Synthesis and Local Anesthetic Activity of Several Dialkylaminoalkyl Esters of Indole Carboxylic Acids

By SAMUEL ELKIN† and FRANCIS M. MILLER

The largest number of compounds synthesized for local anesthetic purposes are the alkamine esters of aromatic acids. In this work, two indole carboxylic acids were incorporated as the acid portion of the ester. All the compounds were effective as topical anesthetics, but had no action on unbroken skin. Nitration of indole-3-carboxylic acid reduced the duration of activity of the esters. The esters of indole-2-carboxylic acid showed a marked decrease in duration of local anesthetic activity.

At present, most of the compounds synthesized for local anesthetic purposes are alkamine esters of aromatic acids. They furnish the preponderant number of marketable local anesthetics.

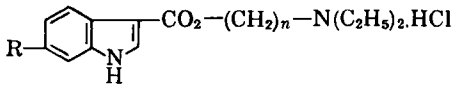
While procaine is relatively low in toxicity and very effective when given hypodermically (1), it requires the addition of a vasopressor substance to help localize the drug at the nerve and thereby prolong the period of anesthesia. Procaine is also only very slightly active as a topical anesthetic. Hence, many compounds of the same general type have been synthesized to improve these properties.

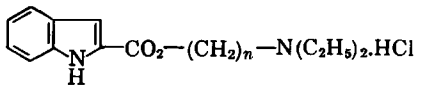
Among the modifications studied are included those which contain a heterocyclic aromatic ring in the acid portion of the molecule. Blicke and Jenner (2) prepared several dialkylaminoalkyl nicotinates, 2-alkyl acid quinolates, and 2-alkyl-3-dialkylaminoalkyl quinolates. They reported that none of these compounds possessed marked activity as local anesthetics.

Blicke and Blake (3) found that the local anesthetic action of a procaine-type compound can be retained by the substitution of a 2-pyrrolyl moiety for the benzoyl and 4-aminobenzoyl groups and by the replacement of dimethyl and diethylamino groupings by 1-pyrrolyl and 1-pyrollidinyl nuclei.

Burtner and Lehmann (4) investigated a series of alkylaminoalkyl esters of carbazole, dibenzfuran, and dibenzthiophene carboxylic acids. They prepared several effective local anesthetics. The best one of the series was β - diethylaminoethyl - 5 - ethylcarbazole - 3 - carboxylate hydrochloride. However, all of the foregoing were irritating and could not be regarded as useful anesthetics. An interesting conclusion which Burtner and Lehmann were able to derive from their investigations was that the activity of the compounds they prepared appeared to be predominantly a function of the carboxyl group rather than of other structural features. That is, equal concentrations of derivatives of carbazole-2- and carbazole-3-carboxylic acids were equally effective. However, the derivatives of carbazole-4-carboxylic acid showed no anesthetic activity.

In this investigation the following dialkylaminoalkyl esters of indole-3-carboxylic acid and indole-2-carboxylic acid have been prepared





I, R = H, n = 2; II, R = H, n = 3; III, R = NO_2, n = 2; IV, R = NO_2, n = 3; V, n = 2; VI, n = 3. The effectiveness of these compounds as local anesthetics has been determined. II showed the most pronounced activity followed by I.

The esters were prepared essentially according to the method of Burtner and Cusic (5). The indole carboxylic acids were dissolved in hot isopropanol and either 2-diethylaminoethyl chloride or 3-diethylamino-1-propyl chloride was added to the refluxing solution. The mixture was allowed to reflux for $2^1/_2$ hours and then cooled overnight. The method of isolation of the resulting compounds varied because of the difference in their solubility.

EXPERIMENTAL

Indole-3-carboxylic Acid (6, 7).—Into a thoroughly dried 1-L. flask equipped with stirrer, dropping funnel, and condenser (drying tube) were placed 12 Gm. (0.5 mole) of magnesium turnings, 100 ml. of anhydrous ether, and a small crystal of iodine as catalyst. Ethyl iodide, 5 Gm., was added all at

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TABLE I.—COMPILED DATA ON THE ESTERS PREPARED

Ester	Yield, %	M.p., °C.	Formula	Analysis N Calcd.	Analysis N Found
I	25.0	174–175	$C_{15}H_{21}N_2O_2Cl$	9.44	9.27
II	21.8	165–167	$C_{16}H_{23}N_2O_2Cl$	9.01	8.80
III	15.6	210–212	$C_{15}H_{20}N_3O_4Cl$	12.30	12.62
IV	15.1	208–210	$C_{16}H_{22}N_3O_4Cl$	11.81	12.13
V	6.2	178–180	$C_{15}H_{21}N_2O_2Cl$	9.44	9.31
VI	17.5	170–171	$C_{16}H_{23}N_2O_2Cl$	9.01	9.06

once and, after a few moments, the yellow color of the iodine disappeared and the ether began to boil. The reaction was controlled by periodic cooling in an ice bath. An additional 75 Gm. (0.5 mole, total) of ethyl iodide was then added dropwise. Stirring was maintained after the addition of the ethyl iodide for about 1/2 hour or until the reaction mixture cooled to room temperature.

An ice-salt bath was applied and 29.5 Gm. (0.25 mole) of indole in 40 ml. of anhydrous ether was added gradually with vigorous stirring. Ethyl chlorocarbonate, 30 Gm. (0.28 mole), was then added dropwise to the cooled solution of indolylmagnesium iodide. The mixture was kept cold and stirring was maintained for an hour after the addition of the ethyl chlorocarbonate. Ice water was added very slowly and the resulting mixture was acidified with acetic acid and the ether layer separated. The ether solution was washed with sodium bicarbonate and dried over sodium sulfate.

Removal of the ether under reduced pressure left a red oily residue of the ethyl ester. This was not purified, but was hydrolyzed by refluxing for 2 1/2 hours with 100 ml. of 0.5 *N* potassium hydroxide. The aqueous solution was separated from a gummy residue that formed, acidified with acetic acid whereby indole-3-carboxylic acid precipitated. The product was transferred to a beaker and washed with a little ether and petroleum ether to remove any unreacted indole. The acid was filtered and recrystallized from a 40% aqueous ethanol solution. Yield, 19 Gm. (47.5%); m.p., 218–220°. Reported m.p., 218–220° (6); 220–224° (8).

6-Nitroindole-3-carboxylic Acid.—Ten grams (0.06 mole) of indole-3-carboxylic acid was suspended in 50 ml. of glacial acetic acid contained in a 600-ml. beaker. A 50-ml. quantity of concentrated nitric acid was added dropwise with stirring. During the addition of the nitric acid the mixture turned a deep red and began to boil. The reddish-brown residue was collected after cooling overnight. This was dissolved in hot ethanol and treated with charcoal. After filtering, water was added to the alcoholic solution and a bright yellow product precipitated. Yield, 4 Gm. (31.2%); darkened at 223° and decomposed at 275–280°. Reported, darkening at 227° and decomposing at 275–280° (7).

Indole-2-carboxylic Acid.—Prepared from *o*-nitrophenyl-pyruvic acid (9) upon boiling with ferrous sulfate in ammonium hydroxide (10). M.p. 197–200°. Reported m.p., 202–204° (10).

2-Diethylaminoethyl Chloride.—Prepared according to Shirley (11) from 2-diethylaminoethyl chloride hydrochloride by treatment with sodium hydroxide and extraction with ether; b.p., 146–148°/756 mm. Reported b.p., 146–147°/750 mm. (11).

3-Diethylamino-1-propyl Chloride.—Prepared in the same manner as indicated under 2-diethylaminoethyl chloride. The free base, a colorless oil distilled at 94–95°/42 mm. Reported b.p., 82°/28 mm. (12).

2-Diethylaminoethyl Indole-3-carboxylate Hydrochloride (I)[1].—Into a 300-ml. flask equipped with stirrer, dropping funnel, and condenser were placed 5 Gm. (0.031 mole) of indole-3-carboxylic acid and 80 ml. of isopropanol. The acid dissolved upon heating. The solution was allowed to reflux and 4.2 Gm. (0.03 mole) of 2-diethylaminoethyl chloride was added dropwise. The mixture was refluxed for 2 1/2 hours and allowed to cool overnight. A white precipitate formed which was filtered off and washed with anhydrous ether. Recrystallization from isopropanol gave a product which was very readily soluble in water.

3-Diethylaminopropyl Indole-3-carboxylate Hydrochloride (II).—Into a 300-ml. flask equipped with stirrer, dropping funnel, and condenser were placed 4.5 Gm. (0.028 mole) of indole-3-carboxylic acid and 75 ml. of isopropanol. The acid dissolved upon heating. The solution was allowed to reflux and 4.2 Gm. (0.028 mole) of 3-diethylamino-1-propyl chloride was added dropwise. The mixture was refluxed for 2 1/2 hours and allowed to cool overnight. No precipitation resulted. The solvent was removed under reduced pressure leaving a reddish oil. The oil was washed several times with anhydrous ether whereupon it became semisolid and almost white. The compound was then treated with isopropanol and a small amount of anhydrous ether, and a white solid precipitated upon scratching. The product was recrystallized from absolute ethanol and ether.

All esters were prepared in a manner described above. Pertinent data are presented in Table I.

Pharmacological Procedures.—The hair around the rabbit's eye was carefully clipped. The winking reflex was tested by gently touching the center of the cornea with a bluntly pointed glass rod. Four drops (equivalent to 1.4 mg.) of 1% aqueous test

TABLE II.—LOCAL ANESTHETIC ACTIVITY OF THE DIALKYLAMINOALKYL ESTERS PREPARED

Ester	Trials	Minimum Duration, min.	Maximum Duration, min.	Average
I	35	68	152	94.2
II	18	83	141	117.0
III	6	49	73	57.4
IV	11	64	105	80.7
V	8	5	11	7.0
VI	7	25	47	36.0

[1] *Note added in galley proof:* J. Büche, *et al.*, *Arch. Pharmazie*, **295**, 209(1962), report the preparation of 2-diethylaminoethyl indole-3-carboxylate hydrochloride and the corresponding 6-nitro derivative.

solution was instilled into the conjunctival sac of the left eye by means of a pipet (28 drops per ml.). The right eye was maintained as a control. The solution was allowed to remain in contact with the surface of the eyeball for 2 minutes by gently pressing the lids together. The time of abolishment of the wink reflex was noted and the duration of anesthesia was tested at 2-minute intervals.

RESULTS

None of the compounds gave any evidence of any deleterious action on the eye. The eyes were carefully checked for corneal pitting, excessive lacrimation, and hyperemia. None of these was present. Pharmacological data are presented in Table II.

SUMMARY

Several dialkylaminoalkyl esters of two indole carboxylic acids were prepared. All of the compounds were effective as topical anesthetics, but had no action on unbroken skin. Nitration of indole-3-carboxylic acid reduced the duration of activity of the esters. The esters of indole-2-carboxylic acid showed a marked decrease in duration of local anesthetic activity.

REFERENCES

(1) Moore, M. B., THIS JOURNAL, 33, 194(1944).
(2) Blicke, F. F., and Jenner, E. L., *J. Am. Chem. Soc.*, 64, 1721(1942).
(3) Blicke, F. F., and Blake, E. S., *ibid.*, 53, 1015(1931).
(4) Burtner, R. R., and Lehmann, G., *ibid.*, 62, 527(1940).
(5) Burtner, R. R., and Cusic, J. W., *ibid.*, 65, 262(1943).
(6) Majima, R., and Kotake, M., *Ber.*, 55, 3861(1922).
(7) Majima, R., and Kotake, M., *ibid.*, 63, 2240(1930).
(8) Doyle, F. P., *et al.*, *J. Chem. Soc.*, 1956, 2855.
(9) DiCarlo, F. J., *J. Am. Chem. Soc.*, 66, 1420(1944).
(10) Kermach, W. O., *et al.*, *J. Chem. Soc.*, 119, 1602(1921).
(11) Shirley, D. A., "Preparation of Organic Intermediates," John Wiley & Sons, Inc., New York 16, N. Y., 1951, pp. 116–117.
(12) Slotta, K. H., and Behnisch, R., *Ber.*, 68, 754(1935).

Synthesis of Some Hydrazono Derivatives of *p*-[N,N-Bis(β-chloroethyl)amino]benzaldehyde

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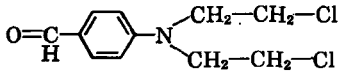
THE CONDENSATION of *p*-[N,N-bis(β-chloroethyl)amino]benzaldehyde (1, 2) (I, benzaldehyde nitrogen mustard) with active methylene groups, (2, 3, 4) hydrazides (2) and amines (5, 6) have been reported. Recent discovery of the activity of some anil derivatives against Dunning leukemia in rats (6) and the inhibitory effect of 8-[bis(β-chloroethyl)triazeno]theophylline (II) (7) on spontaneous tumor (8) prompted the synthesis of some benzalhydrazone derivatives (III) for biological evaluation.



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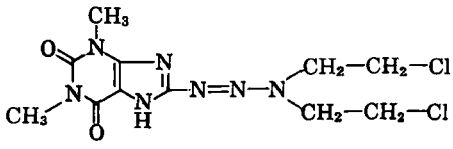

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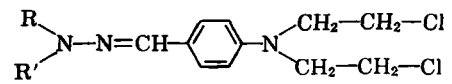

III

The preparation of III, together with the starting materials used, is described in the experimental section.

EXPERIMENTAL[1]

Synthesis of Hydrazinopyrimidines.—To a mixture of 35 Gm. of chloropyrimidine in 70 ml. of absolute ethanol was added, with stirring, 35 ml. of anhydrous hydrazine at such a rate that the reaction temperature remained at 65–75° (occasional cooling in an ice bath may be necessary). After the addition was complete, the resulting solution was stirred at room temperature for 30 minutes, during

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[1] All melting points were taken on the Thomas-Hoover melting point apparatus.