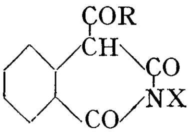
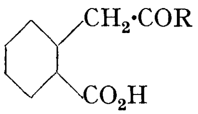
266. *Some Derivatives of Homophthalimide.*

By Robert D. Haworth.

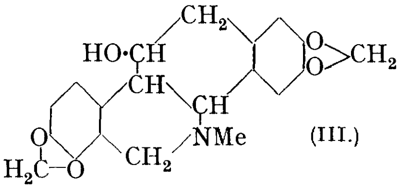
The reactivity of the methylene group of homophthalimide allows of facile condensation with aldehydes, diazotates, and alkyl halides, and it has now been shown that, in the presence of alkalis, reaction readily occurs with a variety of acid anhydrides or chlorides. The 4-monoacyl derivatives (I; X = H) are readily soluble in alkali, and the structure is established by the conversion of the benzoyl derivative (I; R = C_6H_5, X = H) into *o*-carboxybenzyl phenyl ketone (II), and confirmed by the preparation of a series of similar products (I; X = Me) from 2-methylhomophthalimide.



(I.)



(II.)



(III.)

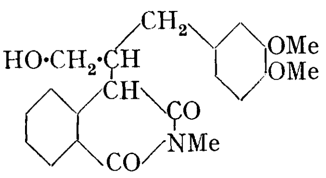
The phenylacetyl derivatives (I; R = $C_6H_5·CH_2$, X = Me) were of interest as offering a possible method for the synthesis of alkaloids of the chelidonine type (III) (Bruchhausen and Bersch, *Ber.*, 1930, **63**, 2520; 1931, **64**, 947; Späth and Kuffner, *Ber.*, 1931, **64**, 370, 1123, 2034), and the route was particularly attractive, as substituted homophthalic acids of appropriate orientation for the alkaloidal synthesis are available (Haworth, Perkin, and Stevens, J., 1926, 1769; Haworth, Koepfli, and Perkin, J., 1927, 551). Such phenylacetyl derivatives are readily prepared, but cyclisation experiments have been unsuccessful, in spite of the fact that favourable cases, such as those in which R is 3 : 4-dimethoxyphenyl or 3 : 4-methylenedioxyphenyl, have been investigated. Compounds of type (I; R = $C_6H_5·CH_2$, X = Me) are quantitatively converted into 2-methylhomophthalimide and methyl phenylacetate by warming with methyl-alcoholic hydrogen chloride and the cyclisation failures are probably to be ascribed to the instability of substances of type (I) towards acidic reagents.

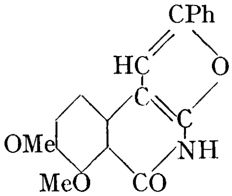
The condensation of ω-bromoacetophenone with 2-methylhomophthalimide gave the 4 : 4-diphenacyl derivative. The formation of 2 : 4 : 4-trialkyl derivatives by the action of alkylating agents on 2-methylhomophthalimide is in accordance with general experience

(Gabriel, *Ber.*, 1886, **19**, 2364; 1887, **20**, 1199; Haworth, Perkin, and Pink, J., 1925, **127**, 1710) and the preparation of 2 : 4-dialkylhomophthalimides presents considerable difficulties. It has been shown that the phenylacetyl derivative (I; R = $C_6H_5{\cdot}CH_2$, X = Me) can be converted into the 4-monomethyl derivative, which on hydrolysis with methyl-alcoholic hydrogen chloride yields 2 : 4-dimethylhomophthalimide, and the method should prove generally useful for the preparation of 2 : 4-dialkylhomophthalimides.

2-Methylhomophthalimide condenses with *O*-methyleugenol oxide, yielding a *compound*, probably (IV), but preliminary cyclisation experiments were discouraging. An attempt has been made to utilise opianic acid in the synthesis of alkaloids of the chelidonine class. Potassium cyanide and 6 : 7-dimethoxy-3-phenacylphthalide (Goldschmidt, *Monatsh.*, 1891, **12**, 476) reacted to give an oil, which was converted by warm concentrated hydrochloric acid into a yellow crystalline *compound*, $C_{19}H_{15}O_4N$, for which structure (V), based on its neutral nature and analysis, is suggested, but as potassium cyanide did not react with 6 : 7-dimethoxy-3-(3′ : 4′-dimethoxyphenacyl)phthalide, this line of attack was abandoned.

(IV.)





(V.)

Most of the experiments described in this communication were carried out in 1932, and the publication of the results appears desirable, as experiments with a similar objective have reached a more advanced stage in the Oxford laboratories (see Richardson, Robinson, and Seijo, this vol., p. 835).

EXPERIMENTAL.

General Methods for Preparation of Compounds of Type (I).—(a) The appropriate acid chloride or anhydride (1·1 mols.) was added with cooling and stirring to a solution of homophthalimide or 2-methylhomophthalimide (1 mol.) in 5% potassium hydroxide solution (1·1 mols.). After 1½ hours, the product was collected and washed with water. (b) In some cases excess of 5% potassium hydroxide solution (2·5 mols.) was employed; after 2 hours, the product was liberated by acidification of the filtered solution, collected, and washed.

4-*Acetyl*-2-*methylhomophthalimide* (I; R = X = Me), obtained in 70% yields from acetic anhydride by method (a), crystallised from methyl alcohol in long needles or stout prisms, the latter form being favoured by slow crystallisation. Both forms melted at 113° (Found : C, 66·2; H, 5·2. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%).

4-*Benzoyl*-2-*methylhomophthalimide* (I; R = C_6H_5, X = Me), obtained in 75% yields from benzoyl chloride by method (a), crystallised from methyl alcohol in long, pale yellow needles, m. p. 114—115° (Found : C, 72·9; H, 4·5. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%).

4-*Phenylacetyl*-2-*methylhomophthalimide* (I; R = $C_6H_5{\cdot}CH_2$, X = Me), obtained in 60% yields by method (b), crystallised from methyl alcohol in colourless needles, m. p. 125—126° (Found : C, 73·7; H, 5·0. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2%). This imide, which is soluble in sodium hydroxide solution, was refluxed for 1 hour with methyl-alcoholic hydrogen chloride and converted quantitatively into methyl phenylacetate and 2-methylhomophthalimide. The phenylacetyl derivative was refluxed for 12 hours with excess of methyl iodide in methyl alcohol containing potassium hydroxide (1·1 mols.). The methyl alcohol and the excess of methyl iodide were removed, the residue diluted with water, and the alkali-insoluble 4-*phenylacetyl*-2 : 4-*dimethylhomophthalimide* collected and crystallised from methyl alcohol; it separated in long rectangular prisms, m. p. 127—128° (Found : C, 74·4; H, 5·3. $C_{19}H_{17}O_3N$ requires C, 74·3; H, 5·5%). Hydrolysis with methyl-alcoholic hydrogen chloride yielded methyl phenylacetate and 2 : 4-dimethylhomophthalimide, which separated from dilute methyl alcohol in colourless needles, m. p. 64—65°. Gabriel and Posner (*Ber.*, 1894, **27**, 2496) give m. p. 64—66°.

4-(3′ : 4′-*Dimethoxyphenyl*)*acetyl*-2-*methylhomophthalimide* [I; R = $C_6H_3(OMe)_2{\cdot}CH_2$, X = Me], obtained in 60% yields by method (b), separated from methyl alcohol in colourless needles, m. p. 133—134° (Found : C, 67·8; H, 5·3. $C_{20}H_{19}O_5N$ requires C, 67·7; H, 5·4%). Unsuccessful attempts were made to cyclise this imide with 80% sulphuric acid, phosphoric oxide in toluene and xylene, phosphorus oxychloride and pentachloride in chloroform.

4-(3′ : *4′-Methylenedioxyphenyl)acetyl-2-methylhomophthalimide* (I; $R = CH_2{:}O_2{:}C_6H_3{\cdot}CH_2$, X = Me), obtained in 65% yields, separated from methyl alcohol in colourless needles, m. p. 141—142° (Found : C, 67·4; H, 4·6. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·5%).

4 : *4-Diphenacyl-2-methylhomophthalimide.*—2-Methylhomophthalimide (2 g.) was dissolved in methyl alcohol (20 c.c.) containing sodium methoxide, prepared from sodium (0·4 g.), and ω-bromoacetophenone (3 g.) was added to the cold solution. Heat was evolved and a solid rapidly separated. After the mixture had been warmed on the water-bath for ½ hour, water was added; the solid obtained (3·5 g.) crystallised from glacial acetic acid in colourless prisms, m. p. 247—248° [Found : C, 75·7; H, 5·4; *M* (Rast), 402. $C_{26}H_{21}O_4N$ requires C, 75·9; H, 5·4%; *M*, 411]. The yield was increased to 5 g. by employing ω-bromoacetophenone (5 g.) in the experiment.

4-*Benzoylhomophthalimide* (I; $R = C_6H_5$, X = H), obtained in 70% yields by method (b), crystallised from glacial acetic acid in colourless needles, m. p. 280° (Found: C, 72·4; H, 4·3. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·2%). This imide was boiled for 6 hours with 10% sodium hydroxide solution (5 parts); ammonia was evolved and acidification of the solution yielded *o*-carboxybenzyl phenyl ketone (II), which separated from aqueous alcohol in slender needles, m. p. 163—164°. Graebe and Trumpy (*Ber.*, 1898, **31**, 377) give m. p. 162—163° (Found : equiv., 238. Calc. for $C_{15}H_{12}O_3$, equiv., 240).

4-*Phenylacetylhomophthalimide* (I; $R = C_6H_5{\cdot}CH_2$, X = H), obtained in 65% yields, crystallised from acetic acid in colourless needles, m. p. 274—275° (Found : C, 73·1; H, 5·0. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%).

4-(3′ : *4′-Dimethoxyphenyl)acetylhomophthalimide* [I; $R = C_6H_3(OMe)_2{\cdot}CH_2$, X = H], obtained in 60% yields, separated from acetic acid in colourless needles, m. p. 282—283° (Found : C, 67·5; H, 5·1. $C_{19}H_{17}O_5N$ requires C, 67·3; H, 5·1%).

Condensation of 2-Methylhomophthalimide with O-*Methyleugenol Oxide.*—This experiment was carried out by Mr. W. Kelly, B.Sc. A solution of 2-methylhomophthalimide (2 g.) and *O*-methyleugenol oxide (2 g.) in methyl alcohol (10 c.c.) containing sodium methoxide (from sodium, 0·28 g.) was allowed to react at room temperature for 7 days. Water was added and neutral substances were removed in ether. The alkaline layer was acidified and extracted with ether. The extract was dried, and the solvent removed; the *product* (IV) crystallised from methyl alcohol in colourless rectangular prisms (1·0 g.), m. p. 135—136° (Found : C, 68·4; H, 6·2. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·2%). After standing overnight in the cold with 80% sulphuric acid, the compound (IV) was converted into homophthalic acid.

Action of Potassium Cyanide on 6 : 7-*Dimethoxy*-3-*phenacylphthalide.*—Potassium cyanide (2·2 g.) in water (10 c.c.) was added to a solution of 6 : 7-dimethoxy-3-phenacylphthalide (5 g., prepared from opianic acid and acetophenone as described by Goldschmidt, *loc. cit.*) in 3·5% sodium hydroxide solution (15 c.c.). Glacial acetic acid (1 c.c.) was added to the cold solution and after 24 hours the brown solution was acidified and the supernatant liquid decanted from the brown oil. The latter was warmed on the water-bath for 1 hour with concentrated hydrochloric acid (25 c.c.), the yellow solid was collected, washed first with water and then with methyl alcohol, and crystallised from glacial acetic acid or better from nitrobenzene; the *compound* (V) separated in bright yellow needles (6·2 g.), m. p. 282° (Found : C, 71·2; H, 4·9; N, 4·4. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7; N, 4·4%). This compound (V) (2 g.) was boiled with 10% sodium hydroxide solution (40 c.c.); ammonia was rapidly evolved and after ½ hour the solution was filtered from traces of insoluble material and acidified. The white precipitate obtained crystallised from methyl alcohol in colourless prisms (1·5 g.), m. p. 184—185° (decomp.) (Found : C, 61·3; H, 5·0%), which have not been identified.

6 : 7-*Dimethoxy*-3-(3′ : *4′-dimethoxy)phenacylphthalide.*—Methyl alcohol was added to a suspension of acetoveratrone (10 g.) and opianic acid (12 g.) in 10% sodium hydroxide solution (36 c.c.) until a homogeneous solution was obtained. After 24 hours, the mixture was acidified with hydrochloric acid and warmed for a few minutes; the product crystallised from methyl alcohol or acetic acid in colourless needles (14 g.), m. p. 165—167° (Found : C, 64·3; H, 5·5. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%).

UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE.

[*Received, June 2nd*, 1937.]