Anal.[a] Calcd. for $C_{17}H_{18}O$: C, 85.6; H, 7.6. Found: C, 85.3; H, 7.4.

α-Methyldesoxybenzoin, IV.—To a solution of the Grignard reagent prepared from 157 g. (1 mole) of bromobenzene and 30 g. of magnesium in 400 cc. of ether was added dropwise during one hour a solution of 63 g. (0.48 mole) of hydratropanitrile[9] in 100 cc. of benzene. After replacing 200 cc. of ether, which was allowed to distil, with an equal volume of benzene, the mixture was refluxed for five hours. The complex was decomposed with dilute hydrochloric acid, 200 cc. of concentrated hydrochloric acid was added, and the mixture refluxed for two hours to hydrolyze the imine hydrochloride. The ketone, IV, was finally isolated in 57% yield as a colorless oil, b. p. 136–137° at 2 mm., which soon crystallized to a solid. On recrystallization this ketone was obtained as feathery needles, m. p. 52–53°.[10]

3-Carboxy-4,5-diphenyl-4-hexenoic Acid.[11]—A solution of 10.3 g. (0.05 mole) of IV and 15.5 g. (0.09 mole) of ethyl succinate in 30 cc. of *t*-butyl alcohol was added to a cooled stirred solution of 2.2 g. (0.055 mole) of potassium in 30 cc. of *t*-butyl alcohol maintained under nitrogen. After refluxing for one and three-quarters hours, the mixture was cooled and treated with 12 cc. of 6 *N* hydrochloric acid. Since the crude half ester did not crystallize, it was saponified and the acid obtained in 42% yield as colorless needles, m. p. 174–176°. More acid was present, but no attempt to isolate the maximum amount was made. The pure acid, obtained on recrystallization from aqueous methanol, melted at 174.6–175.7°. From the neutral reaction products, 19% of IV was recovered.

Anal.[c] Calcd. for $C_{19}H_{18}O_4$: C, 73.8; H, 6.0. Found: C, 74.0; H, 6.2.

α,α-Dimethyldesoxybenzoin, V.—On methylation[8] IV was converted into V in 84% yield. The product boiled at 137–138° at 2 mm. and crystallized on standing to give thin rods, m. p. 45–47°.[12] The attempted Stobbe condensation failed, 79% of V being recovered.

2,5-Dimethylphenyl Benzyl Ketone, VI.—To a stirred cooled solution of 77.3 g. (0.5 mole) of phenylacetyl chloride and 90 g. of pure *p*-xylene[1] in one pound of carbon disulfide was added 110 g. of aluminum chloride during one hour. After heating to reflux during one hour and stirring at room temperature for two more, the mixture was decomposed with ice and hydrochloric acid. The ketone, VI, obtained in 86% yield, boiled at 147–148° at 2 mm. and melted at 30.5–32.0°. The Stobbe reaction failed, an 82% yield of VI being recovered from the reaction mixture.

Anal.[c] Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.8; H, 7.4.

Summary

Steric hindrance in the Stobbe condensation of several methylated desoxybenzoins has been observed. A methyl group ortho to the carbonyl effectively hinders the reaction as do two methyl groups in any positions adjacent to the carbonyl group.

(9) Newman and Closson, THIS JOURNAL, **66**, 1553 (1944).
(10) Kayser, *Ann. Chim.*, (11) **6**, 188 (1936).
(11) The position of the double bond in this acid is assumed.
(12) Bruzan, *Ann. chim.*, [11] **1**, 335 (1934), reports m. p. 46–47°.

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[CONTRIBUTION FROM THE SMITH, KLINE AND FRENCH LABORATORIES]

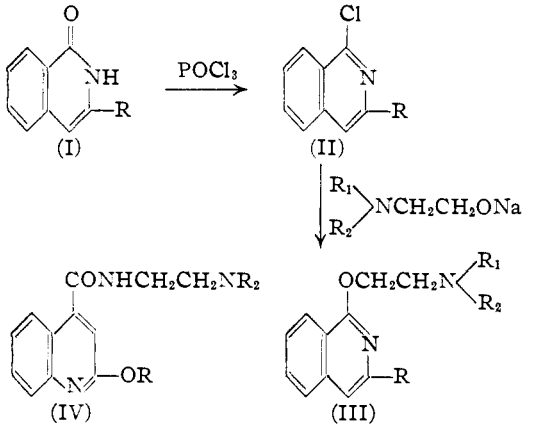
Local Anesthetics. Aminoalkoxyisoquinoline Derivatives

BY JAMES W. WILSON, III, NORMAN D. DAWSON,[1] WALTER BROOKS[2] AND GLENN E. ULLYOT

Aminoalkyl ethers of phenols have been reported to possess local anesthetic activity.[3,4]

As far as we can find, however, no one has investigated the pharmacological properties of aminoalkoxy derivatives of isoquinolines. Previous work in this Laboratory[5] provided an excellent method for preparing a group of isocarbostyrils (I) from which a series of aminoalkoxy derivatives (III) has been obtained according to the procedure outlined by formulas I–III.

In order to be able to study the effect of modifying the lipophylic and hydrophylic character of the terminal groups of the molecule (III) on the pharmacological properties, we have varied the nature of the R, R_1 and R_2 groups as shown in Table I. That such factors play a role is demonstrated by the effect of varying the R groups in the known local anesthetics of the quinoline type (IV),[6] and by gradations in the local anesthetic activity among our compounds, as indicated in the last column of Table I.



The 1-chloroisoquinolines which are intermediates in our syntheses are listed in Table II.

Experimental

Preparation of 1-Chloroisoquinolines.—All of these compounds were prepared from the corresponding isocarbostyrils by the action of phosphorus oxychloride[7] using essentially the same procedure in each case.

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(2) Present address: University of Pennsylvania, Philadelphia, Pennsylvania.
(3) Merck, German Patent 184,968 (1907).
(4) I. G. Farbenindustrie, Swiss Patents 135,890 (1929), 136,186 (1930).
(5) To be reported in a forthcoming paper.
(6) Miescher, *Helv. Chim. Acta*, **15**, 163 (1932).
(7) See Footnote [e], Table II.

TABLE I

AMINOETHOXYISOQUINOLINES (FORMULA III)

	R	R_1	R_2	Formula	B. p. °C.	Mm.	n_D	°C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration of local anesthetic activity in min. by a 0.1% soln. on the rabbit's cornea[e]
1	H	CH_3	CH_3	$C_{13}H_{18}N_2O$	133–134	2	1.5708	20	80	72.18	7.45	72.12	7.31	9.6
2	H	n-C_4H_9	n-C_4H_9	$C_{19}H_{28}N_2O$	172–173	2	1.5355	20	76	75.96	9.39[a]	76.16	9.59	27.8
3	CH_3	C_2H_5	C_2H_5	$C_{16}H_{22}N_2O$	153–154	1–2	1.5530	21	91	74.36	8.58	74.38	8.70	76.0
4	CH_3	—$(CH_2)_5$—		$C_{17}H_{22}N_2O$	175–178	1	1.5715	21	83	75.51	8.20	75.60	8.32	26.4
5	C_2H_5	C_2H_5	C_2H_5	$C_{17}H_{24}N_2O$	154–157	1	1.5481	21	89	74.98	8.88	74.77	8.70	141.8
6	C_2H_5	—$(CH_2)_5$—		$C_{18}H_{24}N_2O$	175–178	1	1.5654	21	93	76.01	8.51	75.86	8.44	180+
7	C_2H_5	H	$CH_2C_6H_5$	$C_{20}H_{23}N_2OCl$[b]					82	70.05	6.76	69.83	6.94	121
8	n-C_3H_7	CH_3	CH_3	$C_{18}H_{22}N_2O$[c]	150–152	2	1.5525	21	92	74.36	8.58[d]	74.38	8.55	72.0
9	n-C_4H_9	CH_3	CH_3	$C_{17}H_{24}N_2O$	155–157	3	1.5486	20	87	74.95	8.88	74.99	8.81	138+

[a] Calcd.: N, 9.33. Found: N, 9.07. [b] This product was isolated as the monohydrochloride, m. p. 154–155°. Calcd.: Cl^-, 10.34. Found: Cl^-, 10.22. [c] Forms a solid dihydrochloride which under prolonged vacuum drying loses one molecule of hydrogen chloride. This product melts at 113–116°. *Anal.* Calcd. for $C_{16}H_{23}N_2OCl$: Cl^-, 12.05. Found: Cl^-, 12.00. [d] Calcd.: N, 10.84. Found: N, 10.61. [e] Anesthetic activity was appraised after topical application to the rabbit's eye. For comparative purposes the durations of anesthesia produced by a 1.0% solution of cocaine or procaine were eighteen and two minutes, respectively.

TABLE II

1-CHLORO-3-SUBSTITUTED-ISOQUINOLINES

3-Substituent	Formula	B. p. °C.	Mm.	M. p., °C.	Yield, %
H	C_9H_6NCl	114–116[a]	8–9	31	79
CH_3	$C_{10}H_8NCl$	108–110[b]	1	32	94
C_2H_5	$C_{11}H_{10}NCl$	148–150[c]	9–10	26	96
n-C_3H_7	$C_{12}H_{12}NCl$	157–161[d]	9		96[e]
n-C_4H_9	$C_{14}H_{14}NCl$[f]	155–158	6		77

[a] Gabriel and Colman, *Ber.*, **33**, 985 (1900). [b] Gabriel and Neumann, *Ber.*, **25**, 3569 (1892). [c] Damerow, *Ber.*, **27**, 2236 (1894). [d] Albahary, *Ber.*, **29**, 2395 (1896). [e] $n^{21}D$ 1.5968. [f] Calcd.: C, 71.06; H, 6.42. Found: C, 71.23, H, 6.48.

3-*n*-Butyl-1-chloroisoquinoline.—A solution of 56 g. of 3-*n*-butylisocarbostyril in 86 g. of phosphorus oxychloride was refluxed for sixteen hours, cooled, and poured into 300 g. of cracked ice. The cold solution was carefully neutralized with 40% sodium hydroxide and the product extracted into ether. After drying over anhydrous sodium sulfate, the ether was removed, and the product distilled to yield 47 g. of colorless liquid.

Preparation of Aminoalkyl Ethers.—In each case a solution of the sodium derivative of the amino alcohol in toluene or xylene was condensed with the chloroisoquinoline. The ethers, with the exception of the 1-(β-benzylaminoethoxy)-3-ethylisoquinoline, were isolated by distillation.

1-(β-Dimethylaminoethoxy)-3-propylisoquinoline.—A mixture of 3.4 g. of finely divided sodium metal and 17.6 g. of β-dimethylaminoethanol in 100 ml. of dry xylene was heated at 60–80° with efficient stirring for three hours. While maintaining the resulting solution at 75–85°, 26 g. of 1-chloro-3-propylisoquinoline was added, with stirring, over a period of six hours. The heating was continued for an additional two hours, the sodium chloride was removed by filtration, the filtrate washed with water and the product extracted with 2 *N* hydrochloric acid. This acid solution was made alkaline and the product extracted with ether. After drying, the ether was removed and the product distilled to yield 29.4 g. of colorless oil, b. p. 150–152° (2 mm.).

1-(β-Benzylaminoethoxy)-3-ethylisoquinoline Monohydrochloride.—The initial condensation was carried out as described above, employing 2.3 g. of sodium, 18 g. of benzylaminoethanol, and 19.2 g. of 1-chloro-3-ethylisoquinoline. When this reaction mixture was extracted with acid, the hydrochloride of the product crystallized, yielding 28 g. (82%) of white solid. Crystallization from acetone–alcohol and vacuum drying gave 22 g., m. p. 154–155°.

Pharmacological.—We are indebted to Dr. Edwin J. Fellows of the Pharmacology Department of Temple University for the pharmacological results reported in Table I: the detailed results will be published elsewhere. Compounds (5), (6), and (9), were superior. Of these (9) appeared outstanding in that it exhibited local anesthetic activity in concentrations as low as 0.001%.

Summary

The properties of five 1-chloroisoquinolines, including one not previously reported, are given.

Eight new 1-(β-dialkylaminoethoxy)-3-alkylisoquinolines and one secondary amine of the same type are described, and their local anesthetic activity is reported. The most effective agent in this series is the 3-butyl-1-(β-dimethylaminoethoxy)-isoquinoline.

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