

*dl*-Ethyl-*n*-butylcyanoethyl Acetate.—This ester was prepared in a manner similar to that used for the isoamyl compound.

*dl*-Ethyl-*n*-butylcyanoacetic Acid.—This acid was prepared from the corresponding ethyl ester in a manner similar to that used for the *dl*-ethylisoamylcyanoacetic acid.

Resolution of *dl*-Ethyl-*n*-butylcyanoacetic Acid.—The method followed in the resolution of this compound was essentially the same as that for the isoamyl compound, using strychnine. The less soluble salt in alcohol gave  $[\alpha]_D^{25} -25.5^\circ$  in alcohol. Owing to the oily nature of the more soluble salt a rotation could not be obtained upon the pure material.

*d*-Ethyl-*n*-butylcyanoacetic Acid.—The less soluble salt was decomposed and purified, as in the case of the ethylisoamylcyanoacetic acid.

*l*-Ethyl-*n*-butylcyanoacetic Acid.—The solution of the more soluble salt was decomposed and purified as in the case of the *d*-ethylisoamylcyanoacetic acid.

*dl*-Ethyl-*n*-butyl-*N*-methylbarbituric Acid.—This compound was prepared according to the directions published by Dox and Hjort.<sup>6</sup> It was also prepared, using *dl*-ethyl-*n*-butylcyanoethyl acetate, *N*-methyl urea and sodium followed by hydrolysis of the imido group. Both methods yielded barbituric acids of the same melting point, and mixed melting points of these compounds showed no depression.

*d* and *l*-Ethyl-*n*-butyl-*N*-methylbarbituric Acids.—These compounds were prepared from the corresponding cyanoethyl acetates in the manner described for the ethyl isoamyl-*N*-methylbarbituric acids.

The *d* form of 5,5-*n*-propylmethylcarbinyloethylbarbituric acid was less effective and less toxic than the *l* or the *dl* forms, but the ratio or margin of safety was lower. Preanesthetic excitement was marked with the *d*, present with the *dl* form and absent with the *l* form.

The *d*, *l* and *dl* forms of the 1-methyl-5,5-isoamylbarbituric acid showed no anesthetic action, the *d* form being slightly more toxic than the *dl* or *l* forms. The *d* isomer in sublethal doses, in contrast to the *l* or the *dl* isomer, caused difficulty in breathing and severe convulsive contractions of the thorax, head and neck.

The *d*, *l* and *dl* forms of the 1-methyl-5,5-*n*-butylethylbarbituric acid were found to have anesthetic properties. The *dl* form had a lower M. A. D. and M. L. D. than either the *d* or *l* forms and caused severe convulsions before and after anesthesia, an effect which was not noticed in the case of the *d* or the *l* isomer.

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### Conclusions

1. The dextro and levo forms of 5,5-*n*-propylmethylcarbinyloethylbarbituric acid, 1-methyl-5,5-isoamylethylbarbituric acid and 1-methyl-5,5-*n*-butylethylbarbituric acid were prepared.

2. These compounds were tested pharmacologically and the effective and the lethal doses were determined. Moderate differences were noted between the doses and the effects produced by the active and racemic forms.

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## The 1,2-Dibenzoylcyclobutanes

BY ELLSWORTH ELLINGBOE AND REYNOLD C. FUSON

Three different 1,2-dibenzoylcyclobutanes have been reported although only two are theoretically possible. This structure has been definitely proved only for the so-called *alpha* form.<sup>1</sup> However, in a parallel study it has been possible to show that the supposititious 1,2-dibenzoylcyclobutane of Conant and Lutz<sup>2</sup> is really a cyclopentane derivative.<sup>3</sup> The lack of evidence upon which to assign the *cis* and *trans* configurations to the two remaining diketones made it desirable to

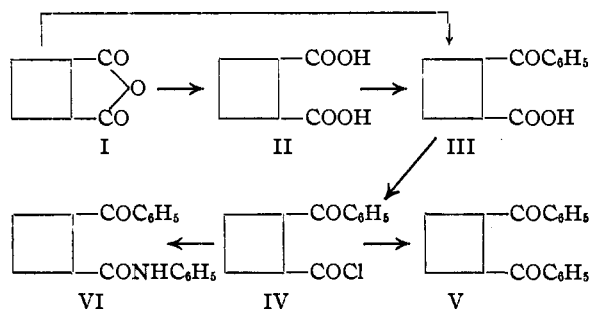
synthesize the so-called  $\beta$ -diketone by a clearcut method. This has now been accomplished, and the identification of the  $\alpha$ - and  $\beta$ -diketones of Kao and Fuson as the *trans* and *cis* isomers, respectively, has been completed.

A repetition of the work of Kao and Fuson, undertaken with the hope of isolating a larger amount of the *cis* diketone, was carried out; but instead of the pure *trans*-1,2-cyclobutanedicarboxylic acid there were used (1) the mixture obtained from the decarboxylation of 1,1,2-cyclobutanetricarboxylic acid, and (2) the pure *cis* acid.

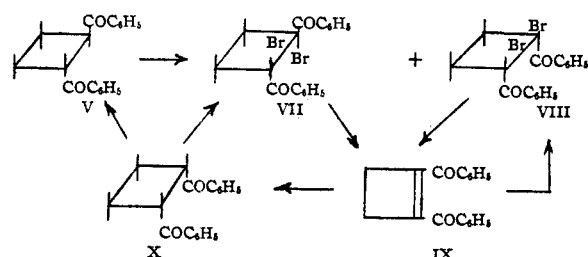
(1) Kao and Fuson, *THIS JOURNAL*, **54**, 1120 (1932).

(2) Conant and Lutz, *ibid.*, **49**, 1090 (1927).

(3) Fuson and Farlow, *ibid.*, **56**, 1593 (1934).



From the mixture only the *trans* diketone (V) was obtained. From the *cis* dibasic acid (II), prepared through its anhydride by the procedure of Perkin,<sup>4</sup> the keto acid, 2-benzoylcyclobutanecarboxylic acid (III) described in the preceding paper was the sole product. The latter result indicated that the thionyl chloride acted as a dehydrating agent<sup>5</sup> since III was also obtained directly from the anhydride (I) by means of benzene and aluminum chloride. The acid chloride (IV) of the keto acid gave V when treated with benzene in the presence of aluminum chloride. The anilide (VI) of III has already been shown (preceding paper) to have the *trans* configuration.



Bromination of *trans*-1,2-dibenzoylcyclobutane (V)<sup>1</sup> upon reinvestigation was found to produce two isomeric dibromides, the *trans* modification (VII) melting at 155–156° (6° higher than that previously reported) and the *cis* form (VIII) melting at 111–112°. Both of these compounds were utilized in the synthesis of *cis*-1,2-dibenzoylcyclobutane (X). The bromine atoms were removed with potassium iodide by Kohler's method<sup>6</sup> to give the unsaturated 1,2-dibenzoyl-1,2-cyclobutene (IX), the debromination taking place

(4) Perkin, *J. Chem. Soc.*, **65**, 580 (1894). The experimental work in this connection corroborates the work of Perkin (*loc. cit.*) and Bode [*Ber.*, **67**, 332 (1934)] and refutes the argument of Kuhn and Wassermann [*Helv. Chim. Acta*, **11**, 600 (1928)], who have reported *cis*-1,2-cyclobutanedicarboxylic acid, m. p. 97–98°.

(5) H. Meyer [*Monatsh.*, **22**, 421 (1901)] studied the use of thionyl chloride in the preparation of acid chlorides, and found that the anhydride was always produced in the case of a dibasic acid whose carboxyl groups were adjacent and in a *cis* configuration. Thus maleic, citraconic, itaconic and phthalic acids all gave anhydrides.

(6) Kohler, *Am. Chem. J.*, **42**, 375 (1909).

much more rapidly from the *cis* than from the *trans* dibromide. Addition of bromine to the unsaturated diketone yielded only the *cis* dibromide. Similarly, catalytic hydrogenation with platinum gave X.

The *cis* diketone was readily converted into the *trans* isomer either by heating for a short time with concentrated hydrochloric acid or by standing for an hour at room temperature in alcohol solution containing a small amount of alkali. Aqueous sodium carbonate partially isomerized it after a few hours' digestion on a steam-bath. Direct bromination yielded a mixture of *cis* and *trans* dibromo diketones, the latter in the predominating amount.

The foregoing transformations and methods of synthesis are believed to constitute adequate evidence for the configurations assigned to the two diketones.

### Experimental

**Preparation of 1,1,2-Cyclobutanetricarboxylic Acid.**—Fifty grams of 1-cyano-1,2-dicarbethoxycyclobutane was converted into the barium salt of the tricarboxylic acid by the procedure of Fuson and Kao.<sup>7</sup> Following the treatment of the pink barium salt with slightly less than the theoretical amount of dilute sulfuric acid and removal of the precipitated barium sulfate, a modification of Fuson and Kao's procedure was employed. The filtrate was put into a 2-liter filter flask and concentrated by drawing air over the surface of the solution by means of suction; the air-intake consisted of large diameter glass tubing stuffed with cotton to filter the air, and the flask was kept at 40–50° on a steam-bath. When the solution had become viscous the air flow was stopped and the solution was allowed to cool. In a short time the tricarboxylic acid began to crystallize, and after standing overnight the mixture was almost solid. The yield was 75% of the theoretical amount. More of the acid was obtained upon further evaporation of the mother liquor.

**Cis-1,2-cyclobutanedicarboxylic Acid.**—Thirty grams of 1,1,2-cyclobutanetricarboxylic acid was heated at 150° in an oil-bath until no more carbon dioxide was evolved. Following the procedure of Perkin (*loc. cit.*) the crude mixture of dibasic acids (m. p. 90–115°) was converted into the anhydride and thence into the pure *cis* dibasic acid. The yield of *cis*-1,2-cyclobutanedicarboxylic acid was 75% of the theoretical amount; m. p. 138–139°.

**The Action of Benzene and Aluminum Chloride on the Mixture of 1,2-Cyclobutanedicarboxylic Acids.**—Twenty-eight and eight-tenths grams of the crude mixture of dibasic acids was treated with thionyl chloride and then with benzene and aluminum chloride according to the procedure given by Kao and Fuson.<sup>1</sup> About a 75% yield was obtained of a product which proved to be the *trans*-1,2-dibenzoylcyclobutane; m. p. 96–97.5°. No other product could be isolated from the mother liquors.

(7) Fuson and Kao, *This Journal*, **51**, 1536 (1929). See also Perkin, *J. Chem. Soc.*, **65**, 580 (1894).

**The Action of Benzene and Aluminum Chloride on *Cis*-1,2-Cyclobutanedicarboxylic Acid.**—Fourteen and four-tenths grams of the *cis* acid was treated with thionyl chloride and then with benzene and aluminum chloride by the foregoing procedure. When the mixture was decomposed with ice and hydrochloric acid the product was largely insoluble in both the acid and benzene layers. After several recrystallizations from alcohol the product melted at 127–128°; it was soluble in dilute sodium hydroxide but insoluble in water. It proved to be 2-benzoylcyclobutanedicarboxylic acid, described in the preceding paper.

**The Action of Benzene and Aluminum Chloride on *Cis*-1,2-cyclobutanedicarboxylic Anhydride.**—Twelve and six-tenths grams of *cis*-1,2-cyclobutanedicarboxylic anhydride (m. p. 77°) was dissolved in 150 cc. of dry benzene in a 500-cc. three-necked, round-bottomed flask equipped with a mercury-sealed stirrer and a reflux condenser. Thirty grams of anhydrous aluminum chloride was then added and the mixture was stirred for ten hours while it was maintained at a temperature of 70°; stirring was continued at room temperature for eleven hours. At the end of this time the reaction mixture was greenish-black. The product obtained by decomposition of the mixture with ice and hydrochloric acid was only partially soluble in the benzene layer. After several recrystallizations from alcohol the product melted at 127–128°; it was identical with the keto acid obtained from the *cis* acid.

**The Action of Benzene and Aluminum Chloride on the Acid Chloride of 2-Benzoylcyclobutanedicarboxylic Acid.**—Three grams of the keto acid was refluxed with 5 g. of thionyl chloride until the evolution of hydrogen chloride had ceased. The excess thionyl chloride was removed by vacuum distillation, and the crude acid chloride thus obtained was dissolved in a small amount of dry benzene and added slowly with stirring to a mixture of 5 g. of anhydrous aluminum chloride in 30 cc. of dry benzene. The mixture became dark immediately; it was stirred for four hours at a temperature of 60°. When decomposed with ice and hydrochloric acid, the benzene layer was further extracted with sodium carbonate solution, washed with water and evaporated. After two recrystallizations from alcohol the product melted at 96–97.5°; a mixed melting point showed it to be *trans*-1,2-dibenzoylcyclobutane.

**The Action of Ultraviolet Light on *Trans*-1,2-Dibenzoylcyclobutane.**—A solution of the *trans* diketone in benzene contained in a fused quartz test-tube was exposed to a mercury arc for fourteen days; at the end of this time the solution originally colorless was tinged a light yellow. The *trans* diketone, however, was recovered largely unchanged, and no other product could be isolated.

**Bromination of *Trans*-1,2-Dibenzoylcyclobutane.**—Seven and one-half grams of *trans*-1,2-dibenzoylcyclobutane was dissolved in 125 cc. of carbon tetrachloride and treated with 9 g. of liquid bromine according to the procedure of Kao and Fuson.<sup>1</sup> Three recrystallizations from ethyl acetate gave a colorless product, melting at 155–156°, which was 6° higher than the melting point previously reported. However, a mixture of the two melted at 153–154°, indicating that the original sample was impure.

*Anal.* Calcd. for  $C_{18}H_{14}O_2Br_2$ : Br, 37.9; C, 51.2; H, 3.32. Found: Br, 37.8; C, 51.2; H, 3.33.

The mother liquors from the purification of the *trans*-dibromide were evaporated and the crystalline residue was triturated with about 15 cc. of cold carbon tetrachloride and separated by filtration. Evaporation of the filtrate and repeated recrystallization of the residue from methyl alcohol yielded an isomeric dibromide which crystallized in large colorless prisms (m. p. 111–112°) which proved to be *cis*-1,2-dibenzoyl-1,2-dibromocyclobutane.

*Anal.* Calcd. for  $C_{18}H_{14}O_2Br_2$ : Br, 37.9; C, 51.2; H, 3.32. Found: Br, 38.1; C, 51.0; H, 3.26.

**Preparation of 1,2-Dibenzoyl-1,2-cyclobutene.**—Kohler's method<sup>8</sup> for the removal of the halogen atoms from an  $\alpha,\beta$ -dibromo ketone by means of potassium iodide was applied to the dibromodibenzoylcyclobutanes. Four and one-half grams of *trans*-1,2-dibenzoyl-1,2-dibromocyclobutane was added to 4 g. of potassium iodide partially dissolved in 50 cc. of boiling ethyl alcohol contained in a 200-cc. brominating flask. The mixture was refluxed on a steam-bath; it darkened slowly as iodine was liberated. It was found necessary to reflux for about fifteen hours to complete the reaction. The alcohol solution was then poured into a large volume of water containing an excess of sodium thiosulfate. A yellow product crystallized slowly from the milky suspension. It was boiled with norite and recrystallized several times from methyl alcohol to yield a light yellow, halogen-free solid (m. p. 96–97.5°) which reacted instantly with potassium permanganate and with bromine in carbon tetrachloride.

*Anal.* Calcd. for  $C_{18}H_{14}O_2$ : C, 82.4; H, 5.34. Found: C, 82.2; H, 5.31.

Removal of the bromine atoms from the *cis*-dibromodiketone by means of potassium iodide was carried out exactly as in the case of the *trans* isomer. The reaction proceeded much more rapidly, however, and was complete after two hours of refluxing. A nearly quantitative yield of unsaturated diketone, melting at 95–97°, was obtained.

**Addition of Bromine to 1,2-Dibenzoyl-1,2-cyclobutene.**—One gram of the unsaturated diketone was dissolved in a small amount of carbon tetrachloride, and a 5% solution of bromine in carbon tetrachloride was added until the bromine color was permanent. After recrystallization from methyl alcohol the product melted at 111–112°, and it was identical with the lower melting isomer obtained by direct bromination of *trans*-1,2-dibenzoylcyclobutane.

**Preparation and Properties of *Cis*-1,2-dibenzoylcyclobutane.**—1,2-Dibenzoyl-1,2-cyclobutene was hydrogenated catalytically with platinum. The ordinary apparatus had too small a pressure drop to be of use for the small amount (0.01 mole) of material reduced, so the hydrogen tank was replaced by a reservoir of about 500-cc. capacity with a mercury column approximately 2.44 meters high as the source of pressure. The pressure drop was then 260 mm. of mercury for 0.01 mole of hydrogen, calibration being carried out with maleic acid by the ordinary technique.<sup>8</sup>

(8) "Organic Syntheses," 1932, Coll. Vol. I, p. 56.

Two and sixty-two hundredths grams (0.01 mole) of the unsaturated diketone was dissolved in 50 cc. of absolute alcohol, 0.05 g. of platinum oxide was added, and the system was filled with hydrogen to a pressure of forty-five pounds. The reduction was stopped after shaking for three and one-half minutes, when the mercury column had dropped 260 mm. The alcohol solution, which was still colored a light yellow, was filtered and evaporated at room temperature by means of a water pump. The residue consisted of a mass of fine colorless needles contaminated by a yellow oil; this was washed with a small quantity of cold ether and filtered. The product so obtained melted at 121–122°; recrystallization from ligroin containing a small amount of benzene did not raise the melting point. More of this product was contained in the ether. This compound is evidently identical with the *cis*-1,2-dibenzoylcyclobutane obtained by Kao and Fuson.<sup>1</sup>

*Anal.* Calcd. for  $C_{18}H_{16}O_2$ : C, 81.8; H, 6.06. Found: C, 81.6; H, 6.13.

The ether solution remaining was evaporated to dryness on the steam-bath, and was inadvertently allowed to remain for about five minutes after the ether had evaporated. The residue was then mixed with a little methyl alcohol, whereupon it formed a colorless crystalline product which was only slightly soluble in hot methyl and ethyl alcohols. After several recrystallizations from benzene, the product melted at 222–223°; yield, 1 g.

*Anal.* C, 79.5, 79.6; H, 6.5, 6.3.

*Cis*-1,2-dibenzoylcyclobutane was subjected to the following tests to characterize it and further to substantiate its identity: (1) potassium permanganate in acetone gave no reaction. (2) A solution in ethyl alcohol plus a few drops of dilute sodium hydroxide was allowed to stand at room temperature for one hour. A yellow color developed, and when the solution was poured into water pure *trans*-1,2-dibenzoylcyclobutane was precipitated; m. p. 96–97°. A mixed melting point with an authentic sample of the *trans* diketone showed no depression; a mixture with the original *cis* diketone melted at 85–100°.

(3) A suspension in aqueous sodium carbonate solution was heated in a steam-bath for several hours. The *cis* diketone changed to an oily product which solidified on cooling; m. p. 88–105°. (4) A solution in glacial acetic acid, allowed to stand for one hour at room temperature, yielded the original *cis* diketone unchanged. (5) Anhydrous aluminum chloride was added to a solution of the diketone in dry benzene which was then shaken for about ten minutes. The mixture was worked up in the usual manner for Friedel-Crafts reactions, and the *cis* diketone was recovered only slightly changed; m. p. 114–119°. (6) A suspension in concentrated hydrochloric acid was heated on the steam-bath for one-half hour. Pure *trans* diketone was recovered; m. p. 96–97°. (7) Bromination in carbon tetrachloride yielded a mixture of *cis*- and *trans*-1,2-dibenzoyl-1,2-dibromocyclobutanes, the latter in the predominating amount. This result is the same as that obtained by bromination of the pure *trans* diketone.

**The Dioxime of *Cis*-1,2-dibenzoylcyclobutane.**—The dioxime melted at 174–175°. A mixed melting point showed it to be different from the dioxime of *trans*-1,2-dibenzoylcyclobutane obtained by Kao and Fuson.<sup>1</sup>

*Anal.* Calcd. for  $C_{18}H_{18}O_2N_2$ : C, 73.4; H, 6.2; N, 9.52. Found: C, 73.6; H, 6.2; N, 9.56.

### Summary

*Cis*-1,2-dibenzoylcyclobutane has been synthesized from its *trans* isomer through the dibromide of the latter. The dibromide was converted into 1,2-dibenzoyl-1,2-cyclobutene, which was catalytically hydrogenated to the *cis* diketone.

The ease with which the *cis* diketone is isomerized to the *trans* form offers an explanation for the fact that *cis*-1,2-cyclobutanedicarboxylic acid and its anhydride yield derivatives which have the *trans* configuration.

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## The Action of Phenylmagnesium Bromide on the Anhydride and the Phenylimide of 1,2-Cyclobutanedicarboxylic Acid

BY ELLSWORTH ELLINGBOE AND REYNOLD C. FUSON

The synthesis of 1,2-dibenzoylthane by the action of phenylmagnesium bromide on *N*-methylsuccinimide<sup>1</sup> suggests the possibility of preparing *cis*-1,2-dibenzoylcyclobutane by an application of the same method to analogous derivatives of 1,2-cyclobutanedicarboxylic acid. In the case of the succinimide the addition of two moles of reagent leads to the formation of  $\alpha,\alpha'$ -diphenyl-*N*-methylpyrrole, presumably by

(1) Lukes and Prelog, *Coll. Czech. Chem. Comm.*, **1**, 334 (1929).

the loss of two molecules of water from the primary addition product. For steric reasons the formation of a pyrrole derivative in this manner seemed unlikely in the cyclobutane series.

Experiments with the *N*-phenylimide (V) of 1,2-cyclobutanedicarboxylic acid, however, did not lead to the formation of the diketone. The first molecule of the reagent added normally to yield *cis*-2-benzoylcyclobutanecarboxanilide