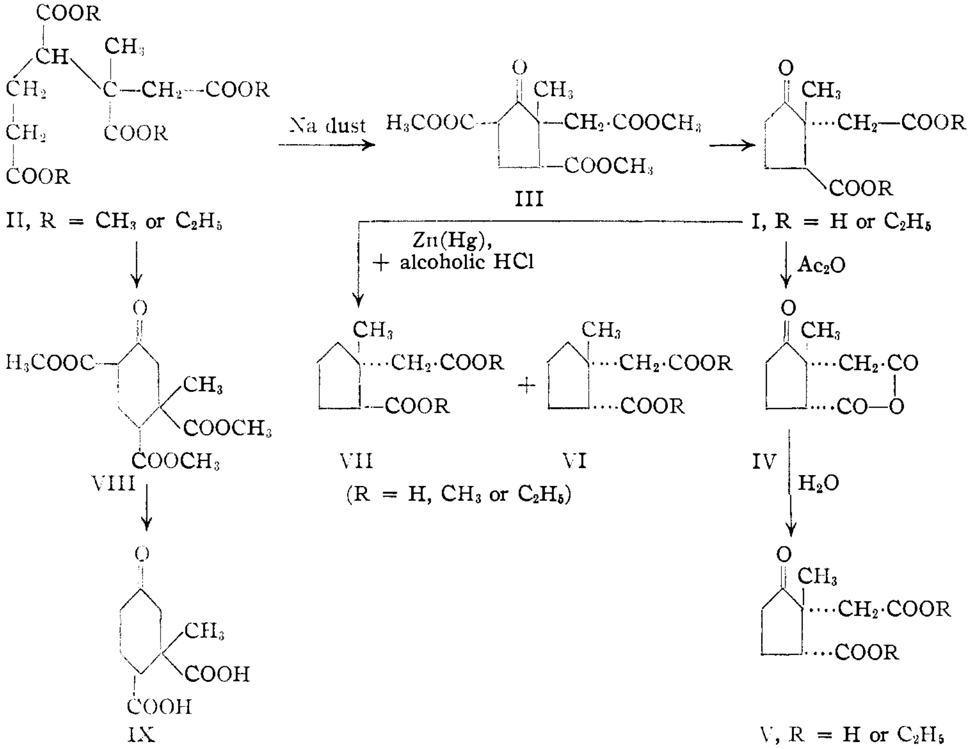
[Contribution from the Organic Chemistry Laboratory of the College of Engineering & Technology, Bengal]

Synthesis of 2-Methyl-3-carboxycyclopentanone-2-acetic Acid

By D. K. Banerjee and S. K. Das Gupta

Both the stereoisomers of 2-methyl-3-carboxycyclopentanone-2-acetic acid (I and V, R = H) have been prepared. In this connection cyclization of methyl 2-methylpentane-1,2,3,5-tetracarboxylate (II) has been studied and it has been found that the desired cyclopentanone derivative (III) is formed almost exclusively. The structure of I has been confirmed by its reduction to the known *cis*- and *trans*-1-methyl-2-carboxycyclopentaneacetic acids and by direct comparison with authentic specimens prepared by a new method.

2-Methyl-3-carboxycyclopentanone-2-acetic acid (I, R = H) a compound which may be useful as an intermediate in steroid synthesis, can be obtained from methyl 2-methylpentane-1,2,3,5-tetracarboxylate (II) if cyclization takes place in the desired fashion. An alternate mode of cyclization, however, would lead to a six-membered compound (VIII). A study of this reaction has been made and has led us to the conclusion that the five-membered ring compound is formed preferentially to the six-membered ring compound. When the tetraester (II) was subjected to a Dieckmann condensation followed by hydrolysis a keto dibasic acid (I, R = H) was obtained in good yield. The conversion of I to its stereoisomer through the anhydride followed by hydrolysis gave compound V. The semicarbazones of the diethyl esters of I and V proved to be different from the semicarbazone of the diethyl ester of IX, previously prepared by Mukharji[1]. A further proof of structure of I resulted from the conversion of its diethyl ester (I, R = C_2H_5), by reduction of the carbonyl group followed by hydrolysis, to a stereoisomeric mixture of known compounds VI and VII, previously prepared by Chuang, Ma and Tien.[2] Presumably the treatment with refluxing alcoholic hydrogen chloride during the reduction experiment was responsible for the conversion of the stereochemically homogeneous I (R = C_2H_5) into a mixture of stereoisomers of the reduced acid.



The authentic samples of VI and VII for direct comparison were prepared by an independent method outlined below. Ethyl 2-methylcyclopentanone-2-acetate, prepared by a method previously described by one of us,[3] was converted into the cyanohydrin (X) with liquid hydrogen cyanide and a few drops of potassium cyanide solution. The unsaturated nitrile (XI), obtained by the dehydration of X with thionyl chloride and pyridine, was hydrolyzed with alkali at high temperature and the resulting crude acidic product was directly esterified with diazomethane. The unsaturated diester (XII), thus obtained, was catalytically hydrogenated, hydrolyzed and finally converted into VI (R = H) through the anhydride (XIV). The dimethyl ester (VI, R = CH_3) was converted into its stereoisomer (VII, R = H) by treatment with a refluxing potassium *t*-butoxide solution, followed by hydrolysis and fractional crystalliza-

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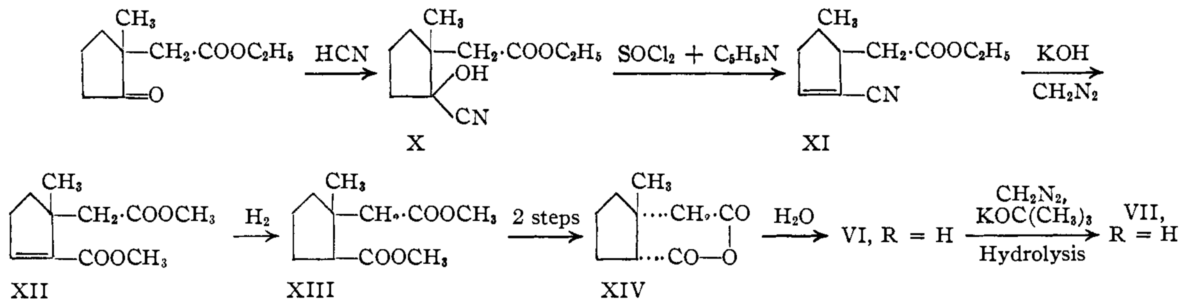
(1) P. C. Mukharji, *J. Indian Chem. Soc.*, **25**, 365 (1948).

(2) C. Chuang, C. Ma and Y. Tien, *Ber.*, **68**, 1946 (1935); *cf.* K. D. Errington and R. P. Linstead, *J. Chem. Soc.*, 666 (1938).

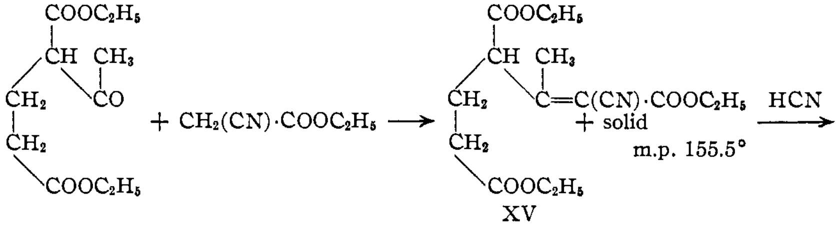
(3) N. K. Chakravarty and D. K. Banerjee, *J. Indian Chem. Soc.*, **23**, 377 (1946); *cf.* M. W. Goldberg, F. Hunziker, J. R. Billeter and M. R. Rosenberg, *Helv. Chim. Acta*, **30**, 200 (1947); R. N. Chakravarty, *Experientia*, **3**, 149 (1947).

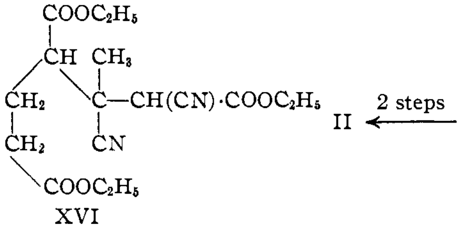


tion. The melting points of the above stereoisomeric acids were not depressed on admixture with the acids obtained from the cyclization product of the tetraester (II).

The tetraester (II) was prepared by the following method. Ethyl α-acetyl-glutarate was condensed with ethyl cyanoacetate using the modified procedure of Cope[4] and the unsaturated cyanoester (XV), λ_{max} 235 mμ (log *E* 3.96), was obtained as a viscous liquid along with a crystalline product. Investigation on the constitution of the crystalline by-product is in progress and will be reported later. The dicyanoester (XVI), obtained by the addition of hydrocyanic acid to XV, was hydrolyzed and the resulting crude gummy acid on esterification furnished the tetraester (II) in moderately good yield.

Acknowledgments.—The authors wish to express their indebtedness to Mr. G. Karmakar and Mr. P. Datta of the All India Institute of Hygiene and Public Health for the ultraviolet absorption data.





Experimental[5]

Ethyl α-Acetylglutarate.—A procedure modified from that of reference 6 was employed. Ethyl sodioacetate, prepared from 11.5 g. (0.5 gram atom) of sodium dust under 250 ml. of dry benzene and 78 g. (0.6 mole) of ethyl acetoacetate, was refluxed for six hours with 70 g. (0.51 mole) of ethyl β-chloropropionate, prepared in 94% yield from β-chloropropionic acid by the azeotrope method. The crude product, obtained in the usual way, was fractionally distilled to yield 87–98 g. (76–85%) of a colorless oil, b.p. 127–130° (4 mm.). The reported yield is 52%, b.p. 132–134° (4 mm.).

Ethyl 1-Cyano-2-methylpentene-1,3,5-tricarboxylate (XV).—For this preparation the procedure described by Banerjee and Shafer[7] was employed except that benzene was replaced by toluene as solvent, which considerably shortened the time of the reaction. From a mixture of 100 g. of ethyl α-acetylglutarate, 52 ml. of ethyl cyanoacetate, 20 g. of ammonium acetate, 43 ml. of glacial acetic acid and 150 ml. of toluene, there was obtained 69 g. (48%) of the unsaturated cyanoester, b.p. 173–175° (1 mm.), as a viscous yellow oil; λ_{max} 235 mμ, log *E* 3.96, ethanol.

Anal. Calcd. for $C_{16}H_{23}NO_6$: C, 59.08; H, 7.08. Found: C, 59.12; H, 7.31.

Twenty-three grams of a crystalline by-product was obtained when the reaction mixture was cooled after completion of the reaction, either when being washed with water or as a forerun at 155–165° (1 mm.) during fractionation through a three-inch Vigreux column. On crystallization from 95% ethanol the product separated as white needles, m.p. 155.5°.

Ethyl 1,2-Dicyano-2-methylpentane-1,3,5-tricarboxylate (XVI).—The addition of hydrocyanic acid to XV was carried out as described by Banerjee.[8] A solution of 69 g. of XV in 240 ml. of 95% ethanol was treated with a solution of 35.5 g. of potassium cyanide in 196 ml. of water and then with 76 ml. of 20% hydrochloric acid as before.[8] The product, after acidification, was worked up in the usual manner and a small portion of it was purified by evaporative distillation for analysis, bath temperature 180–185° (0.5 mm.).

Anal. Calcd. for $C_{17}H_{24}N_2O_6$: C, 57.95; H, 6.81. Found: C, 58.35; H, 6.82.

Methyl 2-Methylpentane-1,2,3,5-tetracarboxylate (II).—The crude dicyanoester (XVI), obtained from 49.5 g. of the unsaturated cyanoester (XV) as described above, was refluxed for 48 hours with 200 ml. of concentrated hydrochloric acid. The acid solution was extracted with ether by the continuous process. The brown glass, obtained after removal of the solvent followed by drying of the residue by azeotropic distillation with benzene, was free from nitrogen and was refluxed for 50 hours with 200 ml. of methanol and 36 ml. of sulfuric acid (d. 1.84). After working up in the usual manner, there was obtained 28 g. (56% on the basis of the unsaturated cyanoester used) of the tetraester, b.p. 165–170° (0.6 mm.), as an almost colorless thick oil.

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.91. Found: C, 53.08; H, 6.96.

The tetraethyl ester was also prepared, b.p. 194–198° (5 mm.).

Anal. Calcd. for $C_{18}H_{30}O_8$: C, 57.75; H, 8.02. Found: C, 57.68; H, 8.31.

***trans*-2-Methyl-3-carboxycyclopentanone-2-acetic Acid (I, R = H).**—Thirty-four grams of the tetramethyl ester

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[4] A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, This Journal, **63**, 3452 (1941).

[5] All m.p.'s are uncorrected.

[6] *Organic Syntheses*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 263.

[7] D. K. Banerjee and P. R. Shafer, This Journal, **72**, 1931 (1950).

[8] D. K. Banerjee, *J. Indian Chem. Soc.*, **17**, 453 (1940).

(II) containing two drops of methanol was added to 2.8 g. of sodium dust under 240 ml. of dry benzene in an atmosphere of nitrogen and the mixture was refluxed for four hours to complete the reaction, indicated by the disappearance of the sodium particles. After cooling in an ice-bath the reaction mixture was treated with an excess of cooled dilute hydrochloric acid under the nitrogen atmosphere. The organic layer was separated and washed successively with water, sodium bicarbonate solution and water again. The oily residue, obtained after removal of the solvent, gave a strong violet coloration with alcoholic ferric chloride and a small portion of this was purified by evaporative distillation for analysis.

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.29. Found: C, 55.08; H, 6.32.

The rest of the crude β-ketoester (III), obtained from the above experiment, was refluxed for 24 hours with a mixture of 180 ml. of acetic acid, 79 ml. of concentrated hydrochloric acid and 54 ml. of water. The crude brown solid residue, which was left after removal of the volatile hydrolysis mixture under diminished pressure at 100°, weighed 14 g. The product, after two crystallizations from dilute hydrochloric acid, had the constant m.p. 174°.

Anal. Calcd. for $C_9H_{12}O_5$: C, 54.00; H, 6.00; neut. equiv., 100. Found: C, 54.25; H, 6.37; neut. equiv., 101.

***trans*-Ethyl 2-Methyl-3-carbethoxycyclopentanone-2-acetate** (I, R = C_2H_5).—For the preparation of this ester, the crude keto dibasic acid (I, R = H) obtained from II by the Dieckmann condensation followed by hydrolysis, was directly esterified. Thus the β-ketonic ester (III), obtained from 12.8 g. of the tetraester using 0.8 g. of sodium dust, after hydrolysis and removal of the volatile products was refluxed for 30 hours with 100 ml. of ethanol and 10 ml. of concentrated sulfuric acid. The keto diester, worked up in the usual manner, was fractionally distilled to yield 6 g. (69% on the basis of the quantity of the tetraester used) of a colorless mobile oil, b.p. 129–131° (1 mm.).

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.93; H, 7.81. Found: C, 61.19; H, 8.05.

The semicarbazone, prepared by allowing a clear warm solution of the above keto diester and a saturated solution of semicarbazide hydrochloride and sodium acetate in ethanol to stand for several hours, was obtained in 90% yield, crude m.p. 137–140°. After two crystallizations from dilute ethanol the product had the constant m.p. 142°.

Anal. Calcd. for $C_{14}H_{23}N_3O_5$: C, 53.67; H, 7.35. Found: C, 54.15; H, 7.70.

The high yield of the keto diester (69% on three steps) and its semicarbazone and the melting point of the latter in the crude state indicate the stereochemical homogeneity of I (R = C_2H_5) and hence that of the keto diacid (I, R = H) follows.

***cis*-2-Methyl-3-carboxycyclopentanone-2-acetic Acid Anhydride** (IV).—Five grams of the crude acid (I, R = H) was refluxed for 30 hours with 25 ml. of acetic anhydride. The acetic anhydride was removed under diminished pressure. The residue distilled at 160–165° (2 mm.) giving 3 g. (70%) of a crystalline solid, m.p. 125°.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.50. Found: C, 59.88; H, 6.02.

***cis*-2-Methyl-3-carboxycyclopentanone-2-acetic Acid** (V, R = H).—Three grams of the above anhydride was dissolved by heating in 50 ml. of water. The heating was continued for one hour after the addition of a small quantity of charcoal. The solution was evaporated to dryness on a steam-bath, after the filtration from charcoal, to yield 3.1 g. (88%) of a crystalline solid, m.p. 140–141°. The crystallization from water did not improve the melting point.

Anal. Calcd. for $C_9H_{12}O_5$: C, 54.00; H, 6.00; neut. equiv., 100. Found: C, 54.18; H, 6.22; neut. equiv., 102.

***cis*-Ethyl 2-Methyl-3-carbethoxycyclopentanone-2-acetate** (V, R = C_2H_5).—A mixture of 3.5 g. of the *cis*-acid, 30 ml. of ethanol and 3 ml. of concentrated sulfuric acid was refluxed for 24 hours. The ester was worked up in the usual way; b.p. 127° (1.5 mm.); yield 2.4 g. (70%) of a colorless liquid.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.93; H, 7.81. Found: C, 61.06; H, 7.88.

The semicarbazone, prepared as described before, was crystallized from dilute ethanol, m.p. 115°.

Anal. Calcd. for $C_{14}H_{23}N_3O_5$: C, 53.67; H, 7.35. Found: C, 54.22; H, 7.65.

Ethyl 1-Methyl-2-carbethoxycyclopentaneacetate (VI, VII, R = C_2H_5).—Following the procedure employed by Mukharji[1] on the cyclohexanone derivative, a solution of 6 g. of I (R = C_2H_5) in 34 ml. of ethanol and 30 g. of zinc amalgam was refluxed for six hours with 50 ml. of ethanol saturated with dry hydrogen chloride at 0°. The refluxing was continued for another six hours after a fresh addition of 25 ml. of hydrogen chloride saturated ethanol. After removal of a portion of the alcohol the product was worked up in the usual way and was fractionally distilled to yield two fractions; (1) b.p. 116–124° (2.5 mm.), 1.97 g.; (2) b.p. 128–140° (2.5 mm.), 3.4 g. The first fraction was redistilled to yield 1 g. (20%), b.p. 105–110° (2.5 mm.) of a colorless mobile liquid.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 63.99; H, 9.06.

Mixture of *cis*- and *trans*-1-Methyl-2-carboxycyclopentaneacetic Acid.—A mixture of 0.8 g. of the above diester, 10 ml. of concentrated hydrochloric acid and 10 ml. of water was refluxed for 20 hours. The acid solution, after filtration and concentration to a small volume, on cooling deposited 0.33 g. of white crystals, m.p. 105–135°.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.52. Found: C, 57.64; H, 7.52.

***cis*-1-Methyl-2-carboxycyclopentaneacetic Acid** (VI, R = H).—The above product after five crystallizations from dilute hydrochloric acid afforded the *cis*-acid, m.p. 164° (reported,[2] 165–166°, 169°). In another experiment the *cis*-acid, m.p. 165°, was prepared from the stereoisomeric mixture by treatment with acetic anhydride followed by hydrolysis of the anhydride, crude m.p. 90° (reported,[2] 93–94°).

***trans*-1-Methyl-2-carboxycyclopentaneacetic Acid** (VII, R = H).—The mother liquors from the above crystallization experiment, after the initial separation of some stereoisomeric mixture on concentration, yielded on further concentration a crystalline solid, which mostly melted below 95° clearing up at 107°. This product after two crystallizations from the same solvent furnished the pure *trans* acid, m.p. 105° (reported,[2] 101–102°).

Cyanohydrin of Ethyl 2-Methylcyclopentanone-2-acetate (X).—Following the procedure of Linstead and Millidge[9] with slight modifications, 7 ml. of liquid hydrogen cyanide was added all at once to 11.3 g. of ethyl 2-methylcyclopentanone-2-acetate (Chakravarty and Banerjee[3]) containing three drops of aqueous potassium cyanide solution cooled in an ice–salt mixture. After standing in a refrigerator for 16 hours, the mixture was acidified with concentrated sulfuric acid, the excess hydrogen cyanide was removed by passing air through it and the residue was worked up in the usual way and distilled; b.p. 123–126° (1 mm.); yield 11 g. (83%) of a colorless liquid.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.56; H, 8.06. Found: C, 63.08; H, 7.81.

Ethyl 2-Cyano-3-methylcyclopentene-3-acetate (XI).—To a well-cooled mixture of 30.45 g. of the above cyanohydrin and 35 ml. of pyridine was added with constant shaking 13 ml. of thionyl chloride at such a rate that the reaction temperature did not rise above 5°. After standing for 16 hours the reaction mixture was heated on the steam-bath for one hour. The dark reaction mixture, after repeated extraction with ether, was diluted with large volume of water, filtered from a slimy residue and re-extracted with ether–benzene mixture. After the usual washings the solvent was removed from the combined extract and the oily residue was refluxed for two hours with freshly precipitated copper under benzene in order to remove the sulfur which contaminated the product. The benzene was removed after filtration and residue distilled; b.p. 113–115° (1.5 mm.); yield 16 g. (58%) of an almost colorless oil.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77. Found: C, 68,19; H, 7.88.

Methyl 2-Carbomethoxy-3-methylcyclopentene-3-acetate (XII).—A mixture of 9 g. of the above unsaturated nitrile, 23 g. of potassium hydroxide dissolved in 10 ml. of water and 75 ml. of diethylene glycol was heated at 190–200°

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[9] R. P. Linstead and A. F. Millidge, *J. Chem. Soc.*, 478 (1936); *cf.* W. E. Bachmann and W. S. Struve, THIS JOURNAL, **63**, 1262 (1941).

under reflux for 20 hours. The cooled solution, after acidification, was extracted with ether (four times). The ether was removed and the acidic residue was esterified with diazomethane to yield 5.2 g. (52% on the basis of the unsaturated nitrile used) of XII as a colorless oil, b.p. 108° (2 mm.), $n^{36}\text{D}$ 1.4637.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.54. Found: C, 62.94; H, 7.52.

Methyl 1-Methyl-2-carbomethoxycyclopentaneacetate (XIII).—A solution of 4.6 g. of the unsaturated diester (XII) in 15 ml. of glacial acetic acid and 0.5 g. of prereduced Adams platinum catalyst were stirred until a little more than the theoretical amount of hydrogen was absorbed in less than 12 hours. The residue obtained by evaporation of the solvent from the filtered solution was distilled; b.p. 105° (2 mm.); $n^{36.5}\text{D}$ 1.4522; yield 3.82 g.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 62.02; H, 8.40.

1-Methyl-2-carboxycyclopentaneacetic Acid Anhydride (XIV).—A mixture of 3.3 g. of XIII, 15 ml. of acetic acid, 10 ml. of concentrated hydrochloric acid and 7 ml. of water was refluxed for 12 hours. After removal of the acetic acid and hydrochloric acid under reduced pressure the residue was treated with 30 ml. of acetic anhydride as described before to yield the anhydride as a gum, b.p. 130° (2 mm.), which later solidified, crude m.p. 90°; yield 2.1 g. (84%).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 63.70; H, 7.34.

***cis*-1-Methyl-2-carboxycyclopentaneacetic Acid (VI, R = H).**—The above anhydride was converted into the *cis*-acid as described before. One crystallization from water yielded the pure *cis*-acid, m.p. 164° alone and when mixed with the *cis*-acid obtained from I.

Conversion of *cis*-1-Methyl-2-carboxycyclopentaneacetic Acid to the *trans*-Acid.—The dimethyl ester prepared from 0.9 g. of the *cis*-acid by means of diazomethane was refluxed for 12 hours with a solution of potassium *t*-butoxide prepared from 0.8 g. of potassium and 25 ml. of *t*-butyl alcohol. To the brown solution was added 30 ml. of water and the mixture refluxed for four hours longer. The white residue, obtained by evaporation of the reaction mixture to dryness on a steam-bath, was dissolved in a small quantity of water, acidified and again evaporated to dryness. The residue was extracted seven times with dry acetone–ether mixture. The oily residue, obtained after removal of the solvent, was dissolved by dilute hydrochloric acid and allowed to stand in the cold. The first crop of crystals was found to be a mixture of stereoisomers. The second crop, obtained by concentrating the mother liquor, melted at 90–95° and weighed 0.2 g. After three crystallizations the product melted at 105.5° alone and when mixed with the *trans* acid obtained from I.

CALCUTTA 32, INDIA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Methylation of Some Amides in Acetone[1]

BY IRWIN J. PACHTER AND MILTON C. KLOETZEL

Amides were methylated in acetone solution by treatment with potassium hydroxide and a methylating agent. The method was applied to the methylation of an amide in the presence of an amine and also to the methylation of one amino group in the presence of another.

The usual method for the alkylation of amides, involving metallic sodium and an inert solvent,[2] is at best a rather inconvenient and somewhat dangerous procedure. Fones[3] has recently suggested the more convenient use of sodium hydride in place of sodium metal, but this improved method is still subject to certain limitations. For example, *p*-nitroacetanilide was unaffected by six hours of refluxing with sodium hydride in xylene and could not be alkylated.[3] In contrast, it was found in the present study that the methylation of *p*-nitroacetanilide can be accomplished conveniently and in good yield merely by refluxing the anilide in acetone solution with potassium hydroxide and methyl iodide for one minute. In similar fashion *p*'-nitrobenzanilide and acetanilide were methylated in good yield.

The method was also applied to the selective methylation of an amide in the presence of an amine. *p*-Benzamidodiphenylamine yielded *p*-(N-methylbenzamido)-diphenylamine in 90% yield when refluxed in acetone solution with methyl iodide and potassium hydroxide. That the product was not the isomeric *p*-benzamidodiphenylmethylamine was proved when the latter was prepared from *p*-nitrodiphenylamine by methylation, reduction and subsequent benzoylation, and found to be different from *p*-(N-methylbenzamido)-diphenylamine.

When large differences in proton availability exist, the method may also be applied to the selective methylation of one amino group in the presence of another. For example, an acetone solution of *p*-amino-*p*'-nitrodiphenylamine, upon treatment with potassium hydroxide and methyl iodide, yielded *p*-amino-*p*'-nitrodiphenylmethylamine in 83% yield. The structure of the product was proved when it was converted into an alkali-soluble benzenesulfonamide and when, upon reduction, it yielded bis-(*p*-aminophenyl)-methylamine, identical with the compound obtained upon methylation and reduction of bis-(*p*-nitrophenyl)-amine.

Experimental[4]

Methylations of amides were run as described here for the methylation of *p*-nitroacetanilide, with the exceptions that the reflux periods were varied as listed in Table I.

To 5.00 g. (0.028 mole) of *p*-nitroacetanilide dissolved in 100 cc. of warm acetone[5] was added 6 g. (0.1 mole) of powdered potassium hydroxide.[6] The hot mixture was refluxed gently while 6 g. (0.042 mole) of methyl iodide in 15 cc. of acetone was added. After one minute, the solution was

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(1) Abstracted from a portion of the dissertation submitted by Irwin J. Pachter to the Graduate School of the University of Southern California in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

(2) P. Hepp, *Ber.*, **10**, 327 (1877).

(3) W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

(4) Microanalyses are by Mr. Joseph Pirie. Melting points are uncorrected.

(5) In this experiment and in the methylation of *p*'-nitrobenzanilide, analytical grade acetone was used. In all other methylations mentioned in this paper, commercial acetone was employed. It is advantageous to use pure acetone when the amide is easily hydrolyzed.

(6) When half this amount of potassium hydroxide was used in the methylation of *p*'-nitrobenzanilide, a yield of 78% of N-methyl-*p*'-nitrobenzanilide was obtained together with 9% of unchanged starting material.