

698. The Preparation of Some 2-Substituted Diazoacetophenones and their Behaviour towards Acid.

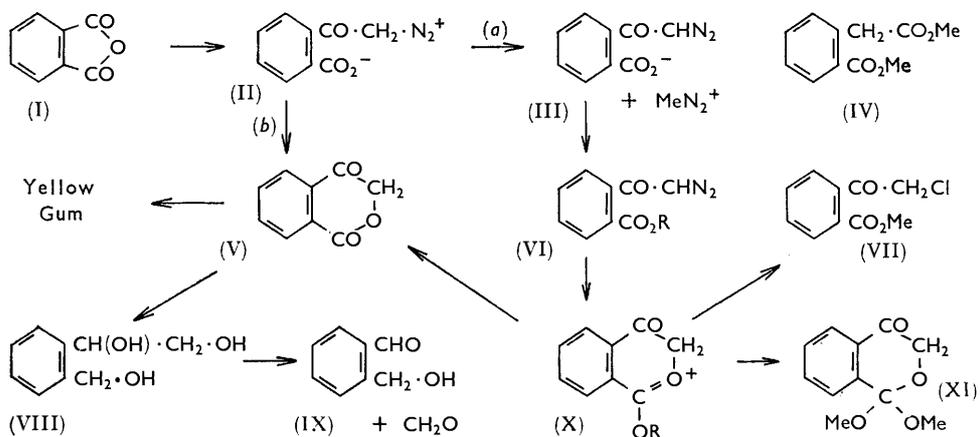
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Phthalic anhydride reacts slowly with diazomethane, to give methyl *o*-diazoacetylbenzoate in only 25% yield. The main reaction seems to give 1,4-dioxoisochroman which reacts further with diazomethane. Methyl, ethyl, and phenyl *o*-diazoacetylbenzoate have been prepared. They react with hydrogen chloride in absolute methanol to give 1,1-dimethoxy-4-oxoisochroman, and 1,4-dioxoisochroman if water is present. These reactions are interpreted in terms of a neighbouring group effect. The action of hydrochloric acid on methyl δ -diazo- γ -oxovalerate gave the δ -chloro-compound, and on ω -diazo-2-phenoxyacetophenone gave the corresponding chloroacetophenone.

THAT the anhydrides of benzoic and trifluoroacetic acid can be used in place of their acid chlorides to provide diazo-ketones through the agency of diazomethane: ^{1,2}



has led to the suggestion ³ that this is a general reaction. Phenylacetic and *p*-nitrophenylacetic anhydride behave similarly.⁴ The anhydrides of dicarboxylic acids can behave differently: Bradley and Robinson¹ have shown that succinic anhydride reacts comparatively slowly with diazomethane and gives mainly dimethyl succinate (73%) and only traces of diazo-compound. We now report that phthalic anhydride reacts only slowly, consumes more than two molecular proportions of diazomethane, and gives the diazoacyl



ester (VI; R = Me) in 25% yield. This compound was not isolated, but its presence was demonstrated by the addition of silver benzoate and triethylamine when, in methanol as solvent, dimethyl homophthalate (IV) was obtained by Wolff rearrangement. Since the product (VI; R = Me) reacts neither with diazomethane nor with phthalic anhydride (see Experimental), its poor yield from these reactants shows their interaction to proceed mainly by another route. No other products could be isolated or identified. Doubtless, the initial interaction involves nucleophilic attack by diazomethane at a carbonyl group of the anhydride (I \rightarrow II); subsequent reaction provides mainly the keto-lactone (V)

¹ Bradley and Robinson, *J. Amer. Chem. Soc.*, 1930, **52**, 1558.

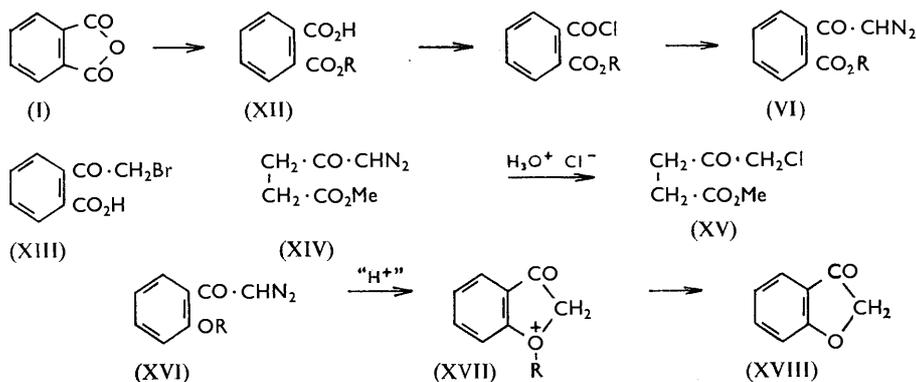
² Weygand and Bestmann, *Angew. Chem.*, 1960, **72**, 537.

³ Eistert, *Ber.*, 1935, **68**, 208, 396; *Angew. Chem.*, 1941, **54**, 124.

⁴ Duggleby and Holt, unpublished work.

[which reacts quickly with diazomethane (see Experimental)] by route (b) and the diazoacyl ester (VI) by route (a) via the anion (III). Route (a) should be favoured by high concentrations of diazomethane.

The diazoacyl esters (VI; R = Me, Et, and Ph) were readily prepared in good yield from the corresponding half esters (XII). The methyl ester (VI) was shown to react with a molecular proportion of dry hydrogen chloride in absolute ether to give the chloroacyl ester (VII). Each ester (VI), in water or moist alcohols, required only catalytic amounts of hydrochloric acid to liberate its nitrogen quantitatively in a few minutes at room temperature and give the keto-lactone (V). This compound was readily identified: it formed a phenyl- and 2,4-dinitrophenyl-hydrazone, it was reduced by lithium aluminium hydride to the triol (VIII) which gave formaldehyde and 2-hydroxymethylbenzaldehyde (IX) on oxidation with periodic acid, it consumed an equivalent of sodium hydroxide in potentiometric titration, and, in accordance with the keto-lactone structure, it has strong infrared absorption bands at 5.77 and 5.88 μ . This keto-lactone has previously been described by Gabriel⁵ who obtained it from *o*-bromoacetylbenzoic acid (XIII) but gave it a different structure.



The diazoacyl esters (VI) in absolute methanol containing a trace of dry hydrogen chloride gave the dimethoxy-compound (XI). These reactions show the oxonium ion (X) to be formed as an intermediate which undergoes nucleophilic attack by methanol to give (XI) directly when R = Me and by subsequent replacement of RO by MeO from the solvent when R = Et or Ph. When water is present, its nucleophilic attack on the ion (X) gives the keto-lactone (V). The interaction of ester and diazoacetyl groups in the presence of acid (see VI \rightarrow X) is a consequence of their juxtaposition: it does not occur in methyl δ -diazo- γ -oxovalerate (XIV), which has greater conformational freedom than have the esters (VI) and with hydrochloric acid gives the chloroacyl ester (XV); nor has it been realised intermolecularly. Thus ω -diazo-4-nitroacetophenone in ethyl benzoate or acetate containing the stoichiometric amount of hydrochloric acid gave only ω -chloro-4-nitroacetophenone (see Experimental). Juxtaposition of diazoacetyl and ether groups is realised in ω -diazo-2-methoxyacetophenone (XVI; R = Me) which, in the presence of hydrochloric acid, forms the oxonium ion (XVII) from which coumaranone (XVIII) is obtained⁶ by nucleophilic attack at the methyl group. We now report that, as expected, the corresponding phenyl ether (XVI; R = Ph) gives only ω -chloro- and ω -hydroxy-2-phenoxyacetophenone.

EXPERIMENTAL

Interaction of Phthalic Anhydride and Diazomethane.—Powdered phthalic anhydride (10 g., 1 mol.) was added to diazomethane (8.5 g., 3 mol.) in ether (900 ml.). The stirred mixture was

⁵ Gabriel, *Ber.*, 1907, **40**, 71.

⁶ Bose and Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 4703.

maintained at 0° until nitrogen (2.500 l. after 3 days) was no longer evolved. After removal of traces of polymethylene, the solvent was evaporated under reduced pressure to leave a dark golden-brown liquid which was dissolved in methanol (60 ml.) and treated dropwise with silver benzoate-triethylamine (1:10)⁷ until nitrogen evolution ceased. The volume of nitrogen evolved (400 ml. at N.T.P.) indicates that methyl *o*-diazoacetylbenzoate (25%) was present. The methanolic solution was worked up in the usual way and gave dimethyl homophthalate⁸ (2.5 g.), b. p. 190—194°/25 mm., from which homophthalic acid⁹ (2.0 g.), m. p. 180—181° (Found: C, 59.8; H, 4.5. Calc. for C₉H₈O₄: C, 60.0; H, 4.4%), was obtained by hydrolysis.

Alkyl and Phenyl o-Diazoacetylbenzoates.—Methyl, ethyl, and phenyl *o*-chloroformylbenzoate were obtained by interaction of the appropriate half esters and thionyl chloride. Excess of the latter was removed under reduced pressure at room temperature and the crude chlorides were added to an excess of ethereal diazomethane at 0° to provide, respectively, *methyl* (75%), m. p. 57—60° (decomp.), yellow needles from benzene (Found: C, 59.0; H, 4.1; N, 13.4. C₁₀H₈N₂O₃ requires C, 58.8; H, 3.9; N, 13.7%), *ethyl*, a yellow oil (which provided 90% of the theoretical volume of nitrogen when treated with hydrochloric acid), and *phenyl o-diazoacetylbenzoate* (75%), m. p. 88—90° (decomp.), yellow needles from ethanol (Found: C, 67.8; H, 3.8; N, 10.6. C₁₅H₁₀N₂O₃ requires C, 67.7; H, 3.8; N, 10.5%).

Action of Anhydrous Hydrogen Chloride on Methyl o-Diazoacetylbenzoate in Ether.—The diazo-ketone (1 g.) was added in portions to dry saturated ethereal hydrogen chloride. There was immediate evolution of nitrogen and plates of 1,4-dioxoisochroman (0.24 g., 30%), m. p. 145—145.5°, were deposited. These were removed and the solution was concentrated to provide off-white needles (0.75 g., 60%, m. p. 100—104°), which on crystallisation from methanol afforded *methyl o-chloroacetylbenzoate*, m. p. 103—104° (Found: C, 56.7; H, 4.5; Cl, 16.7. C₁₀H₉ClO₃ requires C, 56.5; H, 4.3; Cl, 16.7%).

1,4-Dioxoisochroman (V).—To methyl, ethyl, or phenyl *o*-diazoacetylbenzoate (5 g.) in methanol (25 ml.) was added one drop of concentrated hydrochloric acid. The theoretical volume of nitrogen was evolved in 5 min., and plates (70—73%; m. p. 138—140°) separated. Recrystallisation from methanol gave 1,4-dioxoisochroman, m. p. 145—145.5° (Found: C, 67.1; H, 3.8. C₉H₆O₃ requires C, 66.7; H, 3.7%); this gave a *phenylhydrazone*, m. p. 180—180.5°, as yellow needles from ethanol (Found: C, 71.4; H, 4.6; N, 11.1. C₁₅H₁₂N₂O₂ requires C, 71.4; H, 4.8; N, 11.1%), and a 2,4-dinitrophenylhydrazone, m. p. 225—226°, as orange-red needles from ethyl acetate (Found: C, 52.5; H, 2.9; N, 16.4. C₁₅H₁₀N₄O₆ requires C, 52.6; H, 2.9; N, 16.4%).

The solution remaining after treatment of the phenyl ester (5 g.) with a catalytic trace of hydrochloric acid in methanol and removal of the 1,4-dioxoisochroman was freed from methanol, and the residue was steam-distilled. The distillate was acidified and an excess of potassium bromate-potassium bromide solution was added: 2,4,6-tribromophenol (3.74 g.), m. p. and mixed m. p. 94°, was obtained.

Reduction of 1,4-Dioxoisochroman with Lithium Aluminium Hydride and the Action of Periodic Acid on the Product.—1,4-Dioxoisochroman (3 g.) was boiled gently under reflux for 24 hr. with lithium aluminium hydride (3 g.) in tetrahydrofuran (200 ml.). Working up by the standard procedure gave 1-*o*-hydroxymethylphenylethane-1,2-diol (1.2 g.), m. p. 69—69.5° (from ethyl acetate) (Found: C, 64.5; H, 7.3. C₉H₁₂O₃ requires C, 64.3; H, 7.15%). This triol (0.56 g.), in ethanol (5 ml.), was added to 0.2M-periodic acid (17.5 ml.) containing one drop of 2N-sulphuric acid. Next morning, the excess of periodic acid was neutralised with sodium hydrogen carbonate and nitrogen was passed through the warmed solution and then through a dimedone solution: the formaldehyde derivative of dimedone (0.6 g., 63%), m. p. and mixed m. p. 188—189°, was obtained. The aqueous reaction mixture was extracted with ether, the extracts were dried (Na₂SO₄), the ether was volatilised, and the residual oil was dissolved in ethanol (3 ml.) and treated with silver nitrate (0.3 g.) in water (3 ml.) and N-sodium hydroxide solution (2 ml.). The mixture was left overnight. After removal of the silver, and evaporation of the ethanol on the steam-bath, the aqueous residue was washed with ether and gave, by acidification, *o*-hydroxymethylbenzoic acid (0.2 g.) having m. p. and mixed m. p. 120—121° after purification through its sodium salt.¹⁰

⁷ Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

⁸ Wegscheider and Glogau, *Monatsh.*, 1903, **24**, 938.

⁹ Dieckmann and Meiser, *Ber.*, 1908, **41**, 3258.

¹⁰ Hessert, *Ber.*, 1877, **10**, 1446.

Interaction of 1,4-Dioxoisochroman and Diazomethane.—1,4-Dioxoisochroman (1.7 g.) in dioxan (60 ml.) was added to an ethereal solution (450 ml.) of diazomethane (3.5 g.). Steady evolution of nitrogen (260 ml., 1.1 mol.) was observed which ended overnight. Removal of the ether, dioxan, and excess of diazomethane left a yellow gum which was soluble in alkali and most organic solvents and gave a *very slight* precipitate when treated with 2,4-dinitrophenylhydrazine reagent. Its infrared spectrum shows the presence of hydroxyl, carbonyl, and ethylenic groups, and its oxidation with alkaline permanganate gave a high yield of phthalic acid.

Decomposition of Methyl o-Diazoacetylbenzoate by Hydrogen Chloride in Anhydrous Methanol.—The diazo-ketone (10 g.) in absolute methanol (100 ml.) at 0° evolved all its nitrogen when treated dropwise during 10 min. with a solution of hydrogen chloride (0.016 mole) in absolute methanol. The mixture was filtered and gave, on evaporation under reduced pressure, 1,1-dimethoxy-4-oxoisochroman (7 g.), having m. p. 88—90° after repeated recrystallisation from absolute methanol. The infrared spectrum of this product shows it to be contaminated with a small amount of 1,4-dioxoisochroman. The filtrate from which the crude dimethoxy-compound had been separated provided, on further concentration, 1,4-dioxoisochroman (0.5 g.), and methyl *o*-chloroacetylbenzoate (0.15 g.).

The dimethoxy-compound, when warmed on a steam-bath with aqueous dioxan for 30 min., quantitatively provided 1,4-dioxoisochroman, m. p. and mixed m. p. 145—145.5°.

Phenyl *o*-diazoacetylbenzoate with anhydrous hydrogen chloride in methanol gave, as the only crystalline product, 1,1-dimethoxy-4-oxoisochroman (40%), m. p. and mixed m. p. 91—92° (cf. above) (Found: C, 63.0; H, 5.3. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.7%).

Decomposition of Methyl δ -Diazo- γ -oxovalerate with Hydrogen Chloride.—This diazo-ketone was obtained as a yellow oil (Found: diazo-N, 17.6. Calc. for $C_6H_8O_3N_2$: diazo-N, 18.0%) by the addition of β -methoxycarbonylpropionyl chloride to an excess of ethereal diazomethane. With hydrogen chloride in methanol or ethereal hydrogen chloride it provided methyl δ -chloro- γ -oxovalerate (85%), b. p. 118°/13 mm., m. p. 21—22° (Found: C, 44.0; H, 5.4; Cl, 21.7. $C_6H_9ClO_3$ requires C, 43.8; H, 5.5; Cl, 21.6%). When methanol was used as solvent, the stoichiometric quantity of hydrogen chloride was needed to complete the evolution of the nitrogen.

ω -Diazo-2-phenoxyacetophenone and its Decomposition by Hydrochloric Acid.— ω -Diazo-2-phenoxyacetophenone (2 g.), obtained as a dark yellow oil by the addition of *o*-phenoxybenzoyl chloride to an excess of ethereal diazomethane, in ether (50 ml.) was treated dropwise with concentrated hydrochloric acid. The nitrogen was evolved in about 1 min., and the ethereal solution, when washed with water and dried, gave ω -chloro-2-phenoxyacetophenone (1.7 g.), m. p. 55—56° (from methanol) (Found: C, 69.3; H, 4.5; Cl, 14.2. $C_{14}H_{11}ClO_2$ requires C, 68.2; H, 4.5; Cl, 14.4%), $\nu_{max.}$ 5.91 (C=O) and 13.62 μ (C-Cl).

ω -Diazo-2-phenoxyacetophenone (5 g.) was added with vigorous stirring to water (25 ml.) and 2N-hydrochloric acid (2.5 ml., 0.25 mole). The theoretical volume of nitrogen was evolved in 3.5 hr. and the mixture gave a yellow oil (4.5 g.), which decomposed on distillation. It is probably ω -hydroxy-2-phenoxyacetophenone: it has the appropriate absorption bands and quantitatively provides *o*-phenoxybenzoic acid, m. p. and mixed m. p. 113°,¹¹ on oxidation with alkaline potassium permanganate.

Microanalyses were carried out by Mr. V. Manohin.

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[Received, March 19th, 1962.]

¹¹ Ullmann and Slokasow, *Ber.*, 1905, **38**, 2112.