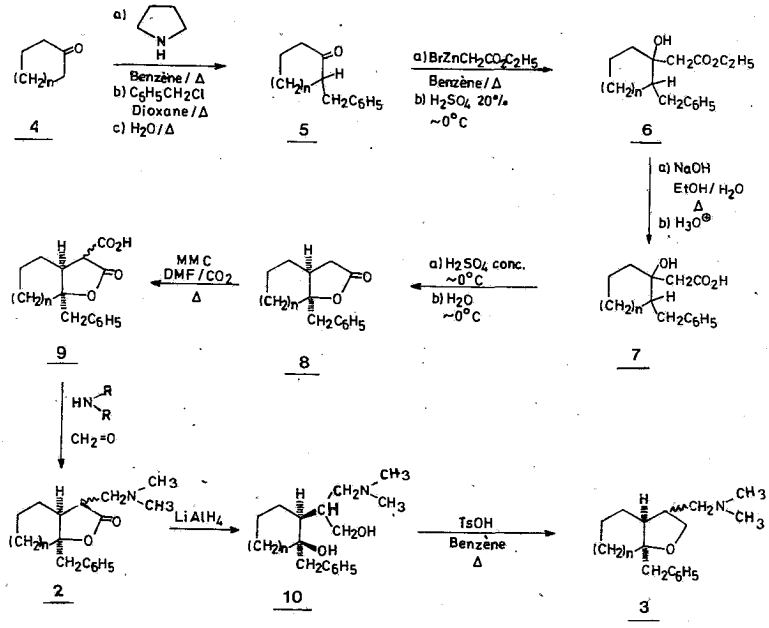

SCHÉMA 1 (n=1,2,3)

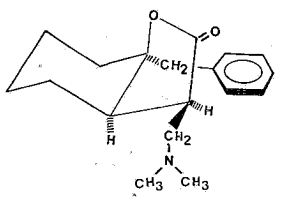

SCHÉMA II

formation du noyau γ-lactonique en milieu acide par l'intermédiaire d'un ion de carbonium. Par ailleurs, les trans-lactones bicycliques, qui se préparent d'habitude par action de diéthyl malonate sodé sur les époxydes des cycloalkènes, se transforment en leurs isomères cis, particulièrement par action des acides forts ou par chauffage.[11-13]

Plus specialement, dans le cas de γ-lactones 8 la structure trans présuppose une trans-configuration diaxiale du groupement benzyle par rapport au 3α-H, c.a.d. une disposition axiale du groupement benzyle et par rapport aux deux noyaux, ce qui paraît improbable à cause de son volume.

La carboxylation des lactones 8 avec le carbonate de méthyle et de magnésium (MMC)[14-17] conduit aux acides-lactones 9 . La transformation des acides 9 aux aminolactones correspondantes 2 est réalisée avec la réaction de Mannich.

Toutes les bases de Mannich sont obtenues avec des rendements satisfaisants sauf la base avec la pipéridine 11 qui est obtenue avec un faible rendement à cause de sa transformation partielle en dérivé méthylénique 12 (Schéma 3).

La réduction des bases de Mannich avec le $LiAlH_4$ fournit les aminodiols 10 avec des rendements quantitatifs. Les ami-

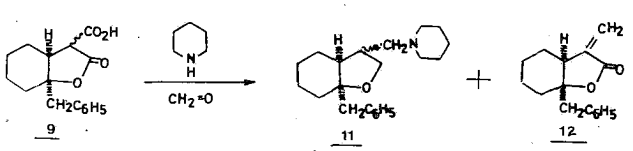

SCHÉMA III

nodiols 10 sont transformés aux dérivés aminés oxabicycliques correspondants 3 par chauffage dans le benzène en présence d'acide p-toluènesulfonique[19-21].

Dans les molécules des aminolactones 2 , il est plus probable que le groupement diméthylaminométhyle volumineux aura la configuration pseudoequatoriale par rapport au noyau lactonique (Schéma 2). Par ailleurs, comme il résulte par les modèles Dreidings la configuration pseudoaxiale du groupement diméthylaminométhyle provoque un empêchement stérique considérable par la présence du groupement benzyle.De plus l'étude des spectres RMN des aminolactones 2 , mais aussi des aminodiols 10 et des aminotétrahydrofurannes 3 n'a pas décélé un mélangle de diastéréoisomères (simple absorption pour la fonction $(CH_3)_2N$), tandis que la chromatographie sur couche mince des aminotétrahydrofurannes 3 révèle un seul produit (la chromatographie sur couche mince des aminolactones 2 conduit à une décomposition progressive aux α-méthylènelactones correspondantes). Cependant la stéréochimie du C_3 aux produits 2 et 3 n'a pas été élucidé d'avantage.

PARTIE EXPÉRIMENTALE

Les points de fusion des produits préparés ont été déterminés dans les tubes capillaires de l'appareil de Büchi et ils ne sont pas corrigés. Les analyses élémentaires ont été réalisées par le Centre de Microanalyse du C.N.R.S. (France). Les spectres IR ont été obtenus avec le spectrophotomètre Perkin-Elmer 177 et les spectres RMN avec le spectrophotomètre Varian FT-80A dans $CDCl_3$ en utilisant le TMS comme référence interne.

(Benzyl-2, hydroxy-1, cyclohexan)acétate d'éthyle 6 (n=2)

On couvre 10.5 g (0.16 gratom) de poudre de zinc activée avec une petite quantité d'un mélange de 29 g (0.154 mole) de benzyl-2, cyclohexanone 5 (n=2), de 26 g (0.154 mole) de bromacétate d'éthyle et de 120 ml de benzène anhydre. Le mélange est chauffé pour démarrer la réaction, puis on ajoute le reste au goutte à goutte et sous agitation de façon à mainte-

nir une vive ébullition. Après addition, on chauffe le mélange pendant 2hrs, puis hydrolyse sous refroidissement avec H_2SO_4 à 10% . On sépare la couche benzénique et extrait l'aqueuse au benzène. On lave les couches benzéniques unies à l'eau, au Na_2CO_3 à 5%, de nouveau à l'eau et sèche sur Na_2SO_4.

Après avoir évaporé le solvant, on distille le résidu sous pression réduite. Rdt: 30 g (72%). Eb:150-152°C/0.03 mm **IR** (film), ν(OH) 3500 cm^{-1}, ν(C=O) 1720 cm^{-1}.
Analyse ($C_{17}H_{24}O_3$):%Calc. C:73.88,H:8.75, %Tr. C:73.60,H:8.84

En utilisant la même méthode nous avons préparé les hydroxyesters suivants :

(Benzyl-2, hydroxy-1, cyclopentan)acétate d'éthyle 6 (n=1)
Rdt: 56%, Eb: 120°C/0.01 mm. **IR** (film)ν(OH) 3500 cm^{-1}, ν(C=O) 1720 cm^{-1}. **Analyse** ($C_{16}H_{22}O_3$): %Calc. C:73.25, H:8.45, %Tr. C:73.40,H:8.39.

(Benzyl-2, hydroxy-1, cycloheptan)acétate d'éthyle 6 (n=3)
Rdt: 50%. Eb:164-166°C/0.05 mm. **IR** (film)ν(OH) 3500 cm^{-1}; ν(C=O) 1720 cm^{-1}. **Analyse** ($C_{18}H_{26}O_3$): %Calc. C:74.45, H:9.03 %Tr. C:74.26,H:9.08.

Acide (benzyl-2, hydroxy-1, cyclohexan)acétique 7 (n=2)

On saponifie 30 g (0.109 mole) d'hydroxyester 6 (n=2) avec 400 ml d'une solution hydroalcoolique de NaOH à 20% pendant 5hrs à reflux. On évapore l'éthanol et dilue le reste avec de l'eau. On extrait à l'éther, sépare la couche aqueuse et l'acidifie sous refroidissement avec HCl à 18%. On extrait le produit huileux qui se forme à l'éther, lave les couches éthérées unies à l'eau, les sèche sur Na_2SO_4 et évapore le solvant. Le résidu est recristallisé dans un mélange éther-n-pentane. Rdt: 24g (88%). F: 90-92°C. **IR** (Nujol)ν(OH) 3535, 3515 cm^{-1}, ν(C=O) 1695 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 0.98-2.10(m, 9H, H-cyclohexaniques), 2.21-3.25 (m, 4H, $C\underline{H}_2CO_2H$, $C\underline{H}_2C_6H_5$), 6.88-7.25(s, 5H, $C_6\underline{H}_5$), 7.45(s large, 2H, $O\underline{H}$; $CO_2\underline{H}$).
Analyse ($C_{15}H_{20}O_3$):%Calc. C:72.55,H:8.12, %Tr. C:72.32,H:8.17

De la même façon nous avons obtenu les hydroxyacides suivants

Acide (benzyl-2, hydroxy-1, cyclopentan)acétique 7 (n=1)
Rdt: 75%. F: 103-105°C (Et_2O-n-pentane). **IR** (Nujol)ν(OH) 3540 cm^{-1}, ν(C=O) 1699 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.38-2.18(m, 7H, H-cyclopentaniques), 2.25-3.05(m, 4H, CH_2CO_2H, $CH_2C_6H_5$), 7.00(s large, 2H, OH , CO_2H), 7.19(s, 5H, C_6H_5). **Analyse** ($C_{14}H_{18}O_3$): %Calc. C:71.77,H:7.74, %Tr. C:71.58,H:7.70.

Acide (benzyl-2, hydroxy-1, cycloheptan)acétique 7 (n=3)
Rdt : 85%. F: 94-96°C (Et_2O-n-pentane). **IR** (Nujol)ν(OH) 3520 cm^{-1}, ν(C=O) 1690 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.02-2.15(m, 11H, H-cycloheptaniques), 2.20-3.10(m, 4H, CH_2CO_2H, $CH_2C_6H_5$), 6.73-7.39(m, 7H, C_6H_5, OH ,CO_2H). **Analyse** ($C_{16}H_{22}O_3$): %Calc. C:73.25,H:8.45, %Tr. C:73.00,H:8.51.

cis-3a,7a, Benzyl-7a, hexahydrobenzofurannone-2(3H) 8 (n=2)

On ajoute 17 g (0.0685 mole) d'hydroxyacide 7 (n=2) par petites quantités, agitation et refroidissement dans 120 ml d'acide sulfurique concentré. Après dissolution complète, on agite le mélange réactionnel pendant 30 min à 0°C, puis hydrolyse sous refroidissement et au goutte à goutte avec 200 ml d'eau. On extrait le produit qui se forme à l'éther, lave les couches éthérées unies à l'eau, au Na_2CO_3 à 5% et de nouveau à l'eau, les sèche sur Na_2SO_4 et les évapore.
On distille le résidu huileux. Rdt: 12.5g(80%). Eb:150-152°C/0.01 mm. **IR** (film)ν(C=O) 1772 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.05-2.00(m, 8H, H-4,5,6,7), 2.34(s, 3H, H-3, 3a), 2.97(s, 2H, $CH_2C_6H_5$),7.20(s, 5H, C_6H_5). **Analyse** ($C_{15}H_{18}O_2$):%Calc. C:78.23, H:7.88, %Tr. C:78.34,H:7.79.

En utilisant la même méthode nous avons préparé les γ-lactones suivantes :

cis-3a,6a, Benzyl-6a, hexahydro-2H-cyclopenta[b]furannone-2 8 (n=1)
Rdt: 81%. Eb: 136-138°C/0.1 mm. **IR** (film)ν(C=O) 1770 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.40-2.20(m, 6H, H-4,5,6), 2.26-2.80 (m, 3H, H-3, 3a), 3.00(q, 2H, AB, J_{AB}=13Hz, $CH_2C_6H_5$),7.25 (s, 5H,

$C_6\underline{H}_5$). **Analyse** ($C_{14}H_{16}O_2$):%Calc. C:77.75,H:7.46, %Tr. C:77.70, H:7.49.

cis-3a,8a, Benzyl-8a, octahydro-2H-cyclopenta[b]furannone-2 8 (n=3)
Rdt: 74%. Eb: 160-162°C/0.01 mm. **IR** (film)ν(C=O) 1775 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.00-2.60(m complex, 13H, H-3, 3a,4,5,6,7, 8),2.93(s, 2H, $C\underline{H}_2C_6H_5$),7.23(s, 5H, $C_6\underline{H}_5$). **Analyse** ($C_{16}H_{20}O_2$): %Calc. C:78.65,H:8.25, %Tr. C:78.51,H:8.32.

Acide cis-3a,7a, benzyl-7a, oxo-2, octahydrobenzofurannecarboxylique-3 9 (n=2)

On chauffe à reflux et sous barbotement de CO_2 pendant 8hrs un mélange de 10 g (0.0454 mole) de γ-lactone 8 (n=2) et de 120 ml d'une solution de carbonate de méthyle et de magnésium dans le DMF. Après refroidissement on verse ce mélange dans un grand volume d'eau et de glace et acidifie sous refroidissement, agitation et au goutte à goutte avec HCl à 10% jusqu'à pH nettement acide.
On filtre le produit solide qui se forme, le lave à l'eau et le sèche. Rdt: 12g (presque quantitatif). F: 159-161°C (déc) (Benzène-MeOH 20:1). **IR** (Nujol)ν(C=O) 1773 cm^{-1} (γ-lactone), ν(C=O) 1717 cm^{-1} (carboxyle). **RMN** ($CDCl_3$)δ(ppm): 1.10-2.02(m, 8H, H-4,5,6,7), 2.60-2.81(m, 1H, H-3a), 3.08(s, 2H, $C\underline{H}_2C_6H_5$), 3.63(d, 1H, J=12Hz, H-3), 7.25(s, 5H, $C_6\underline{H}_5$), 9.73 (s large, 1H, $CO_2\underline{H}$). **Analyse** ($C_{16}H_{18}O_4$): %Calc. C:70.05, H:6.61, %Tr. C=70.25,H:6.56.

En utilisant la même méthode nous avons préparé les acides suivants :

Acide cis-3a,6a, benzyl-6a, oxo-2, hexahydro-2H-cyclopenta[b]furannecarboxylique-3 9 (n=1)
Produit visqueux. Rdt:84%. **IR** ($CHCl_3$)ν(C=O) 1770 cm^{-1} (γ-lactone) ν(C=O) 1725 cm^{-1} (carboxyle), **RMN** ($CDCl_3$)δ(ppm): 1.35-2.10(m, 6H, H-4,5,6), 2.45-2.90(m, 1H, H-3a), 2.95(s, 2H, $C\underline{H}_2C_6H_5$), 3.20(d, 1H, J=4Hz, H-3), 7.15(m, 5H, $C_6\underline{H}_5$), 10.1(s, 1H, $CO_2\underline{H}$).

Acide cis-3a,8a, benzyl-8a, oxo-2, octahydro-2H-cyclohepta[b]furanne-carboxylique-3 9 (n=3)

Rdt: 58%. F: 105-108°C (Et_2O-n-pentane). **IR** ($CHCl_3$) ν(C=O) 1772 cm^{-1} (γ-lactone), ν(C=O) 1725 cm^{-1} (carboxyle). **RMN** ($CDCl_3$) δ(ppm): 1.15-2.07(m, 10H, H-4,5,6,7,8), 2.62-2.83(m, 1H, H-3a), 3.10(s, 2H, $C\underline{H}_2C_6H_5$), 3.65(d, 1H, J=12Hz, H-3), 7.30 (s, 5H, $C_6\underline{H}_5$), 9.81(s, 1H, $CO_2\underline{H}$). **Analyse** ($C_{17}H_{20}O_4$): %Calc C:70.81,H:6.99, %Tr. C:71.02,H:6.91.

cis-3a,7a, Benzyl-7a, (diméthylaminométhyl)-3, hexahydrobenzofurannone-2(3H) 2 (n=2)

On traite 5 g (0.0182 mole) d'acide 9 (n=2) avec 30 ml d'éthanol et 15 ml d'une solution aqueuse de diméthylamine à 40%. Dans la solution obtenue on ajoute au goutte à goutte, sous agitation et refroidissement, 5 ml d'une solution saturée de formol. On agite pendant 1hr à 0°C puis 24hrs à la température ambiante. On verse ensuite le mélange réactionnel dans une grande quantité d'eau et extrait à l'éther. On lave les couches éthérées unies à l'eau, les sèche sur Na_2SO_4 et les évapore.

On obtient 4g d'un produit huileux. Rdt: 77%. **IR** (film) ν(C=O) 1765 cm^{-1}. **RMN** ($CDCl_3$) δ(ppm): 1.25-2.92(mm, 12H, $C\underline{H}_2N$, H-3, 3a, 4,5,6,7), 2.18(s, 6H, $(C\underline{H}_3)_2N$), 3.10(s, 2H, $C\underline{H}_2C_6H_5$), 7.35 (s, 5H, $C_6\underline{H}_5$). **Chlorhydrate** . F: 209-211°C (EtOH-Et_2O). **Analyse** ($C_{18}H_{26}ClNO_2$): %Calc. C:66.75, H:8.09 N:4.34, %Tr. C:66.98,H:8.30,N:4.21.

En utilisant la même méthode nous avons préparé les aminolactones suivantes :

cis-3a,6a, Benzyl-6a, (diméthylaminométhyl)-3, hexahydro-2H-cyclopenta[b]furannone-2. 2 (n=1)

Produit huileux. Rdt: 81%. **IR** (film) ν(C=O) 1762 cm^{-1}. **RMN** ($CDCl_3$) δ(ppm): 1.40-3.08(mm, 10H, $C\underline{H}_2N$, H-3, 3a,4,5,6), 2.10 (s, 6H, $(C\underline{H}_3)_2N$), 3.22(q, 2H, AB, J_{AB}=13Hz, $C\underline{H}_2C_6H_5$), 7.38(m, 5H, $C_6\underline{H}_5$). **Chlorhydrate** .F: 211-213°C (dec) (EtOH-Et_2O). **Analyse** ($C_{17}H_{24}ClNO_2$): %Calc. C:65.90, H:7.81, N:4.52, %Tr. C:66.01,H:7.92,N:4.39.

cis-3a,8a, Benzyl-8a, (diméthylaminométhyl)-3, octahydro-2H-cyclohepta[b]furannone-2. 2 (n=3)

Produit huileux. Rdt: 74%. **IR** (film)ν(C=O) 1765 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.20-2.62(mm, 14H, $C\underline{H}_2N$, H-3, 3a,4,5,6,7,8), 2.09(s, 6H, $(C\underline{H}_3)_2N$), 2.94(q, 2H, AB, J_{AB}=13Hz, $C\underline{H}_2C_6\underline{H}_5$), 7.26(m, 5H, $C_6\underline{H}_5$). **Chlorhydrate** .F: 189-191°C (EtOH-Et_2O). **Analyse** ($C_{19}H_{28}ClNO_2$): %Calc. C:67.54, H:8.35. N:4.15. %Tr. C:67.35,H:8.45,N:4.06.

cis-3a,7a, Benzyl-7a, (pipéridinéméthyl)-3, hexahydrobenzofurannone-2(3H).

En faisant réagir une solution de 2.47 g (0.029 mole) de pipéridine dans 30 ml d'éthanol et 5 ml d'une solution aqueuse de formol à 40% avec 5 g (0.018 mole) d'acide 9 (n=2), comme il est décrit pour l'aminolactone 2 (n=2), on obtient un produit huileux **IR** (film)ν(C=O) 1767,1755 cm^{-1}, ν(C=C) 1660 cm^{-1}. On dissout ce produit dans l'éther et extrait la solution éthérée obtenue au HCl à 5%. On alcalinise les couches aqueuses unies avec $NaHCO_3$ et extrait à l'éther. On lave à l'eau les couches éthérées, les sèche sur Na_2SO_4 et les évapore. On obtient 1 g (Rdt: 17%) de produit huileux. **IR** (film)ν(C=O) 1767 cm^{-1}. **Oxalate** . F: 145-147°C (EtOH). **Analyse** ($C_{23}H_{31}NO_6$):%Calc. C:66.17,H:7.48,N:3.36. %Tr. C:66.31, H:7.50,N:3.21.

cis-3a,7a, Benzyl-7a, méthyléne-3, hexahydrobenzofurannone-2 (3H). 12

Après avoir lavé la couche éthérée à l'acide chlorhydrique à 5% pour éliminer l'aminolactone 11 , on lave cette couche organique à l'eau, la sèche, et l'évapore. On recristallise le résidu dans un mélange éther-n-pentane. F: 89-91°C. Rdt: 3 g (68%). **IR** (Nujol)ν(C=O) 1755 cm^{-1}, ν(C=C) 1660 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.20-2.00(dm, 8H, H-4,5,6,7), 2.70(m,1H, région X, AMX, H-3a), 3.00(s, 2H, $C\underline{H}_2C_6\underline{H}_5$), 5.33(d, 1H, région AM, AMX, $J_{AX}=J_{MX}$=4-5Hz, J_{AM}=0Hz,=$C\underline{H}_A\underline{H}_M$), 6.10(d, 1H, région AM, AMX, $J_{AX}=J_{MX}$=4-5Hz, J_{AM}=0Hz,=$CH_A\underline{H}_M$), 7.20(s, 5H, $C_6\underline{H}_5$) **Analyse** ($C_{16}H_{18}O_2$):%Calc. C:79.31,H:7.49, %Tr. C:79.39,H:7.51

Benzyl-1, [(diméthylaminométhyl)-1, hydroxy-2, éthyl]-2, cyclohexanol 10 (n=2)

On ajoute au goutte à goutte et sous agitation une solu-

tion de 2.9 g (0.01 mole) de l'aminolactone 2 (n=2) dans 60ml de THF anhydre dans une suspension de 1.5 g (0.04 mole) de $LiAlH_4$ dans 80 ml de THF. On chauffe à reflux doux pendant 4hrs puis hydrolyse, sous refroidissement, avec de l'eau et de NaOH à 20%. On filtre les minéraux, les lave au THF et sèche la solution organique sur Na_2SO_4. Après évaporation on obtient 2.7 g d'un produit visqueux. Rdt: 93%. **IR** (film)ν(OH) 3450-3100 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.10-1.76(m, 9H, H-cyclohexaniques),1.95-2.50(m, 3H, -CH CH_2N), 2.26(s, 6H, $(CH_3)_2N$), 2.77(q, 2H, AB, J_{AB}=13Hz, $CH_2C_6H_5$), 3.25-3.65(m, 2H, CH_2OH), 4.00-5.05(s large, 2H, 2xOH), 7.22(s, 5H, C_6H_5).

En utilisant la même méthode on obtient les aminalcools suivants :

Benzyl-1, [(diméthylaminométhyl)-1, hydroxy-2, éthyl]-2, cyclopentanol 10 (n=1)

Produit visqueux. Rdt: 95%. **IR** (film)ν(OH) 3440-3160 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.45-2.60 (m, 10H, H-cyclopentaniques, CH CH_2N), 2.23(s, 6H, $(CH_3)_2N$), 2.80(q, 2H, AB, J_{AB}=13Hz, $CH_2C_6H_5$), 3.20-3.62(m, 2H, CH_2OH), 4.10-5.15(s large, 2H, 2xOH), 7.30(s, 5H, C_6H_5).

Benzyl-1, [(diméthylaminométhyl)-1, hydroxy-2, éthyl]-2, cycloheptanol 10 (n=3)

Produit visqueux. Rdt: 98%. **IR** (film)ν(OH) 3440-3160 cm^{-1}. **RMN** ($CDCl_3$)δ(ppm): 1.15-2.50(m, 14H, H-cycloheptaniques, CH CH_2N), 2.22(s, 6H, $(CH_3)_2N$), 2.82(q, 2H, AB, J_{AB}=13Hz, $CH_2C_6H_5$), 3.18-3.60(m, 2H, CH_2OH), 4.08-5.16(s large, 2H, 2xOH), 7.24(s, 5H, C_6H_5).

cis-3a,7a, Benzyl-7a, (diméthylaminométhyl)-3, octahydrobenzofuranne. 3 (n=2)

On chauffe pendant 5hrs avec élimination azéotropique de l'eau 2 g (0.007 mole) d'aminodiol 10 (n=2) et 3.94 g (0.021 mole) de monohydrate de l'acide p-toluènesulfonique dans 100 ml de benzène anhydre. On verse le mélange réactionnel dans 200 ml de NaOH à 20%, sépare la couche benzènique et extrait l'aqueuse à l'éther. On lave les couches organiques

unies à l'eau, les sèche sur Na_2SO_4 et les évapore. On chromatographie le résidu huileux sur colonne d'alumine neutre en utilisant un mélange éther-hexane 1:3 comme solvant d'élution. Après évaporation des solvants on obtient 1.55 g de produit huileux. Rdt: 82%. **RMN** ($CDCl_3$)δ(ppm): 1.10-1.75(m, 8H, H-4,5,6,7), 2.10-3.05(m, 6H, $C\underline{H}_2N$, $C\underline{H}_2C_6H_5$, H-3, 3a), 2.22(s, 6H, $(C\underline{H}_3)_2N$), 3.28-4.24(dm, 2H, H-2), 7.13-7.20(m, 5H, $C_6\underline{H}_5$). **Chlorhydrate** F: 187-189°C ($EtOH-Et_2O$). **Analyse** ($C_{18}H_{28}ClNO$): %Calc. C:69.77,H:9.11,N:4.52, %Tr. C:69.97,H:9.25,N:4.42.

En utilisant la même méthode nous avont synthétisé les dérivés 3 suivants:

cis-3a,6a, Benzyl-6a, (diméthylaminométhyl)-3, hexahydro-2H-cyclopenta[b]furanne. 3 (n=1)

Produit huileux. Rdt: 60%. **RMN** ($CDCl_3$)δ(ppm): 1.45-2.50(mm, 10H, $C\underline{H}_2N$, H-3,3a,4,5,6,), 2.17(s, 6H,$(C\underline{H}_3)_2N$), 2.85(q, 2H, AB, J_{AB}=13Hz, $C\underline{H}_2C_6H_5$), 3.20-4.00(dm, 2H, H-2), 7.23(s, 5H, $C_6\underline{H}_5$). **Chlorhydrate** F: 168-170°C ($EtOH-Et_2O$). **Analyse** ($C_{17}H_{26}ClNO$): %Calc. C:69.01, H:8.86, N:4.73, %Tr. C:69.19, H:8.91,N:4.52.

cis-3a,8a, Benzyl-8a, (diméthylaminométhyl)-3, octahydro-2H-cyclohepta[b]furanne. 3 (n=3)

Produit huileux. Rdt: 67%. **RMN** ($CDCl_3$)δ(ppm): 1.10-2.45(mm, 14H, CH_2N, H-3, 3a,4,5,6,7,8), 2.18(s, 6H, $(C\underline{H}_3)_2N$), 2.80(q, 2H, AB, J_{AB}=13Hz, $C\underline{H}_2C_6H_5$), 3.20-4.19(dm, 2H, H-2), 7.22(s, 5H, $C_6\underline{H}_5$). **Chlorhydrate** . F: 223-225°C ($EtOH-Et_2O$). **Analyse** ($C_{19}H_{30}ClNO$): %Calc. C:70.45, H:9.34, N:4.32, %Tr. C:70.35, H:9.36,N:4.12.

SUMMARY

Oxabicyclic aminoderivatives

The bicyclic γ-benzyl-α-(dimethylaminomethyl)-γ-lactones 2 and their tetrahydrofuran analogues 3 were prepared. The synthesis of the aminolactones 2 includes benzylation of cycloalkanones via enamines, Reformatskii reaction, lactonization, carboxylation and application of the Mannich reaction. The conversion of the aminolactones 2 to their aminotetrahydrofuran analogues 3 was performed by reduction with $LiAlH_4$

and cyclisation of the intermediate aminodiols.

ΠΕΡΙΛΗΨΗ

Οξαδικυκλικά αμινοπαράγωγα

Περιγράφεται η σύνθεση των δικυκλικών γ-βενζυλο-α-(διμεθυλαμινόμεθυλο)-γ-λακτονών 2 και των αντίστοιχων τετραϋδροφουρανικών αναλόγων τους 3 . Η σύνθεση των αμινολακτονών 2 περιλαμβάνει βενζυλίωση των κυκλοαλκανονών μέσω των εναμινών τους, αντίδραση Reformatskii, λακτονοποίηση, καρβοξυλίωση και εφαρμογή της αντιδράσεως Mannich. Η μετατροπή των αμινολακτονών 2 προς τα αμινοτετραϋδροφουρανικά παράγωγα 3 πραγματοποιείται με αναγωγική διάνοιξη και επανακύκλωση.

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SHORT PAPER

NEW COMPLEXES OF COBALT(II) WITH RING SUBSTITUTED BENZOYLHYDRAZINES AND THEIR BEHAVIOR IN NON AQUEOUS SOLVENTS

C. YOURI-TSOCHATZI AND G.E. MANOUSSAKIS

Faculty of Chemistry, University of Thessaloniki, Thessaloniki 54006, P.O.B. 135, GREECE

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SUMMARY

A series of seventeen new complexes of cobalt(II) with o-, m-, and p-ring substituted benzoylhydrazines have been prepared and studied. The general type of the studied complexes are $|(CoL_3)|X_2$, (where L=o-, m-, p-ring substituted benzoylhydrazines and X=halogen, $^2NO_3^-$, $\frac{1}{2}SO_4^{2-}$). Also in some cases benzoylhydrazines are abbreviated as Bh).

The characterization of the solid compounds was carried out by stoichiometry, conductivity, magnetic susceptibility, infrared and electronic spectra. The behavior of the soluble complexes in non aqueous solvents were studied by spectrophotometry. The effect of the solvents was found to depend on the "acceptor number" (AN) of the solvents.

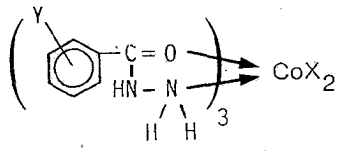
Key words. Substituted benzoylhydrazine cobalt(II) complexes, "acceptor number", Equilibrium tetrahedral-octahedral structure.

INTRODUCTION

Benzoylhydrazines have been known to form complexes that exhibit therapeutic action[1] as well as properties useful in analytical applications[2]. The knowledge of the mode of coordination of these ligands is very useful to understand their properties[3].

Benzoylhydrazines under our experimental conditions act as bidentate ligands with coordination sites the carbonyl oxygen and the terminal nitrogen atom with result the formation of a five membered chelate ring[4-9].

In the present study seventeen new complexes of cobalt(II) with ring substituted benzoylhydrazines were prepared and studied. The general formula of these complexes in the solid state is :



where Y=halogen, $-OCH_3$, $-NO_2$ and X=halogen, NO_3^-, $\frac{1}{2}SO_4^{2-}$.

Also these complexes are studied in some non aqueous media, with the aim of investigating the effect of solvent properties on the formation equilibrium of the complexes. The solvents considered are ethanol, acetonitrile, dimethylsulfoxide, dioxan, tetrahydrofuran which posses different "acceptor number" (AN)[10].

EXPERIMENTAL

Halogen benzoylhydrazines were prepared as described in our previous work[11].

The cobalt(II) complexes of ring substituted benzoylhydrazines were prepared using a method already reported[8]. The prepared complexes are listed in TABLE 1.

The solvents were purified prior to their use properly. All other chemicals were analytical pure.

The infrared absorption spectra (4000-200 cm^{-1}) were measured on a Perkin-Elmer model 1430 recording spectrophotometer in KBr disks.

Electronic absorption spectra in the region 200-800 nm were recorded at ca. 25°C using a Perkin-Elmer model 200 spectrophotometer. The spectra in solid state were obtained using a Varian 634 diffuse reflectance spectrophotometer with MgO as reference.

Magnetic susceptibility measurements were performed at ambient temperature on an ALPHA SCIENTIFIC INC system employing the Faraday method with $Hg|Co(SCN)_4|$ as calibrant.

Molar conductivity were measured using a WTW conductivity bridge.

RESULTS AND DISCUSSION

Complexes in the solid state

The reaction of the studied ring substituted benzoylhydrazines with cobalt(II) salts, CoX_2, in ethanolic solution afforded pink solids[9]. Analyses of the solids (TABLE 1) indicated that the stoichiometry of the new complexes corresponded invariably to the general formula $|CoL_3|X_2$ in-

T A B L E I. Melting point, solid state magnetic moment and analytical data of o-, m-, p-ring substituted benzoylhydrazines cobalt(II) complexes.

Compound	M.Point °C	μ_{eff}/m_B	N %	C %	H %	M %	X %
$[Co(o\text{-}FBh)_3]Cl_2$	225d	4.6	13.9(14.2)	42.2(42.6)	3.7(3.6)	9.8(9.9)	11.6(11.9)
$[Co(m\text{-}FBh)_3]Cl_2$	250-251	4.9	14.0(14.2)	42.3(42.6)	3.5(3.6)	9.7(9.9)	11.7(11.9)
$[Co(p\text{-}FBh)_3]Cl_2$	276-280	4.7	13.9(14.2)	42.2(42.6)	3.5(3.6)	9.6(9.9)	11.8(11.9)
$[Co(o\text{-}ClBh)_3]Cl_2$	134-136	4.9	13.1(13.1)	39.3(39.3)	3.1(3.3)	9.0(9.2)	11.8(11.0)
$[Co(o\text{-}ClBh)_3]Br_2$	181-184	5.0	11.2(11.5)	34.1(34.5)	2.9(2.9)	8.0(8.1)	21.7(21.9)
$[Co(o\text{-}ClBh)_3]I_2$	190-192	5.1	10.0(10.2)	30.1(30.6)	2.3(2.6)	6.9(7.1)	30.4(30.8)
$[Co(m\text{-}ClBh)_3]Cl_2$	230-232	4.8	12.9(13.1)	39.1(39.3)	3.2(3.3)	9.3(9.2)	11.1(11.0)
$[Co(p\text{-}ClBh)_3]Cl_2$	263-265	5.1	12.9(13.1)	39.1(39.3)	3.3(3.3)	9.2(9.2)	10.9(11.0)
$[Co(p\text{-}ClBh)_3]SO_4$	>330	5.2	12.3(12.6)	37.5(37.8)	3.0(3.2)	8.6(8.8)	-
$[Co(o\text{-}BrBh)_3]Cl_2$	293-296	4.8	10.7(10.8)	32.1(32.5)	2.6(2.7)	7.5(7.6)	9.0(9.1)
$[Co(m\text{-}BrBh)_3]Cl_2$	253-254	5.1	10.5(10.8)	31.9(32.5)	2.6(2.7)	7.5(7.6)	8.0(8.1)
$[Co(p\text{-}BrBh)_3]Cl_2$	272-273	4.9	10.5(10.8)	32.1(32.5)	2.5(2.7)	7.5(7.6)	8.0(8.1)
$[Co(o\text{-}IBh)_3]Cl_2$	234-237	5.2	9.3(9.2)	27.8(27.5)	2.4(2,3)	6.2(6.4)	7.5(7.7)
$[Co(m\text{-}IBh)_3]Cl_2$	256-258	4.9	8.9(9.2)	27.1(27.5)	2.1(2,3)	6.3(6.4)	7.4(7.7)
$[Co(p\text{-}IBh)_3]Cl_2$	287-290	5.4	8.9(9.2)	27.0(27.5)	2.2(2.3)	6.1(6.4)	7.6(7.7)
$[Co(m\text{-}OCH_3Bh)_3]Cl_2$	111-113	4.8	13.2(13.4)	39.9(40.1)	3.5(3.4)	9.1(9.4)	11.1(11.3)
$[Co(o\text{-}NO_2Bh)_3]Cl_2$	136-140	4.9	12.0(12.5)	37.8(37.5)	3.3(3.2)	8.6(8.8)	10.1(11.5)

dependent of the ligand-to-metal ratio in the reaction mixture. Conductivity measurements suggested ionic character of the complexes. The molar conductivity of the compounds (A=235-237 $mho \cdot cm^2 \cdot mol^{-1}$) conform with 1:2 electrolytes and the variations in the experimental values suggest dissociation with dilution.

The magnetic moments values (TABLE 1), corrected for diamagnetism using Pascal constants, lied in the range 4.6-5.2 m_B. These values and the pink colour of the solid complexes indicate that the arrangement of the ligand is octahedral and that the resulting field is weak.

The infrared spectra measured in the solid state showed distinct features of coordination of the ligands. The presence of strong absorption bands at about 1660 cm^{-1} and the absence of bands associated with the enolic form[12,13] at wavenumbers higher than 3500 cm^{-1} are strong evidence that the ligands exist in the keto form[11]. The pattern of the ir spectra of the free ligands is rather repeated in the spectra of the complexes with small changes. Thus, the bands in the region 3400-3250 cm^{-1}, exhibit a bathochromic shift and became broader. In the region 1665-1625 cm^{-1} the "amide I" band is shifted by 25-40 cm^{-1} to lower frequencies. The "amide II" band (~1500 cm^{-1}) showed a minor shift while the "amide III" band at about 1250 cm^{-1} arising mainly from N-H in-plane deformation, is shifted by more than 60 cm^{-1} to lower frequencies and is accompanied by splitting[6].

The changes in the band associated with the N-H stretching vibrations and in the "amide" bands suggest that at least in the solid state the substituted benzoylhydrazines coordinate through the carbonyl oxygen and the terminal nitrogen atom[4-9].

The diffuse reflectance electronic specta (Fig.1), of the solid complexes showed the "red" spectrum, characterized by a broad band with maximum at ~530 nm attributed to the $^4A_{2g}(F) \leftarrow {}^4T_{1g}(F)$ transition. Another characteristic band appears at about 1170 nm and using notation appropriate to octahedral symmetry should be assigned to the $^4T_{2g}(F) \leftarrow {}^4T_{1g}(F)$ excitation.

In conclusion, the structure of the studied solid complexes is distorted octahedral. This distortion is probably due to the inequality of the M-O and M-N bonds as well as to the result of Jahn Teller's effect.

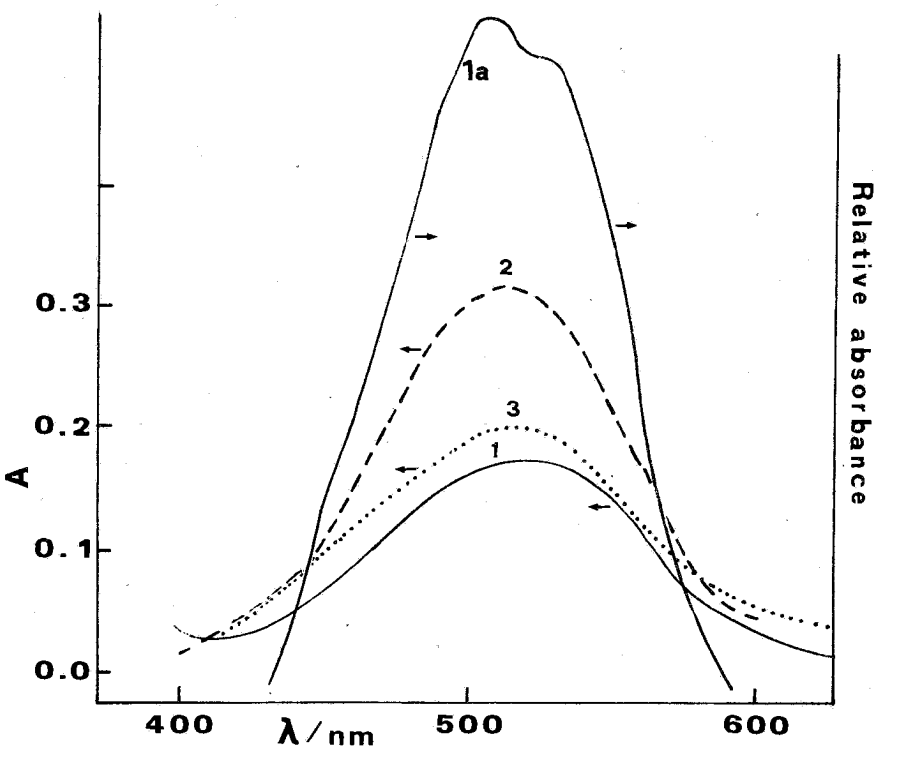


FIG. 1. *Electronic absorption spectra of* $|Co(o\text{-}ClBh)_3|X_2$ *(1a)* $|Co(o\text{-}ClBh)_3|Cl_2$ *in the solid state (___) and in ethanolic solutions (1) 5.00 mM* $|Co(o\text{-}ClBh)_3|Cl_2$ *(___), (2) 2.50 mM* $|Co(o\text{-}ClBh)_3|Br_2$ *(---), (3) 1.80 mM* $|Co(o\text{-}ClBh)_3|I_2$ *(...).*

Complexes in solution

Spectral changes were appeared in solution when a series of solvents of varying dielectric corstant, $\varepsilon/\varepsilon_0$ and "acceptor number" (AN) were emloyed.

The "red" electronic absorption spectra persist as well as in ethanolic solution, (AN=37.9) (Fig.1), water (AN=54.8) or chloroformic solutions (AN=23.1). In dilute acetonitrile (AN=18.9), acetone (AN=12.5),dimethyl sulfoxide (AN=19.3), dioxan (AN=10.8) or tetrahydrofuran(AN=8.0) solutions[10], the "red" spectrum was not observed. Instead, a new envelope at about 560-740 nm appeared which characterizes the "blue" spectrum indicative of tetrahedral structure (Fig.2). Specifically the "blue" spectrum appeared when complexes of the type $|CoL_3|X_2$ (where X in only halo-

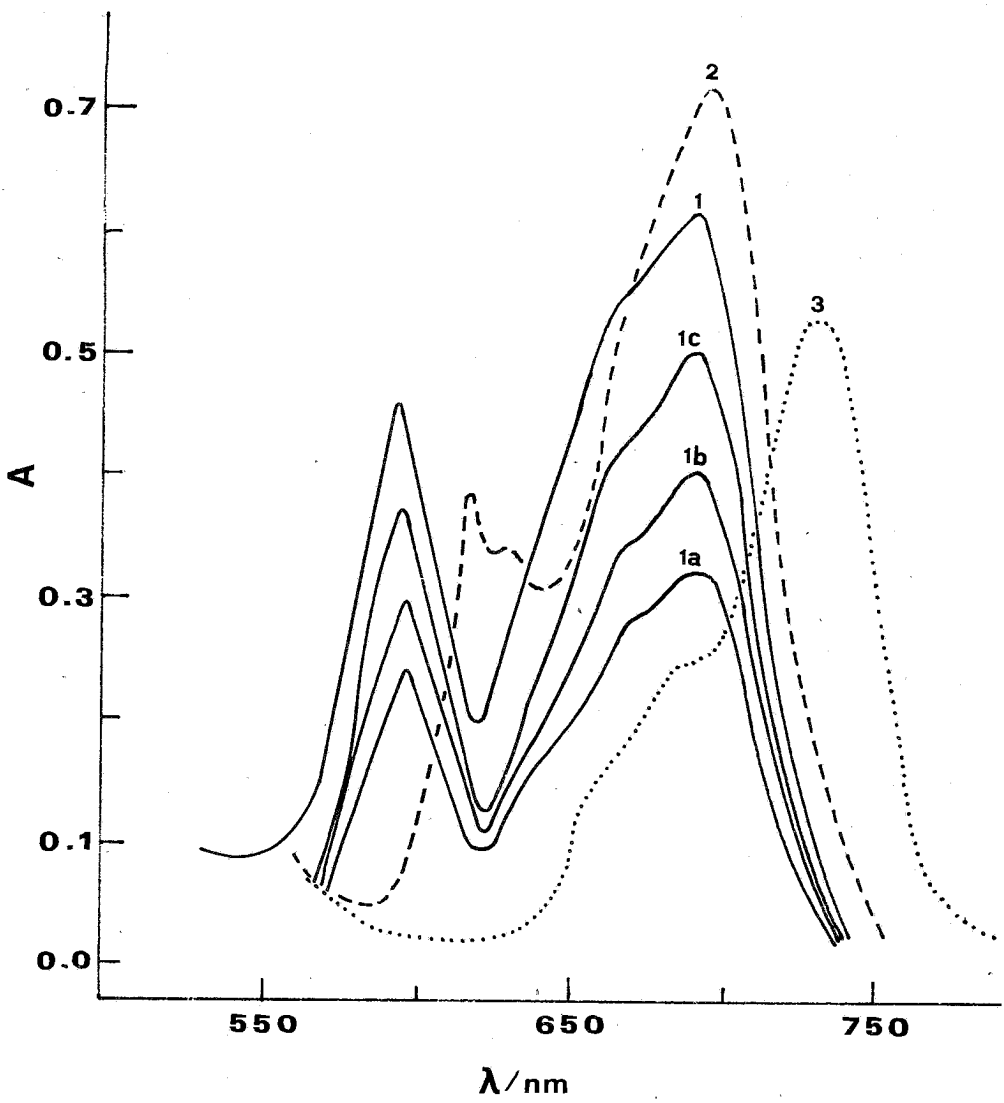


FIG. 2. *Electronic absorption spectra of* $|Co(o\text{-}ClBh)_3|X_2$ *in acetonitrile solutions.*

(1) 2.50 mM $|Co(o\text{-}ClBh)_3|Cl_2$ (___), *(1a) 1.25 mM* $|Co(o\text{-}ClBh)_3|Cl_2$ (___), *(1b) 1.25 mM* $|Co(o\text{-}ClBh)_3|Cl_2$ *+ 0.33 mM LiCl* (___), *(1c) 1.25 mM* $|Co(o\text{-}ClBh)_3|Cl_2$ *+ 1.00 mM LiCl* (___), *(2) 2.50 mM* $|Co(o\text{-}ClBh)_3|Br_2$ (---), *(3) 1.80 mM* $|Co(o\text{-}ClBh)_3|I_2$ (...).

gen) were dissolved in solvents of "acceptor number" (AN) less than 20 (better π* acceptors). This suggests that the rather weak metal - ligand bonds are ruptured by a shift of charge density due to ligand-solvent in teractions. However, extensive charge redistribution, which is envisaged to occur in solvents with "acceptor number" (AN) greater than 20 would impart negative charge on the ligand at the coordination sites which has as result the strenghten of the metal-ligand bonds in the resulting octahedral structure.

Complexes with anions other than halides e.g. $|Co(o\text{-}ClBh)_3|(NO_3)_2$ or $Co(o\text{-}ClBh)_3\ SO_4$ give only the "red" spectrum. The anions NO_3^- and SO_4^{2-} do not favor the tetrahedral structure possible of their greater size. Addition, however, of halogen anions in these solutions effected the appearance of the "blue" spectrum.

The position, shape and intensity of the "blue" spectrum bands, depends on the nature of the halogen anions of the complexes. The intensity and the position (bathochromic shifts) (Fig.2) are increasing according to the sequence $I^->Br^->Cl^-$. This is in agreement with previous observations[14-17].

In our case the dependence of the intensity of the bands on both the solvents and the nature of halogens is a strong evidence that halogen anions are coordinated to cobalt(II). The shape, position and intensity of the "blue" spectrum of the studied complexes suggested that in solution the species CoX_4^{2-} is predominated[15-18] and possible an equilibrium pertains between the tetrahedral and the octahedral structures. This equili brium may be described by the reversible reaction :

$$CoX_4^{2-} + 3L \rightleftharpoons CoL_3^{2+} + 3L$$

where X=halogen.

The equilibrium constants K of this reversible equation were determined spectrophotometrically at 25°C and ionic strength μ=0 by altering concentrations of complexes, halogen, ligand and solvent. The concentration of the dissolved complex CoL_3^{2+} in different solvents is known about 1.0-5.0 mM as well as the concentrations of halogen X(LiCl, KBr, KI) and ligands are 0.1-1.0 mM each one. Absorbance measurements at λ_{max} about 690 nm enabled the determination of the concentrations of the species CoX_4^{2-} which was valid. The values of extinction coefficient,ε, of CoX_4^{2-} were determined from a solution of CoX_2 saturated with halogen in the corresponding solvent. In acetonitrile solutions the resulted values of ε

are for $CoCl_4^{2-}$ and $CoBr_4^{2-}$ 614 and 683 $mol^{-1}.dm^3.cm^{-1}$ respectivelly.

The K value of complex $|Co(o\text{-}ClBh)|Cl_2$ is $1.37x10^{-5}\pm0.05$ in acetonitrile solution under our experimental conditions. Changing the anion to Br^-, the equilibrium constant K is altered and becomes $1.41x10^{-7}\pm0.05$ in the same solvent. Similar measurements involving the complex $|Co(o\text{-}ClBh)_3|I_2$ indicated that the stability of this compound in acetonitrile was much less than that of the other complexes.

The lower equilibrium constant of the bromo-complex as compared to the corresponding chloro-complex is in agreement with the "softer" character of Br, that makes its replacement by the ligand (o-ClBh) more difficult in the coordination sphere of the rather "hard" metal Co(II).

ΠΕΡΙΛΗΨΗ

Μελέτη της συμπεριφοράς συμπλόκων του κοβαλτίου(II) με υποκαταστημένες βενζοϋλοϋδραζίνες σε μη υδατικούς διαλύτες.

Έχει παρασκευαστεί και έχει μελετηθεί μια σειρά νέων συμπλόκων ενώσεων του κοβαλτίου(II) με υποκαταστημένες στον αρωματικό δακτύλιο βενζοϋλοϋδραζίνες. Από τη στοιχειομετρία των ενώσεων καθώς και από τις τιμές της αγωγιμότητας, της μαγνητικής επιδεκτικότητας, των φασμάτων υπερύθρου και των ηλεκτρονικών φασμάτων έχει αποδειχθεί ότι, σε στερεά κατάσταση τα σύμπλοκα έχουν δομή παραμορφωμένη οκταεδρική και ανταποκρίνονται στο γενικό τύπο, $|CoL_3|X_2$ όπου L=ο-, μ- και π-υποκατεστημένες βενζοϋλοϋδραζίνες και X=αλογόνο, NO_3^- και $\frac{1}{2}SO_4^=$.

Μελετήθηκε επίσης φασματοφωτομετρικά η συμπεριφορά των συμπλόκων του κοβαλτίου(II) σε διάφορους διαλύτες και βρέθηκε ότι εξαρτάται από τον "αριθμό δέκτη" ("acceptor number"), (AN), του διαλύτη.

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SHORT PAPER

3-(3-ALKYLAMINO-2-HYDROXYPROPOXY)-DERIVATIVES OF ESTRATRIENE. SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL STUDY.

M.KAZANIS, P.MACHERAS, A.VAVAYANNIS

University of Athens, Department of Pharmacy, Division of Pharmaceutical Chemistry, Solonos 104, GR-106 80 Athens, Greece.

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SUMMARY

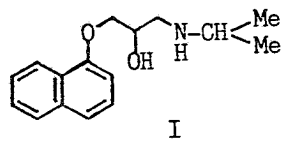
17β-hydroxy and 17-hydroxyimino derivatives of 3-(3-alkylamino-2-hydroxypropoxy)-estrone were synthesized.The title compounds were examined for β-blocking activity.

Key words: estratriene, β-adrenoreceptor blocking activity.

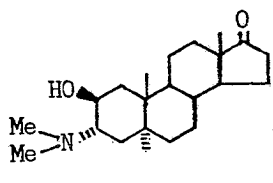
INTRODUCTION

Compounds combining an aromatic or heteroaromatic system with a 3-alkylamino-2-hydroxypropoxy moiety (the alkyl being an i-propyl or a tert-butyl group) are potent sympatholytic agents. Propranolol (I) is the most important representative of these compounds which exert their action by blocking β-adrenoreceptors and are widely used in the treatment of cardiac arrhythmias, angina pectoris etc. It has also been reported[1,2,3] that steroid derivatives bearing an aminalcohol system (II,III) have been studied for similar activity.

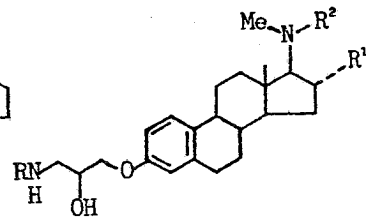
Considering the above data we synthesized derivatives of estrone coupling the propanolamine group with the aromatic ring of the steroid molecule. Our aim was the study of the biological behaviour of these compounds (*3a,3b,4a,4b,5a and 5b* , FIG. 1) which have a bulkier and more extended system in the place of the napthalene group of propranolol. We also modified the 17 ketone group of estrone to 17β alcohol and 17 oxime in order to examine if these modifications influence



I



II



III

R: i-Pr,t-Bu
R^1: H,OH
R^2: H,Me

their biological activity.

The pathways followed for the synthesis of the target compounds are depicted in FIG. 1. Estrone (*1*) was condensed with epichlorhydrine[3] in alkaline medium to yield the epoxypropyl ether *2* . The epoxide ring was opened with isopropylamine or *tert* -butylamine leading to the corresponding amino compounds *3a* and *3b* . Reduction of the latter with $NaBH_4$ in methanol gave the alcohols *4a* and *4b* .The oximes were obtained by reaction of *3a* and *3b* with $NH_2OH.HCl$ in the presence of CH_3COONa. The title compounds were purified by means of their hydrochloric salts.

EXPERIMENTAL

Melting points were determined on a Buchi capillary apparatus and are not corrected. IR spectra were recorded in Nujol on a Perkin-Elmer 177 spectrophotometer. NMR spectra were taken on a Varian EM 360A spectrometer in $CDCl_3$ containing TMS as internal standard. Elemental analyses were performed in the microanalytical laboratories of Centre National de la Recherche Scientifique (France) and of the Nuclear Research Centre "Demokritos" (Greece). The analytical results obtained were within ±0.4% of the theoretical values. Hydrochloric salts were prepared with addition of ethereal solution of HCl in solutions of the bases in absolute ethanol

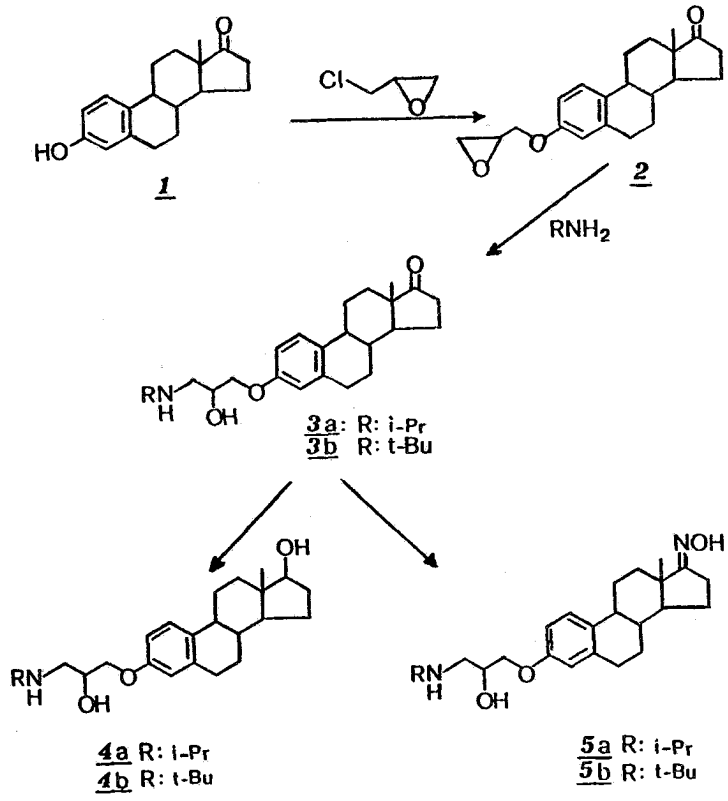


FIG. 1

and were recrystallized from absolute ethanol-anhydrous ether.

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-one , 3b .

1.65 gr (5 mmol) 3-epoxypropoxy-estra-1,3,5(10)-trien--17-one[3] was dissolved in 50 ml methanol and 3.6 gr (50 mmol) tert-butylamine were added. The mixture was refluxed for 20 h, the solvent and excess tert-butylamine were distilled off and the solid residue (1.7 gr, 85%), m.p. 125-30 °C was recrystallized twice from methanol-water and once from ethyl ether-methanol to reach a melting point of 152-53 °C. HCl salt: M.p. 211-13 °C (dec.). Elemental analysis: $C_{25}H_{39}ClNO_3$: 436 (C,H,N).

3-(3-Isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-one[3], *3a* .

Its preparation was similar to the above. HCl salt: M.p. 318-21 °C (~300 °C[3]). Elemental analysis: $C_{24}H_{36}ClNO_3$: 422·(C,H,N).

3-(3-Isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17β-ol , 4a .

In a solution of 0.96 gr (2.5 mmol) 3a in 50 ml methanol were added 0.28 gr (7.5 mmol) $NaBH_4$ and the mixture was stirred at room temperature for 1 h. Following addition of water the resulting mixture was extracted with $CHCl_3$, the chloroform layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to give 0.77 gr (80%) of the crude base. HCl salt: M.p. 326-27 °C. Elemental analysis: $C_{24}H_{38}ClNO_3$: 424 (C,H,N).

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17β-ol , 4b .

It was prepared in a similar way from 1.2 gr (3 mmol) *4a* yielding 1.0 gr (83%) of the base, m.p. 188-90 °C. HCl salt: M.p. 254-56 °C (dec). Elemental analysis: $C_{25}H_{40}ClN_2O_3$: 438 (C,H,N).

3-(3-isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-oxime , 5a .

In 20 ml ethanol were dissolved 1.93 gr (5 mmol) 3a and a solution of 1.4 gr (20 mmol) $NH_2OH.HCl$ and 3.3 gr (40 mmol) sodium acetate in 20 ml ethanol was added. The mixture was refluxed for 2h, cooled, diluted with water and extracted twice with $CHCl_3$. The chloroform layer was dried over anhydrous Na_2SO_4 and the solid residue (1.6 gr,80%),m.p. 147-50 °C was recrystallized from MeOH/n-C_5H_{12} to reach a melting point of 166-68 °C. HCl salt: M.p. 272-73 °C (dec.). Elemental analysis: $C_{24}H_{37}ClN_2O_3$:437 (C,H,N).

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-oxime ,5b .

It was prepared employing the same method. 1,5 gr (3,75 mmol *3b* gave 1.25 gr (80%) *5b* , m.p. 188-90 °C. HCl salt: M.p. 254-56 °C (dec.). Elemental analysis: $C_{25}H_{39}ClN_2O_3$: 451 (C,H,N).

SPECTRA

IR (cm^{-1})

3a , 3b : 3360-3260 ν(OH,NH), 1600-1560 ν(C=C), 1725 ν(C=O).
4a , 4b : 3400-3260 ν(OH,NH), 1600-1560 ν(C=C).
5a , 5b : 3480-3160 ν(OH,NH), 1600-1560 ν(C=C), 1660 ν(C=N).

NMR (d,ppm)- Bases.

3a : 0.9(s,3H,18-CH_3), 1.05 (d,6H,CH_3,i-Pr), 2.2 (t,2H,16--CH_2), 2.9-3.3(m,2H,CH_2NH), 4.0(d,2H,CH_2O), 4.5 (m,1H,CHOH), 6.6-7.2 (m,3H.aromatic).
3b : 0.9(s,H,18-CH_3), 1.45(s,9H,CH_3,t-Bu), 2.2(t,2H,16-CH_2), 3.0 (d,2H,CH_2NH), 4.0 (d,2H,CH_2O), 4.5 (m,1H,CHOH), 6.6-7.2 (m,3H, aromatic).
4a : 0.85 (s,3H,18-CH_3), 1.15 (d,6H,CH_3,i-Pr),1.6 (m,2H, 16-CH_2), 2.8-3.3 (m,3H,CH_2NCH), 3.8 (t,1H,17-CH), 4.15 (d,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).
4b : 0.9 (s,3H,18-CH_3), 1.45 (s,9H,t-Bu), 1.6 (m,2H,16-CH_2), 3.1 (d,2H,CH_2NH), 3.8 (t,1H,17-CH), 4.0 (d,2H,OCH_2), 4.5 (m,1H, CHOH), 6.6-7.2 (m,3H,aromatic).
5a : 0.9 (s,3H,18-CH_3),1.05 (d,6H,CH_3,i-Pr), 2.0 (t,2H, 16-CH_2), 2.85-3.3 (m,3H,CH_2NCH), 3.95 (m,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).
5b : 0.9 (s,3H,18-CH_3), 1.45(s,9H,t-Bu), 2.0 (t,2H,16-CH_2), 3.2 (d, 3H,CH_2NH), 3.95 (m,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).

PHARMACOLOGY

β_1-Blocking activity was determined on isolated right and left atria of male guinea pig (~500 gr) using isoprenaline hydrochloride as agonist[4,5]. β_2-blocking activity was determined on isolated trachea strip of male guinea pig (400-600 gr), using methacholine chloride as spasmogen and salbutamol as agonist[6-8]. None of the tested compounds *3a,3b,4a,4b,5a* and *5b* showed significant β-blocking activity.

ΠΕΡΙΛΗΨΗ

3-(3-Αλκυλαμινο-2-υδροξυπροποξυ)-παράγωγα του οιστρατριενίου. Σύνθεση και προκαταρκτική φαρμακολογική μελέτη.

Παρασκευάστηκαν τα 17β-υδροξυ και 17-υδροξυιμινο παράγωγα της 3-(3-αλκυλαμινο-2-υδροξυπροποξυ)-οιστρόνης και μελετήθηκε η ανταγωνιστική δράση τους στους β-αδρενεργικούς υποδοχείς.

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SHORT PAPER

AMINOÉTHERS DE QUELQUES ARYLADAMANTANOLS

G.FYTAS, N.KOLOCOURIS, G.B.FOSCOLOS et N.POULI

Laboratoire de Pharmacie Chimique
Univercité d'Athènes, 104, rue Solonos, 10680, Athènes, Grèce

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PARTIE THÉORIQUE

La synthèse de dérivés 5 a été effectuée suivant le schéma 1. Comme matière première nous avons utilisé l'adamantanone-2 1 qui par action de bromures d'aryls et de magnésium fournit les aryls-2 adamantanols-2 2 . La transformation des alcools 2 en aminoéthers 4 est réalisée suivant deux méthodes différentes. Selon la première les alcools 2 réagissent avec l'hydrure de sodium pour donner les alcoxydes correspondants; ces derniers réagissent avec les chlorures des dialkylaminoalkyles suivant un mécanisme S_N2 pour donner les aminoéthers 4 .

Key words : 2-(Dialkylaminoalkoxy)-2-aryladamantanes, cleavage in acidic media, antimicrobial testing of.

INTRODUCTION

Il est prouvé que l'introduction du noyau adamantanique dans certaines molécules est souvent intéressante au point de vue pharmacologique. Ainsi nous observons fréquemment l'apparition d'une activité antivirale et anticancéreuse [1-5] et plus rarement d'une activité antimicrobienne [6-9]. Dans le cadre de nos recherches sur la synthèse de dérivés adamantaniques pourvus de propriétés pharmacologiques, nous avons synthétisé quelques sels iodométhyliques d' aminoéthers dérivés de l'adamantane de formule générale 5 afin d'étudier leur activité antimicrobienne éventuelle.

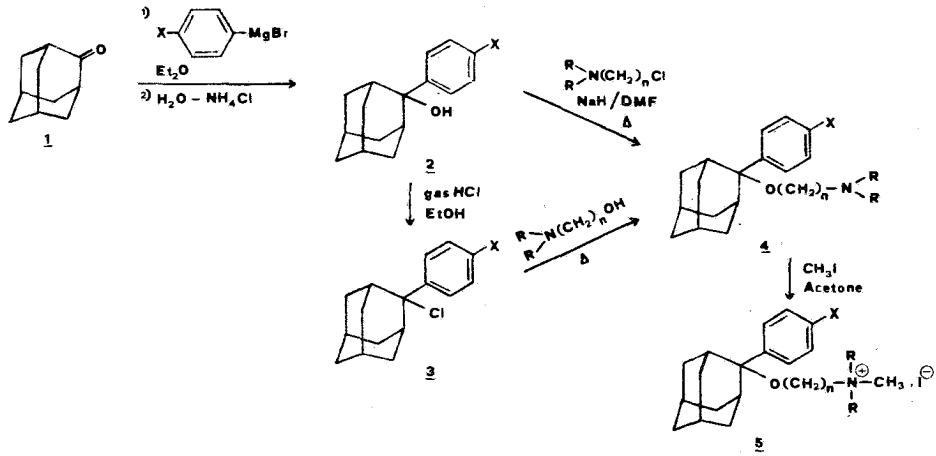


SCHÉMA 1

Selon la deuxième méthode les alcools 2 sont transformés en chlorures 3 avec une solution éthanolique saturée d'acide chlorhydrique gaseux. Ces chlorures 3 réagissent avec un excès d'un dialkylaminoalkanol et fournissent suivant un mécanisme S_N1 les aminoéthers 4 . Enfin les aminoéthers 4 sont transformés en sels iodométhyliques 5 selon les méthodes courantes.

Des efforts pour la préparation des chlorhydrates des bases 4 à l'aide d'une solution éthanolique ou éthérée d' acide chlorhydrique gaseux ont conduit à une décomposition des aminoéthers et formation des chlorures 3 . Par ailleurs, un traitement des aminoéthers 4 avec une solution aqueuse diluée d'acide chlorhydrique fournit les alcools 2 . Il paraît donc que les aminoéthers 4 présentent une instabilité en milieu acide qui est due à leur décomposition facile selon un mécanisme S_N1 (schéma 2). Cette décomposition facile pourrait se mettre en relation avec l'empêchement stérique qui est observé entre les groupements aryle et dialkylaminoalcoxy. Ce point de vue est renforcé par le déplacement chimique du groupement CH_2O au spectre RMN (δ: 2.93-2.97 ppm). Il paraît donc que l'impossibilité de rotation du noyau benzénique est

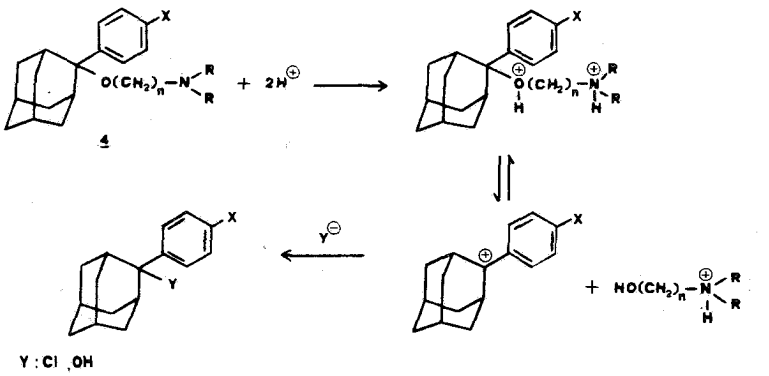


SCHÉMA 2

à l'origine de l'influence des protons CH_2O par sa zone de protection diamagnétique.

L'étude de l'activité antimicrobienne a été réalisée [10] sur les iodométhylates 5 en évaluant la concentration minimum inhibitrice (C.M.I.) selon la technique des dilutions en milieu gélosé [11]. Les espèces bactériennes utilisées sont : Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus, Streptococcus faecalis et Escherichia coli. Aucun de produits testés n'a révélé une C.M.I. < 1mg/ml tandis que la plus forte activité a été présentée par le dérivé 5h vis à vis de l' Escherichia coli avec une C.M.I. de l'ordre de 1.5 mg/ml.

PARTIE EXPÉRIMENTALE

Les points de fusion ont été pris à l'appareil de Büchi et ne sont pas corrigés. Les spectres I.R. ont été enregistrés sur un appareil Perkin-Elmer 177. Les spectres RMN ont été réalisés sur un appareil Varian FT-80A en utilisant le TMS comme référence interne. Les microanalyses ont été réalisées au Service Central de Microanalyse du C.N.R.S.

Phényl-2 adamantanol-2 [11] 2 (X=H)

Dans une solution agitée de bromure de phényl et de magnésium préparé à partir de 1.58 g (0.066 gratom) de tournures de magnésium et de 10.36 g (0.066 Mole) de bromobenzène dans 120 ml d'éther anhydre, on ajoute au goutte à goutte et sous

atmosphère d'azote une solution de 5 g d'adamantanone-2 1 (0.0033 Mole) dans 60 ml d'éther anhydre. Le mélange réactionnel est agité pendant 24 h et par la suite hydrolysé avec une solution saturée de chlorure d' ammonium. La couche éthérée est separée lavée à l'eau, au NaOH à 10 % et de nouveau à l'eau, séchée sur Na_2SO_4 et évaporée. Le résidu cristallise dans un mélange éther-n-pentane.
F: 80-81° C, Rdt: 6.25 g (82 %), **I.R.** (Nujol): ν(OH) 3420 et 3300 cm^{-1}, **RMN-^{1}H** ($CDCl_3$) δ ppm: 1.48-1.92 (m, 11H, H-adamantaniques, OH) 2.32 (s,1H, H-adamantaniques) 2.5(s.large, 3H, H-adamantaniques) 7.15-7.65 (m, 5H, C_6H_5).

En utilisant la même méthode nous avons préparé les alcools suivants:

(p-Fluorophényl)-2 adamantanol-2 2 (X=F)

F: 83° C (n-pentane), Rdt: 90 %, **I.R.** (Nujol): ν(OH) 3589 et 3430 cm^{-1}. **RMN-^{1}H** ($CDCl_3$) δ ppm: 1.45-1.95 (m, 11H, H-adamantaniques, OH) 2.20-2.57 (m, 4H, H-adamantaniques) 6.80-7.57 (dm, 4H, C_6H_4). **Analyse** ($C_{16}H_{19}FO$): % Calc.C:78.01, H:7.78, F:7.71, % Tr.C:77.89, H:7.75, F:7.90.

(p-Méthylphényl)-2 adamantanol-2 2 (X=CH_3)

F: 72° C (n-pentane), Rdt:86 %, **I.R.** (Nujol): ν(OH) 3470, 3300 cm^{-1}, **RMN-^{1}H** ($CDCl_3$) δ ppm : 1.40-1.90 (m, 11H, H-adamantaniques, OH) 2.30 (s, 3H, CH_3) 2.12-2.55 (m, 4H, H-adamantaniques) 6.92-7.42 (q, 4H, AA'BB', $J_{AA'}=J_{BB'}$=OHz, $J_{AB}=J_{A'B'}$=8Hz, C_6H_4), **Analyse** ($C_{17}H_{22}O$): % Calc. C:84.25, H:9.15 % Tr. C:84.05, H:9.17.

Chloro-2 phényl-2 adamantane 3 (X=H)

2 g (0.0088 Mole) de phényl-2 adamantanol-2 (X=H) sont traités avec 40 ml d'une solution éthanolique saturée d'acide chlorhydrique gaseux. Le mélange réactionnel est agité pendant 24 h à la température ambiante, l'éthanol est chassé sous vide et dans le résidu on ajoute de l'eau. On extrait à l'éther, lave les couches éthérées unies à l'eau, sèche sur Na_2SO_4 et évapore le solvant. Le dérivé chloré cristallise

dans le n-pentane.
F: 69° C, Rdt:1.95 g (90 %), **RMN-^{1}H** ($CDCl_3$) δ ppm : 1.50-2.00 (m, 10H, H-adamantaniques) 2.40-2.95 (m, 4H, H-adamantaniques) 7.00-7.56 (m, 5H, $C_6\underline{H}_5$), **Analyse** ($C_{16}H_{19}Cl$): % Calc. C:77.87,H:7.76, % Tr. C:77.52,H:7.82.

Chloro-2 (p-fluorophényl)-2 adamantane 3 (X=F)

Il est préparé comme le dérivé précédent.
F: 62° C (n-pentane), Rdt: 92 %, **RMN-^{1}H** ($CDCl_3$) δ ppm : 1.52-2.01 (m, 10H, H-adamantaniques) 2.41-2.96 (m, 4H, H-adamantaniques) 6.85-7.58 (dm, 4H, $C_6\underline{H}_4$), **Analyse** ($C_{16}H_{18}ClF$): % Calc. C:72.58,H:6.85, % Tr. C:72.50,H:6.90.

Chloro-2 (p-méthylphényl)-2 adamantane 3 (X=CH_3)

2 g (0.0083 Mole) de (p-méthylphényl)-2 adamantanol-2 2 (X=CH_3) et 60 ml d'une solution éthanolique saturée d'acide chlorhydrique gaseux sont chauffés à l'ebullition jusqu'à dissolution du produit. Le mélange réactionnel est par la suite évaporé jusqu'à la moitié de son volume. Le dérivé chloré qui précipite en refroidissant est filtré et recristallisé dans le n-pentane.
F: 100° C, Rdt: 1.85 g (86 %), **RMN-^{1}H** ($CDCl_3$) δ ppm : 1.35-2.10 (m, 10H, H-adamantaniques) 2.28 (s, 3H, $C\underline{H}_3$) 2.30-3.00 (dm, 4H, H-adamantaniques) 6.84-7.40 (q, 4H, AA'BB', $J_{AA'}=J_{BB'}=0Hz$, $J_{AB}=J_{A'B'}=8Hz$, $C_6\underline{H}_4$), **Analyse** ($C_{17}H_{21}Cl$): % Calc. C:78.29,H:8.12, % Tr. C:78.39,H:8.09.

Iodométhylates des (dialkylaminoalkoxy)-2 aryl-2 adamantanes 5

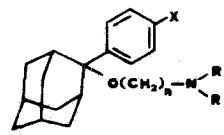
Méthode A : Dans une solution agitée de 0.017 Mole d'aryl-2 adamantanol-2 2 dans 60 ml de DMF anhydre et sous atmosphère d'azote on ajoute en petites quantités 1.68 g (0.035 Mole) d'hydrure de sodium à 55 % dans l'huile minérale et préalablement lavé à l'hexane. Le mélange est agité vers 50° C pendant 1 h et par la suite on ajoute 0.017 Mole de chlorhydrate de chlorure de dialkylaminoalkyle correspondant. L'agitation est poursuivie pendant 10 h vers 70-80°C, puis le melange réactionnel est versé dans un excès d'eau-glace. On extrait à l'éther et les couches éthérées unies sont la-

vées à l'eau et séchées sur Na_2SO_4. Après évaporation du solvant on obtient un résidu huileux qui est transformé en iodométhylate par dissolution dans l'acétone, addition d'un excès d'iodure de méthyle et repos pendant 24 h. Après addition de l'éther, l'iodométhylate qui se forme est filtré et lavé à l'éther.

Méthode B : On chauffe un mélange de 0.008 Mole d'aryl-2 chloro-2 adamantane 3 et de 25ml de dialkylaminoalkanol correspondant vers 130° C pendant 8 h, puis on verse le mélange dans un excès d'eau-glace. On extrait à l'éther et les couches éthérées unies sont lavées à l'eau, séchées sur Na_2SO_4 et evaporées. Le résidu huileux est transformé en iodométhylate suivant la méthode utilisée précédemment.

Les parametres des spectres RMN pour les bases 4 sont présentés dans le tableau I. Les constantes physiques et les analyses sont cités respectivement dans les tableaux II et III

TABLEAU I : Constantes spectroscopiques RMN-^{1}H des (dialkylaminoalcoxy)-2 aryl-2 adamantanes 4



N°	R_2N	n	X	Constantes RMN-^{1}H ($CDCl_3$-δppm)
5a	$(CH_3)_2N$	2	H	1.50-1.98(m, 10H, H adamantaniques), 2.00(s, 6H, $(CH_3)_2N$), 2.07-2.62(m, 6H, H adamantaniques, CH_2N), (2.95(t, 2H, J=6Hz, OCH_2), 7.10-7.50(m, 5H, C_6H_5).
5b	$(C_2H_5)_2N$	2	H	0.94(t, 6H, J=7Hz, 2xCH_3 de Et_2N), 1.42-2.05(m, 10H, H adamantaniques), 2.14-2.67 (m complex, 10H, H adamantaniques, 3xCH_2N), 2.96(t, 2H, J=6Hz, OCH_2), 7.12-7.56(m, 5H, C_6H_5)

TABLEAU I (suite)

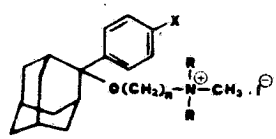
5c		2	H	1.07-1.99(m, 14H, H adamantaniques, H pyrrolidiniques-3,4), 2.08-2.68(m complexe, 10H, H adamantaniques, H pyrrolidiniques-2,5, CH_2N), 2.94(t, 2H, J=6Hz, OCH_2), 7.15-7.60 (m, 5H, C_6H_5).
5d		2	H	1.25-2.02(m, 16H, H adamantaniques, H pipéridiniques-3,4,5), 2.09-2.69(m complexe, 10H, H adamantaniques, H pipéridiniques-2,6, CH_2N), 2.95(t, 2H, J=6Hz, OCH_2), 7.13-7.61 (m, 5H, C_6H_5).
5e		2	H	1.47-2.00(m, 10H, H adamantaniques), 2.06-2.65(m complexe, 10H, H adamantaniques, H morpholiniques-3,5, CH_2N), 2.93(t, 2H, J=6Hz, OCH_2), 3.67(t, 4H, H morpholiniques-2,6), 7.09-7.58(m, 5H, C_6H_5).
5f	$(CH_3)_2N$	2	F	1.51-1.97(m, 10H, H adamantaniques), 2.01 (s, 6H, $(CH_3)_2N$), 2.10-2.68(m complexe, 6H, H adamantaniques, CH_2N), 2.93(t, 2H, J=6Hz, OCH_2), 6.83-7.52(dm, 4H, C_6H_4).
5g	$(CH_3)_2N$	2	CH_3	1.52-1.98(m, 10H, H adamantaniques), 2.02 (s, 6H, $(CH_3)_2N$), 2.10-2.66(m complexe, 6H, H adamantaniques, CH_2N), 2.29(s, 3H, p-CH_3), 2.96(t, 2H, J=6Hz, OCH_2), 6.87-7.38(q, 4H, AA'BB', $J_{AA'}=J_{BB'}=0Hz$, $J_{AB}=J_{A'B'}=8Hz$, C_6H_4).
5h		2	CH_3	1.26-2.03(m, 16H, H adamantaniques, H pipéridiniques-3,4,5), 2.10-2.67(m complexe, 10H, H adamantaniques, H pipéridiniques-2,6, CH_2N), 2.31(s, 3H, CH_3), 2.97(t, 2H, J=6Hz, OCH_2), 6.85-7.40(q, 4H, AA'BB', $J_{AA'}=J_{BB'}=0Hz$, $J_{AB}=J_{A'B'}=8Hz$, C_6H_4).
5i	$(CH_3)_2N$	3	H	1.30-2.00(m,12H, H adamantaniques, CH_2CH_2N), 2.09(s, 6H, $(CH_3)_2N$), 2.12-2.68(m complexe, 6H, H adamantaniques, CH_2N), 2.94(t, 2H, J=6Hz, OCH_2), 7.09-7.57(m, 5H, C_6H_5).

TABLEAU I (suite)

5j $(C_2H_5)_2N$ 3 H 0.96(t, 6H, J=7Hz, 2xCH_3 de Et_2N), 1.32-2.08(m, 12H, H adamantaniques, CH_2CH_2N), 2.12-2.68(m complex, 10H, H adamantaniques, 3xCH_2N), 2.97(t, 2H, J=6Hz, OCH_2), 7.11-7.60(m, 5H, C_6H_5).

5k $(CH_3)_2N$ 3 F 1.34-2.01(m,12H, H adamantaniques, CH_2CH_2N) 2.08(s, 6H, $(CH_3)_2N$), 2.11-2.69 (m complex, 6H, H adamantaniques, CH_2N), 2.94(t, 2H, J=6Hz, OCH_2), 6.83-7.49 (dm, 4H, C_6H_4).

TABLEAU II : Iodométhylates des (dialkylaminoalcoxy)-2 aryl-2 adamantanes 5



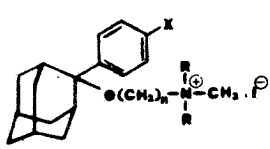
N°	R_2N	n	X	Rdt%	F°C (°C)
5a	$(CH_3)_2N$	2	H	50[a] (81)[b]	191
5b	$(C_2H_5)_2N$	2	H	52[a] (80)[b]	164-165(déc.)
5c		2	H	69[b]	188-190(déc.)
5d		2	H	70[a]	203-204(déc.)
5e		2	H	56[a] (82)[b]	218
5f	$(CH_3)_2N$	2	F	49[a] (77)[b]	228
5g	$(CH_3)_2N$	2	CH_3	51[a] (79)[b]	137

TABLEAU II (suite)

5h		2	CH_3	72[a]	230-232(déc.)
5i	$(CH_3)_2N$	3	H	30[a] (74)[b]	206
5j	$(C_2H_5)_2N$	3	H	70[b]	126-128
5k	$(CH_3)_2N$	3	F	32[a] (73)[b]	179

[a] Rdts obtenus par la méthode A
[b] " " " " " B
[c] Recristallisation dans l'acétone-éther

TABLEAU III : Iodométhylates des (dialkylaminoalcoxy)-2 aryl-2 adamantanes 5



N°	R_2N	n	X	Formule	Analyse % Calc. C	H	I	N	% Tr. C	H	I	N
5a	$(CH_3)_2N$	2	H	$C_{21}H_{32}INO$	57.14	7.31	28.75	3.17	56.92	7.37	28.90	3.14
5b	$(C_2H_5)_2N$	2	H	$C_{23}H_{36}INO$	58.84	7.73	27.03	2.98	58.52	7.90	26.85	3.12
5c		2	H	$C_{23}H_{34}INO$	59,10	7.33	27.15	3.00	59.24	7.28	27.00	3.08
5d		2	H	$C_{24}H_{36}INO$	59.87	7.54	26.36	2.91	59.92	7.57	26.26	2.80
5e		2	H	$C_{23}H_{34}INO_2$	57.14	7.09	26.25	2.90	57.47	7.20	26.04	2.78

TABLEAU III (suite)

5f	$(CH_3)_2N$	2	F	$C_{21}H_{31}FINO$	54.90	6.80	27.63	3.05	54.92	6.84	27.57	3.01
5g	$(CH_3)_2N$	2	CH_3	$C_{22}H_{34}INO$	58.02	7.53	27.87	3.08	58.00	7.36	27.95	3.26
5h		2	CH_3	$C_{25}H_{36}INO$	60.23	7.68	26.06	2.81	60.42	7.72	26.20	2.98
5i	$(CH_3)_2N$	3	H	$C_{22}H_{34}INO$	58.02	7.53	27.87	3.08	57.97	7.45	28.06	3.20
5j	$(C_2H_5)_2N$	3	H	$C_{24}H_{38}INO$	59.62	7.92	26.25	2.90	59.32	7.75	26.36	2.69
5k	$(CH_3)_2N$	3	F	$C_{22}H_{33}FINO$	55.81	7.03	26.80	2.96	55.98	6.99	26.72	3.07

Décomposition des aminoéthers 4 en milieu acide

On dissout 1g de base 4 dans 100 ml d'éther anhydre, puis ajoute au goutte à goutte une solution éthanolique saturée d'acide chlorhydrique gaseux jusqu'à pH acide. Après agitation du mélange pendant 15 min on ajoute de l'eau, sépare la couche éthérée et séche sur Na_2SO_4. Après évaporation du solvant le résidu cristallise dans le n-pentane. Les spectres IR et RMN sont identiques à ceux du chlorure authentique 3 . Rendement: quantitatif.

D'une manière analogue le traitement des bases 4 avec l'acide chlorhydrique à 5 % suivie par une extraction à l'éther conduit presque quantitativement à l'alcool 2 correspondant.

RÉSUMÉ

On décrit la synthèse de quelques (dialkylaminoalcoxy)-2 aryl-2 adamantanes et leur décomposition en milieu acide. Leur étude antimicrobienne a révélé une faible activité vis à vis des espèces : Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus, Streptococcus faecalis et Escherichia coli, le plus actif étant le composé 5h vis à vis de la dernière espèce.

SUMMARY

Aminoethers of aryladamantanols

In this paper the synthesis of some 2-(dialkylaminoalkoxy)-2-aryladamantanes and their cleavage in acidic media are described. The antimicrobial testing of their methiodides showed a weak activity against : Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus, Streptococcus faecalis and Escherichia coli. The highest activity was observed for the product 5h against Escherichia coli.

ΠΕΡΙΛΗΨΗ

Αμινοαιθέρες αρυλαδαμανταναλών

Περιγράφεται η σύνθεση 2-(διαλκυλαμινοαλκοξυ)-2-αρυλαδαμαντανίων κι η διάσπασή τους σε όξινο περιβάλλον. Ο αντιμικροβιακός έλεγχος των ιωδομεθυλικών αλάτων τους έδειξε ασθενή δράση έναντι στελεχών των : Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus, Streptococcus faecalis και Escherichia coli. Τη μεγαλύτερη δράση εμφανίζει το προϊόν 5h έναντι του Escherichia coli.

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SHORT PAPER

DIARYLMORPHOLINES - ANALOGUES CYCLIQUES DE LA DIPHÉNHYDRAMINE

G.B. FOSCOLOS, G. FYTAS, A. VYZAS et S. GAROYFALIAS

Laboratoire de Pharmacie Chimique
Université d' Athènes. 104 Rue Solonos, G.R. 106 80, Athènes. GRÈCE.

J. BASTIDE et P. BASTIDE

Laboratoire de Pharmacologie et Pharmacie Clinique*, Faculté de Pharmacie, Clermont-Ferrand FRANCE.
* Avec la collaboration technique de Anne-Marie PRIVAT.

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INTRODUCTION

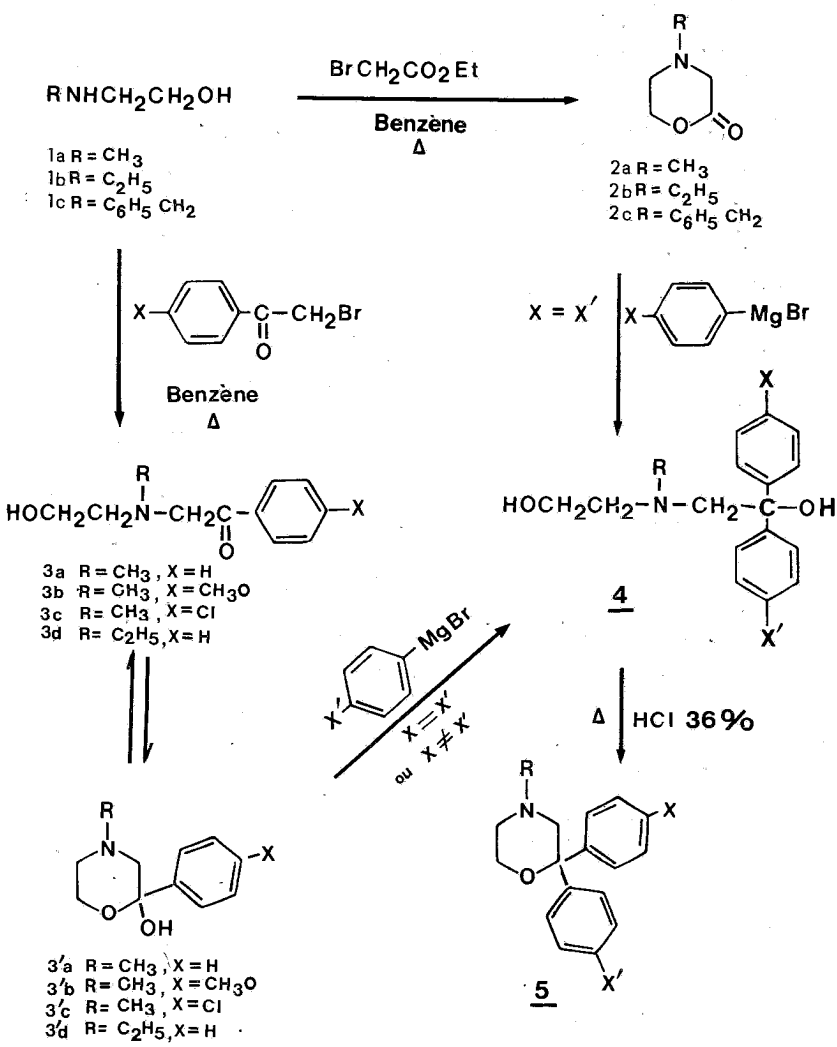
Dans ce travail nous décrivons la synthèse de quelques diaryl-2,2, morpholines 5 ,analogues cycliques des antihistaminiques du type de la Diphénhydramine. Cette synthèse a été réalisée afin d'étudier l'activité pharmacologique des dérivés antihistaminiques de l'éthanolamine sous forme cyclique.

Key words. 4-Substituted 2,2-diarylmorpholines-antihistaminic and antiallergic testing of

CHIMIE

La synthèse du produit 5a (X=X'=H, R:CH_3) a déjà été effectuée par action de N-méthyléthanolamine sur le diphényl-2,2 oxirane et cyclisation de l'aminodiol intermédiaire 4a au sein de l'acide sulfurique[1]. Dans ce mémoire nous avons réalisé la synthèse des morpholines 5 suivant deux méthodes différentes qui sont résumées dans le Schéma 1 .

La première méthode peut être utilisée uniquement pour la préparation des diaryl-2,2 morpholines 5 avec les mêmes aryles (X = X') et comprend l'action du bromacétate d'éthyle sur les éthanolamines N-substituées 1 en fournissant les morpholones-2 2 [2,3]. La transformation des morpholones 2 en morpholines 5 est réalisée par l'action de bromure d'aryle et de



SCHEMA I

magnésium correspondant. Nous obtenons ainsi les β,β-diaryl-diéthanolamines 4 avec les mêmes aryles (X = X') qui se cyclisent dans l'acide chlorhydrique à l'ebullition en morpholines 5 (X = X').

La deuxième méthode est générale est peut être appliquée pour la préparation des morpholines 5 avec les mêmes ou dif-

férents aryles (X = X' ou X ≠ X'). Cette méthode comprend l'action des bromures des phénacyles sur les éthanolamines N-substituées 1 correspondants ; elles se forment les N-phénacyléthanolamines 3 [4,5]. Ces aminohydroxycétones 3 se trouvent en equilibre avec les hémicétals cycliques 3' .Plus specialement pour le cas des dérivés 3a (R:CH_3, X:H), 3c (R:CH_3, X:Cl) et 3d (R:C_2H_5, X:H) l'équilibre 3 ⟷ 3' parait être pratiquement déplacé vers la direction des hémicétals cycliques 3'a , 3'c et 3'd , ce qui est prouvé par l'absence totale de l'absorption du carbonyle à l' I.R.

Dans le cas du dérivé 3b (R:CH_3, X:CH_3O) le spectre IR présente à la fois l'absorption de la fonction hydroxyle et carbonyle, tandis que le spectre RMN une double absorption de N-méthyle, ce qui nous amène à la conclusion qu'il s'agit d'un mélange des 3b et 3'b . Il parait donc que le phénomene + R de la fonction méthoxy affaiblit le caractère électrophile du carbone du carbonyle du dérivé 3b et par conséquent la formation de l'hémicétal 3'b cyclique est moins étendue.

L'action des bromures d'aryles et de magnésium sur les dérivés 3 ou 3' fournit les diaryldiéthanolamines 4 , qui par chauffage dans l'acide chlorhydrique concentré sont cyclisées en morpholines 5 .

RÉSULTATS ET CONCLUSION

L'évaluation de l'activité antihistaminique qui a été effectuée sur l'iléon isolé de cobaye a montré que les chlorhydrates des diaryl-2,2, morpholines 5 présentent une très faible activité antihistaminique-environ 10^3 fois moins actives que le maléate de Mépyramine. Il se conçoit donc que la structure cyclique du squelette de l'éthanolamine entraîne une diminution substantielle de l'activité.

Les chlorhydrates des diaryl-2,2 , morpholines 5 ont été aussi testés pour une éventuelle activité antiallergique; le test de l'anaphylaxie cutanée passive (ACP) a montré que seul le produit 5a (R:CH_3, X=X'=H) présente une légère activité antiallergique-environ 35 fois plus faible de celle de Cromoglycate disodique, tandis que les autres produits 5 se com-

portent, au contraire, comme allergisants.

PROTOCOLES EXPÉRIMENTAUX

CHIMIE

Les points de fussion ont été déterminés dans les tubes capillaires de l'appareil de Büchi et ils ne sont pas corrigés. Les analyses élémentaires ont été réalisées par le Centre de Microanalyse du C.N.R.S. (France). Les spectres IR ont été obtenus avec le spectrophotomètre Perkin-Elmer 177 et les spectres RMN-^{1}H avec le spectrophotomètre Varian FT-80A dans $CDCl_3$ en utilisant le TMS comme référence interne.

Méthyl-4, morpholone-2. 2a

46.8g (0.28 mole) de bromacétate d'éthyle sont ajoutés au goutte à goutte et sous agitation dans une solution de 42g (0.56 mole) de N-méthyléthanolamine 1a dans 300 ml de benzène anhydre. Après reflux pendant 8 hrs, la couche benzénique est evaporée sous pression réduite et le résidu distillé.
Eb:112-114°C/15mm Rdt:12g (38%). IR (film) ν(C=O) 1740 cm^{-1}.

En utilisant la même méthode nous avons préparé les morpholones 2b :Eb:114-116°C/12mm. Rdt: 83% et le 2c :Eb:133-138°C/0.02mm. Rdt:60%.

Méthyl-4, phényl-2, morpholinol-2. 3'a [4] (R:CH_3, X:H)

Ce dérivé se prépare d'une manière analogue que les morpholones 2 en faisant réagir le bromure de phénacyle avec une quantité bimoléculaire de N-méthyléthanolamine au sein de benzène anhydre. F:53-54°C (éther-n-pentane). Rdt:52%.
IR (Nujol):ν(OH) 3410-3380 cm^{-1}.

Méthyl-4, (p-méthoxyphényl)-2, morpholinol-2. 3'b (R:CH_3, X:CH_3O)

Liquide visqueux qui se décompose pendant sa distillation Rdt:80%. IR (film) ν (OH) 3480-3280 cm^{-1}. ν(C=O) 1675 cm^{-1} RMN-^{1}H , δ(ppm) : 2.10-2.25 (d, $C\underline{H}_3N$), 2.02-2.82(m, H-5, H-3, $C\underline{H}_2N$), 3.38-4.35 (m, H-6, $C\underline{H}_2CO$, $C\underline{H}_2OH$), 3.73-3.75 (d, $C\underline{H}_3O$) 7.20-7.58 (dq, $C_6\underline{H}_4$).

Méthyl-4, (p-chlorophényl)-2, morpholinol-2, 3'c (R:CH_3, X:Cl)
F:89-91°C (éther-n-pentane). Rdt:76% **IR** (Nujol): ν (OH) 3390 cm^{-1}. **RMN-^{1}H** δ(ppm): 2.25 (s, 3H, CH_3), 2.05-2.40 (m, 2H, H-5), 2.55-2.80 (m, 2H, H-3), 3.75-4.30 (m, 2H, H-6), 4.82 (s, 1H, OH), 7.20-7.52 (q, 4H, AA'BB', $J_{AA'}=J_{BB'}$=OHz, $J_{AB}=J_{A'B'}$=11Hz, C_6H_4) **Analyse** ($C_{11}H_{14}ClNO_2$) : % Calc. C:58.02, H:6.20, Cl:15.57, N:6.15. % Tr. C:57.94, H:6.31, Cl:15.69, N:6.23.

Éthyl-4, phényl-2, morpholinol-2. 3'd =(R:C_2H_5, X:H)
F:52-53°C (éther-n-pentane). Rdt:70%. **IR** (Nujol): ν(OH) 3410-3390 cm^{-1}.

β,β'-Diaryldiéthanolamines N-substituées 4

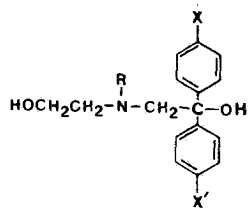
Dans une solution agitée de bromure d'arylmagnésium préparée à partir de 5g (0.21 gratom) de tournures de magnésium et de 0.22 mole de bromure d'aryle dans 300 ml d'éther anhydre, on ajoute au goutte à goutte et sous atmosphère d'azote une solution de 0.065 mole de morpholone-2 2 ou de morpholinol-2 3 correspondant dans 100 ml d'éther anhydre. Le mélange est agité pendant 6 hrs, puis hydrolysé avec une solution saturée de NH_4Cl. La couche étherée est lavée à la soude à 10% et à l'eau, séchée sur Na_2SO_4 et évaporée. Le résidu est recristallisé dans un mélange éther-n-pentane.

Dans le tableau I on trouve les constantes physiques et les rendements des aminodiols 4 ; dans le tableau II sont cités les paramètres spectroscopiques en IR et en RMN-^{1}H.

Diaryl-2,2 morpholines 5

0.019 mole de β,β'-diaryldiéthanolamine 4 sont traités avec 80 ml d'acide chlorhydrique concentré. Le mélange est chauffé à reflux pendant 1,5-2 hrs. Après dilution avec de l'eau ce mélange est lavé à l'éther et la phase aqueuse est alcalinisée avec du Na_2CO_3 solide. La base liberée est extraite à l'éther et les couches éthérées unies sont lavées à l'eau, séchées sur Na_2SO_4 et évaporées. Le résidu huileux est

TABLEAU I: β,β'-Diaryldiéthanolamines N-substituées



No	R	X	X'	Rdt %	F(°C)[a]	Formule brute	Analyse %Calc. C	H	N	%Tr. C	H	N
4a	CH_3	H	H	63	112-113	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.30	7.78	5.10
4b	CH_3	CH_3O	H	75	huileux	$C_{18}H_{23}NO_3$[b]	---	--	--	---	--	--
4c	CH_3	Cl	H	98	96-98	$C_{17}H_{20}ClNO_2$	66.77	6.59	4.58	66.87	6.59	4.50
4d	CH_3	CH_3O	CH_3O	82	huileux	$C_{19}H_{25}NO_4$[b]	---	--	--	---	--	--
4e	C_2H_5	H	H	78	60-62	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.64	8.11	4.84
4f	$C_6H_5CH_2$	H	H	89	105-107	$C_{23}H_{25}NO_2$	79.50	7.25	4.03	79.59	7.18	4.09

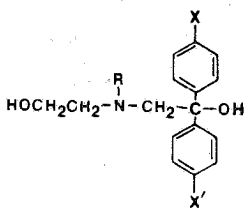
[a] Recristallisation dans l'éther-n-pentane

[b] il se décompose durant la distillation; chlorhydrate hygroscopique

chromatographié sur colonne d'alumine neutre en utilisant un mélange éther-hexane 1:1 comme solvant d'élution.

Les constantes physiques, les analyses et les paramètres des spectres RMN-^{1}H pour les morpholines 5 sont présentés réspectivement dans les tableaux III, IV et V.

TABLEAU II : Constantes spectroscopiques des β,β'-Diaryldiéthanolamines N-substituées 4



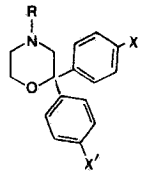
N°	R	X	X'	IR ν(OH)cm⁻¹	RMN-¹H [CDCl₃-δ(ppm)]
4a	CH_3	H	H	3410[a], 3280	2.0(s, 3H, CH_3N), 2.45(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.24(s, 2H, Ph_2C-CH_2N), 3.25-4.50(s large, 1H, OH), 3.40(t, 2H, J=7Hz. $HOCH_2CH_2N$), 7.05-7.50 (m, 10H, 2xC_6H_5), 7.20-8.50(s large, 1H, OH)
4b	CH_3	CH_3O	H	3410-3300[b]	2.0(s, 3H, CH_3N), 2.46(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.26(s, 2H, Ar_2C-CH_2N), 3.27-4.52(s large, 1H, OH), 3.41(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.76(s, 3H, p-CH_3O), 6.60-7.50(m, 9H, H aromatiques), 7.22-8.54(s large, 1H, OH).
4c	CH_3	Cl	H	3367[a]	2.0(s, 3H, CH_3N), 2.46(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.25(s, 2H, Ar_2C-CH_2N), 3.25-4.51(s large, 1H, OH), 3.41(t, 2H, J=7Hz, $HOCH_2CH_2N$), 7.04-7.60(m, 9H, H aromatiques), 7.20-8.46 (s large, 1H, OH).
4d	CH_3	CH_3O	CH_3O	3480-3242[b]	2.01(s, 3H, CH_3N),2.48(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.27(s, 2H, Ar_2C-CH_2N), 3.28-4.53(s large, 1H, OH), 3.43(t, 2H, J=7Hz, $HOCH_2CH_2N$), 3.75(s, 6H, 2xp-CH_3O),6.62-7.40(q,8H,AA'BB', $J_{AA'}=J_{BB'}=0$ Hz $J_{AB}=J_{A'B'}=8Hz$, 2xC_6H_4), 7.15-8.20 (s large, 1H, OH).
4e	C_2H_5	H	H	3465[a], 3345-3140	1.02(t,3H, J=7Hz, CH_3CH_2N),2.50(m, 4H, CH_3CH_2N, $HOCH_2CH_2N$), 3.26(s, 2H, Ph_2C-CH_2N), 3.27-4.52 (s large 1H, OH),3.42(t, 2H, J=7Hz, $HOCH_2CH_2N$), 7.08-7.53(m, 10H, 2xC_6H_5), 7.22-8.40 (s large, 1H, OH).

TABLEAU II (suite)

4f	$C_6H_5CH_2$	H	H	3420-3200[a]	2.63(t, 2H, J=7Hz, $HOCH_2\underline{CH_2}N$), 3.30-4.60(s large. 1H, $\underline{OH}$), 3.44(t, 2H, J=7Hz, $HO\underline{CH_2}CH_2N$), 3.44(s, 2H, $Ph_2C\text{-}\underline{CH_2}N$), 3.51(s, 2H, $C_6H_5\underline{CH_2}N$), 6.95-7.65 (m, 15H, $3XC_6\underline{H_5}$), 7.25-8.60(s large, 1H, $\underline{OH}$).

[a]: Nujol, [b]: Film

TABLEAU III : Diaryl-2,2 morpholines 5



N°	R	X	X'	Rdt%	F(°C) des bases	F(°C)[a] des chlorhydrates
5a	CH_3	H	H	90	76-78[b]	280-282
5b	CH_3	CH_3O	H	60	87-89[c]	227-229
5c	CH_3	Cl	H	65	92-94[b]	275-277
5d	CH_3	CH_3O	CH_3O	45	98-100[b]	241-242
5e	C_2H_5	H	H	61	57-59[c]	234-236
5f	$C_6H_5CH_2$	H	H	50	108-110[b]	---

[a] Recristallisation dans l'éthanol-éther

[b] " " l'éther-n-pentane

[c] " " le n-pentane

MÉTHODES PHARMACOLOGIQUES

Étude de l'activité antihistaminique H_1

L' étude de l'activité antihistaminique est réalisée avec

TABLEAU IV : Diaryl-2,2morpholines 5

N°	R	X	X'	Formule brute des chlorhydrates	Analyses % Calc. C	H	Cl	N	% Tr. C	H	Cl	N
5a	CH_3	H	H	$C_{17}H_{20}ClNO$	70.45	6.96	12.24	4.83	70.40	6.93	12.16	4.90
5b	CH_3	CH_3O	H	$C_{18}H_{21}ClNO_2$	67.60	6.93	11.08	4.38	67.53	6.90	10.99	4.29
5c	CH_3	Cl	H	$C_{17}H_{19}Cl_2NO$	62.97	5,91	21.87	4.32	62.84	5.96	21.55	4.39
5d	CH_3	CH_3O	CH_3O	$C_{19}H_{24}ClNO_3$	65.23	6.92	10.14	4.00	65.22	6.91	10.09	4.04
5e	C_2H_5	H	H	$C_{18}H_{22}ClNO$	71.15	7.30	11.67	4.61	70.98	7.42	11.80	4.38
5f	$C_6H_5CH_2$	H	H	$C_{23}H_{23}NO$ *	83.85	7.04		4.25	83.92	7.08		4.16

* Formule brute de la base

TABLEAU V: Constantes spectroscopiques RMN-^{1}H des Diaryl-2,2 morpholines 5

N°	R	X	X'	Constantes RMN-^{1}H [$CDCl_3$-δ(ppm)]
5a	CH_3	H	H	2.26(s, 3H, CH_3N), 2.40(t, 2H, J=6Hz, H-5), 2.88(s, 2H, H-3), 3.65(t, 2H, J=6H, H-6), 7.10-7.48(m, 10H, 2xC_6H_5).
5b	CH_3	CH_3O	H	2.27(s, 3H, CH_3N), 2.40(t, 2H, J=6Hz, H-5), 2.89 (s, 2H, H-3), 3.67(t, 2H, J=6Hz, H-6), 3.75(s, 3H, p-CH_3O), 6.58-7.51(m, 10H, H aromatiques).
5c	CH_3	Cl	H	2.26(s, 3H, CH_3N), 2.40(~t, 2H, H-5), 2.84(s, 2H, H-3), 3.68(~t, 2H, J=6Hz, H-6), 7.05-7.50(m, 9H, H aromatiques)

TABLEAU V (suite)

5d	CH_3	CH_3O	CH_3O	2.25(s, 3H, CH_3N), 2.42 (~t, 2H, J=6Hz, H-5), 2.82(s, 2H, H-3), 3.73 (~t, 2H, H-6), 3.75 (s, 6H, 2xp-CH_3O), 6.55-7.35(~q, 8H, AA'BB', $J_{AA'}=J_{BB'}=0Hz$, $J_{AB}=J_{A'B'}=8Hz$, 2xC_6H_4)
5e	C_2H_5	H	H	1.08(t, 3H, J=7Hz, CH_3CH_2N), 2.46(m, 4H, CH_3CH_2N, H-5), 2.87(s, 2H, H-3), 3.76(t, 2H, J=6Hz, H-6), 7.08-7.51(m, 10H, 2xC_6H_5).
5f	$C_6H_5CH_2$	H	H	2.49(~t, 2H, J=6Hz, H-5), 2.88(s, 2H, H-3), 3.45(s, 2H, $C_6H_5CH_2N$), 3.67(~t, 2H, J=6Hz, H-6), 6.90-7.50(m, 15H, 3xC_6H_5).

la méthode de Huidobro[6], sur l'iléon isolé de cobaye dans le liquide de Tyrode à une température de 33°C, un utilisant le maléate de Mépyramine comme substance de référence. Les résultats sont résumés dans le Tableau VI.

TABLEAU VI : Activité antihistaminique H_1 des diarylmorpholines 5

Produit N°	DE_{50} (mg dans la cuve de 10ml)	Dose d'Histamine (mcg)
5a	0.19	1
5b	0.08	1
5c	1.07	0.5
5d	0.17	0.5
5e	0.05	1
Mépyramine maléate	0.14×10^{-2}	0.5

Étude de l'activité antiallergique

Pour le contrôle de l'activité antiallergique nous utilisons le test de l'anaphylaxie cutanée passive (ACP) selon la technique de Goose et Blair[7], precisée par Bitteau et Hertz[8]. Des rats mâles de souche iffa Credo OFA d'un poids de 100 à 120 g sont utilisés pour la préparation de l'antisérum. Des animaux de la même souche, mais d'un poids de 200 g mis à

jeûn la veille du test, servent à la titration de l'antisérum et à la recherche d'un effet protecteur. Les produits sont testés après administration i.p. à des doses de 100 mg/Kg. Des lots de 6 animaux sont utilisés pour chaque dose. Le produit de référence utilisé est le Cromoglycate disodique.

Nous indiquons dans le Tableau VII les moyennes arithmétiques M accompagnées de leur intervalle de confiance ΔM au risque 5%. Nous évaluons les pourcentages de variations d'activités après traitement antiallergique, les différences constatées sur les moyennes obtenues, entre les séries de rats témoins et traités in vivo, sont comparées par un test de Student accompagné du risque d'erreur p.

TABLEAU VII Test de l' ACP sur les diarylmorpholines 5 .Résultats moyens comparés

Substances expérimentées	Dose en mg/Kg I.P.	Surface moyenne de l'ellipse en mm^2 M	ΔM	Pourcentage d'inhibition de la réaction	Analyse statistique des résultats
Témoins	-	147.6	19.7	-	-
Cromoglycate disodique	10	89.9	9.5	39.1	p<0.001
5a	100	130.3	11.7	11.7	0.025<p <0.05
5b	100	212.1	17.6	-	p<0.001
5c	100	168.9	19.2	-	0.025<p <0.05
5d	100	285.1	39.2	-	p<0.001
5e	100	184.9	13.3		0.001<p <0.005

RÉSUMÉ

Nous avons préparé des diaryl-2,2 morpholines substituées en-4 5 qui présentent une analogie structurale avec la Diphénhydramine. Le test pharmacologique a montré que les produits 5 présentent une très faible activité antihistaminique et que seul le produit 5a présente une faible activité antiallergique.

SUMMARY

Diarylmorpholines - cyclic analogs of Diphenhydramine

Some 4-substituted 2,2-diarylmorpholines 5 with structural analogy to the Diphenhydramine were prepared. The pharmacological testing of these products showed a very weak antihistaminic action and only for the product 5a a weak antiallergic activity.

ΠΕΡΙΛΗΨΗ

Διαρυλομορφολίνες - κυκλικά ανάλογα της Διφαινυδραμίνης

Παρασκευάσθηκαν μερικές 4-υποκατεστημένες 2,2-διαρυλομορφολίνες 5 με δομική αναλογία προς τη Διφαινυδραμίνη.

Ο φαρμακολογικός έλεγχος απέδειξε πολύ ασθενή αντιϊσταμινική δράση και μόνο για το προϊόν 5α ασθενή αντιαλλεργική ενέργεια.

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