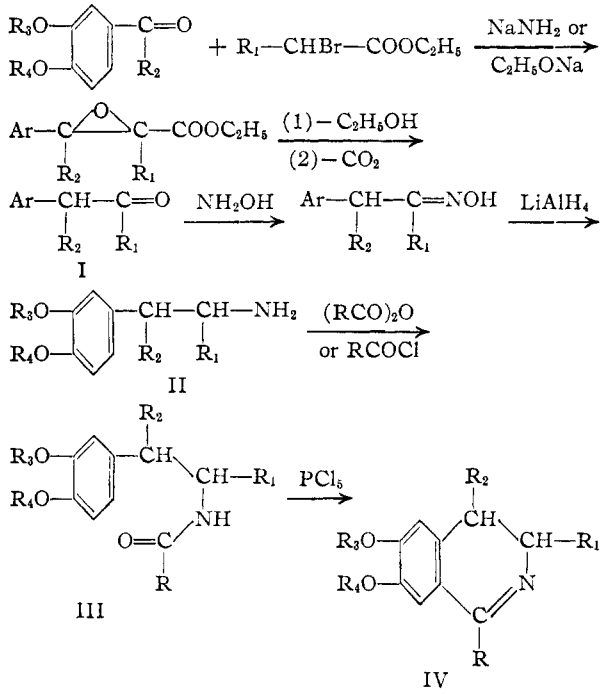
[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Preparation of Some Substituted 3,4-Dihydroisoquinolines[1]

BY ARMIGER H. SOMMERS AND ARTHUR W. WESTON

The synthesis of eleven 3- or 4-methyl-3,4-dihydroisoquinolines with ether substituents in the 6,7-positions, by the Bischler–Napieralski reaction, is described. The branched-chain phenethylamines required as intermediates were prepared by reduction of the corresponding oximes with lithium aluminum hydride. The parent carbonyl compounds were obtained through the Darzens glycidic ester condensation.

Although many 3,4-dihydroisoquinolines having ether substituents in the 6,7-positions have been prepared, little attention has been given the 3- or 4-alkyl derivatives,[2] which may differ significantly in physiological activity from the corresponding non-alkylated dihydroisoquinolines.[3] Eleven such compounds (IV; R is lower alkyl, R_1 and R_2 include hydrogen and methyl, and R_3 and R_4 include methyl and benzyl or *n*-butyl) were prepared by the sequence of reactions



The reactions leading to the intermediate benzyloxymethoxyphenethylamines (II) were used by Robinson and Lowe[4] to synthesize 4-benzyloxy-3-methoxy - α - methylphenethylamine. However, these workers reduced 4-benzyloxy-3-methoxyphenylacetone oxime to the amine with sodium amalgam. We have found that lithium aluminum hydride is a more convenient agent for the reduction of such oximes and that the benzyl ether bond is not cleaved. Publications[5] which appeared after the completion of this work have described the reduction of other oximes with lithium aluminum hydride.

The condensation of substituted benzaldehydes and α-bromo esters occurred in the presence of sodium ethoxide[4] but 4-benzyloxy-3-methoxyacetophenone failed to react under these conditions. Sodamide proved to be an effective catalyst for this reaction.[6]

Basic hydrolysis of the glycidic esters was carried out in aqueous potassium hydroxide[4] or alcoholic sodium ethoxide.[7] Decarboxylation to yield an aldehyde or ketone (I) took place when the resulting acids were heated with copper chromite catalyst[4] or warmed with dilute acid.[7] The carbonyl compounds and their oximes are described in Tables I and II.

Reductions with lithium aluminum hydride were carried out in ether. In some cases the low solubility of the oxime made it necessary to use a continuous extraction technique.[8] The usual isolation procedure for amines which involves extraction from an alkaline aqueous suspension was simplified by the addition of only enough water to completely hydrolyze the reaction mixture. All inorganic material was then removed by filtration and the amine was extracted from the filtrate with dilute acid, regenerated with base and distilled.

One amine which did not contain the benzyl group, 4-*n*-butoxy-3-methoxy-α-methylphenethylamine, was prepared by catalytic hydrogenation of the oxime. Table III describes the amines and their hydrochloride salts.

The amides (III), which are listed in Table IV, were in most cases prepared by acylation of the corresponding amine with an acid anhydride in ether solution or by the Schotten–Baumann procedure. N-Formyl-α-methyl-4-benzyloxy-3-methoxyphenethylamine was obtained by interaction of the amine and formic acid. N-Acetyl-α-methyl-4-*n*-butoxy-3-methoxyphenethylamine was prepared from the amine and acetic anhydride and also by the reaction[9] of O-*n*-butyleugenol with acetonitrile in concentrated sulfuric acid. The latter method could not be extended to the preparation of the corresponding amide from O-benzyleugenol. All the amides possess the 3-methoxy configuration of vanillin with the exception of Compound 10 which has that of iso-vanillin.

The dihydroisoquinolines (IV), all of which were prepared from the corresponding amides by cyclization with phosphorus pentachloride in chloroform,[3]

(1) Presented in part before the Medicinal Division of the American Chemical Society, Cleveland, 1951.

(2) (a) W. S. Ide and J. S. Buck, THIS JOURNAL, **62**, 425 (1940); (b) S. Sugasawa and N. Sugimoto, *J. Pharm. Soc. Japan*, **61**, 62 (1941); *C. A.*, **36**, 92 (1942).

(3) M. B. Moore, H. B. Wright and M. R. Vernsten, private communication.

(4) R. Robinson, A. Lowe and Imperial Chemical Industries, Ltd., British Patent 519,894, April 9, 1940; *C. A.*, **36**, 873 (1942).

(5) (a) F. A. Hochstein, THIS JOURNAL, **71**, 305 (1949); (b) H. Felkin, *Compt. rend.*, **230**, 304 (1950); (c) E. Larsson, *Svensk Kem. Tid.*, **61**, 242 (1949); *C. A.* **44**, 1898 (1950).

(6) C. F. H. Allen and J. Van Allan, *Org. Syntheses*, **24**, 82 (1944).

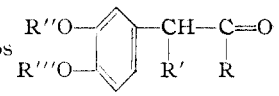
(7) C. F. H. Allen and J. Van Allan, *ibid.*, **24**, 87 (1944).

(8) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(9) J. J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948).

TABLE I

CARBONYL COMPOUNDS



No.	R'''	R''	R'	R	Formula	B.p., °C.	Mm.	Yield, %[a]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	CH_3	$C_6H_5CH_2$	H	CH_3	$C_{17}H_{18}O_3$	175-176[b]	0.4	26	75.53	75.35	6.71	6.84
2	$C_6H_5CH_2$	CH_3	H	CH_3	$C_{17}H_{18}O_3$	192[c]	0.7	50	...	...	..	..
3	$C_6H_5CH_2$	CH_3	CH_3	CH_3	$C_{18}H_{20}O_3$	162-164	0.3	32	76.03	75.96	7.09	7.12
4	$C_6H_5CH_2$	CH_3	CH_3	H	$C_{17}H_{18}O_3$	193-194	1.0	20	75.53	75.28	6.71	6.90
5	$CH_3(CH_2)_3$	CH_3	H	CH_3	$C_{14}H_{20}O_3$	133-138[d]	0.4	30	71.16	71.22	8.53	8.53

[a] Based on the original aldehyde or ketone. [b] M.p. 73-74°. [c] M.p. 60-61° from alcohol-water. Ref. (4) gives m.p. 58°. $n^{25}D$ 1.5149.

TABLE II

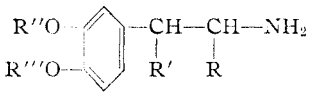
OXIMES

No.	Formula	M.p., °C.	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	$C_{17}H_{19}NO_3$	69-70	71.56	71.63	6.71	6.58	4.91	4.87
		93-94	71.56	71.39	6.71	6.45	4.91	4.96
2	$C_{17}H_{19}NO_3$	118-120[b]	71.56	71.30	6.49	6.71	4.91	4.83
3	$C_{18}H_{21}NO_3$	79.5-80.5	72.21	72.12	7.07	6.95	4.68	4.86
4	$C_{17}H_{19}NO_3$	Oil	...	...	..	..	4.91	4.35[c]
5	$C_{14}H_{21}NO_3$	103.5-104.5	66.90	67.14	8.42	8.29	5.57	5.54

[a] The oximes were recrystallized from aqueous alcohol before analysis. [b] Described by ref. (4) as an oil. [c] Analysis of crude oxime.

TABLE III

SUBSTITUTED PHENETHYLAMINES

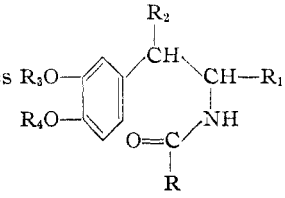


No.	R'''	R''	R'	R	B.p., °C.	Mm.	Yield, %	Hydrochlorides Formula	M.p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	CH_3	$C_6H_5CH_2$	H	CH_3	.....	...	40	$C_{17}H_{22}ClNO_2$	175-177	66.33	66.11	7.21	7.40
2[a]	$C_6H_5CH_2$	CH_3	H	CH_3	172-173	0.3	56	$C_{17}H_{22}ClNO_2$	172-174	66.33	66.16	7.21	7.36
3	$C_6H_5CH_2$	CH_3	CH_3	CH_3	172-175	.4	17	$C_{18}H_{24}ClNO_2$	175-180	67.17	67.64	7.52	7.50
4	$C_6H_5CH_2$	CH_3	CH_3	H	162-166	.3	31	$C_{17}H_{22}ClN_2O$	126-127	66.33	66.66	7.21	7.05
5	$CH_3(CH_2)_3$	CH_3	H	CH_3	133-137[b]	.7	50	$C_{14}H_{24}ClNO_2$	137-139	61.41	61.68	8.84	8.60

[a] This amine is described in ref. (4) as a slightly hygroscopic solid, b.p. 195-196° at 1 mm., m.p. 57-58°. [b] $n^{25}D$ 1.5137.

TABLE IV

SUBSTITUTED N-PHENETHYLAMIDES



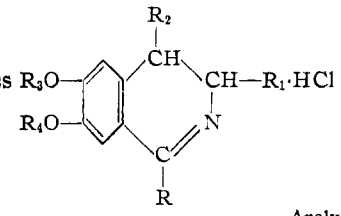
No.	R	R_1	R_2	R_3	R_4	Yield	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	H	CH_3	H	CH_3	$C_6H_5CH_2$	[a]	129-132	$C_{18}H_{21}NO_3$	72.21	72.82	7.07	6.92
2	CH_3	CH_3	H	CH_3	$C_6H_5CH_2$	70	111-112	$C_{19}H_{23}NO_3$	72.81	72.92	7.40	7.32
3	C_2H_5	CH_3	H	CH_3	$C_6H_5CH_2$	75	124-125	$C_{20}H_{25}NO_3$	73.36	73.05	7.70	7.41
4	n-C_3H_7	CH_3	H	CH_3	$C_6H_5CH_2$	91	118-119	$C_{21}H_{27}NO_3$	73.88	74.12	7.97	7.94
5	i-C_3H_7	CH_3	H	CH_3	$C_6H_5CH_2$	51	139-141	$C_{21}H_{27}NO_3$	73.88	74.10	7.97	7.75
6	i-C_4H_9	CH_3	H	CH_3	$C_6H_5CH_2$	76	119-121	$C_{22}H_{29}NO_3$	74.33	74.41	8.22	8.05
7	CH_3	H	CH_3	CH_3	$C_6H_5CH_2$	80	92	$C_{19}H_{23}NO_3$	72.81	73.16	7.40	7.25
8	C_2H_5	H	CH_3	CH_3	$C_6H_5CH_2$	67	95	$C_{20}H_{25}NO_3$	73.36	73.72	7.70	7.61
9	CH_3	CH_3	CH_3	CH_3	$C_6H_5CH_2$	77	125-135	$C_{20}H_{25}NO_3$	73.36	73.76	7.70	7.61
10	CH_3	CH_3	H	$C_6H_5CH_2$	CH_3	75	142-143	$C_{19}H_{23}NO_3$	72.81	72.80	7.40	7.43
11	CH_3	CH_3	H	CH_3	n-C_4H_9	97	85-86	$C_{16}H_{25}NO_3$	68.78	68.82	9.02	8.82

[a] See experimental section.

are described by Table V. The free bases were in most cases oils, and were converted to the crystalline hydrochloride salts. Dilute aqueous solutions of these salts are fluorescent.

TABLE V

SUBSTITUTED 3,4-DIHYDROISOQUINOLINE HYDROCHLORIDES



No.	R	R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	H	CH_3	H	CH_3	$C_6H_5CH_2$	[a]	194	$C_{18}H_{20}ClNO_2$	68.02	68.17	6.34	6.65
2[b]	CH_3	CH_3	H	CH_3	$C_6H_5CH_2$	58	207–208	$C_{19}H_{22}ClNO_2$	68.77	68.69	6.69	6.78
3[c]	C_2H_5	CH_3	H	CH_3	$C_6H_5CH_2$	19	194	$C_{20}H_{24}ClNO_2$	69.45	69.40	6.99	6.67
4	*n*-C_3H_7	CH_3	H	CH_3	$C_6H_5CH_2$	58	165–166	$C_{21}H_{26}ClNO_2$	70.08	70.15	7.28	7.44
5	*i*-C_3H_7	CH_3	H	CH_3	$C_6H_5CH_2$	26	160–162	$C_{21}H_{26}ClNO_2$	70.08	70.15	7.28	7.11
6	*i*-C_4H_9	CH_3	H	CH_3	$C_6H_5CH_2$	18	184–185	$C_{22}H_{28}ClNO_2$	70.66	70.97	7.55	7.26
7	CH_3	H	CH_3	CH_3	$C_6H_5CH_2$	57	191	$C_{19}H_{22}ClNO_2$	68.77	68.94	6.69	6.75
8	C_2H_5	H	CH_3	CH_3	$C_6H_5CH_2$	55	173–174	$C_{20}H_{24}ClNO_2$	69.45	69.62	6.99	6.92
9	CH_3	CH_3	CH_3	CH_3	$C_6H_5CH_2$	11	164–166	$C_{20}H_{24}ClNO_2$	69.45	69.31	6.99	6.88
10[d]	CH_3	CH_3	H	$C_6H_5CH_2$	CH_3	59	191	$C_{19}H_{22}ClNO_2$	68.77	68.53	6.69	7.10
11	CH_3	CH_3	H	CH_3	*n*-C_4H_9	62	155–156	$C_{16}H_{24}ClNO_2$	64.52	64.22	8.12	7.98

[a] See experimental section. [b] Free base m.p. 91–92°. *Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.43; H, 7.17. Found: C, 77.53; H, 7.12. [c] Free base m.p. 99–100°. *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.86; H, 7.49. [d] Free base m.p. 87–88°. *Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.43; H, 7.17. Found: C, 77.49; H, 7.50.

The compounds described in this paper exhibit unexpected and interesting local anesthetic activity, and are undergoing further investigation. We are grateful to Dr. R. K. Richards and members of the Department of Pharmacology for this preliminary report of their findings.

Acknowledgments.—We are indebted to Mr. Morris Freifelder for carrying out the catalytic hydrogenation. We are also grateful to Mr. E. F. Shelberg, Head of the Microanalytical Department, and staff for the analyses reported here.

Experimental

4-Benzyloxy-3-methoxyacetophenone.—A mixture of 46 g. (0.28 mole) of 4-hydroxy-3-methoxyacetophenone,[10] 48 g. (0.38 mole) of benzyl chloride, 42 g. (0.30 mole) of anhydrous potassium carbonate and 370 ml. of methanol was stirred and refluxed for six hours. The hot mixture was filtered and the product which precipitated in the cooled filtrate was collected; weight 60 g. (83%), m.p. 85–87°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.97; H, 6.29. Found: C, 75.06; H, 6.21.

The semicarbazone was recrystallized from aqueous alcohol; m.p. 165–168°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: N, 13.41. Found: N, 13.24.

4-Benzyloxy-3-methoxybenzaldehyde[11] and 3-benzyloxy-4-methoxybenzaldehyde[12] were prepared in yields of 70 to 80% from vanillin and isovanillin (Monsanto Chemical Co.). 4-*n*-Butoxy-3-methoxybenzaldehyde[13] was prepared by M. B. Moore and M. R. Vernsten of these Laboratories.

Carbonyl Compounds.—The Darzens condensations were carried out by the following general procedure: A mixture of 0.4 mole of aldehyde or ketone, 0.4 mole of α-bromo ester and 400 ml. of sodium-dried toluene was stirred at −5 to −10° while either 0.4 mole of sodium ethylate or a toluene slurry of 0.4 mole of sodamide[14] was added during one hour. The bath temperature was allowed to rise to room temperature and after 24 hours the reaction mixture was poured into 500 ml. of water. The glycidic ester was obtained as an oily liquid by separation and concentration of the organic layer.

The hydrolysis of the ester was accomplished by one of two methods: (a) The ester was stirred for 24 hours with a solution of 55 g. of potassium hydroxide in 500 ml. of water. The mixture was cooled during acidification with concentrated hydrochloric acid and the glycidic acid which formed as an oil was extracted with ether. (b) The ester was stirred with a solution of 10 g. of sodium in 250 ml. of absolute ethanol for 30 minutes and then was cooled while 10 ml. of water was added dropwise. The mixture was stirred for 15 hours longer and was then diluted with 1 l. of anhydrous ether. The resulting solid, the sodium salt of the glycidic acid, was collected and washed with dry ether.

Two methods were employed for decarboxylation of the acid: (a) The acid was mixed with 2 g. of copper chromite and heated in an oil-bath at 140–150° for 2 hours at a pressure of less than 1 mm. The bath temperature was then raised and the ketone was distilled. (b) The sodium salt of the acid was warmed with 150 ml. of 3 *N* hydrochloric acid until there was no further evolution of carbon dioxide. The product was extracted with ether, concentrated and distilled.

In both the hydrolysis and the decarboxylation, procedure (b) was found to be more satisfactory, and was used for compounds 3, 4 and 5 in Table I.

Oximes.—A 25% solution of the aldehyde or ketone in 95% ethanol was shaken for 15 minutes with an aqueous solution of about the same volume containing 2 moles of hydroxylamine per mole of carbonyl compound. The hydroxylamine was prepared by combining solutions of equimolar amounts of hydroxylamine hydrochloride and potassium acetate. The ketoximes precipitated as white solids while the aldoxime was an oil which was extracted with ether. Only in the case of 3-benzyloxy-4-methoxyphenylacetone was the derivative obtained in two forms. The yields were nearly quantitative.

Phenethylamines.—A solution of 0.5 mole of lithium aluminum hydride in about one liter of anhydrous ether was stirred under nitrogen during the gradual addition of 0.1 mole of the oxime in ether solution. The mixture was refluxed for 15 to 20 hours and was then hydrolyzed by the cautious addition of about 70 ml. of water. The milky white mixture was filtered and the filtrate was shaken with 100 ml. of 2 *N* hydrochloric acid and 50 ml. of water. The aqueous solutions were made strongly basic with sodium hydroxide and the amine was extracted with ether. The extract was dried over potassium carbonate, concentrated and distilled. The hydrochloride salt was prepared from an ether solution by the addition of ethereal hydrogen chloride and was recrystallized from *n*-propanol and ether.

(10) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).

(11) R. M. Anker, A. H. Cook and I. M. Heilbron, *ibid.*, 917 (1945).

(12) R. Robinson and S. Sugasawa, *ibid.*, 3163 (1931).

(13) G. Kubiczek, M. Pohl and A. Smahel, *Monatsh.*, **77**, 52 (1947).

(14) T. R. Vaughn, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

4-*n*-Butoxy-3-methoxy-α-methylphenethylamine.—A solution of 12.6 g. (0.05 mole) of 4-*n*-butoxy-3-methoxyphenylacetone oxime in 150 cc. of glacial acetic acid was shaken with 0.25 g. of platinum oxide under 20 lb. pressure of hydrogen until reduction was complete. The mixture was filtered, the solvent was removed from the filtrate under vacuum, and the residue was treated with 100 ml. of 2 *N* hydrochloric acid. The acidic solution was washed with ether and made basic with 25% sodium hydroxide. The liberated amine was extracted with ether and distilled.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.74; H, 9.98.

Amides. By the Use of Acid Anhydrides.—The amine was dissolved in ten volumes of dry ether and treated with an equal weight of acetic, propionic or butyric anhydride. In most cases the crystalline amide soon precipitated. If it did not, the ether was removed and the residual oil was stirred with aqueous sodium hydroxide until the amide solidified, after which it was collected by filtration and washed with water.

By the Schotten-Baumann Reaction.—The amide was prepared from the amine and isobutyryl chloride or isovaleryl chloride in the usual manner, and was crystallized from aqueous alcohol.

N-Formyl-α-methyl-4-benzyloxy-3-methoxyphenethylamine.—A mixture of 5 g. (0.02 mole) of 4-benzyloxy-3-methoxy-α-methylphenethylamine and 5 ml. of 100% formic acid was heated at 100° for 45 minutes. The resulting brown oil was poured into dry ether whereupon a solid formed which proved to be the formate salt of the amine. A sample after crystallization from alcohol and ether melted at 151°.

Anal. Calcd. for $C_{17}H_{21}NO_2 \cdot HCOOH$: C, 68.12; H, 7.30. Found: C, 68.29; H, 7.22.

This material was dissolved in 50 ml. of formic acid, and the mixture was allowed to reflux for 30 minutes in an oil-bath at 165°. Then 25 ml. of distillate was removed and replaced by an equal volume of formic acid. The solution was heated for two more hours and was then concentrated under vacuum. The oily residue was treated with water and the mixture was shaken with ether. Evaporation of the dried ethereal extract gave a brown oil which partially dissolved in hot Skellysolve C. In the cooled decantate there separated crystals, m.p. 129–132°, and an oil which slowly crystallized. The total amount of solid thus obtained was small; therefore it was subjected to ring-closure without further purification.

N-Acetyl-α-methyl-4-*n*-butoxy-3-methoxyphenethylamine.—The method applied to allylbenzene by Ritter and Kalish[9] was followed using O-*n*-butyleugenol. The product did not solidify when the reaction mixture was made alkaline and was therefore extracted with ether. When the extract was evaporated a mixture of oil and crystals remained which was converted to the isoquinoline without further purification. The yield of amide was about 50%.

3,4-Dihydroisoquinolines.—A solution of 2 g. of amide in 15 ml. of dry chloroform was added dropwise with stirring to a solution of 4 g. of phosphorus pentachloride in 50 cc. of chloroform. The reaction flask was heated in an oil-bath at 48–50° during the addition and for one hour longer. The solvent was then removed under vacuum and the residual yellow solid was treated with 50 ml. of water. After the mixture had been warmed on a steam-bath for 30 minutes it was cooled and shaken with ether. The aqueous layer was made strongly basic with sodium hydroxide whereupon the dihydroisoquinoline separated. It was extracted with ether and the extract was dried over potassium hydroxide pellets. The product was obtained by evaporation, and, if solid, was recrystallized from Skellysolve B. The hydrochloride salts were prepared in ether, and were crystallized from a mixture of *n*-propanol and ether.

NORTH CHICAGO, ILL. RECEIVED JUNE 4, 1951

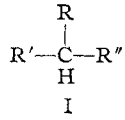
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Histamine Antagonists. γ,γ-Disubstituted N,N-Dialkylpropylamines[1]

BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK, MARGARET SHERLOCK AND ROSEMARIE FRICANO

A series of substituted dialkylaminoalkanes have been synthesized by various methods and tested as histamine antagonists. Two compounds, γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine and γ-(*p*-chlorophenyl)-γ-(2-pyridyl)-N,N-dimethylpropylamine, have been found to be effective clinically. In general the most active compounds were derivatives of N,N-dimethylpropylamine, having a 2-pyridyl and a phenyl, para-substituted phenyl or heterocyclic group in the gamma position.

Following the preliminary clinical success of β-dimethylaminoethyl benzhydryl ether[2] and N′-benzyl-N′-(2-pyridyl)-N,N-dimethylethylenediamine[3] as histamine antagonists, we undertook an extensive chemical program[4] to establish whether antihistaminic activity was limited to compounds derived from ethanolamine and ethylenediamine.[5] As part of our study, a new series of substituted dialkylaminoalkanes of general formula I, wherein



I

R is alkyl, cycloalkyl, aralkyl, heterocyclic, R′ is heterocyclic, R″ is dialkylaminoalkyl or N-piperidinoalkyl were synthesized and a number of these compounds were found to be potent histamine antagonists.

One of the general methods for the synthesis of substituted dialkylaminoalkanes involved the preparation and conversion of tertiary nitriles V to I. When phenylacetonitrile (II, R = phenyl) was alkylated with a dialkylaminoalkyl chloride and sodamide in toluene, the desired α-(β-dialkylaminoalkyl)-phenylacetonitrile III was obtained in good yield[6] (Method A). Upon further alkylation of III with 2-chloro- or 2-bromopyridine and sodamide in toluene, α-phenyl-α-(β-dialkylaminoalkyl)-2-pyridylacetonitrile (V) was obtained. The synthesis

(1) Presented in abstract before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, April 21, 1948.

(2) E. R. Loew, M. E. Kaiser and V. Moore, *J. Pharmacol. Exptl. Therap.*, **88**, 120 (1945); E. R. Loew and M. E. Kaiser, *Proc. Soc. Exper. Biol. and Med.*, **58**, 235 (1945); G. Rieveschl, Jr., U. S. Patent 2,421,714, June 3, 1947.

(3) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946).

(4) N. Sperber and D. Papa, *ibid.*, **71**, 886 (1949); N. Sperber, D. Papa, E. Schwenk and M. Sherlock, *ibid.*, **71**, 887 (1949); D. Papa, N. Sperber and M. Sherlock, *ibid.*, **73**, 1279 (1951).

(5) Excellent discussions of histamine antagonists may be found in the reviews of C. P. Huttrer, *Enzymologia*, **12**, 277 (1948); *Experientia*, **5**, 53 (1949); F. Leonard and C. P. Huttrer, CBCC Review No. 3, National Research Council (1950) and B. Idson, *Chem. Revs.*, **47**, 307 (1950).

(6) O. Eisleb, *Ber.*, **74**, 1433 (1941); C. E. Kwartler and P. Lucas, THIS JOURNAL, **68**, 2395 (1946).