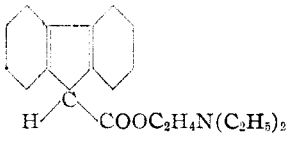
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE & Co.]

Antispasmodics. II. Basic Esters of Some Polynuclear Carboxylic Acids[1]

BY ROBERT R. BURTNER AND JOHN W. CUSIC

In the previous paper[2] it was observed that the formation of a carbon–carbon bond or bridge between the two benzene nuclei in certain basic esters of diphenylacetic acid resulted in a marked increase in spasmolytic activity without increasing the toxicity. Thus β-diethylaminoethyl fluorene-9-carboxylate which possessed the highest therapeutic index of the series, is approximately six times as effective as the corresponding ester of diphenylacetic acid. Seeking further to explore the possibilities of such polycyclic structures, we have prepared a series of esters in which the bridge between the benzene nuclei has been extended to include —CH_2—, —NH—, oxygen and sulfur.



Since the dihydroanthracene-9-carboxylic acid ester possessed extraordinarily high activity against spasm due to histamine, it was of interest to determine whether such activity might persist in analogous structures of a simpler type. Consequently, several derivatives of naphthoic acid were studied. The fluorene molecule was modified in a similar manner. Hypothetical removal of one of the benzene nuclei yields the analogous derivative of indene-1-carboxylic acid, while the biphenyl-2-acetic acid ester represents the product of cleavage at the methylene or 9-carbon atom.

Pharmacological Part

The pharmacological studies were carried out by Dr. Gerhard Lehmann of the Department of Physiology and Pharmacology, University of Louisville and will be described in detail in a future paper. Spasmolytic activity was determined on the isolated rabbit intestinal muscle by measuring the relaxation produced by the drug in question against spasm induced by 10^{-6} acetylcholine bromide and spasm caused by 2×10^{-4} histamine acid phosphate. The activities are expressed as reciprocal functions and are referred to β-diethylaminoethyl fluorene-9-carboxylate which had the most favorable therapeutic coefficient of our previous series and whose activity is arbitrarily designated as unity. Thus, the smaller the number a given compound shows under the heading Reciprocal Spasmolytic Activity, the greater is its activity. Toxicities were determined by intraperitoneal injection in mice and are expressed as the L. D.$_{50}$.

Experimental Part

Preparation of the Acids

9,10-Dihydroanthracene-9-carboxylic Acid.—Although Schlenk[3] first prepared this acid by the addition of sodium to anthracene followed by carbonation, a modification of the method of Gilman[4] offers a more convenient and productive synthesis.

A solution of *n*-butyllithium, prepared in the usual manner[5] from 127.4 g. (0.93 mole) of *n*-butyl bromide and 10 g. (1.44 atoms) of lithium in 1000 cc. of absolute ether, was siphoned under a stream of nitrogen into a stirred suspension of 82 g. (0.45 mole) of 9,10-dihydroanthracene[6] in 400 cc. of ether. The rate of addition of the butyllithium solution was regulated to produce moderate refluxing. The mixture was then stirred for one hour at laboratory temperature and finally refluxed for three hours. Carbonation with crushed dry-ice followed by extraction with water and acidification yielded 77 g. of the desired acid melting at 203–204°. (The pure acid melts at 209°.)

Xanthene-9-carboxylic Acid.—Five and three-tenths grams (0.029 mole) of finely powdered xanthene[7] was added to a solution of *n*-butyllithium prepared from 12.8 g. of *n*-butyl bromide and 1 g. of lithium in 100 cc. of ether. The deep red solution was refluxed for one hour and carbonated with dry-ice to give 4.5 g. of acid melting at 222°.[8]

Thioxanthene-10-carboxylic Acid.—Eleven and one-half grams (0.058 mole) of thioxanthene[9] was metalated with *n*-

(1) Presented before the Medicinal Section of the American Chemical Society at the Memphis meeting, April, 1942.

(2) Burtner and Cusic, THIS JOURNAL, **65**, 262 (1943).

(3) Schlenk, *et al.*, *Ber.*, **47**, 473 (1914).

(4) Gilman and Bebb, THIS JOURNAL, **61**, 109 (1939).

(5) Gilman, Zoellner and Selby, *ibid.*, **54**, 1957 (1932).

(6) Wieland, *Ber.*, **45**, 492 (1912). A purer product is obtained if three parts by weight of sodium are used in the reduction of anthracene.

(7) *o*-Phenoxybenzoic acid, prepared according to Brewster and Strain, THIS JOURNAL, **56**, 120 (1934), was converted to xanthone by the method of Graebe, *Ber.*, **21**, 503 (1888), and reduced to xanthene according to Keller and Kostanecki, *ibid.*, **41**, 1325 (1908). Two parts by weight of sodium were sufficient to complete this reduction.

(8) Conant, THIS JOURNAL, **49**, 2085 (1927), who obtained this acid by metalation of xanthene with sodium–potassium alloy followed by carbonation, reported a m. p. of 222–223°.

(9) Thiosalicylic acid, *Org. Syn.*, **12**, 76 (1932), was converted to thioxanthone according to Gomberg and Britton, THIS JOURNAL, **43**, 1946 (1921), and reduced to thioxanthene by Graebe's method, *Ann.*, **263**, 1 (1891).

TABLE I

Basic ester hydrochlorides Acid[a]	Basic alcohol	Melting point, °C.	Crystallization solvent	Chlorine analyses Calculated	Chlorine analyses Observed	Reciprocal spasmolytic activity Acetylcholine	Reciprocal spasmolytic activity Histamine	LD_{50}
9,10-Dihydroanthracene-9-carboxylic	β-Diethylaminoethanol	170–1	*i*-PrOH	9.86	9.80	5	0.05	0.15
9,10-Dihydroanthracene-9-carboxylic	γ-Diethylaminopropanol	136	EtOAc	9.48	9.43	3	2	0.15
9,10-Dihydroanthracene-9-carboxylic	β-Diethylaminopropanol	185	EtOAc	9.48	9.64	10	0.5	0.24
9,10-Dihydroanthracene-9-carboxylic	β-Di-*n*-butylaminoethanol	130	EtOAc	8.52	8.62	>100	25	0.53
9,10-Dihydroanthracene-9-carboxylic	β-Morpholinoethanol	142	Dioxane	9.48	9.60	> 50	2	0.50
9,10-Dihydroanthracene-9.10-dicarboxylic	(bis)β-Diethylaminoethanol	192–3	EtOAc–*i*-PrOH	13.17	12.81	30	1	0.13
9,10-Dihydro-10-methylanthracene-9-carboxylic	β-Diethylaminoethanol	202	*i*-PrOH	9.50	9.52	> 20	0.1	0.17
9,10-Dihydro-9-methylanthracene-9-carboxylic	β-Diethylaminoethanol	157–9	*i*-PrOH–Ether	(N) 3.75	(N) 3.84	5	0.1	0.15
Xanthene-9-carboxylic	β-Diethylaminoethanol	159–160	*i*-PrOH–EtOAc	10.03	9.85	0.5	0.4	0.25
Thioxanthene-10-carboxylic	β-Diethylaminoethanol	195	*i*-PrOH	9.38	9.49	6	0.33	0.22
Acridan-9-carboxylic	β-Diethylaminoethanol	201	*i*-PrOH	10.2	9.82	3	2	0.14
10-Methylacridan-9-carboxylic	β-Diethylaminoethanol	157–8	*i*-PrOH–EtOAc	9.45	9.68	40	1	0.14
Acridine-9-carboxylic	β-Diethylaminoethanol	190[b]	MeOH–Ether	9.89	9.71	30	4	0.28
9-Ethylfluorene-9-carboxylic	β-Diethylaminoethanol	168–9	EtOAc	(N) 3.75	(N) 4.0	10	0.5	0.14
9-Cyclohexylfluorene-9-carboxylic	β-Diethylaminoethanol	184	Acetone	8.30	8.50	> 50	1	0.15
Indene-1-carboxylic	β-Diethylaminoethanol	141–3	*i*-PrOH	(N) 4.74	(N) 4.88	100	3	0.23
1-Naphthoic	β-Diethylaminoethanol	159–161	*i*-PrOH	[c]		50	3	0.45
1,4-Dihydro-1-naphthoic	β-Diethylaminoethanol	152	*i*-PrOH–EtOAc	11.46	11.75	50	3	0.66
1,2,3,4-Tetrahydro-1-naphthoic	β-Diethylaminoethanol	137–8	*i*-PrOH	(N) 4.5	(N) 4.85	40	3	0.45
Biphenyl-2-acetic	β-Diethylaminoethanol	108–9	[d]	(N) 4.03	(N) 4.05	20	1	0.20
Phenanthrene-9-carboxylic	β-Diethylaminoethanol	169–170[e]	*i*-PrOH	9.90	10.4	> 50	2	0.24
Atropine sulfate						0.14	4	0.24
Papaverine						> 10	1	

[a] See "The Ring Index" by Patterson and Capell (Reinhold Publishing Corp., New York, N. Y., 1942) for nomenclature of the acids. [b] Samdahl and Weider, *Bull. soc. chim.*, [5] **2**, 2008 (1935), report m. p. 179–180°. [c] Prepared by Bjerregaard and Houston, *C. A.*, **28**, 6851 (1934). [d] Could not be crystallized; wash with ether after pptn. [e] Van de Kamp, Burger and Mosettig, THIS JOURNAL, **60**, 1321 (1938), report m. p. 171–171.5°.

butyllithium as above to yield upon carbonation 12.5 g. of acid melting at 218–219°. Crystallization from 50 cc. of isopropanol gave 10 g. of thioxanthene-10-carboxylic acid, m. p. 227°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.4; H, 4.16. Found: C, 69.8; H, 4.43.

9,10-Dihydroacridine-9-carboxylic Acid.—A stirred suspension of 25.8 g. of acridine-9-carboxylic acid[10] in 250 cc. of water containing 6.5 g. of sodium carbonate monohydrate was treated portionwise with 400 g. of 3% sodium amalgam at 10°. The deep red color soon faded to a light brown. After the addition of the amalgam, the mixture was stirred for one-half hour at 10° and then decanted from the mercury. Decoloration with Darco and acidification gave 18 g. of the desired acid, m. p. 205° (dec.).[11]

10-Methyl-9,10-dihydroacridine-9-carboxylic Acid.—Twelve and three-tenths grams (0.064 mole) of 10-methyl-9,10-dihydroacridine was added to a solution of *n*-butyllithium prepared from 28 g. of *n*-butyl bromide and 2.2 g. of lithium in 220 cc. of ether. The dark red solution was refluxed for one hour and then carbonated with dry-ice. The crude product thus obtained was crystallized from 200 cc. of 50% acetic acid to give 5 g. of the desired acid, m. p. 184° (dec.), which darkened on long standing even in an evacuated desiccator in diffused light.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.92.

(10) Lehmstedt and Wirth, *Ber.*, **61**, 2044 (1928).

(11) E. Bergmann, *et al.*, *Ann.*, **483**, 80 (1930), report a m. p. of 205°. Their method of reduction using hydrogen and Pd–$BaSO_4$ catalyst was unsatisfactory in our hands.

9,10-Dihydro-10-methylanthracene-9-carboxylic Acid.—Twenty-seven grams (0.14 mole) of 9-methyl-9,10-dihydroanthracene dissolved in 75 cc. of benzene was added all at once to a solution of *n*-butyllithium derived from 41.1 g. (0.3 mole) of *n*-butyl bromide and 4.2 g. (0.6 atom) of lithium. The mixture was refluxed for two hours and then stirred overnight at laboratory temperature. Carbonation with dry-ice gave 15 g. of crude product which was crystallized from 100 cc. of 50% ethanol to yield 6 g. of the desired acid, m. p. 204–207°. When mixed with a sample of 9-methyl-9,10-dihydroanthracene-9-carboxylic acid the m. p. was depressed to 175°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.5; H, 5.88. Found: C, 80.0; H, 5.74.

9,10-Dihydro-9-methylanthracene-9-carboxylic Acid.—Three and one-half grams (0.09 atom) of potassium was added in small pieces to a solution of 23 g. (0.09 mole) of ethyl 9,10-dihydroanthracene-9-carboxylate in 80 cc. of absolute ether. When the reaction ceased (about thirty minutes), 10 cc. of absolute ethanol was added and the mixture stirred for one hour by which time the potassium had completely dissolved; 12.8 g. (0.09 mole) of methyl iodide was then added all at once causing vigorous refluxing. After stirring for four hours, the mixture was poured into water, acidified, extracted with ether and the ethereal solution distilled to yield an oily residue. Saponification with a solution of 10 g. of potassium hydroxide in 150 cc. of ethanol for seventy-five minutes gave upon dilution and acidification 15 g. of a colorless acid, m. p. 193–195°. Crystallization from dilute ethanol yielded 13 g. of the acid melting at 194–196°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.5; H, 5.88. Found: C, 80.9; H, 5.96.

9-Cyclohexylfluorene-9-carboxylic Acid.—Twenty grams (0.08 mole) of 9-cyclohexylfluorenene[12] was added all at once to a solution of *n*-butyllithium prepared from 2.6 g. (0.37 atom) of lithium and 33.8 g. (0.24 mole) of *n*-butyl bromide. The dark red solution was refluxed for two and one-half hours and then carbonated with dry-ice. Water was added and the solvent evaporated on a steam-bath. Since the lithium salt was relatively insoluble, it was necessary to add 500 cc. of water and heat to boiling to effect solution. After filtration the hot solution was acidified to precipitate the crude acid, m. p. 210°, which upon crystallization from a 1:1 solution of benzene and ligroin weighed 17 g. and melted at 220–222°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.17; H, 6.90. Found: C, 82.65; H, 7.20.

Indene-1-carboxylic Acid.—Thirty-four and eight-tenths grams (0.3 mole) of indene was added all at one time to a solution of phenylsodium prepared from 23 g. of sodium and 45 g. of chlorobenzene in the manner described in our previous paper. The mixture was refluxed with stirring for fifteen hours, diluted with an equal volume of absolute ether and carbonated by pouring onto crushed dry-ice. After dissolving the excess sodium in 50% ethanol and extracting with water the aqueous layer was acidified to precipitate 25.5 g. of the acid, m. p. 149–151°.[13]

The following acids were prepared according to known methods: 1,4-dihydro-1-naphthoic acid,[14] 1,2,3,4-tetrahydro-1-naphthoic acid,[15] biphenyl-2-acetic acid,[16] 9,10-dihydroanthracene-9,10-dicarboxylic acid[5] and 9-ethylfluorene-9-carboxylic acid.[17]

Preparation of the Esters

In each instance the ester was prepared by the interaction of the acid with corresponding dialkylaminoalkyl chloride in isopropanol solution according to the method of Hörenstein and Pählicke.[18,19]

Discussion of Results

The extension or expansion of the carbon-carbon bond or bridge between the benzene nuclei in the parent fluorene ester to include —CH_2—, —NH—, oxygen and sulfur produced some rather unusual pharmacological results. For example, the insertion of a methylene group in this position, thus forming the 9,10-dihydroanthracene derivative, causes a twenty-fold increase in the anti-histamine activity accompanied by a decrease in the effectiveness against acetylcholine. To our knowledge this compound, being twenty times as potent as papaverine, is one of the most powerful spasmolytics that has been reported to date. Subsequent animal experiments have shown it to be approximately one-fifth as effective as epinephrine in relaxing spasm of the bronchioles induced by histamine.

The introduction of an oxygen atom in the bridge of the fluorene ester gives rise to a less spectacular yet highly significant improvement in spasmolytic activity, since the resulting xanthene derivative is at least twice as effective against *both* types of spasm with only a relatively small increase in toxicity. In clinical practice, such a dual type of activity would be of obvious value. Replacement of oxygen by sulfur in the bridge produced a net decrease in activity with no essential change in toxicity. The latter effect was quite unexpected, since substitution of sulfur for oxygen in a comparable case involving basic esters of dibenzofuran- and dibenzothiophene-carboxylic acids caused a fifty per cent. reduction in toxicity.[20] The introduction of an —NH— linkage between the two benzene nuclei in the parent fluorene ester repressed both types of spasmolytic activity and markedly increased the toxicity.

The marked anti-histamine activity of the 9,10-dihydroanthracene ester is evidently inherent to that structure, since removal of one of the benzene nuclei, as represented by the 1,4-dihydronaphthalene derivative, results in a sixty-fold decrease in this effect. When a similar modification is effected in the case of the fluorene carboxylic acid ester, thus forming the analogous indene derivative, the spasmolytic activity suffers to even a greater extent. Cleavage of the fluorene nucleus at the 9-carbon atom likewise exerts a deleterious effect, as evidenced by the low activity of the biphenylacetic acid ester.

The introduction of an alkyl group in the dihydroanthracene and fluorene derivatives in the 9-position, thus forming a tertiary carbon atom at the point of attachment of the carboxyl group, lowers the over-all spasmolytic activity. As in previous studies the reduction of toxicity resulting from the elaboration or expansion of the amino alcohol generally fails to offset the accompanying decrease in potency.

We wish to express our appreciation to Mr. William W. Jenkins for his assistance with the synthesis of these compounds.

(12) Miller and Bachman, THIS JOURNAL, **57**, 769 (1935).

(13) This acid was sufficiently pure for our purposes. Weissgerber, *Ber.*, **44**, 1436 (1911), reports the m. p. of the pure acid as 156–157°.

(14) Kamm and McClugage, THIS JOURNAL, **38**, 425 (1916).

(15) Kay and Morton, *J. Chem. Soc.*, **105**, 1571 (1914).

(16) Schonberg and Warren, *Chemistry & Industry*, 199 (1939).

(17) Wislicenus and Mocker, *Ber.*, **46**, 2777 (1913).

(18) Hörenstein and Pählicke, *ibid.*, **71**, 1644 (1938).

(19) See Burtner and Cusic, ref. 2, for a more detailed description of this synthesis and the purification of the products.

(20) Burtner and Lehmann, THIS JOURNAL, **62**, 527 (1940).

Summary

The synthesis and antispasmotic properties of twenty-one esters are described. Variation of the acid portion of these esters to include unsaturated and partially saturated derivatives of naphthalene, indene, 9-alkylfluorene, anthracene, xanthene, thioxanthene, acridine and phenanthrene in some instances causes pronounced changes in pharmacological properties.

Of this series, β-diethylaminoethyl xanthene-9-carboxylate appears to possess the greatest activity against spasm induced by acetylcholine, while the corresponding ester of 9,10-dihydroanthracene-9-carboxylic acid is the most effective against histamine.

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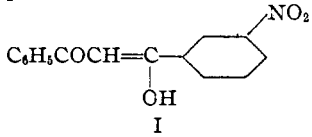
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, HOWARD UNIVERSITY]

The Properties of *m*-Nitrodibenzoylmethane

BY R. PERCY BARNES AND LOUIS B. DODSON[1]

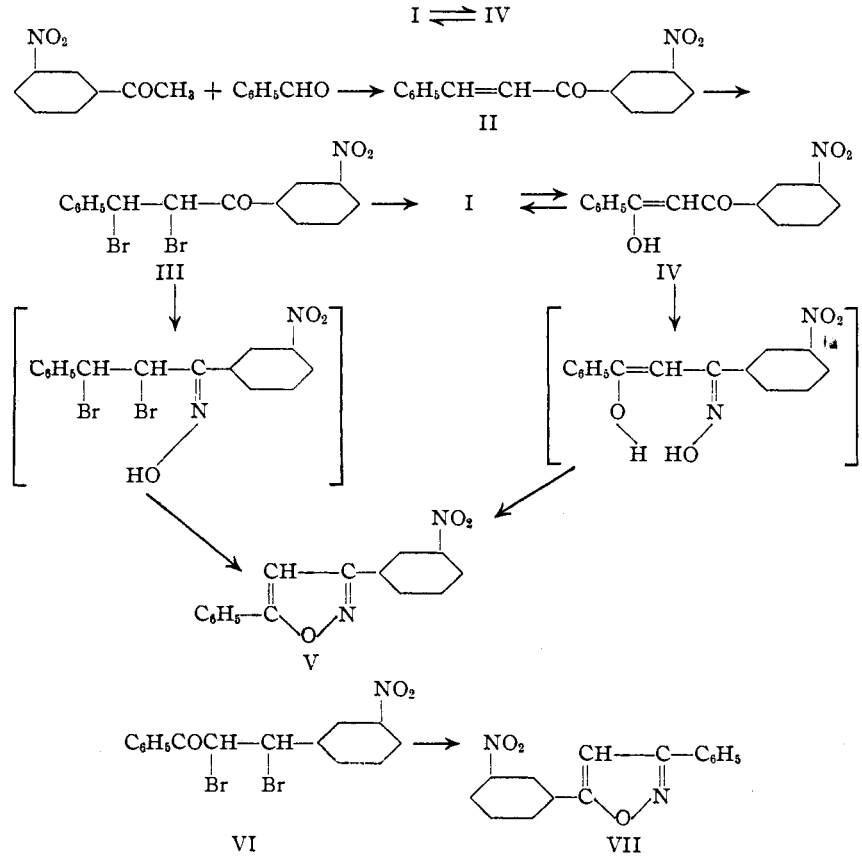
In a recent communication[2] we established the fact that *p*-methoxydibenzoylmethane reacts as 1-phenyl-3-*p*-methoxyphenylpropene-one-3-ol-1 in isoxazole formation. Because of the effect of the nitro group on the acetylation of desoxybenzoins,[3] we decided to test the behavior of *m*-nitrodibenzoylmethane in isoxazole and pyrazole formation.

By starting with the dibromide of *m*-nitrobenzalacetophenone (VI), Bodforss[4] prepared *m*-nitrodibenzoylmethane and showed that on permanganate oxidation in alkaline medium it gives *m*-nitrobenzoic and phenylglyoxylic acids, thus establishing that under these conditions *m*-nitrodibenzoylmethane behaves as *m*-nitro-α-oxy-benzalacetophenone (I).



I

We have condensed *m*-nitroacetophenone with benzaldehyde producing benzal-*m*-nitroacetophenone (II). This substance was brominated to the corresponding dibromo compound (III),



which was refluxed with sodium methylate and hydrochloric acid in turn, giving rise to a pale yellow enolic substance, melting and mix-melting identically with the enol as prepared by Bodforss.

m-Nitrodibenzoylmethane gives rise to an

(1) Candidate for the Master's Degree.

(2) R. Percy Barnes and Alfred Brandon, THIS JOURNAL, **65**, 1070 (1943).

(3) R. P. Barnes, S. R. Cooper, Victor J. Tulane and Harold Delaney, *J. Org. Chem.*, **8**, 153 (1943).

(4) Bodforss, *Ber.*, **49**, 2795 (1916).