

203°, and at 212.5–213.5° after recrystallization from acetone.

When the reaction was carried out with 0.1 mole each of potassium amide and methyl benzoate and 0.05 mole of bis-acetylferrocene (III) (ether suspension stirred for 6 hr.), there was obtained 11 g. (46%) of bis- β -diketone IV, m.p. 213–214°. Since 6 g. (45%) of the bisacetylferrocene (III) was recovered the conversion yield was 84%.

When the reaction was carried out with 0.05 mole of potassium amide and 0.025 mole each of bisacetylferrocene (III) and methyl benzoate (ether suspension stirred for 8 hr.), there was obtained 1.8 g. (20%, 40% based on the ester) of bis- β -diketone IV, m.p. 212.5–214°. Since 4.5 g. (67%) of bis-acetylferrocene (III) was recovered, the conversion yield of IV based on III was 61%.

Cyclization of bis- β -diketone IV with hydrazine to form bis-pyrazole VII. To a solution of 5 g. (0.01 mole) of bis- β -diketone IV in 1.5 l. of absolute ethanol was added 20 g. (0.6 mole) of 95% hydrazine in 20 ml. of absolute ethanol. The resulting deep red solution was refluxed for 1 hr., during which time the color changed to a deep orange. After cooling to room temperature and standing overnight in a refrigerator, the reaction mixture was filtered (cold) to yield 3.1 g. of bispyrazole VII (orange crystalline solid), m.p. >300° dec. Reduction of the volume of the filtrate under vacuum gave an additional 0.9 g. of an orange powder, m.p. >300° dec.; total yield 4.0 g. (82%). This compound failed to dissolve appreciably (as would be indicated by color) in various refluxing solvents including benzene,

acetone, hexane, ethanol, chloroform, and dioxane. However, unrecrystallized samples from both fractions gave satisfactory analytical values.

Anal. Calcd. for $C_{28}H_{22}N_4Fe$: C, 71.49; H, 4.71; N, 11.91; Fe, 11.90. Found for orange crystals: C, 71.43; H, 4.90; N, 11.88; Fe, 11.73. Found for orange powder: C, 71.37; H, 4.88; N, 11.79; Fe, 12.14.

Formation of the copper-chelate XI of bis- β -diketone IV. To a solution of 1 g. of the bis- β -diketone IV in 500 ml. of refluxing acetone was added 20 ml. of a saturated solution (large excess) of warm, aqueous copper acetate. After refluxing for 15 min., the reaction mixture was cooled and filtered. The solid was washed with water and dried. After washing with petroleum ether and recrystallizing from benzene there was obtained 1 g. (88%) of a yellow powder, m.p. >300°.

Anal. Calcd. for $C_{28}H_{20}O_4FeCu$: C, 62.08; H, 4.09. Found: C, 62.29; H, 3.99. Mol. wt. determinations¹⁸: Calcd. for $C_{28}H_{20}O_4FeCu$: 541.9. Found: 529, 514, 509, 521. Limit of error, $\pm 10\%$.

A portion of the chelate was reconverted to the original bis- β -diketone by stirring overnight in 20% phosphoric acid. It was identified by infrared spectrum and melting point.

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(18) Mol. wt. determination by Laboratory of Microchemistry, Dr. Carl Tiedcke, Teaneck, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

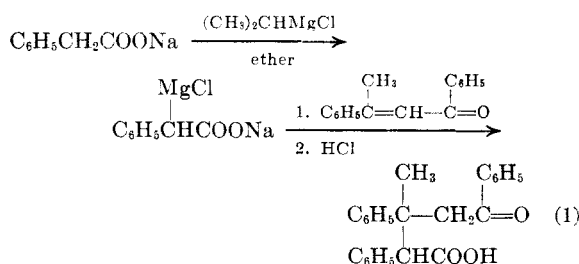
Conjugate Addition of Phenylacetic Acid and Derivatives with α,β -Unsaturated Carbonyl Compounds by Means of Sodium Amide

CHARLES R. HAUSER AND MARVIN T. TETENBAUM¹

Received October 24, 1957

Disodio phenylacetic acid prepared by means of two equivalents of sodium amide in liquid ammonia underwent conjugate addition with benzalacetophenone and ethyl cinnamate to give excellent yields of products. Addition of cold acid to the reaction mixture from the α,β -unsaturated ester produced the corresponding di-acid instead of the intermediate mono-acid-ester. Similarly the disodium salt of phenylacetamide gave with ethyl cinnamate under these conditions the mono-acid-amide. However the monosodium salt of ethyl phenylacetate formed with this α,β -unsaturated ester the corresponding diester.

Ivanoff and co-workers² have effected the conjugate additions of phenylacetic acid to dypnone and phorone by means of isopropylmagnesium chloride. This Grignard reagent was employed to convert the sodium salt of phenylacetic acid to its magnesium chloride derivative which was condensed with the α,β -unsaturated ketones. The reaction may be illustrated with dypnone (Equation 1).

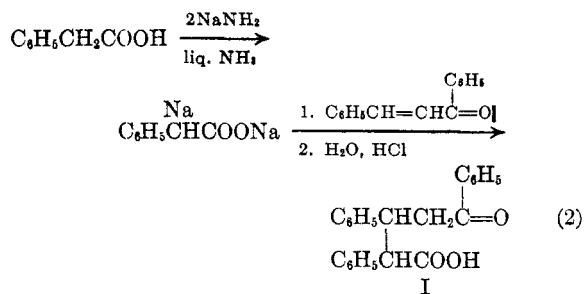


(1) American Cyanamid Company Fellow, 1956–1957.

Although the yield was not given in this reaction, a 75% yield was reported for the corresponding reaction with phorone.²

In the present investigation the conjugate additions of phenylacetic acid and certain of its derivatives to benzalacetophenone and ethyl cinnamate were effected by means of sodium amide in liquid ammonia. Two molecular equivalents of this reagent were employed to convert the phenylacetic acid to its disodium derivative which was then condensed with the α,β -unsaturated carbonyl compound. The reaction with benzalacetophenone produced ketone-acid I in excellent yield (Equation 2).

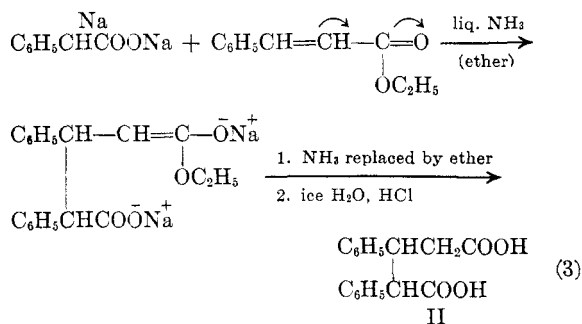
(2) D. Ivanoff, M. Mihova, and T. Christova, *Bull. soc. chim. France*, [4], 51, 1321 (1932).



The product evidently consisted largely of the lower melting of the two possible diastereoisomers of I. In an unsuccessful attempt to effect cyclization of this isomer³ by means of polyphosphoric acid, the recovered ketone-acid melted at the temperature reported for the higher melting isomer.

The two diastereoisomers of ketone-acid I have previously been prepared⁴ by the conjugate addition of methyl phenylacetate with benzalacetophenone by means of sodium methoxide, followed by the hydrolysis of the esters and separation of the resulting isomeric ketone-acids both of which were obtained in these reactions.

The conjugate addition of disodio phenylacetic acid with ethyl cinnamate produced, on adding ice water and acid, diacid II in 95% yield (Equation 3).



The corresponding mono-acid-ester was presumably an intermediate, but it was not isolated under the above conditions.⁵

Whereas the conjugate addition with benzalacetophenone gave largely one of the diastereoisomers of I, this reaction (Equation 3) produced a mixture of the two possible isomers of II.⁶

Like many Michael-type condensations, the present conjugate addition was realized by means of only a catalytic amount of sodium amide, although the yield of product was lower. Thus, a 46% yield of diacid II was obtained when 20 mole

(3) Treatment of this compound with hydrogen fluoride at room temperature produced an orange powder (m.p. 214–215°) which was not identified.

(4) S. Avery and G. C. Jorgensen, *J. Am. Chem. Soc.*, **52**, 3628 (1930).

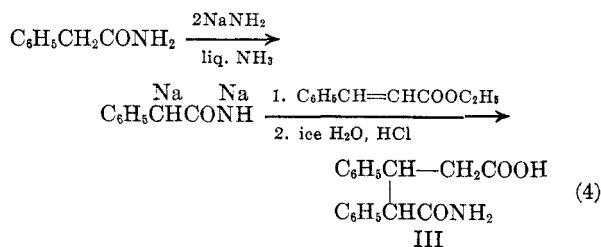
(5) The unexpected ease of hydrolysis of the ester group is being investigated.

(6) D. Lednicer of this laboratory has found, by fractional recrystallizations, that the crude conjugate addition product consists of approximately equal amounts of the two diastereoisomers.

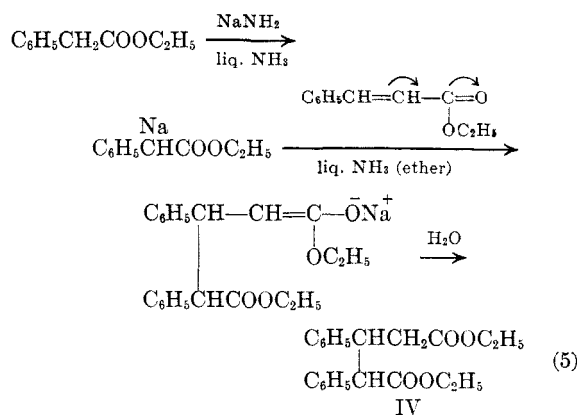
percent of this base was used to effect the ionization of the α -hydrogen of sodium phenylacetate. Actually 1.2 equivalents of sodium amide were employed to one equivalent each of phenylacetic acid and ethyl cinnamate, but one equivalent of this base was neutralized in converting the acid to sodium phenylacetate.

Similarly, disodio phenylacetic acid underwent conjugate addition with benzyl cinnamate to give, after treatment with cold acid, diacid II, and benzyl alcohol.

Also the disodium or dipotassium salt of phenylacetamide underwent conjugate addition with ethyl cinnamate to form the acid-amide III (71–89%) (Equation 4). None of the corresponding ester-amide, which would presumably be an intermediate, was isolated under the condition employed.⁵



On the other hand, sodio ethyl phenylacetate prepared by means of one equivalent of sodium amide was found to produce with ethyl cinnamate under similar conditions the corresponding diester IV in 65% yield (Equation 5).



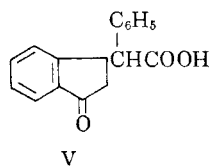
The product apparently consisted largely of the lower melting diastereoisomer of IV. Saponification of this diester IV with approximately one equivalent of potassium hydroxide gave about a 50% yield of diacid II, and none of the corresponding mono-acid-ester was isolated.

The lower melting isomer of diester IV has previously been obtained in low yield from ethyl phenylacetate and ethyl cinnamate employing sodium triphenylmethide.⁷ The higher melting isomer of

(7) C. R. Hauser and B. Abramovitch, *J. Am. Chem. Soc.*, **62**, 1763 (1940).

IV has been obtained in high yield from this conjugate addition using sodium ethoxide.⁸

It should be mentioned that diacid II (isomeric mixture) was cyclized by means of hydrogen fluoride to form apparently hydrindone V (48%).



This five membered ring product has previously been obtained from the anhydride of diacid II by means of aluminum chloride.^{8,9} Since the anhydride has yielded the lower melting isomer¹⁰ of diacid II on hydrolysis with alkaline carbonate, cyclic product V might have arisen from this isomer.

EXPERIMENTAL¹¹

Conjugate addition of phenylacetic acid with benzalacetophenone. To a stirred suspension of 0.2 mole of sodium amide in 300 ml. of liquid ammonia¹² was added 13.6 g. (0.1 mole) of solid phenylacetic acid. After the resulting green solution of the disodium salt of the acid was stirred for 15 min., 20.8 g. (0.1 mole) of solid benzalacetophenone was added, and the stirring continued for 1 hr. The liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added. The resulting ether suspension was refluxed for 1 hr., and then decomposed with ice water. The mixture, which contained a white precipitate, was filtered, and most of the solid was washed through the filter into the filtrate with dilute potassium hydroxide. The aqueous alkaline layer of the filtrate was separated from the ethereal layer, and acidified in the cold with hydrochloric acid. There was obtained an excellent yield of ketone-acid I, m.p. 185–187° and at 186–187° after two recrystallizations from methanol. This was evidently the lower melting diastereoisomer of I which has been reported to melt at 186–187°.⁴ The higher melting isomer of I has been reported to melt at 260–261°,⁴ and a mixture of the two isomers at 240°.⁴

When a sample of our product (m.p. 186–187°) was heated with polyphosphoric acid¹³ at 125–130° for 30 min., and the reaction mixture then treated with iced hydrochloric acid, there was recovered ketone-acid I melting at 263–265° which was apparently the higher melting isomer.

Conjugate addition of phenylacetic acid with ethyl cinnamate. The disodium salt of phenylacetic acid was prepared from 0.2 mole of sodium amide and 0.1 mole of the acid in 300 ml. of liquid ammonia as described above, and a solution of 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of anhydrous ether was added with stirring. The

green color of the disodium salt of the acid was discharged, and a white precipitate was produced. After stirring for 1 hr., the liquid ammonia was replaced by ether (see above), and the resulting ether suspension was refluxed for 30 min. Ice water was then added, and the aqueous alkaline layer was separated and combined with three alkaline extracts of the ether layer. After filtering to remove a small amount of tar, iced hydrochloric acid was added to produce a white precipitate which was dried overnight on the funnel. There was obtained 27 g. (95%) of α,β -diphenylglutaric acid (II) m.p. 190–233°. This mixture of isomers of diacid II was crystallized four times from a mixture of ether and petroleum ether (b.p. 30–60°) to give the higher melting isomer of II, m.p. 228–233° (reported m.p. 226–228°).^{10,14}

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.97; H, 5.70.

Similar results were obtained when solid ammonium chloride was added to the reaction mixture in liquid ammonia within a few minutes after the ethyl cinnamate was added. The ammonia was then replaced by ether, and cold water and acid added to the resulting ether suspension.

Conjugate addition with catalytic amount of base. To a stirred suspension of 0.12 mole of sodium amide in 300 ml. of liquid ammonia was added 0.1 mole of phenylacetic acid, followed after 15 min. by 0.1 mole of ethyl cinnamate in an equal volume of ether. After 2 hr. the reaction mixture was worked up to give a 46% yield of di-acid II, m.p. 195–198°. Some (34%) ethyl cinnamate was recovered. Regenerated phenylacetic acid was detected.

Conjugate addition of phenylacetic acid with benzyl cinnamate. Benzyl cinnamate was prepared in 92% yield from one mole each of cinnamoyl chloride and benzyl alcohol, the reaction mixture being heated on the steam bath for 1 hr. and then at 200° for 30 min. The ester boiled at 183° at 3 mm. (reported boiling point 195–200° at 5 mm.).¹⁵

The ester (0.1 mole) in an equal volume of ether was added to a stirred solution of disodio phenylacetic acid in liquid ammonia prepared from 0.1 mole of the acid and 0.2 mole of sodium amide as described above. After 1 hr. the liquid ammonia was replaced by ether, and the resulting suspension stirred for 30 min. Ice water was added, and the layers were separated. The solvent was removed from the ether layer and the residue was distilled *in vacuo* to give a 65% yield of benzyl alcohol, b.p. 83–85° at 5 mm. (reported b.p. 92° at 10 mm.).¹⁶ Acidification of the alkaline aqueous layer precipitated a good yield of di-acid II.

Conjugate addition of phenylacetamide with ethyl cinnamate. To a stirred suspension of 0.2 mole of sodium amide in 300 ml. of liquid ammonia was added 13.5 g. (0.1 mole) of solid phenylacetamide. The resulting bright green solution of the disodium salt of the amide was stirred for 15 min., and 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of ether was then added. The liquid ammonia was replaced by ether, and the resulting ether suspension was stirred for 1 hr. Ice water was added, and the aqueous alkaline layer (after filtering) was acidified with iced hydrochloric acid to precipitate 20 g. (71%) of mono-acid-amide III, melting at 196–197°. One recrystallization from ethanol raised the melting point to 204–205° (reported m.p. 200–205°).¹⁰ A mixed melting point with diacid II was depressed to about 185°.

When the conjugate addition of phenylacetamide with ethyl cinnamate was similarly effected by means of potassium amide (instead of sodium amide), there was obtained an 89% yield of the mono-acid-amide III, m.p. 204–205°.

(14) The lower melting isomer of II is reported to melt at 208–210°; see Ref. 10.

(15) See Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. I, p. 272.

(16) J. Meisenheimer, *Ber.*, **41**, 1420 (1908).

(8) G. M. Badger, J. E. Campbell, and J. W. Cook, *J. Chem. Soc.*, 1087 (1949).

(9) For another preferential five-membered ring cyclization (over the usual six-membered ring cyclization) see D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(10) S. Avery and W. D. Maclay, *J. Am. Chem. Soc.*, **51**, 2833 (1929).

(11) Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(12) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **VIII**, 122 (1954).

(13) We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of polyphosphoric acid.

A 2 g. sample of the mono-acid-amide III readily dissolved in cold dilute potassium hydroxide solution. On refluxing this solution for 3 hr., ammonia was evolved, and there was obtained, on acidification of the cooled solution, 1.6 g. (80%) of diacid II, m.p. 216–217°. This melting point was not depressed on admixture with diacid II prepared from the conjugate addition of phenylacetic acid and ethyl cinnamate as described above. A mixed melting point with the mono-acid-amide III was depressed to 185–190°.

Conjugate addition of ethyl phenylacetate with ethyl cinnamate. To a stirred solution of 0.1 mole of sodium amide in 300 ml. of liquid ammonia was added 16.4 g. (0.1 mole) of ethyl phenylacetate in an equal volume of ether, and the resulting solution stirred for 15 min. A solution of 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of ether was added, and the ammonia was replaced by ether. The resulting ether suspension was refluxed on the steam bath for 30 min., cooled, and decomposed with ice water. The ethereal layer (with which was combined three ether extracts of the aqueous layer) was dried over Drierite, and the solvent removed. The residue was distilled *in vacuo* to give 6.5 g. of recovered ethyl cinnamate, leaving a residue that solidified after standing at room temperature for one day. This solid was recrystallized from ethanol to give 22 g. (65%) of white diester IV, m.p. 76–77° (lit. m.p. 75–75.5°).⁷ The higher melting isomer of diester IV is reported to melt at 92–93°.¹⁷

A 6 g. sample of diester IV was refluxed 6 hr. with an

aqueous solution of potassium hydroxide containing approximately an equimolar amount of this base. After cooling and removing a small amount of gummy residue, the alkaline solution was acidified with iced hydrochloric acid. The resulting white precipitate was recrystallized from a mixture of ether and petroleum ether (b.p. 30–60°) to give 2.5 g. (50%) of diacid II, m.p. 193–196°. This melting point was not depressed on admixture with a sample of diacid II.

Cyclization of diacid II. A solution of 5 g. of diacid II in 150 g. of liquid hydrogen fluoride contained in a polyethylene bottle was allowed to stand in a hood at room temperature overnight, during which time the hydrogen fluoride had evaporated. The resulting gummy residue was dissolved in ether, and the yellow solution was poured into dilute potassium hydroxide. The two layers were separated. The orange-red aqueous alkaline layer was cooled in an ice bath and acidified with iced hydrochloric acid to precipitate 4.5 g. of a white semi-solid which was presumably hydrindone V. This product resisted crystallization from the usual organic solvents, but it readily gave a yellow-orange 2,4-dinitrophenylhydrazone in 48% over-all yield. After two recrystallizations from ethanol, this derivative melted at 262–263° (softened at 258°) in agreement with the melting point reported for it when hydrindone V was prepared by the cyclization of the anhydride of II by means of aluminum chloride.⁸

Anal. Calcd. for C₂₃H₁₈O₆N₄: C, 61.88; H, 4.06; N, 12.55. Found: C, 61.66; H, 4.17; N, 12.75.

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(17) W. Borsche, *Ber.*, **42**, 4497 (1909).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Stability of Mixed Carboxylic-Carbonic Anhydrides

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Preparation of a considerable number of mixed carboxylic-carbonic anhydrides shows that they are more stable than previously supposed. Some are stable crystalline solids, and many of the liquid ones can be distilled without decomposition. They have been characterized by analysis, except in the case of some liquids which could not be distilled, and by the preparation of solid derivatives.

The mixed carboxylic-carbonic anhydrides, RCOOCOOR, have been widely used for the preparation of amide and particularly of peptide linkages.^{2,3} It has also been found that they can be used for numerous acylation reactions on carbon, such as acylation of malonic and acetoacetic ester,⁴ the formation of ketones from organocadmium compounds,⁴ and preparation of diazoketones from

diazomethane.^{4,5} In the recent work in which the mixed anhydrides were utilized,^{2–5} generally no attempts were made to isolate them, and the impression is given that they are unstable compounds.^{2,3} In early work,⁶ several mixed anhydrides were prepared from the acid and ethyl chlorocarbonate; they were described as unstable oils and were not characterized suitably. More recently, the mixed anhydride has been isolated from benzylpenicillin in the form of a rather unstable gum.⁷ Small yields of the mixed anhydrides III and IV have been obtained by oxidation of α -keto esters I and II by

(1) Monsanto Fellow, 1956–57.

(2) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951)

(3) *E.g.*, J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952); J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953); **76**, 2474 (1954); V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953); **76**, 3107 (1954); B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(4) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

(5) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **18**, 161 (1953).

(6) Knoll and Co., German Patent **117,267** [*Chem. Zentr.*, **72**, 347 (1901); *Friedländer*, **VI**, 146].

(7) R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jensen, M. E. Trevelt, and G. B. Webb, *J. Chem. Soc.*, 3733 (1953); D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3636 (1953).