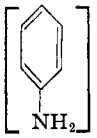
[CONTRIBUTION FROM THE UNIVERSITY OF MICHIGAN COLLEGE OF PHARMACY]

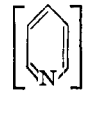
Esters of Pyridinecarboxylic Acids as Local Anesthetics

BY F. F. BLICKE AND E. L. JENNER[1,2]

The nuclear amino group in dialkylaminoalkyl aminobenzoates (I)[3] contributes in some manner which is not understood to the local anesthetic activity of these compounds. It is a matter of interest to know the extent to which this activity would be affected by a shift of the nitrogen atom into the ring. Some information relative to this point could be gained by pharmacological examination of dialkylaminoalkyl esters of pyridinemonocarboxylic acids (II)[4]



I



II

It has been reported by Ingersoll and Robbins[5] that β-diethylaminoethyl and γ-diethylaminopropyl nicotinate are inactive as local anesthetics. They stated that these esters were prepared by them by interaction of the required basic alcohol with nicotinyl chloride; the "nicotinyl chloride" which was employed melted at 264–265° and was preserved over calcium chloride and paraffin. It has been shown by Meyer and Graf[6] that the true nicotinyl chloride melts at 15–16° and that it is so sensitive to moisture that it cannot be kept unchanged in a desiccator over alkali.

It seems that the material which Ingersoll and Robbins used as "nicotinyl chloride" was somewhat impure nicotinic acid hydrochloride; the latter, when pure, melts at 273–274°.[7]

We prepared nicotinyl chloride according to the procedure of Meyer and Graf and also by the method of Douglass and Forman.[8] In one instance the acid chloride was allowed to react with β-diethylaminoethanol and, in another, nicotinic acid was heated with β-diethylaminoethyl chloride in isopropyl alcohol. β-Diethylaminoethyl nicotinate hydrochloride was obtained in both cases but the properties of our ester hydrochloride were markedly different from those mentioned by Ingersoll and Robbins. When the ester salt was converted into the ester base, the latter was found to boil at a temperature which corresponds to that reported for this product by Knunyantz and Katznel'son.[9]

An examination of β-diethylaminoethyl nicotinate by L. W. Rowe, who tested all of our products in the Parke, Davis and Company Laboratories, showed that the base, as well as the hydrochloride, was practically inactive when applied to the rabbit's cornea. Local anesthesia was produced by injection of a 1–2% solution of the hydrochloride but the activity by this route of administration is greatly inferior to that of procaine or cocaine.

The fact that β-diethylaminoethyl nicotinate is soluble in about three parts of cold water, whereas bases of active esters are fairly insoluble, may account to some extent for its lack of action.

Although ethyl nicotinate has been known for some time, no statement relative to its effectiveness as a local anesthetic could be found. We submitted this ester for examination and it was shown to be practically inactive by topical application. Ethyl *p*-aminobenzoate is the well-known and widely used local anesthetic anesthesin (benzocaine).

Several other esters of nicotinic acid which we prepared are listed in Table I. Their potency is very slight.

In view of the fact that 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates,[10] 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates[11] and 1-alkyl 2-dialkylaminoalkyl 4-aminophthalates[12] are active local anesthetics it seemed desirable to prepare corre-

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by E. L. Jenner in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis and Company Fellow.

(3) β-Diethylaminoethyl *p*-aminobenzoate is procaine. Corresponding esters of *o*- and *m*-aminobenzoic acids exhibit local anesthesia according to the German Patent 170,587 [*Frdl.*, **8**, 1002 (1906)].

(4) In the naphthalene series it has been found that β-diethylaminoethyl 4-amino-1-naphthoate is a strong local anesthetic [Blicke and Parke, THIS JOURNAL, **61**, 1200 (1939); Rowe, *J. Am. Pharm. Assoc.*, **29**, 241 (1940); Haury, Gruber and Drake, *J. Pharmacol. Exp. Therap.*, **70**, 315 (1940)]. We have been unable to find any reference with regard to the activity of dialkylaminoalkyl esters of quinoline-4-carboxylic acid, however, 2-alkyloxy derivatives of the latter are potent products [Wojahn, *Arch. Pharm.*, **269**, 422 (1931)].

(5) Ingersoll and Robbins, THIS JOURNAL, **48**, 2449 (1926).

(6) Meyer and Graf, *Ber.*, **61**, 2202 (1928).

(7) McElvain, "Organic Syntheses," Coll. Vol. I, p. 378.

(8) Douglass and Forman, THIS JOURNAL, **56**, 1609 (1934).

(9) Knunyantz and Katznel'son, Russian Patent, 35,836 [*C. A.* **29**, 8001 (1935)]. According to the abstract, the ester was made from the acid chloride and the basic alcohol; it was said to be of therapeutic value but it was not mentioned specifically that it exhibits local anesthetic action.

(10) Blicke and Otsuki, THIS JOURNAL, **63**, 1945 (1941).

(11) Blicke and Otsuki, *ibid.*, **63**, 2435 (1941).

(12) Blicke and Castro, *ibid.*, **63**, 2437 (1941).

sponding esters in the pyridine series. Accordingly, we synthesized a series of 2-alkyl 3-dialkylaminoalkyl quinolinates (Table III) in the following manner. 8-Hydroxyquinoline was oxidized to quinolinic acid (pyridine-2,3-dicarboxylic acid), the latter converted into quinoline anhydride and the anhydride heated with the required alkanol. The 2-alkyl acid quinolinates[13] obtained (Table II) were treated with a dialkylaminoalkyl chloride whereby the 2-alkyl 3-dialkylaminoalkyl esters were produced.

The local anesthetic activity of these esters, in comparison with those of the aminophthalic acid esters mentioned above, is relatively low. The most active product is 2-amyl 3-(γ-dibutylaminopropyl)-quinolinate.

Bis-(β-diethylaminoethyl) quinolinate dihydrobromide was found to be inactive, even in 4% solution, when applied to the rabbit's cornea.

Experimental Part

Dialkylaminoalkyl Nicotinate Hydrochlorides.—(A) To 0.05 mole of nicotinyl chloride, dissolved in 75 cc. of dry benzene, there was added 0.05 mole of the dialkylaminoalkanol dissolved in an equal amount of the same solvent. In some instances the product separated almost immediately as an oil or solid. After one to four days the precipitate was isolated and recrystallized.

(B)[14] A mixture of 0.05 mole of the dialkylaminoalkyl chloride and 0.05 mole of nicotinic acid in 50 cc. of dry isopropyl alcohol was refluxed on a steam-bath for twelve hours. After removal of the solvent under reduced pressure, the residue was triturated with anhydrous ether. In the event that the product remained oily, it was dissolved in water, the cold solution treated with Norit, filtered, the solution extracted with ether and the base liberated from the aqueous layer with concd. potassium carbonate solution. The oily base was extracted with ether and the solution dried over anhydrous magnesium sulfate. The solvent was removed and the base treated with the calculated amount of concentrated hydrobromic acid necessary for the formation of the hydrobromide. The material became crystalline when rubbed under dry ether.

Our β-diethylaminoethyl nicotinate hydrochloride melted at 128–129°, after recrystallization from acetone, was not hygroscopic, and could be recrystallized from ethyl or isopropyl alcohol. The "β-diethylaminoethyl nicotinate hydrochloride" described in the literature[5] melted at 140–160°, after recrystallization from acetone, was hygroscopic, and could not be recrystallized from the lower alcohols.

We found that the ester base is soluble in about three parts of cold water and precipitates upon the addition of solid potassium carbonate to the solution. It boiled at 120–125° (2 mm.); the boiling point 155–157° (10 mm.) has been reported.[9] The ester base produced a burning sensation when placed on the tip of the tongue but no anesthesia was experienced.

α-Phenyl-γ-diethylaminopropanol.—A solution of 24.2 g. of phenyl diethylaminoethyl ketone hydrochloride[15] in 50 cc. of water was treated with hydrogen under an initial pressure of three atmospheres in the presence of Raney nickel catalyst.[16] The calculated amount of hydrogen was absorbed in eight hours. The solution was filtered and the cold filtrate shaken with Norit, then with Filter-Cel, filtered again and the filtrate made strongly alkaline by addition of solid sodium hydroxide. After extraction of the product with ether the solution was dried over anhydrous magnesium sulfate. The product boiled at 122–124° (2 mm.).

When hydrogen chloride was passed into an ether solution of the basic alcohol, the hydrochloride precipitated as an oil. The latter was cooled and rubbed under dry ether whereupon it became crystalline; m. p. 84–86° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{22}ONCl$: Cl, 14.54. Found: Cl, 14.57.

β-Dicyclohexylaminoethanol.—A mixture of 25.0 g. of ethylene bromohydrin and 72.4 g. of dicyclohexylamine[17] was heated for three days on a steam-bath, the precipitated dicyclohexylamine hydrobromide filtered and washed with toluene. From the filtrate there was obtained 28.0 g. (62%) of the desired ethanol; b. p. 131–134° (2 mm.).[18]

2-Alkyl Acidquinolinates.—The necessary quinolinic acid was obtained by oxidation of 8-hydroxyquinoline according to the procedure of Sucharda[19] but the purification of the acid was effected in the following manner. The residue of crude, moist quinolinic acid nitrate obtained from 250 g. of 8-hydroxyquinoline was pulverized, placed on a Jena funnel and washed thoroughly with five 20-cc. portions of 30% nitric acid. After recrystallization from 500 cc. of 40% acetic acid, 212 g. of dark orange product was obtained. The latter was dissolved in 2 liters of boiling water and treated successively with Norit and Filter-Cel. A large portion of the material separated from the cold solution and a further amount was obtained by concentration of the mother liquor; the total yield of nearly colorless acid was 178 g. (62%); m. p. 185–190° (decomp.).[20]

In order to convert quinolinic acid into quinolinic anhydride, a mixture of 100 g. of finely powdered acid and 200 cc. of acetic anhydride was maintained at 65° and fifteen 1-cc. portions of concd. hydrochloric acid[21] were added over a three hour period. The solution was poured into 2 liters of carbon tetrachloride and the precipitated, crystalline anhydride was recrystallized from 600 cc. of dry benzene; yield 64 g. (72%); m. p. 136–138°.[22]

(13) According to Kirpal [*Monatsh.*, **21**, 957 (1900)] the major product formed from quinolinic anhydride is the 2-alkyl ester and not the isomeric 3-alkyl compound.

(14) This general procedure was used originally by Horenstein and Pählicke [*Ber.*, **71**, 1644 (1938)] for the preparation of basic alkyl esters of hydroxy acids.

(15) Blicke and Burckhalter, THIS JOURNAL, **64**, 453 (1942).

(16) "Organic Syntheses," **21**, 15 (1941).

(17) The amine was dried for three days over stick sodium hydroxide prior to use; b. p. 129–134° (121 mm.).

(18) The boiling point reported is 135° (2 mm.) (German Patent 556,324). The method of preparation was not mentioned.

(19) Sucharda, *Ber.*, **58**, 1728 (1925).

(20) Skraup [*Monatsh.*, **2**, 148 (1881)] reported 190–195° (decomp.).

(21) German Patent, 442,221; *Frdl.*, **15**, 1632 (1927).

(22) Dox [THIS JOURNAL, **37**, 1948 (1915)] found 134°.

TABLE I

DIALKYLAMINOALKYL NICOTINATE HYDROCHLORIDES, C_5H_4N-COOR·HCl

	R	M. p., °C.[a]	Formula	Chlorine, % Calcd.	Chlorine, % Found
1	$CH_2CH_2N(C_2H_5)_2$	127–128[b]	$C_{12}H_{19}O_2N_2Cl$	13.71	13.77
2	$CH_2CH_2CH_2N(C_4H_9)_2$	104–105	$C_{17}H_{29}O_2N_2Cl$	10.78	10.79
3	$CH_2CH_2N(C_6H_{11})_2$[c]	163–165	$C_{20}H_{31}O_2N_2Cl$	9.66	9.75
4	$CH(C_6H_5)CH_2CH_2N(C_2H_5)_2$	145–146	$C_{19}H_{25}O_2N_2Cl$	10.16	10.20

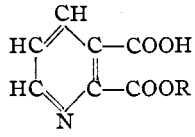
[a] Compound 1 was recrystallized from isopropyl alcohol; 2 from ethyl acetate; 3 and 4 from a mixture of absolute alcohol and ethyl acetate. [b] The melting point 140–160° has been reported (ref. 5). [c] C_6H_{11} = cyclohexyl.

2-Methyl acidquinolinate was obtained when a solution of 38 g. of quinolinic anhydride in 200 cc. of absolute methyl alcohol was refluxed for eight hours, the excess alcohol removed and the oily residue dissolved in 100 cc. of hot water. When the solution was cooled with ice, 39.8 g. of crude, crystalline ester separated. The latter was recrystallized from 40 cc. of water and then from 100 cc. of ethyl acetate; yield 19.1 g. (41%).

2-Amyl acidquinolinate was prepared by the same general procedure.

TABLE II

2-ALKYL ACIDQUINOLINATES



	R	M. p., °C.[a]	Formula	Neutralization equivalent Calcd.	Neutralization equivalent Found
1	CH_3	125–126[b]	$C_8H_7O_4N$	181.1	180.4
2	$CH_2(CH_2)_3CH_3$	110–111	$C_{12}H_{15}O_4N$	237.2	237.5
3	$CH_2(CH_2)_6CH_3$	104–105	$C_{15}H_{21}O_4N$	279.3	279.7
4	$CH_2(CH_2)_{10}CH_3$	106–107	$C_{19}H_{29}O_4N$	335.4	335.2
5	$CH_2CH_2C_6H_5$	139–140	$C_{15}H_{13}O_4N$	271.3	271.1

[a] Compounds 1, 3 and 4 were recrystallized from ethyl acetate; compounds 2 and 5 from water. [b] Kirpal [*Monatsh.*, **20**, 766 (1899)] reported 123°.

In the case of the 2-octyl, 2-lauryl and 2-β-phenylethyl esters, the calculated amount of the required alcohol was refluxed with the anhydride in dry toluene (50 cc. for 0.1 mole of anhydride). The crude esters were washed thoroughly with hot water before recrystallization.

2-Alkyl 3-Dialkylaminoalkyl Quinolinates.—These diesters were prepared from the dialkylaminoalkyl chloride and the 2-alkyl acidquinolinates by general procedure B, described under dialkylaminoalkyl nicotinate hydrochlorides.

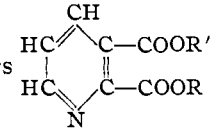
To obtain γ-dibutylaminopropyl chloride, the hydrochloride[23] of this compound obtained from 18.7 g. of γ-dibutylaminopropyl alcohol was dissolved in water, the solution made alkaline with solid potassium carbonate, the liberated base extracted with ether and the extract dried with anhydrous magnesium sulfate. Upon distillation there was obtained 16.4 g. (80%) of the basic alkyl halide; b. p. 73–75° (2 mm.).

Bis-(β-diethylaminoethyl) Quinolinate Dihydrobromide.—To 20.4 g. (0.10 mole) of quinolinyl chloride,[24] dissolved in dry benzene, there was added a benzene solution of 46.8 g. (0.40 mole) of β-diethylaminoethanol. The mixture refluxed vigorously during the addition of the ethanol and β-diethylaminoethanol hydrochloride precipitated. The mixture was warmed for eight hours on a steam-bath, the precipitate removed, the benzene solution shaken with water and then with a 10% sodium carbonate solution. The benzene solution was dried with anhydrous magnesium sulfate, the solvent removed and the base triturated with the amount of 48% hydrobromic acid required for the formation of the dihydrobromide. The product became crystalline when rubbed under anhydrous ether; m. p. 157–159° after recrystallization from alcohol.

Anal. Calcd. for $C_{19}H_{33}O_4N_3Br_2$: Br, 30.31. Found: Br, 30.28.

TABLE III

2-ALKYL 3-DIALKYLAMINOALKYL QUINOLINATE SALTS



	R	R'	M. p., °C.[a]	Formula	Halogen, % Calcd.	Halogen, % Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	113–114	$C_{14}H_{21}O_4N_2Cl$	11.19	11.25
2	C_5H_{11}	$CH_2CH_2N(C_2H_5)_2$	98–101	$C_{18}H_{29}O_4N_2Br$	19.15	19.27
3	C_8H_{17}	$CH_2CH_2N(C_2H_5)_2$	59– 62[b]	$C_{21}H_{35}O_4N_2Br$	17.40	17.50
4	$C_{12}H_{23}$	$CH_2CH_2N(C_2H_5)_2$	72– 74	$C_{25}H_{43}O_4N_2Br$	15.50	15.60
5	$CH_2CH_2C_6H_5$	$CH_2CH_2N(C_2H_5)_2$	141–142	$C_{21}H_{27}O_4N_2Cl$	8.71	8.74
6	C_6H_{11}	$CH_2CH_2CH_2N(C_4H_9)_2$	oil	$C_{23}H_{39}O_4N_2Cl$	8.00	8.24

[a] Compounds 1 and 2 were recrystallized from isopropyl alcohol; 5 from ethyl alcohol; 4 from ethyl acetate; 3 from a mixture of acetone and petroleum ether (30–40°); 6 was washed repeatedly with dry ether. [b] Hygroscopic.

Summary

Dialkylaminoalkyl nicotinates, 2-alkyl acidquinolinates and 2-alkyl 3-dialkylaminoalkyl

(23) Blicke and Otsuki, THIS JOURNAL, **63**, 2435 (1941).

(24) Obtained in 84% yield by the method of Scheiber and Knothe [*Ber.*, **45**, 2256 (1912)].

quinolinates have been described. None of the esters possessed marked activity as a local anesthetic.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 10, 1942

[COMMUNICATION NO. 853 FROM THE KODAK RESEARCH LABORATORIES]

The Reaction of β-Isodurylaldehyde Cyanohydrin with Phenylmagnesium Bromide[1]

BY A. WEISSBERGER AND DUDLEY B. GLASS

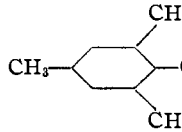
Benzoin and a number of substituted benzoins and other acyloins have been prepared by the reaction of aryl- or alkylmagnesium halides with the cyanohydrins of aryl aldehydes.[2,3] Omitting the reaction of the Grignard reagent with the active hydrogen of the cyanohydrin, and the acid used in decomposing the magnesium complex, the course of the reaction may be represented as

$$ArCHOHCN + RMgX \longrightarrow ArCHOHC(=NMgX)R \quad (1)$$

$$ArCHOHC(=NMgX)R + H_2O \longrightarrow ArCHOHC(=NH)R + Mg(OH)X \quad (2)$$

$$ArCHOHC(=NH)R + H_2O \longrightarrow ArCHOHCOR + NH_3 \quad (3)$$

The yields vary considerably, but no total failure of the reaction is reported in the literature. However, when β-isodurylaldehyde cyanohydrin,



—CHOHCN, was treated with phenylmagnesium bromide in an attempt to prepare 2,4,6-trimethylbenzoin for a study of its oxidation rate, the compound expected was not obtained. Instead, the product of the reaction was a nitrogen-containing substance with the properties of an α-aminoketone; the compound is a monohydric base, is oxidized by Fehling solution and by nitrosobenzene to 2,4,6-trimethylbenzil, and autoxidizes in alkaline solution.[4] The same substance was obtained by the following series of reactions

$$C_6H_3(CH_3)_3 + C_6H_5CH_2COCl \longrightarrow C_6H_2(CH_3)_3COCH_2C_6H_5 + HCl$$

$$C_6H_2(CH_3)_3COCH_2C_6H_5 + C_4H_9NO_2 \longrightarrow C_6H_2(CH_3)_3COC(=NOH)C_6H_5 + C_4H_9OH$$

$$C_6H_2(CH_3)_3COC(=NOH)C_6H_5 + 4H(SnCl_2) \longrightarrow C_6H_2(CH_3)_3COCHNH_2C_6H_5 + H_2O$$

I

This synthesis establishes the position of the oxygen and nitrogen atoms in respect to the mesitylene and benzene nuclei and identifies the compound as 2,4,6-trimethyldesylamine (I) or its tautomer (II).

If one considers the work of Kohler[5] and of Fuson,[6] who have shown that in compounds of the types $C_6H_2(CH_3)_3COCH=$ and $C_6H_2(CH_3)_3CH\text{-}OHC\equiv$ the mesitylene residue promotes the formation and enhances the stability of the enolic form $C_6H_2(CH_3)_3C(OH)=C<$, the anomalous course of the reaction of β-isodurylaldehyde cyanohydrin with phenylmagnesium bromide can be understood. With the mesitylene derivative, the imino compound, which ordinarily undergoes acid hydrolysis, eq. 3, is transformed by enolization into the amino compound II, eq. 4, which resists hydrolysis. This or the tautomeric amine I separates from the acid solution as the hydrochloride.

$$C_6H_2(CH_3)_3CHOHC(=NH)C_6H_5 \longrightarrow C_6H_2(CH_3)_3C(OH)=C(NH_2)C_6H_5 \quad (4)$$

II

The phase in the sequence of reactions in which the enolization occurs is indicated by the reaction of β-isoduraldehyde cyanohydrin with methylmagnesium iodide.[7] β-Isoduraldehyde cyanohydrin consumes two moles of the Grignard reagent and evolves one mole of methane. This agrees with the structure of the resulting complex as that of the imino derivative $ArCH(OMgBr)C(=N\text{-}MgBr)R$. The tautomeric enamino compound $ArC(OMgBr)=C(NHMgBr)—R$ should evolve another mole of methane. Hence, the amino compound is not formed before the hydrolysis of the Grignard complex.

The explanation of the anomalous reaction of β-isoduraldehyde cyanohydrin with phenylmag-

(1) This investigation was started in the Dyson-Perrins Laboratory, Oxford. I wish to express thanks to Sir R. Robinson for his hospitality and to Imperial Chemical Industries, Ltd. for financial assistance.—A. W.

(2) Gauthier, *Compt. rend.*, **152**, 1100, 1259 (1911); Tiffeneau and Levy, *Bull. soc. chim.*, **37**, 1247 (1925); Asahina and Terasaka, *J. Pharm. Soc.* (Japan), **494**, 219 (1923).

(3) Weissberger, Strasser, Mainz and Schwarze, *Ann.*, **478**, 112 (1930).

(4) *Cf.* James and Weissberger, THIS JOURNAL, **59**, 2040 (1937).

(5) Kohler and co-workers, *ibid.*, **57**, 2517 (1935); **58**, 2166 (1936); **59**, 887 (1937).

(6) Fuson and co-workers, *ibid.*, **58**, 1233 (1936), and succeeding papers.

(7) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930). We wish to thank Dr. Alan Bell of these laboratories for the "Grignard Machine" analyses.