then sublimed at 40° (0.1 mm.) and 14.0 g. (84.8%) of product collected, m.p. 41–42°.

Anal. Calcd. for $C_5H_3BrCl_2N_2$: total halogen, 62.3; N, 11.6. Found: total halogen, 62.0; N, 11.5.

Dehalogenation of 5-Bromo-2,4-dichloro-6-methylpyrimidine.—A mixture of 12.05 g. (0.05 mole) of 5-bromo-2,4-dichloro-6-methylpyrimidine, 4.0 g. (0.1 mole) of magnesium oxide, 0.1 g. of 10% palladium-on-charcoal, 50 ml. of ethanol and 100 ml. of water was hydrogenated for 48 hours until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and washed with methylene chloride. The filtrate was then extracted continuously with methylene chloride for 5 hours and dried over anhydrous sodium sulfate. After the drying agent and solvent were removed, the residue was distilled to give a colorless liquid, 2.0 g. (42.8%), b.p. 33–34° (11 mm.), $n^{25}D$ 1.4936; (141–142° (atm.) $d^{16}_{15.9}$ 1.031, no yield reported),[12] (b.p. 86° (114 mm.), $n^{29}D$ 1.4916, no yield reported),[4] (b.p. 141–145° (atm.) $n^{25}D$ 1.4940, (30%)).[3b] The picrate was prepared in the usual manner, m.p. 129–130°. A mixed melting point with an authentic sample, *m.p. 131–132.2°, gave no depression, m.p. 129–130°.*

(12) S. Gabriel and J. Coleman, *Ber.*, **32**, 1533 (1899).

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The Stobbe Condensation with Perinaphthanone-7 and 8-Methylperinaphthanone-7[1]

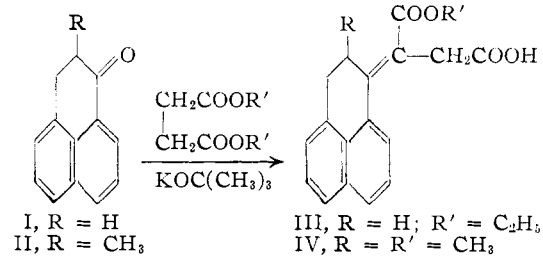
BY JAMES W. PATTON[2] AND GUIDO H. DAUB

RECEIVED DECEMBER 19, 1953

In the course of investigations being carried out in this Laboratory on the synthesis of 3,4-benzpyrenes the Stobbe condensation with perinaphthanone-7 (I) and 8-methylperinaphthanone-7 (II) was investigated. The condensation of diethyl succinate with I was carried out in like manner to the procedure described for tetralone-1 using potassium *t*-butoxide as the condensing agent.[3] From the resulting mixture of half-esters which was obtained in 43% yield, β-carbethoxy-β-(7-perinaphthylidene)-propionic acid (III) was isolated. The structure of III was proved by oxidation of the half-ester with potassium permanganate, perinaphthanone-7 being isolated in 61% yield. The use of larger amounts of potassium *t*-butoxide or sodium hydride[4] as the condensing agent gave only tarry products.

Under the above conditions 8-methylperinaphthanone-7 (II) failed to react, but the modified procedure described for hindered ketones[5] gave a 29% yield of oily half-ester from which a crystalline product, β-carbomethoxy-β-(8-methylperinaphthylidene-7)-propionic acid (IV), was isolated. The double bond in IV was shown to be exocyclic by comparison of the ultraviolet absorption spectra of III and IV.

Attempts to decarbethoxylate the half-ester III with a mixture of hydrobromic and acetic acids[6] or hydrochloric and acetic acids[3] resulted in the formation of intractable tars.



I, R = H
II, R = CH_3

III, R = H; R' = C_2H_5
IV, R = R' = CH_3

Experimental[7]

Perinaphthanone-7 (I).—The preparation of perinaphthanone-7 by the cyclization of 50 g. (0.25 mole) of β-(1-naphthyl)-propionic acid, m.p. 155.5–156°, with 160 ml. of anhydrous hydrogen fluoride was carried out according to the procedure described by Fieser and Gates[8] with some modification. The crude ketone was distilled at reduced pressure, b.p. 136–140° at 0.1 mm., and recrystallized from methanol to give a total of 37.8 g. (83% yield) of pale yellow prisms of comparable purity to that obtained by Fieser and Gates.

β-Carbethoxy-β-(7-perinaphthylidene)-propionic Acid (III).—A solution of 2.00 g. (0.110 mole) of perinaphthanone-7, m.p. 78–80°, in 3.00 g. (0.0172 mole) of diethyl succinate, b.p. 109–112° at 23 mm., was added to a solution of 0.48 g. (0.0123 g.-atom) of potassium in 20 ml. of anhydrous *t*-butyl alcohol with stirring in a nitrogen atmosphere. The solution was stirred at reflux for one hour. The solution was cooled, acidified with 2 ml. of concentrated hydrochloric acid in 50 ml. of water and most of the *t*-butyl alcohol removed at reduced pressure. The product was taken up in ether and the ether solution was extracted several times with a saturated sodium bicarbonate solution. The extracts were washed with ether and acidified giving a dark yellow oil which turned to a tan solid, m.p. 120–155°, 1.45 g. (43% yield). Several recrystallizations from ethyl acetate afforded **β-carbethoxy-β-(7-perinaphthylidene)-propionic acid** as almost colorless prisms, m.p. 172–173°.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.54; H, 5.85; neut. equiv., 310.3. Found: C, 73.61; H, 5.65; neut. equiv., 311.1.

Oxidation of β-Carbethoxy-β-(7-perinaphthylidene)-propionic Acid (III).—A solution of 1.00 g. of β-carbethoxy-β-(7-perinaphthylidene)-propionic acid and 5 ml. of 1 *N* sodium hydroxide in 100 ml. of water was covered with 30 ml. of benzene. A few drops of 0.66% aqueous potassium permanganate solution was added and when the color had disappeared the solution was chilled in an ice-bath and the rest (150 ml.) of the permanganate was added dropwise over a period of two hours with stirring. The solution was then made acid to congo red and 30 ml. of additional benzene was added. The benzene layer was filtered and extracted with 10% sodium bicarbonate. The benzene solution was separated and dried over anhydrous sodium sulfate. The benzene was evaporated under dry nitrogen to give 0.36 g. of ketone, m.p. 81–82°, 61% yield. A mixed melting point with perinaphthanone-7 showed no depression.

β-Carbomethoxy-β-(8-methylperinaphthylidene-7)-propionic Acid (IV).—A solution of 1.62 g. (0.0414 g.-atom) of potassium in 44 ml. of anhydrous *t*-butyl alcohol was mixed with 6.80 g. (0.0465 mole) of dimethyl succinate, b.p. 92–94° at 20 mm., and 10 ml. of this solution was added to 1.96 g. (0.0100 mole) of 8-methylperinaphthanone-7,[9] b.p. 135–136° at 0.1 mm., under dry nitrogen. This mixture was kept at 50° in an oil-bath while the remaining ester solution was added through a Hershberg addition funnel over a period of three hours while the solution was stirred mechanically. The solution was heated an additional two hours, cooled and acidified with 6 ml. of concentrated hydrochloric acid in 50 ml. of water, and most of the *t*-butyl alcohol was removed under reduced pressure. The product was taken up in ether and extracted with 1 *N* ammonium hydroxide. The ammonia extractions were washed with

(1) This work was supported in part by a grant from the Research Corporation.

(2) Graduate Research Assistant, February, 1951, to February, 1952.

(3) W. S. Johnson, H. C. E. Johnson and J. Petersen, THIS JOURNAL, **67**, 1360 (1945).

(4) G. H. Daub and W. S. Johnson, *ibid.*, **72**, 501 (1950).

(5) W. S. Johnson, V. L. Stromberg and J. Petersen, *ibid.*, **71**, 1385 (1949).

(6) B. Riegel and J. G. Burr, *ibid.*, **70**, 1070 (1948).

(7) All melting points are uncorrected.

(8) L. F. Fieser and M. D. Gates, THIS JOURNAL, **62**, 2335 (1940).

(9) L. F. Fieser and F. C. Novello, *ibid.*, **62**, 1855 (1940).

ether and acidified giving a tan oil, 0.92 g., 29% yield. Repeated recrystallizations from ethyl acetate afforded colorless **β-carbomethoxy-β-(8-methylperinaphthylidene-7)-propionic acid (IV)**, m.p. 190–191°.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.54; H, 5.85; neut. equiv., 310.3. Found: C, 73.58; H, 5.95; neut. equiv., 310.6.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of III and IV in 95% ethanol were measured with a Model DU Beckman spectrophotometer. Maxima and (log ε) values are: III, 231 mμ (4.54) and 312 mμ (4.06); IV, 232 mμ (4.53) and 312 mμ (4.04).

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Dialkylaminoethyl Amides of Benzilic Acid and their Quaternary Ammonium Salts as Antispasmodics

BY ARTHUR P. PHILLIPS

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In recent years considerable efforts in numerous laboratories have been directed toward the discovery of powerful new synthetic antispasmodic compounds. These should have, preferably, strong antispasmodic effects of both the atropine and papaverine type, while lacking the numerous undesirable side actions of the former drug.

Of the great variety of structures which have been investigated, many powerful antispasmodics have been found among the dialkylaminoalkyl esters of such acids as diphenylacetic, benzilic and others of similar structure. In only a very few instances[1] have some analogous dialkylaminoalkyl amides been made and tested. The amides reported were usually the diethylaminoethyl amides and they were stated as being less active than the corresponding diethylaminoethyl esters in most instances, at least in atropine-like activity. Miescher, Meisel and Hoffmann[2] have reported a number of dialkylaminoalkyl amides of various aliphatic aromatic acids, and they state that some of these approximate atropine in potency.

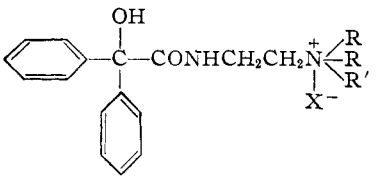
Since some recent work[3] from these laboratories has been concerned with various carboxylic acid aminoalkyl amides, it seemed worthwhile to prepare a series of substituted aminoethyl amides for antispasmodic testing. Benzilic acid was selected as the common acid component, since dialkylaminoalkyl esters of this acid frequently show strong activity, and because in the above-mentioned patent[2] one of the specific compounds claimed was the diethylaminoethyl amide of benzilic acid.

Benzilic acid methyl ester reacted with dimethylaminoethylamine, diethylaminoethylamine, morpholinoethylamine and with piperidinoethylamine to give the series of aminoalkyl amides shown in Table I. The individual tertiary aminoalkyl amides were quaternized with methyl iodide to give the methiodides, also in Table I.

The potency of these compounds as antispasmodics was compared with that of atropine by comparing the amounts of atropine and of compound needed to produce a 50% inhibition of the acetylcholine induced contraction in the isolated guinea pig ileum preparation. The diethylaminoethyl amide of benzilic acid was the most potent member of the present series and showed only 4% of the potency of atropine. The quaternary methiodide of this amide had only 1% of the potency of atropine in this test method, while the other compounds shown in Table I had 1% or less of the potency of atropine. Thus these compounds do not appear to offer any promise as useful antispasmodics. It is interesting to note that the quaternary salts were less potent than the tertiary amines while in the analogous ester series quaternization frequently enhanced activity.

TABLE I

DIALKYLAMINOETHYL AMIDES OF BENZILIC ACID AND SOME DERIVED SALTS



R	R′X	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	...	94–95	$C_{18}H_{22}N_2O_2$	72.4	72.2	7.4	7.1
CH_3	CH_3I	204–205	$C_{19}H_{25}IN_2O_2$	51.7	51.4	5.7	5.8
C_2H_5	...	104–105	$C_{20}H_{26}N_2O_2$	73.6	73.4	8.0	7.8
C_2H_5	CH_3I	189–190	$C_{21}H_{29}IN_2O_2$	53.9	53.8	6.2	6.4
$O(C_2H_4)_2$[b]	...	127–128	$C_{20}H_{24}N_2O_3$	70.6	70.4	7.1	6.9
$O(C_2H_4)_2$[b]	CH_3I	230–231	$C_{21}H_{27}IN_2O_3.H_2O$	50.3	50.4	5.9	5.7
$-(CH_2)_5-$[c]	HCl	201–202	$C_{21}H_{27}ClN_2O_2.H_2O$	64.2	64.6	7.4	7.6
$-(CH_2)_5-$[c]	CH_3I	171–172	$C_{22}H_{29}IN_2O_2.H_2O$	53.0	52.6	6.3	6.5

[a] Yields were all 90% or greater. The tertiary amino amides were recrystallized from mixtures of benzene and Skellysolve B. The methiodides and hydrochloride were recrystallized from mixtures of methanol and ether. [b] Morpholinoethyl amides. [c] Piperidinoethyl amides.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included and to A. E. Light for the pharmacological results which were briefly summarized.

(1) Meier and K. Hoffmann, *Helv. Med. Acta*, **7**, 106 (1941).

(2) K. Miescher, W. Meisel and K. Hoffmann, U. S. Patent 2,009,144 (July 23, 1935).

(3) A. P. Phillips, THIS JOURNAL, **73**, 5822 (1951); **74**, 4320 (1952).