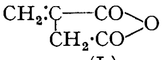
454. *The Friedel–Crafts Reaction with Itaconic Anhydride.* *6-Phenyl-4-methyl-3-pyridazone.*

By S. Dixon, Hilda Gregory, and L. F. Wiggins.

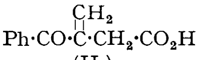
The reaction of itaconic acid with benzene under Friedel–Crafts conditions has been investigated. The product of the reaction has been shown to be β-benzoyl-α-methylacrylic acid by a study of the absorption spectrum of it and allied compounds, and by synthetic methods. This product has been converted into 6-phenyl-4-methyl-3-pyridazone, which has been synthesised from the β-benzoyl*iso*butyric acid obtained by the Friedel–Crafts reaction of methylsuccinic anhydride and benzene.

The observation (Lockwood and Ward, *Ind. Eng. Chem.*, 1945, **37**, 403) that itaconic acid may be obtained by the growth of certain micro-organisms, in particular *Aspergillus terreus*, on solutions of glucose or sucrose makes this substance more readily available than hitherto. Since we have been concerned with the study of materials readily obtainable from sucrose we have turned our attention to itaconic acid. In this paper the reaction of the itaconic anhydride with benzene under the conditions of the Friedel–Crafts reaction and the pyridazine derivatives obtained by condensation of the product of this reaction with hydrazine have been investigated.

When itaconic anhydride (I) is treated with benzene and aluminium chloride in a typical Friedel–Crafts reaction, a crystalline compound (*A*), m. p. 155°, is obtained. This contains a phenyl, a carbonyl, and a carboxyl group, but no halogen atoms. It affords a *semicarbazone*, and analysis of the compound and its semicarbazone show its empirical formula to be $C_{11}H_{10}O_3$.

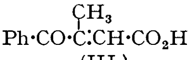


(I.)



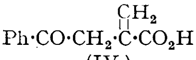
$\mathrm{Ph{\cdot}CO{\cdot}\overset{CH_2}{\overset{\|}{C}}{\cdot}CH_2{\cdot}CO_2H}$

(II.)



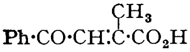
$\mathrm{Ph{\cdot}CO{\cdot}\overset{CH_3}{\overset{|}{C}}{:}CH{\cdot}CO_2H}$

(III.)



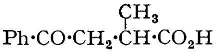
$\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}\overset{CH_2}{\overset{\|}{C}}{\cdot}CO_2H}$

(IV.)



$\mathrm{Ph{\cdot}CO{\cdot}CH{:}\overset{CH_3}{\overset{|}{C}}{\cdot}CO_2H}$

(V.)



$\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}\overset{CH_3}{\overset{|}{C}}H{\cdot}CO_2H}$

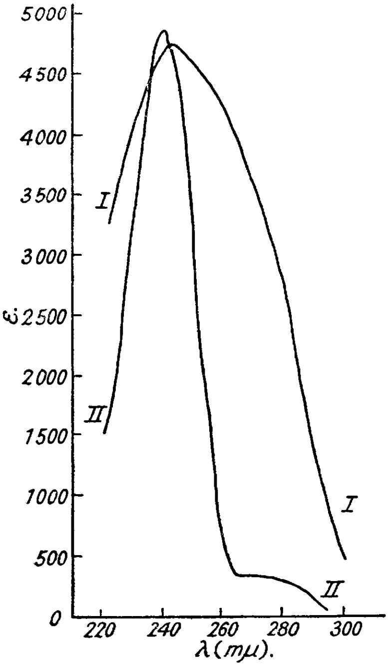
(VI.)

$\mathrm{Ph{\cdot}CO{\cdot}CH{:}CH{\cdot}CO_2H}$

(VII.)

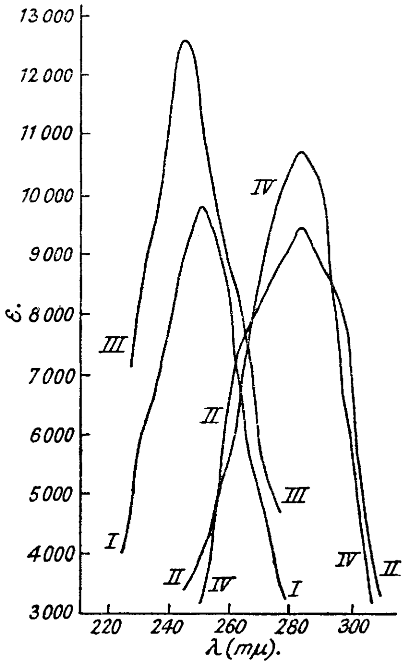
By the method of synthesis employed, (*A*) may have any of the structures (II)—(V). (III) and (V) are fully conjugated structures, whereas (II) and (IV) are not. Hence there should be a marked difference in the absorption spectra of these two types. The Friedel–Crafts condensation of benzene with maleic anhydride gives the well-known β-benzoylacrylic acid (VII). The absorption spectrum of this would be expected to be very similar to that shown by structures (III) or (V). Compound (*A*) and β-benzoylacrylic acid did indeed exhibit similar absorption spectra; the former showed maximum absorption of light in the ultra-violet region at 2425 A., and the latter at 2450 A. (see Fig. 1). Thus compound (*A*) is represented by (III) or (V). Furthermore, hydrolysis with barium hydroxide yielded acetophenone, characterised as its semicarbazone, which suggests that (*A*) cannot be represented by structures (II) and (III). In conjunction with the absorption spectra data quoted above, this indicates that compound (*A*) is β-benzoyl-α-methylacrylic acid (V), which is confirmed by hydrogenation under mild conditions with a palladium catalyst. The product was the crystalline β-benzoyl*iso*butyric acid (VI) which was synthesised by Klobb (*Bull. Soc. chim.*, 1897, [iii], **17**, 408) by the condensation of ω-bromoacetophenone with ethyl sodiocyanoacetate, treatment of the sodium derivative of the product with methyl iodide, and hydrolysis with sodium hydroxide. A better proof of the constitution of this material was later provided by Oppenheim (*Ber.*, 1901, **34**, 4227), who synthesised it starting from ω-bromoacetophenone and ethyl sodiomethylmalonate.

FIG. 1.



I. β-Benzoylacrylic acid.
II. β-Benzoyl-α-methylacrylic acid.

FIG. 2.

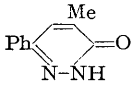


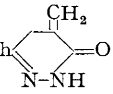
I. 6-Phenyl-3-pyridazone.
II. 6-Phenyl-3-pyridazinone.
III. Condensation product of compound " A " with hydrazine.
IV. 6-Phenyl-4-methyl-3-pyridazinone.

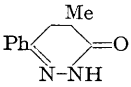
(*Measurements carried out in ethyl alcohol solution.*)

Oppenheim also prepared (VI) by the condensation of methylsuccinic anhydride with benzene in the presence of aluminum chloride. In addition to the α-methyl acid Mayer and Stamm (*Ber.*, 1923, **56**, 1424) later obtained the isomeric β-methyl acid from this reaction. During our preparation of (VI) by Oppenheim's method, we found that methylsuccinic acid was obtained from itaconic acid more expeditiously (and in 82% yield) by catalytic hydrogenation than by the sodium amalgam previously used (Fittig, *Annalen*, 1898, **304**, 156).

If the compound (*A*) is indeed represented by (V) it should yield a pyridazone derivative (VIII) on treatment with hydrazine. This transformation has now been accomplished, although in poor yield (11%). If the compound (*A*) had the methylene structure (IV) this reaction would, of course, lead to a pyridazinone (IX). If, however, prototropic change occurred during the condensation with hydrazine, then the pyridazone (VIII) might also be formed from (IV). It has been observed that pyridazone and pyridazinone derivatives absorb light characteristically in the ultra-violet region of the spectrum, and, moreover, that there is a marked difference in the light absorption of pyridazone and pyridazinone derivatives. 6-Phenyl-3-pyridazone shows one absorption peak at 2515 A., whereas the corresponding pyridazinone derivative shows


(VIII.)


(IX.)


(X.)

maximum absorption at 2840 A. The product of the condensation of compound (*A*) with hydrazine shows an absorption spectrum with the head of the band at 2475 A. and hence closely resembles the pyridazone (see Fig. 2). If the possibilities of prototropic change are discounted, these observations provide further evidence that compound (*A*) is β-benzoyl-α-methylacrylic acid (V). The true 6-phenyl-4-methyl-3-pyridazinone (X) was obtained when β-benzoyl*iso*butyric acid was condensed with hydrazine. This showed maximum absorption of light in the ultra-violet region at 2840 A. and was dehydrogenated by bromine (Overend and Wiggins, *J.*, 1946, 239) to give 6-phenyl-4-methyl-3-pyridazone, identical with that obtained by the condensation of compound (*A*) with hydrazine.

The formation of pyridazone derivatives from γ-keto-acids containing an αβ-unsaturated linkage is always difficult. We have observed this in the case of acetyl- and benzoyl-acrylic acids in addition to the case just described. It would appear, therefore, that these compounds are essentially *trans*-isomers and that conversion into the *cis*-form must take place before cyclisation to a pyridazone derivative.

Some confusion exists in the literature as to the course of the reaction of benzene and citraconic acid anhydride in the presence of aluminium chloride; von Pechmann (*Ber.*, 1882, **15**, 833) obtained β-benzoyl-β-methylacrylic acid, m. p. 113°, and proved its constitution by hydrolysis to propiophenone and glyoxylic acid. On the other hand, Bogert and Ritter (*J. Amer. Chem. Soc.*, 1925, **47**, 526) obtained an acid, m. p. 153°, which was shown to be β-benzoyl-α-methylacrylic acid and is clearly identical with the compound obtained during the work described in this paper. Thus, it would appear that the reaction of citraconic anhydride with benzene can take place in either of the possible directions.

EXPERIMENTAL.

Condensation of Itaconic Anhydride with Benzene in the Presence of Aluminium Chloride.—Itaconic anhydride (28 g.), prepared by the distillation of the acid with phosphoric oxide, was dissolved in dry benzene (200 c.c.) and treated with finely powdered anhydrous aluminium chloride (70 g.). On slight warming of the mixture a vigorous reaction occurred, much hydrogen chloride being evolved. Heating under reflux was continued for 3 hours. The mixture was cooled and the excess of aluminium chloride decomposed by carefully adding dilute hydrochloric acid. Benzene was removed by distillation with steam, and a pale yellow solid remained. This, β-benzoyl-α-methylacrylic acid, was collected and recrystallised from alcohol–water, forming long needles (37 g., 78%), m. p. 155° (Bogert and Ritter, *loc. cit.*, recorded m. p. 153°) (Found: C, 69·0; H, 5·35. Calc. for $C_{11}H_{10}O_3$: C, 69·4; H, 5·21%). Treatment of the acid, dissolved in cold alcohol–water, with an aqueous solution of semicarbazide hydrochloride and sodium acetate afforded the *semicarbazone* which, recrystallised from absolute alcohol, formed needles, m. p. 218° (Found: C, 58·2; H, 5·49; N, 16·9. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·26; N, 17·0%).

Condensation of β-Benzoyl-α-methylacrylic Acid with Hydrazine. 6-Phenyl-4-methyl-3-pyridazone.—β-Benzoyl-α-methylacrylic acid (18 g.), dissolved in hot N-sodium hydroxide solution (90 c.c.), was treated with a solution of hydrazine sulphate (12·5 g.), also dissolved in N-sodium hydroxide solution (90 c.c.). The mixture was heated on a water-bath for 2 hours, an oil appearing in the mixture. On cooling, the oil partly crystallised. The supernatant aqueous layer was decanted and the semi-solid mass dissolved in hot alcohol–water, filtered with charcoal, and allowed to crystallise. The pale yellow crystals of 6-*phenyl*-4-*methyl*-3-*pyridazone*, recrystallised from alcohol–water, formed plates, m. p. 189° (2·0 g., 11·4%) (Found: C, 70·5; H, 5·4; N, 15·4. Calc. for $C_{11}H_{10}ON_2$: C, 71·0; H, 5·38; N, 15·1%).

Alkaline Hydrolysis of β-Benzoyl-α-methylacrylic Acid.—β-Benzoyl-α-methylacrylic acid (2 g.) was heated at 80° for 4 hours with barium hydroxide octahydrate (7 g.) in water (60 c.c.). The mixture was steam-distilled and the distillate extracted with ether. The extract was dried ($MgSO_4$) and evaporated to an oil. A small amount of this was dissolved in alcohol and treated with an aqueous solution of semicarbazide hydrochloride and sodium acetate. After being heated for 2 minutes, the solution was allowed to cool, whereupon a crystalline solid separated. This, recrystallised from absolute alcohol, showed m. p. 198° alone or in admixture with an authentic specimen of acetophenone semicarbazone.

Reduction of β-Benzoyl-α-methylacrylic Acid.—β-Benzoyl-α-methylacrylic acid (2 g.) was dissolved in methanol (25 c.c.) and subjected to hydrogenation over palladium–charcoal at room temperature under a slight pressure of hydrogen. Absorption proceeded rapidly until the theoretical amount of hydrogen necessary for the saturation of the olefinic linkage (250 c.c.) had been absorbed. The hydrogenation was arrested, the catalyst filtered off, and the clear solution evaporated to dryness. β-Benzoyl*iso*butyric acid, recrystallised three times from dilute alcohol, formed needles, m. p. 140° alone or in admixture with an authentic specimen (yield, 1·8 g., 90%).

Hydrogenation of Itaconic Acid.—Itaconic acid (100 g.) in water (600 c.c.) was shaken in an autoclave with hydrogen under pressure in the presence of Raney nickel at room temperature. When absorption of hydrogen had ceased, the solution was filtered and evaporated to dryness. A pale green solid remained which was extracted with benzene–ether. The extract, on evaporation of the solvent, yielded a white crystalline solid which, recrystallised from benzene–ether, formed prisms, m. p. 111°, of methylsuccinic acid (82 g., 82%).

*β-Benzoyl*iso*butyric Acid.*—Methylsuccinic anhydride (37 g.), m. p. 37°, prepared by treatment of methylsuccinic acid with acetyl chloride, was dissolved in dry benzene (185 g.) and mixed, with cooling, with finely gronnd anhydrous aluminium chloride (74 g.). The mixture was heated under reflux on a water-bath for 2 hours. An excess of aluminium chloride was then decomposed with dilute hydrochloric acid, and the benzene removed by steam-distillation. A white solid remained which, recrystallised from alcohol–water, formed long colourless needles, m. p. 140° (37 g., 60%). Oppenheim (*loc. cit.*) records the same m. p.

6-*Phenyl*-4-*methyl*-3-*pyridazinone.*—β-Benzoyl*iso*butyric acid (37 g.) in N-sodium hydroxide solution (190 c.c.) was heated for 2 hours with hydrazine sulphate (25·1 g.), also dissolved in N-sodium hydroxide (190 c.c.). On being cooled the mixture deposited a solid which, recrystallised from alcohol, formed needles, m. p. 157° (34 g., 96%). Oppenheim (*loc. cit.*) records m. p. 157·5°.

6-*Phenyl*-4-*methyl*-3-*pyridazone.*—The pyridazinone (26·5 g.) was dissolved in hot glacial acetic acid (75 c.c.), and bromine (22 g.) added dropwise. Hydrogen bromide was evolved. After addition of all the bromine, the solution was heated at 100° for 15 minutes, then cooled, and poured into ice–water (400 c.c.), whereupon a white solid separated. This, after being kept overnight, was filtered off and recrystallised from dilute alcohol, forming plates, m. p. 189° (22 g., 83%). It was identical with the 6-phenyl-4-methyl-3-pyridazone obtained by condensation of β-benzoyl-α-methylacrylic acid with hydrazine.

β-Benzoylacrylic Acid.—This was prepared according to the following modification of the method of von Pechmann (*Ber.*, 1882, **15**, 883). Maleic anhydride (20 g.) was dissolved in dry benzene (200 c.c.) and treated with finely ground anhydrous aluminium chloride (30 g.), and the mixture heated at 60° for 3 hours. The excess of aluminium chloride was then decomposed with dilute hydrochloric acid, and the solution extracted with benzene. The dried ($MgSO_4$) extract was evaporated and the residue recrystallised from water; β-benzoylacrylic acid formed plates, m. p. 64°; yield, 27 g. (75%).

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