[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF DEPAUW UNIVERSITY]

Diethylaminoalkyl Ester Hydrochlorides of N-Alkyl-4-carbostyrilcarboxylic Acids

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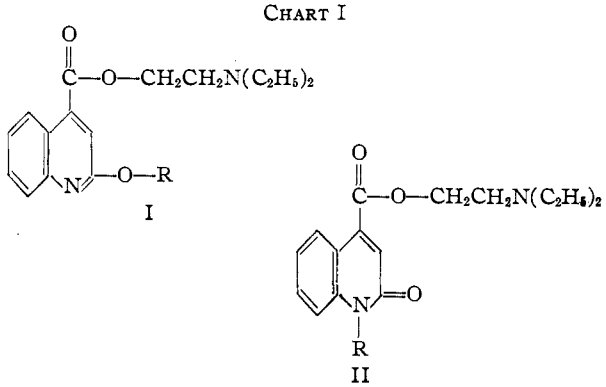
The β-diethylaminoethyl ester hydrochlorides of various 2-alkoxycinchoninic acids are known to possess local anesthetic activity. By a series of reactions the isomeric diethylaminoethyl and propyl ester hydrochlorides of N-alkyl-4-carbostyrilcarboxylic acids have been prepared. Preliminary anesthetic tests on the tongue have indicated that these compounds are devoid of any marked activity. This appears to be in agreement with the studies of Wojahn who postulated that the 2-alkoxyquinoline group must be present for activity.

Wojan[3] has prepared a number of diethylaminoethyl esters of various 2-alkoxycinchoninic acids and has shown these compounds to possess anesthetic values (Chart I, Compound I). The property was best shown by diethylaminoethyl 2-butoxycinchoninate hydrochloride which gave a three-hour anesthesia when 10–20 mg. of the compound was placed on the tongue for three minutes.

CHART I



Gardner and Hammel[4] have also prepared a series of esters from β-morpholinethanol and γ-morpholinepropanol and various 2-alkoxycinchoninic acids. They have found these compounds to possess a local anesthetic value when tested on the tongue.

Since work reported from this Laboratory involved the preparation of N-methyl-4-carbostyrilcarboxylic acid,[5] it was of interest to us to prepare a series of these acids and the subsequent diethylaminoalkyl ester hydrochlorides and test these compounds for possible anesthetic properties (Chart I, Compound II). Although no pharmacological tests have been made on these compounds as yet, preliminary tests indicate that the hydrochlorides do not exhibit any pronounced anesthetic activity when tested on the tongue. This observation appears to be in accordance with Wojan[6] who reported from his studies with 2-alkoxycinchoninic acid amids and 2-alkoxy-4-aminomethylquinolines, that the 2-alkoxyquinoline group is the activating part of the molecule. Apparently, from our studies, the replacement of the 2-alkoxy group by the N-substituted alkyl group destroys the anesthetic principle. It is interesting to note that this change in the molecule will destroy the basic property of the ring nitrogen, since the compound becomes a cyclic anilide.

Attempts first were made to prepare the N-alkyl-4-carbostyrilcarboxylic acids by the method described by Thielepape[7] whereby the N-alkylacetanilide was condensed with diethyl oxalate and the subsequent ethyloxalyl-N-alkylacetanilide treated with concentrated sulfuric acid to form the ethyl ester of the N-alkyl-4-carbostyrilcarboxylic acid. The free acid was then obtained by basic saponification. This preparation was successful for N-methyl-4-carbostyrilcarboxylic acid, but with larger alkyl groups substituted on the nitrogen, the yields of the ethyloxalyl-N-alkylacetanilide were too small for further preparations. The acids were finally obtained by first preparing the N-alkyl-4-methylcarbostyrils as described by Kaslow and Cook,[8] converting these compounds to the corresponding N-alkyl-4-carbostyrilcarboxaldehydes (see Table I) as described by Cook and Stamper[5] and finally oxidizing the aldehydes to the acid (see Table II) with acid sodium dichromate.

TABLE I

N-ALKYL-4-FORMYLCARBOSTYRILS

Alkyl	M.p., °C.	Yield, %	N analyses, % Calcd.	Found
Methyl	179–180	89	[a]	
Ethyl	117.5–119	56	[a]	
Propyl	104–105.5	39	6.79	6.88
Butyl	112–113.5	32	6.11	6.54
Amyl	74–75.5	19	5.76	5.54
i-Amyl	71–72.5	27	5.76	5.89

[a] Previously reported.

TABLE II

N-ALKYL-4-CARBOSTYRILCARBOXYLIC ACIDS

Alkyl	M.p., °C.	Yield, %	N analyses, % Calcd.	Found
Methyl	240–246 (dec.)	60.8	[a]	
Ethyl	204–207 (dec.)	67.4	[b]	
Propyl	198–202 (dec.)	61.3	6.06	6.19
Butyl	178–183 (dec.)	82.5	5.71	5.81
Amyl	161–163 (dec.)	72.1	5.40	5.89
i-Amyl	171–174 (dec.)	36.3	5.40	5.44

[a] Previously reported. [b] F. J. Myers and H. G. Lindwall, THIS JOURNAL, 60, 644 (1938), report m.p. 205–206°.

Attempts to prepare the acid chlorides of these acids for the conventional method of esterification with β-diethylaminoethanol and γ-diethylaminopropanol proved impossible. Also, there was no success in attempts to prepare the esters from the sodium salt of the acid and the diethylaminoalkyl

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(3) H. Wojan, *Arch. Pharm.*, **269**, 422 (1931); *C. A.*, **25**, 5244 (1931).

(4) J. H. Gardner and W. M. Hammel, THIS JOURNAL, **58**, 1360 (1936).

(5) D. J. Cook and M. Stamper, *ibid.*, **69**, 1467 (1947).

(6) H. Wojan, *Arch. Pharm.*, **274**, 83 (1936); *C. A.*, **30**, 4167 (1936).

(7) E. Thielepape, *Ber.*, **55**, 127 (1922).

(8) C. E. Kaslow and D. J. Cook, THIS JOURNAL, **67**, 1969 (1945).

chloride. The ester hydrochlorides were finally prepared according to the method of Burtner and Cusic[9] by refluxing the acid and the diethylaminoalkyl chloride in *i*-propyl alcohol and obtaining the hydrochloride as a precipitate. Isopropyl alcohol proved suitable as a solvent for the preparation of the ester hydrochlorides of 1-methyl- and 1-ethyl-4-carbostyrilcarboxylic acids, but it was found that *i*-amyl alcohol was necessary as the solvent for the acids where the 1-substituent was a larger alkyl group. These ester hydrochlorides are listed in Table III. These compounds are stable under anhydrous conditions, but hydrolyze rapidly in moist air. Attempts were also made to isolate the hydrochlorides of the 1-propyl, 1-amyl and 1-isoamyl derivatives of the diethylaminoethyl carbostyrilcarboxylate, but no analytical pure samples could be recovered. The conversion of the hydrochlorides to the free bases and recrystallization of these products from water–ethanol solution gave a transesterification to the ethyl ester of the 1-alkyl-4-carbostyrilcarboxylate. No free bases were isolated.

TABLE III

β-DIETHYLAMINOETHYL N-ALKYL-4-CARBOSTYRILCARBOXYLATE HYDROCHLORIDES

Alkyl	M.p., °C.	Yield, %	N analyses, % Calcd.	Found
Methyl	196–197.5	72	8.28	8.06
Ethyl	168–170	52	7.95	8.27
Butyl	129–131.5	29	7.36	6.95
γ-Diethylaminopropyl N-alkyl-4-carbostyrilcarboxylate Hydrochloride				
Methyl	182–184	41	7.95	8.02

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Experimental[10]

The starting materials, N-methyl-, N-ethyl-, N-propyl-, N-butyl- and N-isoamylanilines, were all Eastman Kodak products. N-Amylaniline was prepared from the sodium salt of acetanilide with amyl bromide and obtained by saponification of the N-amylacetanilide. The N-alkyl-4-methylcarbostyrils were all prepared by a method described by Kaslow and Cook.[8] All of the N-alkyl-4-methylcarbostyrils except N-isoamyl-4-methylcarbostyril have been previously prepared.

N-Isoamyl-4-methylcarbostyril.—Eighty-one and six-tenths grams (0.50 mole) of N-isoamylaniline was treated with 63 g. (0.75 mole) of diketene in the same manner as previously described.[8] The oil formed after sulfuric acid ring closure and dilution with ice-water was extracted with ether, dried and recrystallized from a 1:1 mixture of benzene and petroleum ether. A white crystalline solid weighing 73.9 g. (69%) and which after a second crystallization melted at 70–71.5° was obtained.

Anal. Calcd. for $C_{15}H_{19}ON$: N, 6.11. Found: N, 6.07.

The **N-alkyl-4-formylcarbostyrils** were all prepared by methods which have been previously described.[5,11] The data concerning these compounds is recorded in Table I.

The N-alkyl-4-carbostyrilcarboxylic acids were all prepared by the oxidation of the aldehyde with acid sodium dichromate. The description of one of these oxidations will illustrate the method.

N-Methyl-4-carbostyrilcarboxylic Acid.—Thirty grams (0.16 mole) of 1-methyl-4-carbostyrilcarboxaldehyde was suspended in 300 ml. of water. Thirteen and nine-tenths grams of sodium dichromate (0.05 mole) was dissolved in the water suspension and with constant stirring 49 g. of concentrated sulfuric acid was added dropwise. After the addition of the acid was complete, the mixture was heated on the steam-bath for 30 minutes. The reaction flask was then cooled in an ice-bath and the solid recovered by filtration. This solid was dissolved in 80 ml. of five per cent. sodium hydroxide, filtered and the filtrate cooled. After cooling the acid was recovered by acidifying the filtrate with five per cent. hydrochloric acid. The recovered acid when dried weighed 19.8 g. (60.8%) and when recrystallized from boiling water was found to melt at 240–246° (dec.).

The data concerning the various acids prepared are recorded in Table II.

The preparation of the **β-diethylaminoethyl and γ-diethylaminopropyl ester hydrochlorides** is illustrated by the following example.

β-Diethylaminoethyl 1-Methyl-4-carbostyrilcarboxylate Hydrochloride.—Five grams (0.03 mole) of 1-methyl-4-carbostyrilcarboxylic acid was heated to reflux in 80 ml. of isopropyl alcohol and to this hot solution was added 3.4 g. (0.03 mole) of β-diethylaminoethyl chloride.[12]

The isopropyl alcohol solution was refluxed for 2.5 hours and upon cooling a pale tan colored precipitate formed. Six grams (72.3%) of the β-diethylaminoethyl 1-methyl-4-carbostyrilcarboxylate hydrochloride was recovered. A 0.5-g. sample was dissolved in a solution containing 10 ml. of dioxane, 10 ml. of ethyl ether and 10 ml. of ethyl alcohol. After filtering hot with a pinch of norite, 5 ml. of ethyl ether was added to the filtrate and white crystals precipitated which melted at 196–197.5°.

Anal. Calcd. for $C_{17}H_{23}O_3N_2Cl$: N, 8.28. Found: N, 8.06.

The other ester hydrochlorides were prepared in an analogous manner except *i*-amyl alcohol was used for the solvent in the preparation of the 1-butyl derivative. The data for these compounds are recorded in Table III.

Ethyl 1-Methyl-4-carbostyrilcarboxylate.—When a 0.5-g. sample of β-diethylaminoethyl 1-methyl-4-carbostyrilcarboxylate hydrochloride was dissolved in 5 ml. of water and made basic with concentrated ammonium hydroxide, an oil separated which crystallized on cooling. This product was redissolved by the addition of 2–3 ml. of ethyl alcohol and heating. Upon cooling tan colored crystals were obtained which melted at 128–130°. Treatment of γ-diethylaminopropyl 1-methyl-4-carbostyrilcarboxylate hydrochloride in the same manner resulted in a similar product melting at 128–130°. A mixed melting point of these two products showed no depression and a mixed melting point of these two products with an authentic sample of ethyl 1-methyl-4-carbostyrilcarboxylate showed no depression.

Ethyl 1-Ethyl-4-carbostyrilcarboxylate.—A 0.2-g. sample of β-diethylaminoethyl 1-ethyl-4-carbostyrilcarboxylate hydrochloride was treated with concentrated ammonium hydroxide and recrystallized from ethyl alcohol in a manner analogous to the previous experiment. Cream colored needles formed which melted at 83–84.5° and with recrystallization melted at 87–88°. By analysis this compound was shown to be the ethyl ester of the 1-ethyl derivative and not the free base. F. J. Myers and H. G. Lindwall reported this compound as melting at 88.5–89°.

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(9) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(10) Melting points were taken on a Fisher–Johns melting block.

(11) D. J. Cook, R. Sears and D. Dock, *Proc. Indiana Acad. Sci.*, **58**, 145 (1948).

(12) Prepared according to Slotta and Behnisch, *Ber.*, **68**, 758 (1935).