[CONTRIBUTION FROM THE RESEARCH DIVISION OF SMITH, KLINE AND FRENCH LABORATORIES]

ANALGESICS. III. AMINOPHTHALIDYLALKANES

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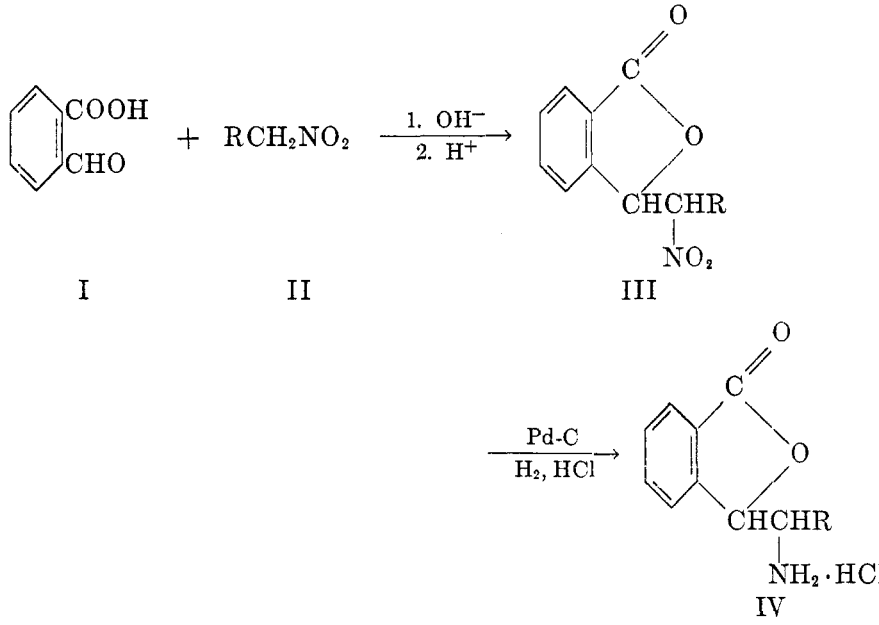
Previous papers (1, 2) in this series have described two methods of synthesis for aminophthalidylalkanes (IV) as shown by I–X. Method *A* is preferred when the proper starting materials are available. In the present work both of these methods have been employed to study the effect of substitution in the benzene ring (by amino, acetylamino, dimethyl, and dimethoxy), as well as the effect of further variations in the nature of the R group (isobutyl, hexyl, phenyl).

A.



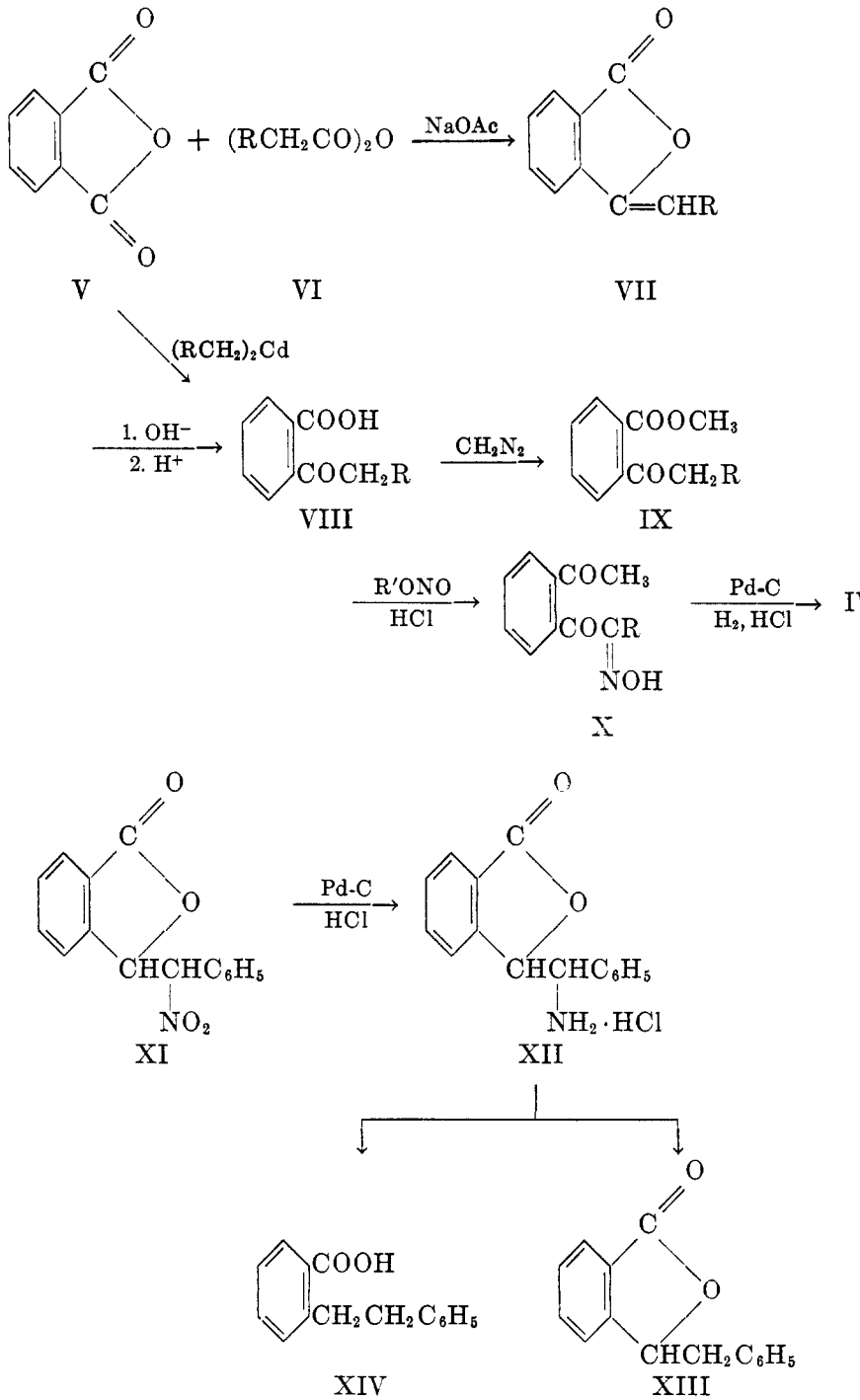
The behavior of phenylphthalidylnitromethane when subjected to catalytic reduction in an acid solution deserves special mention (see XI–XIV). In addition to reduction of the nitro group, reductive debenzylation of both the amino and the hydroxyl (actually the lactone) functions occurred. Presumably both XIII and XIV are formed from the amine salt (XII).

Similar catalytic debenzylations have been described by Baltzly and Buck (3).

The aminophthalidylalkanes (IV) were also of interest as intermediates in the synthesis[1] of aminoalkoxyisoquinolines. Isoquinoline derivatives of this type exhibit pronounced local anesthetic properties (4).

[1] The conversion of aminophthalidylalkanes into substituted isocarbostyrils has already been mentioned [see Ref. (1)]. It will be described in more detail in a later paper.

B.


O
C
O
C
O
+ (RCH2CO)2O
NaOAc
C=CHR
V
VI
VII
(RCH2)2Cd
1. OH−
2. H+
COOH
COCH2R
VIII
CH2N2
COOCH3
COCH2R
IX
R'ONO
HCl
COCH3
COCR
NOH
X
Pd-C
H2, HCl
IV
CHCHC6H5
NO2
XI
Pd-C
HCl
NH2·HCl
XII
COOH
CH2CH2C6H5
XIV
CHCH2C6H5
XIII

A number of those compounds (1) already reported (R = methyl and ethyl) showed moderate ability to elevate the pain threshold in animals. None of the aminophthalidylalkanes described in this investigation appreciably altered the pain threshold of animals.

EXPERIMENTAL

A. PHTHALIDYLNITROALKANES

3-Methyl-1-nitro-1-phthalidylbutane. This compound was obtained as a yellow oil in a 50% yield from phthalaldehydic acid (1) and 3-methyl-1-nitrobutane (5) using the procedure of Ullyot, *et al.* (1). One of the diastereoisomers melted at 107–108.5° after crystallization from alcohol.

Anal. Calc'd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07.
Found: C, 62.58; H, 6.09.

1-Nitro-1-phthalidylheptane. This compound was obtained as above in a crude yield of 63% from phthalaldehydic acid and 1-nitroheptane (5). Neither of the diastereoisomers was obtained in crystalline form.

Phenylphthalidylnitromethane. A mixture of 7.3 g. (0.053 mole) of crude phenylnitromethane (6), 8.0 g. (0.053 mole) of phthalaldehydic acid, and 0.5 ml. (0.005 mole) of piperidine was heated at 80° for five hours. The resulting solid was washed with saturated sodium bicarbonate, dilute hydrochloric acid, and water. Crystallization from acetic acid-water gave 8.7 g. (61%); m.p. 157–162°.

Anal. Calc'd for $C_{15}H_{11}NO_4$: N, 5.20. Found: N, 5.21.

6,7-Dimethoxyphthalide (meconine). The procedure of Edwards, Perkin, and Stoyle (7) was modified as follows. An ice-cold mixture of 182 g. (1.0 mole) of 2,3-dimethoxybenzoic acid, 800 ml. of concentrated hydrochloric acid, and 81 g. (1.0 mole) of 37% formaldehyde was stirred and saturated with hydrogen chloride. The mixture was stirred at room temperature for four hours and then allowed to stand overnight. The resulting dark red solution was concentrated to approximately 700 ml., poured into 600 g. of cracked ice, and brought to *p*H 3–4 with 40% sodium hydroxide. The aqueous phase was decanted from the gummy residue, diluted with 1500 g. of cracked ice, and kept at 0° for three hours. The brown product was separated, triturated with a saturated solution of sodium bicarbonate, and crystallized from 5 l. of water; 46 g.; m.p. 101–102°. Concentration of the mother liquor yielded an additional 19 g. (total yield 33%); m.p. 99–100°. Other preparations gave yields of 30–48%.

When the procedure of Edwards, Perkin, and Stoyle was followed 69 g. (0.38 mole) of 2,3-dimethoxybenzoic acid yielded 46 g. of a product which melted at 106–107° after crystallization from alcohol. None of the desired meconine was obtained. In carrying out this same reaction, Manske and Ledingham (8) obtained a product (m.p. 106°) which they identified as 4-chloromethyl-6,7-dimethoxyphthalide. On the basis of melting point and analytical data (see below) our product was evidently identical with that described by Manske.

Anal. Calc'd for $C_{11}H_{11}ClO_3$: C, 54.45; H, 4.57.
Found: C, 54.30; H, 4.87.

5,6-Dimethoxyphthalaldehydic acid (opianic acid). The procedure described by Perkin, *et al.* (7) gave only traces of opianic acid. The following modification was employed. To 15 g. (0.077 mole) of 6,7-dimethoxyphthalide in 650 ml. of warm water was added 25 g. of finely divided manganese dioxide. Then 37.5 g. of concentrated sulfuric acid in 37.5 g. of water was added slowly with stirring. After refluxing for three hours, the mixture was filtered. Concentration of the filtrate to one-half its original volume gave 10 g. of a mixture of meconine and opianic acid. The acid was separated with sodium bicarbonate; 5.5 g. (34%), m.p. 142–146°. The recovered meconine weighed 3.2 g.; m.p. 100–101°.

1-Nitro-1-(6,7-dimethoxyphthalidyl)propane. A solution of 15 g. (0.071 mole) of opianic

acid and 6.32 g. (0.071 mole) of 1-nitropropane in 100 ml. of methanol was cooled to 3° and 11.9 ml. (0.142 mole) of a 40% sodium hydroxide solution (aqueous) was added dropwise with stirring. After three hours at 3° the solution was acidified by the dropwise addition, with stirring, of 30 ml. of 6 *N* hydrochloric acid, care being taken to keep the temperature below 10°. One half of the solvent was removed by distillation *in vacuo*. The oil was taken into ether and washed with bicarbonate solution and water. Removal of the ether gave an oil which crystallized from alcohol-water; 7.5 g.; m.p. 70–95°. Repeated crystallization from alcohol-water gave a colorless product; m.p. 107–115° (softening at 100°). The bicarbonate wash yielded 3.1 g. of opianic acid; m.p. 142–144°.

Anal. Calc'd for $C_{13}H_{15}NO_6$: N, 4.98; OCH_3, 22.04.

Found: N, 5.14; OCH_3, 22.05.

1-Nitro-1-(6-nitrophthalidyl)propane. A solution of 22.1 g. (0.1 mole) of 1-nitro-1-phthalidylpropane (1) in 25 ml. of concentrated sulfuric acid was added slowly with stirring at 5° to a mixture of 11 g. (0.11 mole) of potassium nitrate and 33 ml. of concentrated sulfuric acid.[2] After stirring at 10° for three hours, and standing at room temperature for 16 hours, the solution was poured over cracked ice. The product, m.p. 93–96°, weighed 26.6 g. (100%). Crystallization from alcohol yielded 24.2 g.; m.p. 95–98°; mixture m.p. with starting material 67–87°.

Anal. Calc'd for $C_{11}H_{10}N_2O_6$: N, 10.52. Found: N, 10.65.

Oxidation with alkaline permanganate gave 4-nitrophthalic acid[3] (9), m.p. 165–166.5° after crystallization from benzene-acetic acid.

B. HYDROGENATION OF THE PHTHALIDYLNITROALKANES

1-Amino-1-phthalidyl-3-methylbutane hydrochloride. Reduction of the nitro compound as previously described (1) gave a 60% yield of a basic water-soluble product which was not obtained in crystalline form. The structure of this product was established beyond doubt by alkaline rearrangement to 3-isobutylisocarbostyril (10); m.p. 137–138°. This rearrangement will be described in detail in a later paper.

1-Amino-1-phthalidylheptane hydrochloride. This product was obtained in a 41% yield, as above, by reduction of the crude nitro compound. After crystallization from dilute 2-propanol it melted at 251–252°.

Anal. Calc'd for $C_{15}H_{22}ClNO_2$: Cl^-, 12.49. Found: Cl^-, 12.33.

Phenylphthalidylmethylamine hydrochloride. A mixture of 10 g. (0.037 mole) of phenylphthalidylnitromethane, 225 ml. of alcohol, and 1 g. of a 9% palladium on zirconium dioxide catalyst (American Platinum Works) was hydrogenated at 52° and 47.5 p.s.i. The theoretical volume of hydrogen (0.111 mole) was absorbed in a period of eight hours. After removing the catalyst, 3.2 ml. (0.037 mole) of concentrated hydrochloric acid was added. The solution was concentrated to a small volume and water was removed by azeotropic distillation with 200 ml. of benzene. The gummy residue was triturated with acetone and filtered. The crude solid (4.4 g.) was dissolved in 110 ml. of warm alcohol, and 0.37 g. (0.016 mole) of sodium in 38 ml. of alcohol was added. The solvent was removed by distillation *in vacuo* and benzene was again added. After removing a small amount of the benzene at atmospheric pressure, the solution was cooled and acidified with dry hydrogen chloride. The hydrochloride was recrystallized from an alcohol-water solution by azeotropically removing water with benzene; 1.0 g. (19%); m.p. 279–280° dec. (sinters at 273°).

Anal. Calc'd for $C_{15}H_{14}ClNO_2$: N, 5.07; Cl^-, 12.86.

Found: N, 5.48; Cl^-, 12.84.

The *p-nitrobenzoyl* derivative, m.p. 218–220°, was crystallized from alcohol.

Anal. Calc'd for $C_{22}H_{16}N_2O_5$: N, 7.21. Found: N, 7.20.

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[2] This procedure was employed by Shriner and Keyser, *J. Org. Chem.*, **5**, 200 (1940), for the nitration of phthalide.

[3] This oxidation product rules out the possibility of nitration in positions four or seven of the ring. It does not eliminate the unlikely possibility of nitration in position five.

Catalytic hydrogenation of the phenylphthalidylnitromethane in acid solution gave chiefly non-basic products. A solution of 13.5 g. (0.05 mole) of the nitro compound in 250 ml. of alcohol containing 4.3 ml. of concentrated hydrochloric acid was hydrogenated at 52° and 50 p.s.i. using 2 g. of a 50% palladium on carbon catalyst. In a period of 2.5 hours the uptake of hydrogen corresponded to 0.20 mole. After removing the catalyst, the solvent was removed by distillation *in vacuo*. Traces of water were removed from the residual material by distillation with benzene. The gummy residue was triturated with acetone to yield 3.7 g. of crystalline water-soluble material which proved to be chiefly ammonium chloride. The acetone was removed from the filtrate and the resulting solid was separated into two fractions with a saturated solution of sodium bicarbonate. The bicarbonate-soluble material after crystallization from benzene-petroleum ether weighed 1.1 g. (10%) and melted at 131.5–132.5°. It did not depress the melting point of an authentic sample of *o*-(β-phenylethyl)benzoic acid (11). The bicarbonate-insoluble material, after crystallization from alcohol-water, melted at 59.0–59.5° and weighed 7.0 g. (62%). It did not depress the melting point of an authentic sample of 3-benzylphthalide (12).

1-Amino-1-(6,7-dimethoxyphthalidyl)propane hydrochloride. This compound was prepared by hydrogenation using the procedure already described (1). After removing the catalyst, the solvent was removed *in vacuo*. Benzene and alcohol were added and the distillation was repeated. Crystallization from acetone-petroleum ether gave 7.0 g. of a water-soluble product. A second crystallization, carried out by dissolving in 60 ml. of alcohol, adding 250 ml. of benzene, concentrating to a volume of 40 ml., and diluting with 35 ml. of acetone yielded 5.6 g. (65%). When heated slowly (closed cap), sintering occurred at 125°, shrinking at 160–164° and melting at 194–198°. The melting point varied (160–190°), depending upon the rate of heating.

Anal. Calc'd for $C_{13}H_{18}ClNO_4$: N, 4.83; OCH_3, 21.55.

Found: N, 4.75; OCH_3, 19.30.

The *p-nitrobenzoyl* derivative, after crystallization from alcohol, melted at 160–165°.

Anal. Calc'd for $C_{20}H_{20}N_2O_7$: N, 6.99; OCH_3, 15.49.

Found: N, 7.14; OCH_3, 15.74.

1-Nitro-1-(6-aminophthalidyl)propane. A solution of 13.3 g. (0.1 mole) of 1-nitro-1-(6-nitrophthalidyl)propane in 75 ml. of glacial acetic acid was hydrogenated at room temperature and 50 p.s.i. using Adam's catalyst. After 20 minutes, the uptake of hydrogen corresponded to 0.3 mole and the rate of reduction decreased abruptly. At this point the hydrogenation was stopped, the mixture was warmed, filtered, and cooled to 10° to yield 8.9 g. (76%) of product; m.p. 181–184°. Crystallization from acetone-alcohol yielded white crystals; m.p. 183–184°.

Anal. Calc'd for $C_{11}H_{12}N_2O_4$: N, 11.86. Found: N, 11.75.

The *acetyl* derivative was prepared in, and crystallized from, glacial acetic acid; m.p. 201–202°.

Anal. Calc'd for $C_{13}H_{14}N_2O_5$: N, 10.07. Found: N, 10.19.

1-Amino-1-(6-acetamidophthalidyl)propane hydrochloride. A mixture of 15 g. (0.054 mole) of 1-nitro-1-(6-acetamidophthalidyl)propane and 12 g. of preformed palladium-on-carbon catalyst (prepared from 10 ml. of 16% palladium chloride solution and 10 g. of activated charcoal) in 150 ml. of glacial acetic acid containing 2 g. (0.055 mole) of anhydrous hydrogen chloride was hydrogenated at 70° and an initial pressure of 50 p.s.i. In a period of four hours, 0.162 mole of hydrogen was absorbed. The catalyst was removed and leached with water. The acetic acid was removed from the filtrate and the water-soluble product was separated. Crystallization of the water-soluble material from alcohol-water was effected by azeotropically removing the water with benzene; 6.1 g. (40%); m.p. 290–291°.

Anal. Calc'd for $C_{13}H_{17}ClN_2O_3$: C, 54.83; H, 6.02; Cl^-, 12.45.

Found: C, 54.89; H, 5.96; Cl^-, 12.45.

The *p-nitrobenzoyl* derivative was crystallized from alcohol; m.p. 270–272.5°.

Anal. Calc'd for $C_{20}H_{19}N_3O_6$: N, 10.57. Found: N, 10.56.

1-Amino-1-(6-aminophthalidyl)propane dihydrochloride. A solution of 11.8 g. (0.05 mole of 1-(6-aminophthalidyl)-1-nitropropane in 10.2 ml. (0.12 mole) of concentrated hydro-

chloric acid was diluted with 110 ml. of water and mixed with 10 ml. of 10% palladium chloride solution and 2.0 g. of activated charcoal. This mixture was hydrogenated at 65° and an initial pressure of 50 p.s.i. In a period of 90 minutes 0.15 mole of hydrogen was absorbed. After removing the catalyst the filtrate was taken to dryness *in vacuo*. The solid residue was suspended in 75 ml. of hot alcohol and enough water was added to give a clear solution. Benzene (40 ml.) was added to this solution and removed by distillation. Dilution with 20 ml. of benzene and cooling yielded 8.7 g. (62%) of product; m.p. 249–250.5°.

Anal. Calc'd for $C_{11}H_{16}Cl_2N_2O_2$: Cl^-, 25.39. Found: Cl^-, 25.07.

The *diacetyl* derivative was crystallized from alcohol; m.p. 273.5–274.5°.

Anal. Calc'd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.68.
Found: C, 62.10; H, 6.32; N, 9.75.

C. PREPARATION OF AMINOPHTHALIDYLALKANES FROM ANHYDRIDES

1. *1-Amino-1-(5,6-dimethylphthalidyl)propane hydrochloride.* a. *2-Carboxy-4,5-dimethylbutyrophenone.* A modification of the general procedure of De Benneville (13) was employed. Ether was replaced by benzene (14) as the solvent, and the molar ratio of di-*n*-propylcadmium to the anhydride was increased. From 41.1 g. (1.69 moles) of magnesium, 258 g. (2.1 moles) of *n*-propyl bromide, 178.4 g. (0.975 mole) of anhydrous cadmium chloride, and 114 g. (0.65 mole) of 4,5-dimethylphthalic anhydride (15), there was obtained 116 g. (81%) of product; m.p. 120–124°. Crystallization from benzene yielded the acid; m.p. 129.5–130°.

Anal. Calc'd for $C_{13}H_{16}O_3$: Neut. equiv., 220.6. Found: Neut. equiv., 219.1.

b. *2-Carbomethoxy-4,5-dimethylbutyrophenone.* The procedure of Ullyot, Taylor, and Dawson (2) gave a 69% yield of product, b.p. 159–163° (3 mm.), n_D^{25} 1.5217, from 50 g. (0.23 mole) of the acid.

Anal. Calc'd for $C_{14}H_{18}O_3$: C, 71.70; H, 7.74.
Found:[4] C, 70.51; H, 7.58.

c. *2-Carbomethoxy-4,5-dimethyl-α-isonitrosobutyrophenone.* A 73% yield of this compound was obtained using essentially the procedure of Ullyot, *et al.* (2). After crystallization from 90% 2-propanol it melted at 154–157°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32.
Found: C, 63.79; H, 6.47; N, 5.31.

d. *1-Amino-1-(5,6-dimethylphthalidyl)propane hydrochloride.* Reduction of the isonitroso compound (38 g., 0.145 mole) following the procedure of Ullyot, *et al.* (2) yielded 15 g. (41%) of product which was purified by conversion to the free base and reprecipitation with anhydrous hydrogen chloride from alcohol; m.p. 288–290° dec.

Anal. Calc'd for $C_{13}H_{18}ClNO_2$: Cl^-, 13.86; N, 5.48.
Found: Cl^-, 13.65; H, 5.47.

The *acetyl* derivative was crystallized from 90% 2-propanol; m.p. 170–171°.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36.
Found: C, 68.79; H, 7.38; N, 5.39.

2. *1-Amino-1-phthalidylpentane hydrochloride.* a. *Caprophenone-o-carboxylic acid.* Pentylidenephthalide, b.p. 158–160° (4 mm.), was prepared in 66% yield from *n*-caproic anhydride, phthalic anhydride, and freshly fused potassium acetate, using essentially the procedure described by Ullyot, Taylor, and Dawson (2) for the preparation of propylidenephthalide. The keto acid was obtained in 76% yield by alkaline hydrolysis of the pentylidenephthalide. It was distilled at 185–186° (5 mm.).

Anal. Calc'd for $C_{13}H_{16}O_3$: Neut. equiv., 220.3; C, 70.89; H, 7.32.
Found:[5] Neut. equiv., 213.6; C, 72.65; H, 7.82.

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[4] The distilled product was contaminated with 3-propylidene-5,6-dimethylphthalide which formed during the distillation from the psuedo form of the ester [see Ref. (2)].

[5] The discrepancy in the analytical data is probably due to the regeneration of pentylidenephthalide during the distillation by the loss of water from the psuedo form of the keto-acid.

b. *Methyl caprophenone-o-carboxylate.* This ester was obtained in 90% yield by esterification (2) of the acid. It distilled without decomposition at 153–155° (4 mm.).

Anal. Calc'd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74.

Found: C, 71.71; H, 8.04.

c. *Methyl α-isonitrosocaprophenone-o-carboxylate.* The isonitroso reaction (2) was carried out in methylene chloride using ethyl nitrite and anhydrous hydrogen chloride. The product (88% crude yield) melted at 95–96° after crystallization from dilute alcohol.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 64.11; H, 6.51; N, 5.34.

Found: C, 64.10; H, 6.65; N, 5.44.

d. *1-Amino-1-phthalidylpentane hydrochloride.* The isonitroso derivative was reduced as previously described. The basic, water-soluble product was obtained in 41% yield as a white crystalline solid. This compound was not characterized as such but its identity was established by rearrangement to 3-*n*-butylisocarbostyril (4).

3. *Attempted preparation of 1-amino-1-(4,7-dimethoxyphthalidyl)propane hydrochloride.* a. *2-Carboxy-3,6-dimethoxybutyrophenone.* The procedure used to prepare the 2-carboxy-4,5-dimethylbutyrophenone was employed in the preparation of this acid. From 10.4 g. (0.05 mole) of 3,6-dimethoxyphthalic anhydride,[6] there was obtained 10.5 g. (83%) of a white product; m.p. 165–166°. Crystallization from benzene did not change the melting point.

Anal. Calc'd for $C_{13}H_{16}O_6$: Neut. equiv., 252.26; C, 61.89; H, 6.39.

Found: Neut. equiv., 250.38; C, 61.89; H, 6.80.

b. *2-Carbomethoxy-3,6-dimethoxybutyrophenone.* A dry solution of 16.8 g. (0.40 mole) of diazomethane [from 63.0 g. (0.61 mole) of nitrosomethylurea (16)] in 350 ml. of methylene chloride was added at 0°, with stirring, to a suspension of 63 g. (0.25 mole) of 2-carboxy-3,6-dimethoxybutyrophenone in 500 ml. of methylene chloride. After standing at room temperature for two hours the yellow solution was dried overnight with sodium sulfate. Removal of the solvent gave 65 g. (98%) of the pale yellow solid; m.p. 52–54°.Crystallization from acetone-isoheptane did not change the melting point.

Anal. Calc'd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81.

Found: C, 62.92; H, 6.54.

c. *Attempted preparation of 2-carbomethoxy-3,6-dimethoxy-α-isonitrosobutyrophenone.* Efforts to carry out the isonitroso reaction on this ketone (5.0 g.) using the procedure of Ullyot, *et al.* (2), gave only a very small quantity (0.4 g.) of nitrogen-containing product; m.p. 201–203°, after recrystallization from 90% 2-propanol. The analytical data on this compound were quite erratic. The starting keto-ester was recovered in 40% yield.

Attempted preparation of 1-amino-1-(dibenzo[e,g]phthalidyl)propane hydrochloride. a. *10-Butyrylphenanthrene-9-carboxylic acid.* Ten grams (0.041 mole) of 9,10-dicarboxyphenanthrene anhydride (17), treated with an excess of dipropylcadmium in toluene yielded 9 g. (75%) of product; m.p. 202–205°. After crystallization from toluene the keto-acid melted at 206–207°.

Anal. Calc'd for $C_{19}H_{16}O_3$: C, 77.80; H, 5.49.

Found: C, 77.95; H, 5.63.

b. *9-Carbomethoxy-10-butyrylphenanthrene.* Esterification of the keto-acid with diazomethane using the procedure employed in preparing 2-carbomethoxy-3,6-dimethoxybutyrophenone gave a 96% yield of product, recrystallized from 90% 2-propanol; m.p. 98–100° (after solidification the product remelted at 108–110°).

Anal. Calc'd for $C_{20}H_{18}O_3$: C, 78.49; H, 5.92.

Found: C, 78.42; H, 6.00.

c. *Attempted preparation of 9-carbomethoxy-10-(α-isonitrosobutyryl)phenanthrene.* Repeated efforts to carry out the isonitroso reaction on the keto-ester using the procedure of Ullyot, *et al.* (2), gave no nitrogen-containing product. The keto-ester was consistently recovered in good yield (60–75%).

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[6] Obtained from Dr. Robert L. Frank, University of Illinois; m.p. 266–268° after crystallization from acetic anhydride.

SUMMARY

The preparation of a group of aminophthalidylalkanes has been described. None of the compounds showed any appreciable analgetic activity.

PHILADELPHIA, PENNA.

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