Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 69.8; H, 9.1.

Pregnanetriol-3(α),16,20 from *epi*-Sarsasapogenin.—*epi*-Sarsasapogenin acetate was treated with potassium persulfate as described above. After hydrolysis with ethanolic potassium hydroxide the neutral fraction yielded a substance which crystallized from ether to give white crystals, m. p. 206–207°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.9; H, 10.7.

With benzoyl chloride in pyridine the product gave a **benzoate** which crystallized from aqueous acetone as small white needles, m. p. 153–155°.

Anal. Calcd. for $C_{42}H_{48}O_6$: C, 77.7; H, 7.5. Found: C, 77.3; H, 7.4.

Conversion of Pregnanetriol-3(β),16,20 to Pregnanediol-3(α),20(α).—To a solution of 900 mg. of pregnanetriol in 35 cc. of acetic acid was added slowly a solution of 400 mg. of chromic anhydride in 5 cc. of water and 15 cc. of acetic acid. The solution was allowed to stand at room temperature for twenty minutes and then diluted with water and the product taken up in ether. The ether solution was washed with sodium hydroxide solution and water and evaporated to dryness to give a colorless neutral oil which was dissolved in 200 cc. of boiling absolute ethanol and reduced with 10 g. of sodium. Water was then added and the neutral fraction extracted with ether. The ether solution was washed with water and evaporated to leave a yellow oily residue which was dissolved in 10 cc. of acetone and allowed to stand overnight. The product which crystallized from the solution was purified by further recrystallization from acetone to give pregnanediol-3(α),-20(α), m. p. 235–238°. It gave no depression with a sample of pregnanediol-3(α),20(α), m. p. 236–239°. It gave a depression of 20° with the original pregnanetriol.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.7; H, 11.2.

Treatment with acetic anhydride gave the **diacetate** of **pregnanediol-3(α),20(α)**, m. p. 177–179°, which gave no depression of the melting point with the known diacetate, m. p. 178–180°.

Summary

Sarsasapogenin has been converted to pregnanetriol-3,16,20 by persulfate oxidation.

STATE COLLEGE, PENNA. RECEIVED DECEMBER 26, 1939

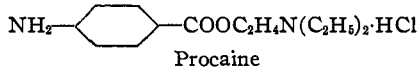
[CONTRIBUTION FROM THE LABORATORY OF G. D. SEARLE & CO., AND DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY, UNIVERSITY OF LOUISVILLE]

Heterocyclic Local Anesthetics. Carbazole, Dibenzofuran and Dibenzothiophene Derivatives[1]

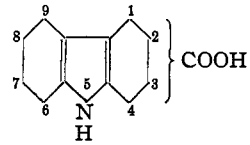
BY ROBERT R. BURTNER AND GERHARD LEHMANN

In any study of local anesthetics of the procaine type one is impressed by the fact that most of the structural variations have been focused upon the amino alcohol portion of the molecule. The effect of alkylation of the nuclear amino group has been studied, and in a few instances useful drugs have resulted, whereas the introduction of an aryl group in this position has received little or no attention.

The carbazole carboxylic acids offered a readily available group of starting materials of the latter type with the interesting variation involving the carbon–carbon bond between the two benzene nuclei.



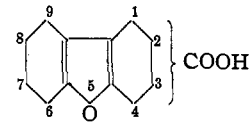
Procaine



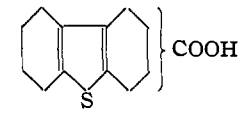
Carbazolecarboxylic acid

Previous investigation of a series of esters of carbazole-N-(or 5)-carboxylic acid by Knoefel[2] led to some rather active compounds of low toxicity. In the present study a series of dialkylaminoalkyl esters of the isomeric carbazolecarboxylic acids was prepared with suitable variations involving the alcohol portion of the molecule as well as nuclear substituents.

Seeking to determine the effect of replacement of the heterocyclic element by oxygen and sulfur an analogous series of esters of dibenzofuran and dibenzothiophenecarboxylic acids was investigated.



Dibenzofurancarboxylic acid



Dibenzothiophenecarboxylic acid

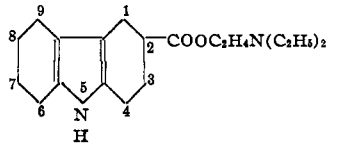
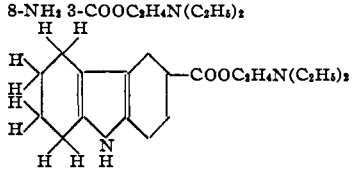
In order to study the effect of the carbon–carbon bond between the two benzene nuclei on the activity of compounds of this type, the correspond-

(1) Presented before the Medicinal Section of the American Chemical Society at the Baltimore Meeting, April, 1939.

(2) Knoefel, *J. Pharmacol.*, **47**, 69 (1933).

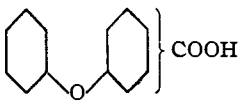
TABLE I

CARBAZOLE LOCAL ANESTHETICS

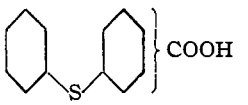
No.	Structure	Hydrochloride m. p., °C.	N analyses, % Calcd.	Obsd.	Min. duration of corneal anesthesia in rabbits[a] 0.1%	0.5%	1.0%	Av. subcutaneous toxicity in mice g./kg.[c]
1		195	8.1	8.3	14[e]+	27++		0.4[d]
2	3-$COOC_2H_4N(C_2H_5)_2$	127 (base)	8.97	8.91	10+	30++		.5
3	4-$COOC_2H_4N(C_2H_5)_2$	Viscous oil	Cl, 10.22	10.38	0		8−	2.0
4	2-$COOC_2H_4N(n\text{-}C_4H_9)_2$	187	6.95	6.99	7−	14−		1.0
5	2-$COOCH_2CH_2CH_2N(C_2H_5)_2$	169	7.96	7.77	17+	36++		0.15
6	5-C_2H_5 2-$COOC_2H_4N(C_2H_5)_2$	204	7.48	7.6	4[e]−		7+	.7
7	5-$n\text{-}C_4H_9$ 2-$COOC_2H_4N(C_2H_5)_2$	Glass (sulfate)	6.74	6.5			0[b]	3.5
8	5-C_2H_5 3-$COOC_2H_4N(C_2H_5)_2$	174	7.48	7.40	36[e]+	43++		0.5[d]
9	5-$n\text{-}C_4H_9$ 3-$COOC_2H_4N(C_2H_5)_2$	Viscous oil	Cl, 8.79	8.91				
10	8-NH_2 3-$COOC_2H_4N(C_2H_5)_2$	146–147 (base)	12.5	12.7				
11		234	8.0	8.0	12+	29++		0.08

[a] 0 = none, − = weak, + = full, ++ = deep. A 1% cocaine solution gave deep anesthesia lasting fifteen minutes. [b] A 5% solution of this compound gave weak anesthesia for three minutes. [c] Dose at which 50% of animals died. The fatal dose of cocaine is 0.08 g./kg. [d] Intravenous M. L. D. in rabbits = 20 mg./kg. [e] The duration of anesthesia for 5% solutions of compounds 1, 6, 8 and procaine applied intracutaneously in man is 69 min., 34 min., 24 hr. and 70 min., respectively.

ing derivatives of diphenyl ether and diphenyl sulfide also were prepared.



Phenoxybenzoic acid



Thiophenoxybenzoic acid

Experimental Part

Carbazole Derivatives.—The unsubstituted carbazolecarboxylic acids were prepared either by carbonation of the N-potassium derivative followed by pyrolytic rearrangement, or by alkali fusion of the corresponding methyl ketones according to known methods.[3,4] 5-Ethylcarbazole-2-carboxylic acid was obtained in good yield by alkylation of the acid with ethyl sulfate followed by saponification.[5]

5-*n*-Butylcarbazole-2-carboxylic Acid.—A mixture of 21 g. of carbazole-2-carboxylic acid, 47 g. of *n*-butyl sulfate, 42 g. of sodium hydroxide (dissolved in 28 cc. of water) and 146 cc. of acetone was shaken vigorously with intermittent cooling for ten minutes. The solid mass was poured into one liter of water containing 50 g. of sodium hydroxide and concentrated to a volume of 500 cc. The resulting solution was chilled, filtered and acidified. The crude product, which became granular on standing overnight, was filtered out, dried and crystallized from petroleum ether. The yield of white needles melting at 157° was 15 g.

(3) German Patent 442,609; British Patent 27,051.

(4) Meitzner, THIS JOURNAL, **57**, 2327 (1935); Plant and Williams, *J. Chem. Soc.*, 1142 (1934); Borsche and Fiese, *Ber.*, **40**, 378 (1907).

(5) Gilman and Kirby, *J. Org. Chem.*, **1**, 146 (1936).

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: N, 5.36.

5-Ethylcarbazole-3-carboxylic Acid.—Repeated attempts to alkylate carbazole-3-carboxylic acid using ethyl sulfate or ethyl iodide were unsuccessful. The desired product, however, was obtained easily by alkali fusion of 5-ethyl-3-acetylcarbazole described below.

Fifteen grams of 3-acetylcarbazole, 15 cc. of ethyl sulfate, 15 g. of sodium hydroxide (dissolved in 10 cc. of water) and 100 cc. of acetone were shaken for fifteen minutes. Dilution with water gave the crude product, which was crystallized from petroleum ether to yield 15 g. of 5-ethyl-3-acetylcarbazole melting at 97°.

Anal. Calcd. for $C_{16}H_{15}ON$: N, 5.9. Found: N, 5.6.

Potassium hydroxide fusion gave a 40% yield of the desired acid melting at 248° after crystallization from toluene.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.82. Found: N, 5.92.

5-*n*-Butylcarbazole-3-carboxylic Acid.—As with the ethyl derivative described above, this acid could not be prepared by direct alkylation but was obtained by alkali fusion of 5-*n*-butyl-3-acetylcarbazole.

A mixture of 28 g. of 3-acetylcarbazole, 70 g. of *n*-butyl iodide, 30 cc. of 66% potassium hydroxide and 140 cc. of acetone was refluxed for twenty-four hours. After dilution with water the acetone and excess butyl iodide were boiled off, the chilled mixture filtered and the crude product crystallized from petroleum ether to yield 28 g. of 5-*n*-butyl-3-acetylcarbazole melting at 74.5–75°.

Anal. Calcd. for $C_{18}H_{19}ON$: N, 5.28. Found: N, 5.41.

Fusion with potassium hydroxide gave an 8% yield of

the desired acid which was crystallized from benzene and melted at 198°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: N, 5.6.

8-Nitrocarbazole-3-carboxylic Acid.—Two grams of sodium nitrite was added in portions, with stirring, to a solution of 5.5 g. of carbazole-3-carboxylic acid in 80 cc. of acetic acid at 90°. A solution of 4.5 cc. of acetic acid and 4.5 cc. of concentrated nitric acid was then added dropwise with stirring at 80–85°. Stirring was continued for one hour at 85°, the resulting mixture chilled and the yellow product filtered out and washed with 50 cc. of alcohol. Refluxing with 100 cc. of alcohol and 40 cc. of 40% sodium hydroxide for thirty minutes gave, after dilution with water and acidification, 6 g. of a yellow amorphous powder, m. p. 335° (dec.). Crystallization from nitrobenzene raised the melting point to 338°.

Anal. Calcd. for $C_{13}H_8O_4N_2$: N, 10.95. Found: N, 11.1.

Decarboxylation with copper bronze in the high boiling fraction (b. p. 300–350°) of technical pyridine gave 2-nitrocarbazole.

6,7,8,9-Tetrahydrocarbazole-2-carboxylic Acid.—Thirty-eight grams of *p*-hydrazinobenzoic acid[6] and 38 cc. of cyclohexanone were heated on a steam-bath for fifteen minutes and then refluxed gently with stirring for fifteen minutes with 400 cc. of 10% (by volume) sulfuric acid. The chilled mixture was filtered, the crude product dissolved in dilute alkali, decolorized with Darco and acidified. The yield of pure product melting at 279° was 40 g.

Anal. Calcd. for $C_{13}H_{13}O_2N$: N, 6.51. Found: N, 6.46.

The dialkylaminoalkyl esters were prepared by conversion to their respective acid chlorides (by means of phosphorus trichloride) followed by treatment with the desired alcohol (method A) or by way of the ω-chloroalkyl ester which was then treated with the appropriate amine (method B).

β-Chloroethyl Carbazole-2-carboxylate.—A slow stream of dry hydrogen chloride was passed into a refluxing solution of 10 g. of carbazole-2-carboxylic acid in 50 cc. of ethylene chlorohydrin for a period of six hours. After standing overnight at laboratory temperature the mixture was poured into 400 cc. of ice water, the crystalline product filtered out, washed with sodium bicarbonate solution and crystallized from benzene to yield 8 g. of the ester melting at 141°.

Anal. Calcd. for $C_{15}H_{12}O_2NCl$: Cl, 12.95. Found: Cl, 13.0.

γ-Chloropropyl Carbazole-2-carboxylate.—A procedure similar to that above starting with 20 g. of the acid and 80 cc. of trimethylene chlorohydrin gave 18 g. of pure product, m. p. 129°.

Anal. Calcd. for $C_{16}H_{14}O_2NCl$: Cl, 12.32. Found: Cl, 12.26.

β-Diethylaminoethyl 5-Ethylcarbazole-2-carboxylate (Method A).—Ten grams of 5-ethylcarbazole-2-carboxylic acid and 40 cc. of phosphorus trichloride were heated on a steam-bath for one and one-half hours. The excess phosphorus trichloride was distilled off under reduced pressure and the acid chloride cautiously treated with 50 cc. of β-diethylaminoethanol. When the initial reaction had subsided, the mixture was heated on a steam-bath for fifteen minutes and then let stand overnight at laboratory temperature. After dilution with 500 cc. of water containing 50 cc. of 10% sodium hydroxide the oily base was extracted with ether, the ethereal extract washed with water and dried over sodium sulfate. The solvent was removed and the excess amino-alcohol distilled off under reduced pressure. The crude base was dissolved in 300 cc. of dry ether, treated with Darco and the filtrate saturated with dry hydrogen chloride. The viscous hydrochloride was taken up in 150 cc. of warm acetone from which it soon precipitated in crystalline form. The acetone filtrate was concentrated to 50 cc. to yield an additional amount of material. Crystallization of the combined products from methanol gave 7 g. of the hydrochloride melting at 204°.

γ-Diethylaminopropyl Carbazole-2-carboxylate (Method B).—Seventeen grams of γ-chloropropyl carbazole-2-carboxylate and 11 g. of diethylamine were heated in a sealed tube at 110° for thirty-six hours. The base was isolated and converted to its hydrochloride in the same manner as described in method A to give 8 g. of the desired compound melting at 169°.

β-Diethylaminoethyl 8-Aminocarbazole-3-carboxylate.—Using the procedure described under method A, β-diethylaminoethyl 8-nitrocarbazole-3-carboxylate hydrochloride was obtained, melting at 225–227°, after crystallization from ethanol.

Anal. Calcd. for $C_{19}H_{22}O_4N_2Cl$: N, 11.8. Found: N, 11.5.

Reduction was effected by means of iron filings and acetic acid in the customary manner. When the reaction was complete, the mixture was poured into water, made alkaline and filtered. The precipitate was extracted with acetone, the extract treated with Darco and the solvent removed. The crude base was then dissolved in ether and precipitated as the hydrochloride. Addition of alkali to an aqueous solution of the salt precipitated the base in crystalline form, which was filtered out and recrystallized from petroleum ether to give yellow plates, m. p. 146–147°.

Dibenzofuran and Dibenzothiophene Derivatives. β-(*p*-Phenoxy)-acrylic Acid.—Thirty-five grams of *p*-phenoxybenzaldehyde,[7] 175 cc. of acetic anhydride and 28 g. of twice fused sodium acetate were refluxed for eight hours and then diluted with 1400 cc. of warm water to destroy excess acetic anhydride. The mixture was made alkaline to phenolphthalein and extracted with ether to remove any oily precipitate. Acidification precipitated the crude acid which was crystallized from petroleum ether to yield 10 g. of acid melting at 135°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.18; H, 4.89. The acid chloride was obtained by treatment with thionyl chloride in benzene solution and boiled at 225° (18 mm.).

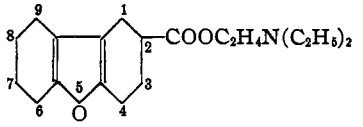
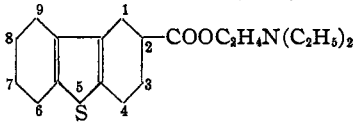
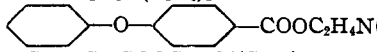
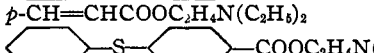
Since this paper was presented, *bis*-(β-diethylaminoethyl)-dibenzofuran-2,8-dicarboxylate dihydrochloride, m. p. 251–253°, has been prepared and found to be only faintly active at a concentration of 5%.

(6) Fischer, *Ann.*, **212**, 337 (1882).

(7) German Patent 650,430.

TABLE II

DIBENZOFURAN AND DIBENZOTHIOPHENE LOCAL ANESTHETICS

No.	Structure	Hydrochloride m. p., °C.	N analyses, % Calcd.	Obsd.	Min. duration of corneal anesthesia in rabbits[a] 0.1%	0.5%	1.0%	Av. subcutaneous toxicity in mice g./kg.[b]
12		185	4.03	4.09	4[d]+	11++	20++	0.45[c]
13	3-$COOC_2H_4N(C_2H_5)_2$	221	4.03	4.05	5+	25++	30++	.5
14	4-$COOC_2H_4N(C_2H_5)_2$	210	4.03	4.12	4−		11+	.45
15	2-$COOCH_2CH_2CH_2N(C_2H_5)_2$	185	3.38	3.51	8−	14+	35++	.3
16	2-$COOC_2H_4NHC_4H_9(i)$	212	4.03	4.2	0	14+	26+	.45
17	2-$COOC_2H_4NHC_5H_{11}(n)$	160	3.38	3.42	0	27+		.6
18	7-NH_2 2-$COOC_2H_4N(C_2H_5)_2$	255	7.72	7.8				
19	2-CH=CHCOOC$_2$H$_4$N(C$_2$H$_5$)$_2$	185	3.75	3.75	0	10+	13+	.5
20		219	3.86	4.1		8−		1.0
21	4-$COOC_2H_4N(C_2H_5)_2$	213	3.86	4.01		9−		0.65
22		136	4.0	4.05	[d]	15++	22++	.15
23	*p*-CH=CHCOOC$_2$H$_4$N(C$_2$H$_5$)$_2$	129–130	3.73	4.0				
24		137	S, 8.75	8.62	0	14+	34++	.35

[a] See (*a*) Table I. [b] See (*c*) Table I. [c] Intravenous M. L. D. in rabbits = 30 mg./kg. [d] The concentration and duration of anesthesia for solutions of compounds 12, 22 and procaine applied intracutaneously in man are, respectively: 0.5%, 60 min.; 0.2%, 53 min.; 0.5%, 70 min.

The other acids used in the preparation of the esters listed in Table II were prepared by known methods.[8,9] Although Courtot prepared dibenzothiophene-2-carboxylic acid by carbonation of the corresponding Grignard reagent,[8d] it also may be obtained by diazotizing the recently accessible 2-aminodibenzothiophene,[10] converting the diazonium halide to the nitrile and hydrolyzing according to the customary procedure.

The esters of the above acids were prepared by either of the two methods described in the case of the carbazolecarboxylic acids.

γ-Chloropropyl Dibenzofuran-2-carboxylate.—Twenty-three grams of dibenzofuran-2-carboxylic acid chloride and 50 cc. of trimethylene chlorohydrin were heated at 150° (bath temp.) for five hours, the excess trimethylene chlorohydrin distilled off under reduced pressure and the residual material poured into water. The crude product was washed with water and crystallized from petroleum ether to give 20 g. of ester melting at 85°.

Anal. Calcd. for $C_{16}H_{13}O_3Cl$: Cl, 12.27. Found: Cl, 12.25.

β-Diethylaminoethyl 7-Aminodibenzofuran-2-carboxylate.—7-Nitrodibenzofuran-2-carboxylic acid chloride, prepared by refluxing the nitro acid with thionyl chloride for ten hours, melted at 225° after crystallization from toluene. The acid chloride was treated in the usual manner with diethylaminoethanol to give an 85% yield of the nitro ester, m. p. 161°. Reduction of the nitro group was effected with iron filings and acetic acid in the usual manner. The crude oily product was dissolved in absolute ethanol and treated with one equivalent of alcoholic hydrogen chloride. Crystallization from ethanol gave the monohydrochloride, m. p. 255°.

β-Isobutylaminoethyl Dibenzofuran-2-carboxylate.—The β-isobutylaminoethanol is most conveniently prepared by the interaction of isobutyl bromide and ethanolamine.[11] The formation of the ester is best carried out in the manner of a Schotten–Baumann reaction according to the procedure of Goldberg and Whitmore.[12] The hydrochloride of this ester as well as the amyl derivative are somewhat unusual in that their aqueous solutions are slightly alkaline to litmus.

The β-*n*-amylaminoethanol and its ester are prepared in the same manner as described above.

Pharmacological Results

Anesthetic potency was determined on rabbits' cornea by applying the solutions for one minute and testing the reflex at each minute thereafter. At least six experiments were carried out for

(8) See the following references for preparation of these acids: (a) Borsche and Bothe, *Ber.*, **41**, 1940 (1908); (b) Kirkpatrick and Parker, THIS JOURNAL, **57**, 1126 (1935); (c) Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 778 (1937); (d) Courtot and Pomonis, *Compt. rend.*, **186**, 1624 (1928); (e) Weedon and Doughty, *Am. Chem. J.*, **33**, 424 (1905).

(9) Dibenzofuran-2-carboxylic acid was prepared by hypochlorite oxidation of 2-acetyldibenzofuran, and 7-nitrodibenzofuran-2-carboxylic acid was obtained by chromic acid oxidation of 7-nitro-2-acetyldibenzofuran in essential accordance with directions kindly supplied by Professor Henry Gilman.

(10) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(11) British Patent 482,886.

(12) Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

each concentration and compared with a 1% solution of cocaine. In most instances the induction period varied from one to three minutes.

Toxicity was determined by subcutaneous injections in white mice. In the carbazole series lethal doses resulted in convulsions preceded by excitement, whereas with the sulfur compounds and no. 22 the symptoms were weakness and depression even in fatal doses. The dibenzofuran derivatives in small doses cause depression, while larger amounts give rise to convulsions. The lethal intravenous dose in rabbits for compounds no. 1, 8 and 12 is 20, 20 and 30 mg./kg., respectively, death being preceded in each instance by clonic-tonic convulsions and dyspnea. Death occurred in all cases through respiratory failure.

Discussion

Of the simple unsubstituted carbazole esters the 2- and 3-isomers (nos. 1 and 2) exhibit about the same degree of anesthetic potency, with the 4-isomer falling considerably behind. Among the analogous dibenzofuran derivatives the 3-isomer (no. 13) possesses the greatest anesthetic potency, while the 2- and 4-isomers follow in order of decreasing activity. This was rather unexpected, since in compounds of the procaine type the para position (corresponding to the 2-position in carbazole) of the carboxyl group with respect to the amino group has been regarded as the most favorable combination, the meta and ortho isomers following in order of decreasing activity. Furthermore, in the case of the dibenzofuran compounds the observed order is likewise at variance with the predictions one might make from a study of the alkoxybenzoic acid esters in which the compounds bearing the side chain para to the ether linkage are the most active. It is possible that the abnormally high activity of the 3-isomer in either series may be due to the fact that the side chain occupies a position para to the *carbon–carbon* bridge and that this position combination exerts a more profound influence than that resulting from the para relationship between the imino group or the ethereal oxygen and the carboxyl group. With the analogous dibenzothiophene derivatives it is evident that these compounds possess a much weaker anesthetic action, exhibiting not only a shorter duration of corneal anesthesia but also a much less profound effect.

In the carbazole series the order of toxicity is quite definitely 2>3>4-isomer, while among the dibenzofuran isomers there is little difference in toxicity, whereas with the dibenzothiophene derivatives the order is reversed, the 4-isomer being the most toxic.

Extending the carbon chain between the carbonyl group and the terminal nitrogen atom in the carbazole or the dibenzofuran series practically doubles the toxicity with a much less significant increase in anesthetic potency. Substitution of *n*-butyl groups for ethyl in the alcohol of the carbazole esters results in a proportional decrease in activity and toxicity. The effect of replacing hydrogen by an alkyl group on the ring nitrogen varies with the position of the side chain. With the carboxyl group in the 3-position the introduction of the N-ethyl group nearly doubles the anesthetic potency without increasing the toxicity. It is interesting to note that this compound (no. 8) is at least three times as potent as cocaine and only one-fifth as toxic. When the carboxyl group is in the 2-position both toxicity and activity are reduced by the introduction of the N-ethyl group and practically lost with the substitution of an N-butyl group. Partial hydrogenation of the carbazole nucleus increases the toxicity by more than two-fold without affecting the potency.

The β-mono-isobutylaminoethyl dibenzofuran-2-carboxylate (no. 16) offers no advantage over the diethylaminoethyl ester (no. 12) and does not exhibit any measurable degree of pressor action. This is somewhat surprising, since the corresponding derivative of the procaine type recently described by Goldberg and Abramson[13] is considerably more active than procaine and possesses definite pressor activity. The mono-*n*-amyl ester (no. 17) is somewhat better than no. 12, since it has a slightly lower toxicity and greater duration of corneal anesthesia. The introduction of an ethylenic linkage between the dibenzofuran nucleus and the carbonyl group as in compound no. 19 results in a slight decrease in toxicity but a much greater drop in activity. This also is at variance with the expected result, since the introduction of an ethylenic linkage at such a point generally enhances the efficacy of the parent compound.

In considering the effect of opening the carbon–carbon bond between the two benzene nuclei as in compounds nos. 22 and 24, it is evident that such a transition in the oxygen derivative results pri-

(13) Goldberg and Abramson, *J. Pharmacol.*, **62**, 69 (1938).

marily in a marked increase in toxicity with only a minor increase in activity. In the case of the diphenyl sulfide ester the toxicity is likewise greater than that of its dibenzothiophene analog, although in this instance the anesthetic potency is substantially enhanced both as to duration and quality.

None of these compounds had a mydriatic action in the concentrations used, whereas they all caused more or less irritation of the cornea and conjunctiva, the extent of the damage depending on the concentration. The pathological changes were conjunctivitis, chemosis, opacity of the cornea and intense secretion with consequent ectropion.

Effect on Blood Pressure and Respiration.—The action on blood pressure and respiration was determined for compounds no. 1, 8 and 12 by intravenous injection of 5 mg./kg. in dogs anesthetized with ether or without anesthesia. All three drugs caused depression of respiration and a sharp fall in blood pressure, the latter effect being only slightly diminished by the addition of epinephrine.

Action on Human Skin.—The anesthetic action of five of these compounds was further examined by means of wheal experiments on human skin under aseptic conditions. The solutions were prepared so as to contain 0.9% sodium chloride and a concentration of epinephrine of 1:250,000. Two-tenths cc. of this solution was used for intracutaneous injection. The duration, quality of anesthesia and side effects were observed and compared with procaine.

The same relative order of activity as was observed in the corneal studies is maintained in this instance. The unusual duration of compound 8 is worthy of note. As might have been predicted from the experiments on the rabbit cornea each of the compounds thus examined was more or less irritating and painful on injection.

The irritating effects of the entire group of compounds appear to be inherent to the nucleus involved, since meticulous purification, variation of the substituent groups and changing the method of synthesis does not materially alter the situation.

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Summary

The investigation of a series of alkylaminoalkyl esters of carbazole-, dibenzofuran- and dibenzothiophenecarboxylic acids led to some powerful local anesthetics. The best one of the series is β-diethylaminoethyl 5-ethylcarbazole-3-carboxylate hydrochloride (no. 8), which is more than thrice as potent as cocaine and only one-fifth as toxic. The activity of these compounds appears to be predominantly a function of the position of the carboxyl group rather than other structural variations. Opening of the carbon–carbon bridge in the dibenzofuran and dibenzothiophene derivatives does not improve the therapeutic efficiency. All of these compounds were more or less irritating to the rabbit's eye and to human skin, so that they cannot be regarded as useful anesthetics.

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Sulfanilamide Derivatives. VI. Substituted N^1-Aliphatic Sulfanilamides[1]

BY M. L. CROSSLEY, E. H. NORTHEY AND M. E. HULTQUIST

A number of N^1-alkyl and hydroxyalkylsulfanilamides have been prepared by Kharasch, Mietzsch, Fourneau, Bauer and others.[2,3,4,5] As part of our program on N^1-substituted sulfanilamides, we have independently synthesized many of the derivatives reported by these authors, as well as a number of others which have not hitherto been published to our knowledge. The latter are sulfanilyl derivatives of aliphatic amines, amino-alcohols, diamino-alcohols, and amino-acids. Closely allied derivatives of morpholine and difurfurylamine are included.

The syntheses of these derivatives followed the

(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., September, 1939.

(2) M. S. Kharasch and O. Reinmuth, U. S. Patents 2,097,414, and 2,097,415, October 26, 1937.

(3) F. Mietzsch and J. Klarer, U. S. Patent 2,085,037, June 29, 1937.

(4) E. Fourneau, J. and Mme. J. Trefouel, F. Nitti and D. Bovet, *Compt. rend. soc. biol.*, **122**, 258 (1936).

(5) S. M. Rosenthal, H. Bauer and S. E. Branham, *Public Health Reports, U. S. Treas. Dept.*, **52**, 662 (1937).