[Contribution from the Department of Chemistry, the University of Texas]

Further Studies with *cis*- and *trans*-β-Benzoyl-α- and β-methylacrylic Acids and β-Benzoyl-α-methylenepropionic Acid[1]

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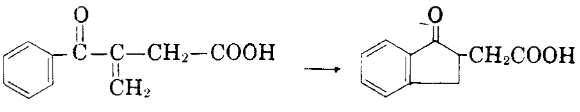
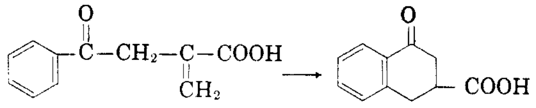
A by-product in the Friedel-Crafts reaction between itaconic anhydride and benzene is identified as 1-keto-2-indanacetic acid. The addition reactions of the β-benzoyl-α- and β-methylacrylic acids and of β-benzoyl-α-methylenepropionic acid with morpholine are described.

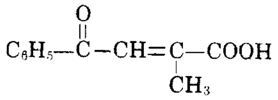
In an earlier paper[3] the syntheses of *cis*- and *trans*-β-benzoyl-α- and β-methylacrylic acids (V and VI) and of β-benzoyl-α-methylenepropionic acid (III) were described. In the preparation of the α-methylenepropionic acid (III) by the Friedel-Crafts reaction between benzene and itaconic anhydride in carbon disulfide solution, an acid isomeric with III, V, and VI was obtained as a by-product. The first portion of the present paper deals with the identification of this substance.



I II

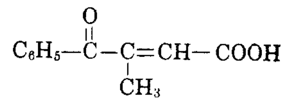


III IV



$C_6H_5-\overset{\overset{O}{\|}}{C}-CH=\underset{\underset{CH_3}{|}}{C}-COOH$

V (a) *cis*
(b) *trans*

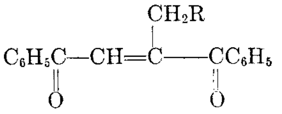


$C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{C}=CH-COOH$

VI (a) *cis*
(b) *trans*

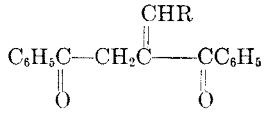
Oxidation of the material with potassium permanganate and with chromic acid gave *o*-phthalic acid and homophthalic acid respectively, showing that the acid in question has a condensed ring system. Although two such acids, possible from the Friedel-Crafts reaction between itaconic acid and benzene and with melting points identical with the acid in question, are reported in the literature, only one of them, 1-keto-2-indanacetic acid (II), could give homophthalic acid upon oxidation. Synthesis by the method of Groves and Swan[4] showed this to be the acid in question. Very likely the substance arose through a cyclization of the expected, but yet unknown, β-benzoyl-β-methylenepropionic acid (I) during the Friedel-Crafts reaction. The ability of such reactions to occur has been demonstrated by the cyclization of certain β-aroylacrylic acids[5] and aryl vinyl ketones[6] to the corresponding indanone derivatives. The other acid with the same melting point, 1-keto-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid (IV) which could have been produced by the cyclization of β-benzoyl-α-methylenepropionic acid (III), upon synthesis[7] gave a large mixture melting point depression with the acid in question.

In earlier papers[8] it has been shown that certain 1,2-dibenzoylalkenes (VII) react with amines to form 3-amino-1,2-dibenzoylalkanes (IX). These reactions involve a 1,3-hydrogen shift and addition of the amine to the resulting isomeric alkene (VIII). The remainder of this paper deals with attempts to ascertain whether or not the β-benzoyl-α- and β-methylacrylic acids (V and VI) behave similarly.



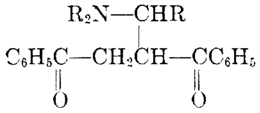
$C_6H_5\underset{\underset{O}{\|}}{C}-CH=\overset{\overset{CH_2R}{|}}{C}-\underset{\underset{O}{\|}}{C}C_6H_5$

VII



$C_6H_5\underset{\underset{O}{\|}}{C}-CH_2\overset{\overset{CHR}{\|}}{C}-\underset{\underset{O}{\|}}{C}C_6H_5$

VIII



$C_6H_5\underset{\underset{O}{\|}}{C}-CH_2\overset{\overset{R_2N-CHR}{|}}{C}H-\underset{\underset{O}{\|}}{C}C_6H_5$

IX

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[1] Taken largely from a portion of the Ph. D. dissertation of C. K. D., The University of Texas, June, 1954.

[2] Holder of an E. C. A. Scholarship from the State Department, 1952–1953.

[3] Lutz, Bailey, Dien, and Rinker, *J. Am. Chem. Soc.*, **75**, 5039 (1953).

[4] Groves and Swan, *J. Chem. Soc.*, 867 (1951).

(5) Baddeley, Holt, and Makar, *J. Chem. Soc.*, 3289 (1952); Baddeley, Makar, and Ivinson, *J. Chem. Soc.*, 3969 (1953).

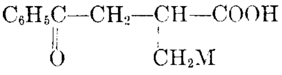
(6) Smith and Pritchard, *J. Am. Chem. Soc.*, **62**, 771 (1940).

(7) Attwood, Stevenson, and Thorpe, *J. Chem. Soc.*, **123**, 1764 (1923).

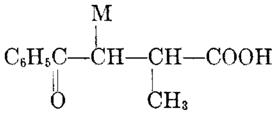
(8) (a) Lutz and Bailey, *J. Am. Chem. Soc.*, **67**, 2229 (1945); (b) Bailey and Nowlin, *J. Am. Chem. Soc.*, **71**, 732 (1949); (c) Bailey and Hakki, *J. Am. Chem. Soc.*, **71**, 2886 (1949); (d) Bailey, Nowlin, Pomerantz, Waggoner, and Kawas, *J. Am. Chem. Soc.*, **73**, 5560 (1951); (e) Bailey, Bath, Thomsen, Nelson, and Kawas, *J. Org. Chem.*, **21**, 297 (1956).

Upon treatment with excess morpholine β-benzoyl-α-methylenepropionic acid (III) and *cis-* and *trans*-β-benzoyl-α-methylacrylic acids (V) all produced the same addition compound and/or its morpholinium salt. Both products reacted with ethereal hydrogen chloride to produce the hydrochloride of the addition compound.

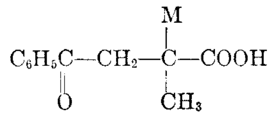
Of the three possible structures for the addition compound (X, XI, or XII) structure X, the one which would be produced by a reaction analogous to the dibenzoylpropene reaction[8] is apparently eliminated for the following reasons. The substance is easily deaminated by means of dilute hydrochloric acid to produce *trans*-β-benzoyl-α-methylacrylic acid (Vb). This is analogous to the easy deamination of 1,2-dibenzoyl-1-morpholinoethane to give *trans*-1,2-dibenzoylethylene,[9] but unlike the deamination of 1,2-dibenzoyl-3-morpholinopropane (type IX) which required considerably stronger conditions and yielded 2,3-dibenzoylpropene (type VIII).[8d] In the present case the deamination to the *trans*-α-methylacrylic acid (Vb) could not have involved the α-methylene compound (III) as an intermediate since the latter is stable to hydrochloric acid. This is evidenced by its method of preparation and by its failure to isomerize when treated with an ethanol-hydrochloric acid mixture. Further, both the α-methylenepropionic acid (III) and the *cis*-α-methylacrylic acid (Va) are isomerized by means of triethylamine to the *trans* acid (Vb).[3] The amine addition, therefore, is most likely to involve the *trans* isomer (Vb) to produce either XI or XII.


$\underset{\overset{\|}{O}}{C_6H_5C}-CH_2-\underset{CH_2M}{CH}-COOH$

X


$\underset{\overset{\|}{O}}{C_6H_5C}-\overset{M}{\overset{|}{C}}H-\underset{CH_3}{CH}-COOH$

XI


$\underset{\overset{\|}{O}}{C_6H_5C}-CH_2-\overset{M}{\underset{CH_3}{C}}-COOH$

XII

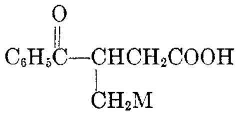
M = morpholino

It proved impossible to decide rigorously between structures XI and XII. By analogy to the addition of ammonia to β-benzoylacrylic acid[10] and of methanol to methyl β-(5-bromo-2,4-dimethoxybenzoyl)acrylate,[11] however, structure XII, which involves addition to the more reactive carbonyl-olefin conjugated system rather than the carboxyl-olefin (or, in the basic medium, the carboxylate ion-olefin) conjugated system, is favored.

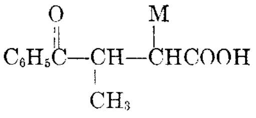
When β-benzoyl-α-methylenepropionic acid (III) was treated with morpholine in ether solution, the morpholinium salt of III was produced instead of the addition compound. The substance was very soluble in water, decolorized an acetone solution of potassium permanganate, regenerated III upon treatment with dilute hydrochloric acid, and reacted with excess morpholine to form the morpholinium salt of the addition compound (XII). On standing, the morpholinium salt of III rearranged to XII.

When either *cis-* or *trans*-β-benzoyl-β-methylacrylic acid (VI) was treated with excess morpholine the morpholinium salt of the addition compound was obtained. In this case it was possible to convert the salt to the addition compound itself by treatment with dilute hydrochloric acid. In order to deaminate the addition compound it was necessary to heat a solution of the compound in dilute hydrochloric acid for several minutes. The product was *trans*-β-benzoyl-β-methylacrylic acid (VIb).

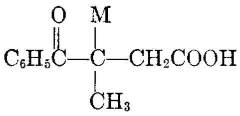
The situation is not as clear cut here as in the α-methyl series since β-benzoyl-β-methylenepropionic acid (I) is still unknown and since triethylamine has no effect on either *cis-*[3] or *trans*-β-benzoyl-β-methylacrylic acid (VI). In spite of this and the fact that the more difficult deamination of the addition compound (in comparison to the α-methyl series) might seem to speak in favor of XIII as its structure, logic requires that structure XIV be assigned to the addition compound on the basis of its deamination to *trans*-β-benzoyl-β-methylacrylic acid (VIb).[12] Structure XV is not likely for the reasons given earlier under the discussion of the addition product in the α-methyl series.


$C_6H_5\overset{\overset{O}{\|}}{C}-\underset{CH_2M}{C}HCH_2COOH$

XIII


$C_6H_5\overset{\overset{O}{\|}}{C}-\underset{CH_3}{CH}-\overset{M}{\overset{|}{C}}HCOOH$

XIV


$C_6H_5\overset{\overset{O}{\|}}{C}-\overset{M}{\underset{CH_3}{C}}-CH_2COOH$

XV

M = morpholino

This then necessitates the conclusion that neither the β-benzoyl-α-methylacrylic acids (V) nor the β-benzoyl-β-methylacrylic acids (VI) undergo addition with amines in the novel fashion that certain 1,2-dibenzoylalkenes do.[8]

EXPERIMENTAL[13]

1-Keto-2-indanacetic acid (II). The procedure was the same as reported in the earlier paper[3] with the exception

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[9] Lutz, Bailey, and Shearer, *J. Am. Chem. Soc.*, **68**, 2224 (1946).

[10] Fraser and Raphael, *J. Chem. Soc.*, **2245** (1950).

[11] Rice, *J. Am. Chem. Soc.*, **50**, 229 (1928).

[12] The greater ease with which deamination of the addition product in the α-methyl series occurs in comparison with that of the β-methyl series also speaks for the structures assigned. The methyl group in structure XII, through its inductive effect, should repel electrons toward the morpholine group and facilitate its removal.

[13] Some of the microanalyses were done by the Clark Microanalytical Laboratory, Urbana, Illinois.

that the yield was increased to 10% by increasing the relative amount of aluminum chloride (170 g. of aluminum chloride, 50 g. of itaconic anhydride, 80 ml. of dry benzene, and 250 ml. of carbon disulfide). In addition it was found advantageous to treat the crude product containing II (from filtrate B in the earlier paper)[3] with boiling barium hydroxide solution for two hours in order to hydrolyze the β-benzoyl-α-methylenepropionic acid (III). The resulting acetophenone was removed by steam-distillation and the remaining barium hydroxide solution was acidified and cooled, giving the indanacetic acid (II) which melted at 147–148°. The substance is colorless, is readily soluble in dilute sodium carbonate solution, and does not decolorize potassium permanganate in acetone solution. A mixture melting point with 1-keto-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid (IV) (m.p. 147–149°) prepared by the method of Attwood, Stevenson, and Thorpe[7] was 115–121°. A mixture melting point with 1-keto-2-indanacetic acid prepared by the method of Groves and Swan[4] showed no depression. The *semicarbazone* derivative melted at 240–241° after recrystallization from ethyl alcohol.

Anal. Calc'd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.38; H, 5.62; N, 16.99.

The *morpholinium salt* precipitated from an ether solution of the acid (II) and morpholine. It melted at 124–125° after recrystallization from an ethanol-ether mixture. It was readily converted back to II by treatment with dilute hydrochloric acid.

Anal. Calc'd for $C_{15}H_{19}NO_4$: N, 5.05. Found: N, 4.94.

Oxidation of 1-keto-2-indanacetic acid (II). (*a*). *To give o-phthalic acid.* A solution of 0.2 g. of II, 0.8 g. of potassium permanganate, 0.2 ml. of 10% sodium hydroxide, and 16 ml. of water was refluxed for 30 minutes, after which the mixture was acidified with sulfuric acid and refluxed another 30 minutes. The manganese dioxide was removed with sodium bisulfite and the resulting solution was extracted with ether. The ether extract was evaporated, the residue (0.12 g.) was recrystallized from water (m.p. 195–199°) and sublimed, yielding material which melted at 127–129° and showed no depression in a mixture melting point with known phthalic anhydride.

(*b*). *To homophthalic acid.*[14] To a boiling solution of 7.5 g. of chromium trioxide in 6.2 ml. of conc'd sulfuric acid and 75 ml. of water, was added with vigorous stirring over a 4-minute period, 2 g. of the indanacetic acid (II). After two more minutes of reflux, the solution was cooled and extracted with ether. The ether extract was washed and then was extracted with a dilute sodium hydroxide solution. Upon acidification of the basic extract and cooling, 0.9 g. of material melting at 154–169° was obtained; recrystallized from water, it had m.p. 174–176° (47% yield). The material was converted to the anhydride by heating with acetic anhydride for an hour. Evaporation of the acetic anhydride and crystallization of the residue from an ether-acetone mixture gave 0.1 g. of material melting at 141–142°. Perkin and Robinson[15] report the melting point of homophthalic acid as 175–177° and Wislicenus[16] reports the anhydride melting point as 140–141°.

β-Benzoyl-α-morpholinoisobutyric acid (XII) *and its morpholinium salt.* A solution of 5 g. of β-benzoyl-α-methylenepropionic acid (III) in 30 ml. of morpholine was set aside for 24 hours, after which it was evaporated to 15 ml. and cooled, yielding 8.2 g. of colorless crystals melting at 100–104°. Trituration with a warm solution of 15 ml. of ether and 15 ml. of ethanol left 2.2 g. of the acid melting at 113–117°; recrystallized from ethanol, m.p. 118–119°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; Neut. equiv., 277. Found: C, 64.69; H, 6.78; Neut. equiv., 280.

From the trituration filtrate, upon evaporation and cooling of the residue in an ice-salt bath and recrystallization of the resulting crystals from a 10:1 ether-ethanol solution, there was obtained 5.5 g. of the morpholinium salt, m.p. 102–104°; recrystallized from ether-ethanol, m.p. 105–106°. The material was soluble in water, insoluble in ether. Total yield of addition compound: 88%.

Anal. Calc'd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.53; H, 7.58; N, 7.48.

Similar results were obtained with *cis*- and *trans*-β-benzoyl-α-methylacrylic acids (V).

The morpholinoisobutyric acid (XII) could be converted to its morpholinium salt by treatment with excess morpholine. Either the morpholinoisobutyric acid (XII) or its morpholinium salt, gave the *hydrochloride* of XII upon treatment in acetone solution with excess ethereal hydrogen chloride solution for 48 hours. The hydrochloride precipitated and melted at 210–212° after recrystallization from acetone, yield 87%.

Anal. Calc'd for $C_{15}H_{20}ClNO_4$: C, 57.42; H, 6.42. Found: C, 57.37; H, 6.33.

Upon treatment of either the morpholinoisobutyric acid (XII) or its morpholinium salt with dilute aqueous hydrochloric acid *trans*-β-benzoyl-α-methylacrylic acid (Vb) precipitated; yield 91%, m.p. 109–110°, no depression in a mixture melting point with an authentic sample. The *trans* acid (Vb) was also obtained when a water solution of the hydrochloride of XII was refluxed over a steam-bath for 1–3 hours. It is noteworthy that β-benzoyl-α-methylenepropionic acid (III) was recovered unchanged in quantitative yield after treatment with an ethanol-hydrochloric acid mixture for one hour.

Morpholinium β-benzoyl-α-methylenepropionate. A solution of 5 g. of β-benzoyl-α-methylenepropionic acid (III), 10 ml. of morpholine, and 50 ml. of anhydrous ether deposited colorless crystals over a period of 10 minutes; 4.8 g. (66%), m.p. 77–78° after dry ether washing. The material was readily soluble in water and difficultly soluble in ether. It quickly decolorized an acetone-potassium permanganate solution.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91. Found: C, 65.11; H, 7.02.

Treatment of the morpholinium β-benzoyl-α-methylenepropionate with dilute hydrochloric acid precipitated the β-benzoyl-α-methylenepropionic acid (III) in 60% yield, m.p. 150–154°, identification by the mixture melting point method.

Upon treatment of morpholinium β-benzoyl-α-methylenepropionate with excess morpholine the morpholinium salt of β-benzoyl-α-morpholinoisobutyric acid (XII) was obtained in 80% yield; m.p. 104–105°, identification by the mixture melting point method; the reaction mixture was worked up as in the previous preparation of the substance.

On standing, the morpholinium β-benzoyl-α-methylene propionate gradually decomposed to a yellow oil which upon treatment with ethyl alcohol yielded β-benzoyl-α-morpholinoisobutyric acid (XII) in 30% yield; m.p. 116–118°, identification by the mixture melting point method.

β-Benzoyl-α-morpholinobutyric acid (XIV). (a). *The morpholinium salt.* To a solution of 1 g. of *trans*-β-benzoyl-β-methylacrylic acid (VIb) in 10 ml. of ether was added 10 ml. of morpholine. A precipitate immediately formed but this redissolved on standing. After 24 hours the solution was cooled in an ice-salt bath whereupon crystallization occurred, yielding 1.6 g. (83% yield) of material melting at 132–136°. Similar results were obtained using the *cis* isomer. The material was soluble in dilute hydrochloric acid. Several recrystallizations from a 1:5 ethanol-ether mixture raised the melting point to 138–139°.

Anal. Calc'd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.78; H, 7.59; N, 7.95.

(*b*). *Conversion to the acid* (XIV). To a solution of 6 g. of

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(14) Method of Ingold and Piggot, *J. Chem. Soc.*, **123**, 1497 (1923).

(15) Perkin and Robinson, *J. Chem. Soc.*, **91**, 1082 (1907).

(16) Wislicenus, *Ann.* **233**, 108 (1886).

the morpholinium salt of XIV in 80 ml. of water was added dropwise 5% hydrochloric acid until the solution was at *p*H 5–6 (indicator paper). Upon cooling the solution 3.2 g. of colorless crystals was obtained. Extraction of the filtrate with ether and evaporation of the ether extract yielded an additional 1 g.; crude yield 94%, m.p. 106–112°. Recrystallization from dilute ethyl alcohol raised the melting point to 115–116°. The material did not decolorize an acetone solution of potassium permanganate and it was soluble in either dilute hydrochloric acid or sodium carbonate solution.

Anal. Calc'd for $C_{15}H_{19}NO_4$: N, 5.05. Found: N, 5.33.

Treatment with excess morpholine converted the acid back to the morpholinium salt in 97% yield, m.p. 135–137°, no depression in melting point in admixture with an authentic sample.

Dilute hydrochloric acid solutions of either XIV *or its* morpholinium salt remained stable for several hours. After 10–15 minutes heating over the steam-bath, however, a crystalline precipitate formed in 80–90% yield; m.p. 100–102°, no depression in melting point in admixture with an authentic sample of *trans*-β-benzoyl-β-methylacrylic acid (VIb).

Attempted conversion of XIV *to a dibenzoylmorpholinopropane* by means of the Friedel-Crafts reaction with benzene resulted in the loss of the morpholino group and the production of tars.

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