warm alcohol. The orange product (microscopic, hair-like crystals) was obtained in 87 and 89% yield, m. p. 320–328° (dec.). No depression was observed in a mixed melting point with a sample of this derivative prepared directly from glyoxal.

Anal. Calcd. for $C_{14}H_{10}O_8N_8$: N, 26.80. Found: N, 26.4, 26.5.

Glyoxal phenylosazone was obtained from IV in poor yield by the following procedure: a solution of 0.5 g. of IV, 10 ml. of glacial acetic acid and 20 ml. of water was heated to boiling and then let stand several minutes. Then 6 ml. of phenylhydrazine–acetic acid reagent (1 vol. of phenylhydrazine, 1 vol. of acetic acid and 2 vol. of water) was added and the reaction mixture was heated to boiling until a brown color developed (about two minutes). A solution of 50 ml. of water and 25 ml. of acetic acid was added and the mixture was cooled and shaken. The light brown product was filtered; m. p. 155–162°. Recrystallized from alcohol plus a little water the derivative was obtained as yellow-brown needles of m. p. 168–169°; a mixed melting point with an authentic sample of glyoxal phenyl osazone (m. p. 169–172°) was 169–170°.

(c) **Isolation of Acids.**—A mixture of acids was isolated as before from the sodium bicarbonate extraction of the paste; yield, 29.8 g.; m. p. 76–93°; mixed m. p. (with benzoic acid) 85–107°; neut. equiv. 159. Since 0.187 equiv. of acids was obtained from an amount of residue originally containing only 0.18 equiv. of free acids, it was assumed that hydrolysis of acylals had occurred during the sodium bicarbonate extraction.[5]

Benzoic acid was separated from the acid mixture by steam distillation. A 24.5-g. sample of the acids was steam distilled, keeping the volume at about 100 ml. Two distillate fractions were collected. The first fraction (800 ml.) on cooling yielded 6.7 g. of impure benzoic acid (m. p. 117–120°; mixed m. p. 119–121°; neut. equiv. 125). The second fraction (300 ml.) gave 0.7 g. of less pure benzoic acid (m. p. 110–117°; mixed m. p. 116–120°; neut. equiv. 127). On cooling the residue from the steam distillation, 8.6 g. crude acids was obtained (m. p. 100–120°; mixed m. p. with benzoic acid 85–97°; neut. equiv. 215). This acid mixture was dissolved in dilute sodium hydroxide solution, treated with decolorizing charcoal and precipitated with hydrochloric acid. The product thus obtained (m. p. 117–138°; mixed m. p. with benzoic acid 100–110°) was recrystallized twice from dilute alcohol and once from water, giving a small amount of product of m. p. 180–185° (the melt was not clear until 250–260°). This product was proved to contain *p*-substituted benzoic acid by oxidation by boiling for about ten minutes in alkaline solution with excess potassium permanganate. The acid obtained from the oxidation was practically insoluble in water and alcohol, did not melt up to 310° and had neut. equiv. 85. It was identified as terephthalic acid (neut. equiv. 83) by its dimethyl ester of m. p. 139–140° (lit. m. p. for dimethyl terephthalate 140°).

Summary

A study has been made of the products of the reaction of benzoyl peroxide with excess diethyl ether, diethyl Cellosolve and dioxane at about 40°. With diethyl ether and diethyl Cellosolve the chief products are carbon dioxide, benzoic acid and acylals, *i. e.*, benzoates of the radicals derived from the respective ethers by loss of methylenic hydrogen. With dioxane the above products are obtained and also considerable amounts of higher molecular weight acids and acylals. These results have been interpreted as being in general agreement with a postulated chain mechanism for the decomposition of benzoyl peroxide in these solvents.

SCHENECTADY, N. Y. RECEIVED SEPTEMBER 26, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY DENTAL SCHOOL, AND DEPARTMENT OF PHARMACOLOGY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL]

Dialkylaminoalkyl Esters of 4,4′-Stilbenedicarboxylic and 4,4′-Dibenzyldicarboxylic Acid[1,2,3]

BY L. S. FOSDICK AND K. F. URBACH

A great number of structurally unrelated compounds are known to produce local anesthesia. No single grouping has been observed to explain this effect although certain substitutions and structural characteristics are known to influence it. For example, Kamm[4] in considering certain derivatives of *p*-aminobenzoic acid has observed that local anesthetic activity is destroyed if the double bond conjugation between the carbonyl group and the aromatic nucleus is interrupted. This suggests that one of the structural characteristics influencing local anesthetic activity is the existence of double bond conjugation between the carbonyl group and the aromatic nucleus in this type of anesthetic. In support of this hypothesis are the observations of Shriner[5] on the vinylogy of *p*-aminobenzoic acid derivatives, the observations on the activities of *p*-amino and *m*-aminomandelic acid esters[6,7] and the studies by Whitacre[8] on the interrelationship between type of linkage of the ester carbonyl group to the aromatic ring and local anesthetic activity.

In addition, Gilman[9] has pointed out that ethylenic linkages in positions other than between the carbonyl group and the aromatic nucleus increase local anesthetic activity.

This suggests that double bond conjugation, in general, plays a marked role in local anesthetic activity of a given compound. In support of this

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society meeting, September 12, 1946.

(2) A part of this material is taken from the thesis of Mr. Urbach submitted at Northwestern University Graduate School. Present address, Department of Pharmacology, Northwestern University Medical School.

(3) This work has, in part, been done under a grant from the Abbott Fund.

(4) Kamm, THIS JOURNAL, **42**, 1030 (1920).

(5) Shriner and Keyser, *ibid.*, **60**, 286 (1938).

(6) Fosdick and Wessinger, *ibid.*, **60**, 1465 (1938).

(7) Fosdick and Calandra, *ibid.*, **63**, 1101 (1941).

(8) Whitacre, *Anesthesia and Analgesia*, **18**, 112 (1939).

(9) Gilman and Pickens, THIS JOURNAL, **47**, 245 (1925).

hypothesis is the observation that "Novocaine-Brown" $H_2NC_6H_4N{=}NC_6H_4COOCH_2CH_2N(C_2H_5)_2$ is as active as procaine itself.[10]

With this point in view it was thought to be desirable to obtain a series of compounds in which conjugated carbonyl groups are linked to an aromatic system containing extensive double bond conjugation and to test them for local anesthetic activity. Such requirements are fulfilled by derivatives of 4,4'-stilbenedicarboxylic acid. In order to determine the influence of interrupting the conjugation between the two aromatic rings on local anesthetic activity in this series, comparable derivatives of 4,4'-dibenzyldicarboxylic acid were prepared.

The symmetrical dialkylaminoalkyl esters of 4,4'-stilbenedicarboxylic and 4,4'-dibenzyldicarboxylic acid were synthesized by treating the corresponding diacid chlorides with the appropriate dialkylamino alcohols. The symmetrical dimethylaminoethyl-, diethylaminoethyl-, and dibutylaminoethyl esters of both dicarboxylic acids and the dibutylaminopropyl ester of 4,4'-stilbenedicarboxylic acid were synthesized and isolated as hydrochlorides.

Preliminary pharmacological data obtained by testing the compounds on the rabbit cornea indicate that the diethylaminoethyl esters of both dicarboxylic acids and the dimethylaminoethyl ester of 4,4'-stilbenedicarboxylic acid are active as topical anesthetics. The other derivatives of the stilbene series are too insoluble to allow accurate appraisal, while the dimethylaminoethyl- and dibutylaminoethyl esters of 4,4'-dibenzyldicarboxylic acid seem to be devoid of topical activity. A comparison between the two diethylaminoethyl esters indicates that there is greater activity associated with the stilbene series than with the dibenzyl series. This suggests the hypothesis that extension of a conjugated system between aromatic rings increases local anesthetic activity. More detailed pharmacological data will be presented elsewhere.

Experimental

Diacid Chloride of 4,4'-Stilbenedicarboxylic Acid.—4,4'-Stilbenedicarboxylic acid was prepared according to the method of Hager[11] who reported on the difficulty of hydrolyzing the intermediary 4,4'-dicyanostilbene to the acid. We were also unable to hydrolyze the dicyanide under a variety of conditions. In several runs the diamide was obtained. When this was dissolved in 85% sulfuric acid and treated with sodium nitrite nothing but a good yield of terephthalic acid was obtained. After 4,4'-stilbenedicarboxylic acid was obtained 20 g. of it was refluxed with excess thionyl chloride for twelve hours. The mixture was filtered hot and some of the diacid chloride crystallized on cooling. The crystals were filtered by suction and the thionyl chloride was removed from the filtrate *in vacuo* as far as possible. A yellow semisolid residue remained. This was dissolved in benzene and the solution was concentrated *in vacuo* to remove remaining thionyl chloride. The residue was combined with the first crop of crystals and was recrystallized from benzene. Thus a 35% yield of fine yellow needles, m. p. 227–230°, was obtained. Several chloride analyses gave high results, probably due to retained thionyl chloride. The identity of the compound was established by converting it into the diethyl 4,4'-stilbenedicarboxylate which has been described previously.[11] The yield of the diacid chloride was raised to 85% by the following procedure. 4,4'-Stilbenedicarboxylic acid (5 g.) was ground in a mortar with a large excess (100 g.) of phosphorus pentachloride and left overnight. Phosphorus trichloride (200 cc.) was added and the mixture refluxed for four hours when solution was complete. The phosphorus trichloride was removed by distillation and the resulting crystalline mass well cooled. This was then decomposed in small portions of ice-cooled ether containing 5% alcohol. The precipitated diacid chloride was filtered by suction, washed with cold alcohol and crystallized from dry benzene.

β-Chloroethyl-4,4'-stilbenedicarboxylate.—This compound was prepared by refluxing the diacid chloride with excess ethylene chlorohydrin for several hours. On cooling the substance was obtained as colorless crystals in 70% yield; m. p. 145–146°.

Anal. Calcd. for $C_{20}H_{18}O_4Cl_2$: Cl, 18.07. Found: Cl, 17.83.

Attempts to convert this compound to the dialkylaminoalkyl esters with the appropriate secondary amines failed.

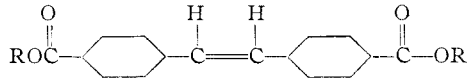
4,4'-Dimethylaminoethyl Stilbenedicarboxylate Hydrochloride.—The diacid chloride of 4,4'-stilbenedicarboxylic acid (0.005 mole) was dissolved in hot benzene and added to dimethylaminoethanol (0.02 mole), also dissolved in benzene. The mixture was refluxed for thirty minutes and cooled. Dimethylaminoethanol hydrochloride was filtered off by suction and dry hydrogen chloride gas was bubbled through the filtrate. The colorless substance obtained was filtered and crystallized from absolute alcohol–dry ether; yield 73%; m. p. 265–267°, with decomposition.

Anal. Calcd. for $C_{24}H_{32}O_4N_2Cl_2$: N, 5.79. Found: N, 5.85.

4,4'-Diethylaminoethyl stilbenedicarboxylate hydrochloride, 4,4'-dibutylaminoethyl stilbenedicarboxylate hydrochloride and 4,4'-dibutylaminopropyl stilbenedicarboxylate hydrochloride were prepared in a manner similar to that described in the preparation of the 4,4'-dimethylaminoethyl ester. The properties of the compounds are summarized in Table I.

TABLE I

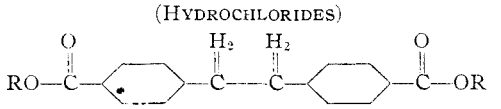
4,4'-DIALKYLAMINOALKYL STILBENEDICARBOXYLATES (HYDROCHLORIDES)



R	M. p., °C.	Yield, %	N Analyses, % Calcd.	Found
$Me_2NCH_2CH_2$—	265–267 dec.	73	5.79	5.85
$Et_2NCH_2CH_2$—	246 dec.	75	5.21	5.23
$Bu_2NCH_2CH_2$—	230–232	82	4.29	4.12
$Bu_2NCH_2CH_2CH_2$—	210–211	79	4.12	4.02

TABLE II

4,4'-DIALKYLAMINOALKYL DIBENZYLDICARBOXYLATES (HYDROCHLORIDES)



R	M. p., °C.	Yield, %	N Analyses, % Calcd.	Found
$Me_2NCH_2CH_2$—	240–242	39	5.77	5.65
$Et_2NCH_2CH_2$—	226–227	38	5.17	5.09
$Bu_2NCH_2CH_2$—	139–140	52	4.28	4.14

(10) Fulton, *Am. J. Physiol.*, **57**, 159 (1921).

(11) Hager, Van Arendonk and Shonle, THIS JOURNAL, **66**, 1982 (1944).

4,4′-Dialkylaminoalkyl Dibenzyldicarboxylates.—The hydrochlorides of these compounds were prepared from the diacid chloride of 4,4′-dibenzyldicarboxylic acid[12] by the method indicated in the preparation of the analogous stilbene compounds above. The properties of these compounds prepared are summarized in Table II.

Summary

1. Several dialkylaminoalkyl esters of 4,4′-stilbenedicarboxylic and 4,4′-dibenzyldicarboxylic acid have been prepared.

2. Two esters of the stilbene series and one of the dibenzyl series show topical anesthetic properties.

3. It is suggested that the activity in the stilbene series is, in part, due to the extensive and continuous conjugation which, if interrupted as in the dibenzyl analogs, results in decreased activity.

(12) Fischer and Wolffenstein, *Ber.*, **37**, 3215 (1904).

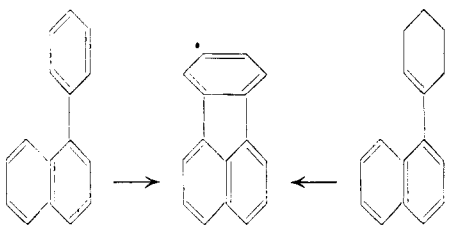
CHICAGO, ILLINOIS RECEIVED SEPTEMBER 23, 1946

[CONTRIBUTION FROM THE U. S. BUREAU OF MINES, CENTRAL EXPERIMENT STATION]

Aromatic Cyclodehydrogenation. V. A Synthesis of Fluoranthene[1]

BY MILTON ORCHIN[2] AND LESLIE REGGEL[2]

In a continuation of the cyclodehydrogenation[3] studies in this Laboratory,[4] we have found that 1-phenylnaphthalene, I, can be readily converted to fluoranthene, II. Since 1-(2′,3′,4′,5′-tetrahydrophenyl)-naphthalene, III, which is an intermediate in the synthesis of I, can be converted directly to II, the isolation of 1-phenylnaphthalene is not required for the successful synthesis of fluoranthene. The tetrahydro compound, III,



I II III

can be obtained in good yield in two steps from 1-naphthylmagnesium bromide and cyclohexanone, so that pure synthetic fluoranthene is now readily available by a three-step process.[5] The cyclodehydrogenations to fluoranthene can be accomplished with a palladium-on-charcoal catalyst, but a pelleted chromia–alumina catalyst[6] seems to be superior.

Cook and Lawrence[7] reported that the attempted liquid-phase dehydrogenation of the tetrahydro compound, III, to 1-phenylnaphthalene, I, with a platinum catalyst gave only a small quantity of hydrogen, but the reaction did result in disproportionation into 1-cyclohexylnaphthalene and 1-phenylnaphthalene. We have found that if a palladium-on-charcoal catalyst is used, nearly quantitative evolution of hydrogen occurs, and 1-phenylnaphthalene can be isolated in 94% yield. The formation of 1-cyclohexylnaphthalene can also be avoided by vapor-phase dehydrogenation of III over a palladium-on-charcoal catalyst at 350°, but considerable fluoranthene is formed in this process.

Cook and Lawrence have commented[7] on the unusual resistance which the tetrahydro compound III displays to hydrogenation under mild conditions with a platinum catalyst. Previously, we have found[8] that small-scale hydrogenation of polynuclear compounds can be achieved in the absence of a hydrogen atmosphere simply by refluxing an ethanol solution of the compound with Raney nickel.[9] We have now found that hydrogenation of III proceeds readily under these conditions, and that 1-cyclohexylnaphthalene can be isolated from the products.

(1) Published by permission of the Director, U. S. Bureau of Mines. Presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, April 8–12, 1946.

(2) Organic Chemist, Central Experiment Station, U. S. Bureau of Mines, Pittsburgh, Pa.

(3) The word "cyclo-dehydrogenation" has been used previously, as, for example, by J. W. Cook, *J. Chem. Soc.*, 369 (1934), but has not been precisely defined. We wish to define "aromatic cyclodehydrogenation" as an intramolecular loss of hydrogen from an aromatic or hydroaromatic compound to form a new compound with a greater number of rings. This definition would include the examples cited in Cook's work.

(4) For the previous publication in this series see Orchin and Friedel, THIS JOURNAL, **68**, 573 (1946).

(5) Only two other syntheses of fluoranthene have been reported. Von Braun and Anton, *Ber.*, **62**, 145 (1929), started with 9-sodium-9-carboethoxyfluorene and built up the additional six-membered ring by a series of six reactions. Cook and Lawrence (ref. 7) obtained an unspecified but "very small" yield of fluoranthene by selenium dehydrogenation of the product obtained by aluminum chloride cyclization of 1-(1′-naphthyl)-2(or 6)-methylcyclohexene-1.

(6) The catalyst, designated as Cr-181, was purchased from the Harshaw Chemical Co., Cleveland, Ohio. It is in the form of ⅛" pellets, stated to consist of alumina impregnated with 12% chromia and 2% magnesia. Indications are that this catalyst is superior to palladium-on-charcoal for the cyclodehydrogenations previously reported from this Laboratory.

(7) Cook and Lawrence, *J. Chem. Soc.*, 1431 (1936).

(8) Orchin, THIS JOURNAL, **66**, 535 (1944).

(9) Mozingo, Spencer and Folkers, *ibid.*, **66**, 1859 (1944), state that benzene rings are not reduced by this procedure. Obviously, this does not apply to benzene rings which are part of a fused ring system. In our studies with Raney nickel, we have found that even in the presence of a hydrogen atmosphere, the hydrogen held on the surface of the nickel participates in the reaction. For example, in a quantitative study it was found that the apparent absorption of hydrogen by cyclohexene is always less than theoretical when hydrogenation is done in the presence of Raney nickel, even though no cyclohexene remains unconverted.