water wash). Aliquots of this solution assayed as follows: *Anal.* Calcd.: N, 8.66; P, 9.6. Found: N, 8.72; P, 9.52. The optical rotation of a 0.5% solution in 0.24 *N* hydrochloric acid, $\alpha^{20}\text{D}$ +8.55°.

Summary

The preparation of uridylic and cytidylic acids from an acid hydrolysate of yeast ribonucleic acid employing the anion exchanger Amberlite IRA-400 and elution with formic and hydrochloric acids is described. From 100 g. of nucleic acid, 4.9 g. of crystalline diammonium uridylate were obtained in a preparation involving formic acid elution and conversion of uridylic acid to the diammonium salt. In another preparation, employing a hydrochloric acid elution, 17.8 g. of a barium uridylate fraction were obtained which, by spectrophotometric assay, contained 52% (9.25 g.) uridylic acid. A method for conversion of barium uridylate to free uridylic acid employing a cation exchange technique is described. Cytidylic acid was readily crystallized from fractions eluted from the column in either dilute formic or hydrochloric acid. The yield was 7.5 g. and 6.9 g. from 100 g., respectively, of yeast ribonucleic acid.

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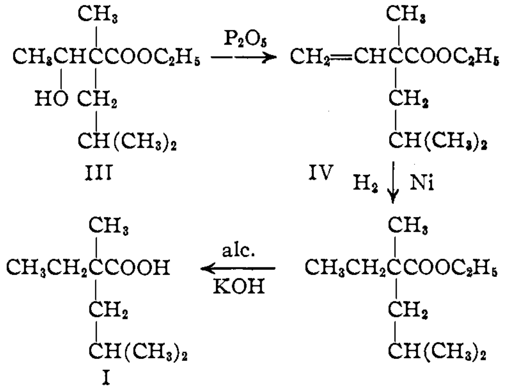
[Contribution from Havemeyer Laboratory, Columbia University]

The Synthesis and Resolution of Methylethylisobutylacetic Acid

By W. von E. Doering and Kenneth B. Wiberg

In connection with the resolution and reactions of (+)methylethylisobutylcarbinol,[1] the corresponding acid, methylethylisobutylacetic acid (I) has been synthesized and resolved.

Attempts to prepare I by carbonation of the Grignard reagent from methylethylisobutylcarbinyl chloride by the conventional method produced I in impractically low yield.[2,3] The absence of rearrangement in the dehydration of β-hydroxy-α,α-disubstituted butyric acids[4,5] encouraged the synthesis of I from methylisobutylacetoacetic ester (II). Catalytic hydrogenation of II,[6] slow with ordinary Raney nickel, but conveniently rapid with "W-5" Raney nickel,[7] produced the requisite β-hydroxyester (III) which was dehydrated with phosphorus pentoxide to methylisobutylvinylacetic ester (IV). Hydrogenation of IV followed by hydrolysis gave the desired acid I. The structure of IV was supported by ozonolysis to an aldehyde, oxidation and hydrolysis of which gave the known methylisobutylmalonic acid (V).[8] It is of interest that the oxidation of the acid derived from IV (VI) with alkaline potassium permanganate gave mainly methylisobutylacetic acid and a small amount of methylisobutyl ketone, but only a trace of V despite the inertness of the latter to permanganate.[9]



The resolution of I, effected by the fractional crystallization of the brucine salt, appears to be the first reported resolution of a trialkyl acetic acid in which the carboxylic acid group is attached to the asymmetric center.[10] The (+) acid obtained by this resolution had an infrared absorption curve which appeared to be identical with that of the *dl*-acid (see Fig. 1).[11] In addition, methylisobutylvinylacetic acid (VI) was partially resolved by means of the (+)α-phenylethylamine salt. Hydrogenation of (+)VI gave (+)I.

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[1] Doering and Zeiss, This Journal, **70**, 3966 (1948), **72**, 147 (1950), and unpublished results.

[2] This result parallels that of Schuerch and Huntress, *ibid.*, **70**, 2824 (1948).

[3] The recent modification of Lester and Proffitt [*ibid.*, **71**, 1877 (1949)] in which methylethyl-*n*-propylacetic acid is prepared by the carbonation of the Grignard reagent under pressure with shaking gives good yields.

[4] Shive, Crouch and Lochte, *ibid.*, **63**, 2979 (1941).

[5] Courtot, *Bull. soc. chim.*, [3] **35**, 118 (1906).

[6] *Cf.* Adkins, Connor and Cramer, This Journal, **52**, 5192 (1930); Covert and Adkins, *ibid.*, **54**, 4116 (1932).

[7] Adkins and Billica, *ibid.*, **70**, 695 (1948).

[8] Burrows and Bentley, *J. Chem. Soc.*, **67**, 510 (1895).

[9] Courtot, ref. 5, reports that dimethylvinylacetic acid is oxidized by alkaline permanganate to dimethylmalonic acid in 72% yield. The anomalous oxidation of IV acid is being investigated.

[10] Conant and Carlson, This Journal, **54**, 4048 (1932), reported the resolution of methyl-*n*-butylphenylacetic acid. In this connection it might be noted that camphene-1-carboxylic acid [Houben and Pfankuch, *Ber.*, **59**, 956 (1926)]; umbellularic acid [Rydon, *J. Chem. Soc.*, 829 (1936)]; and camphoric acid [Debierne, *Compt. rend.*, **128**, 1112 (1899)] have also been resolved. However, each of these contains two asymmetric centers.

[11] The infrared absorption curves were kindly obtained by Mr. A. P. Wolf of these laboratories using a Perkin-Elmer Model 12-B infrared spectrometer modified for automatic ratio recording. [Abraham Savitzky, Doctoral Dissertation, Columbia University, 1949.]

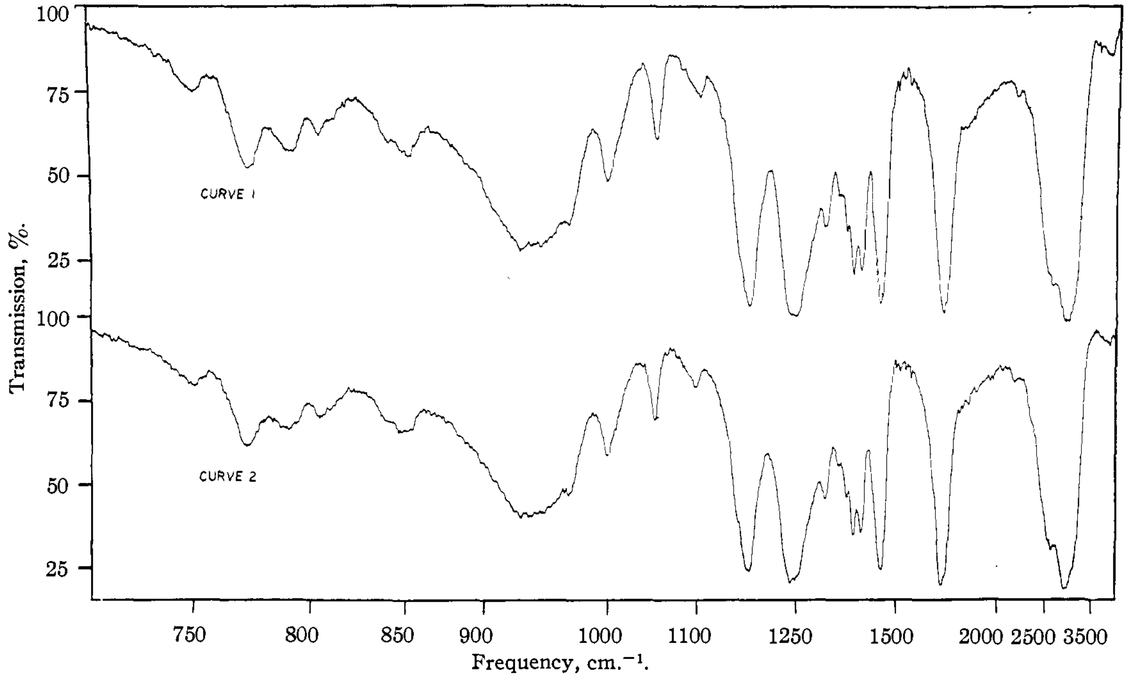

Fig. 1.—Infrared spectra: curve 1, (+)methylethylisobutylacetic acid; curve 2, *dl*-methylethylisobutylacetic acid.

Experimental[12]

Ethyl α-Isobutylacetoacetate.[13]—Three liters of dry *t*-butyl alcohol which had been refluxed two hours with 10 g. of sodium was distilled directly into a 5-l. three-necked flask fitted with a stirrer, condenser and addition funnel. To a slurry of potassium *t*-butoxide obtained by adding 195 g. (5.0 a.) of potassium to the alcohol over a period of one to two hours there was added 650 g. (5.0 m.) of freshly distilled ethyl acetoacetate with stirring. After fifteen minutes of additional stirring, 1 kg. (5.4 m.) of isobutyl iodide was added, the resultant solution being stirred and refluxed for fifteen hours or until neutral. The precipitated potassium iodide was filtered from the cooled solution and washed with *t*-butyl alcohol. The filtrate and washings were distilled through a Vigreux column until the vapor temperature reached 90°. The residue was washed once with an equal volume of water, dried over anhydrous magnesium sulfate and distilled to give 644 g. (69%) of ethyl α-isobutylacetoacetate, b. p. 108–112° at 21 mm.

Ethyl α-Methyl-α-isobutylacetoacetate (II).—For the alkylation the procedure above was employed, using 2.5 l. of *t*-butyl alcohol, 125 g. (3.2 a.) of potassium, 644 g. (3.45 m.) of isobutylacetoacetic ester and 500 g. (3.5 m.) of methyl iodide. The alkylation was very rapid, the solution becoming neutral in fifteen minutes. The material was distilled slowly through a 2-foot Vigreux column, 460 g. (72%) of ethyl α-methyl-α-isobutylacetoacetate, b. p. 115–117° at 21 mm., $n^{25}\text{D}$ 1.4309, being collected.[14]

Ethyl α-Methyl-α-isobutyl-β-hydroxybutyrate (III).—The hydrogenation of 600 g. (3.0 m.) of II was carried out at 120° and 100 atm. pressure using 10 g. of "W-5" Raney nickel.[7] It was sometimes necessary to add a further quantity of catalyst in order to obtain quantitative absorption of hydrogen. The material thus obtained was filtered and distilled, 576 g. (95%) of III, b. p. 126–129° at 23 mm., $n^{25}\text{D}$ 1.4402, d^{25} 0.951, being collected; *M*D calcd., 56.18; found, 56.00.

Ethyl Methylisobutylvinylacetate (IV).—To a suspension of 150 g. (1.05 m.) of phosphorus pentoxide in 300 ml. of dry benzene there was added slowly with stirring and cooling 300 g. (1.5 m.) of III. After the initial reaction had subsided, the benzene was distilled at atmospheric pressure, leaving a residue which was distilled rapidly under reduced pressure. This material was redistilled, 202 g. (74%) of IV, b. p. 85–88° at 17 mm., $n^{25}\text{D}$ 1.4321, d^{25} 0.880, being collected; *M*D calcd., 54.18; found, 54.25.

Ethyl Methylethylisobutylacetate.—IV (338 g.) was hydrogenated at room temperature and 3–4 atm. pressure using 5 g. of "W-5" Raney nickel.[7] The hydrogenation was very rapid and somewhat exothermic. The ester was filtered and distilled, 316 g. (93%) of ethyl methylethylisobutylacetate, b. p. 84–87° at 15 mm., $n^{25}\text{D}$ 1.4200, d^{25} 0.865, being obtained; *M*D calcd., 54.65; found, 54.41.

Methylethylisobutylacetic Acid (I).—A solution of 316 g. of I ethyl ester and 168 g. of potassium hydroxide in 400 ml. of methanol was refluxed for twenty-four hours. The reaction mixture was concentrated to half-volume, diluted with 500 ml. of water, and boiled until the distillate became clear. Acidification of the cooled solution with concentrated hydrochloric acid produced an oil which was extracted with ether, reëxtracted with several portions of 10% potassium carbonate solution, and regenerated by acidification. The crude acid was treated with bromine until saturated, washed with sodium bisulfite solution, and distilled, the fraction, b. p. 121–127° at 12 mm., being collected (242 g., 87%). Redistillation gave 214 g. (81% of the theoretical yield) of pure I, b. p. 124–125° at 12 mm., $n^{25}\text{D}$ 1.4328.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46; neut. equiv., 158.2. Found: C, 68.09; H, 11.48; neut. equiv., 160.2.

Thorough ether extraction of a potassium carbonate solution of the acid gave purer material; neut. equiv., 157.2; b. p. 124° at 11 mm. Purification could also be effected by crystallization of the β-phenylethylamine

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(12) Melting points and boiling points are corrected. Microanalyses were performed by W. Manser.

(13) While this is essentially the procedure of Renfrow and Renfrow, THIS JOURNAL, **68**, 1801 (1946), some modification was necessary.

(14) Material distilled through a 2-foot adiabatic column packed with $^3/_{32}$" glass helices and boiling constantly at 118° at 25 mm. did not give significantly different results in the later experiments than did this material.

salt from ethyl acetate; m. p. 97–97.5°. I obtained in this way had $n^{25}\text{D}$ 1.4323.

Anal. Calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.00; H, 10.45; N, 5.14.

Methylisobutylvinylacetic Acid (VI).—A solution of 150 g. of IV and 90 g. of potassium hydroxide in 200 ml. of methanol was refluxed for twenty-four hours. The reaction mixture was diluted with 400 ml. of water and boiled until the distillate became clear. Acidification of the cooled solution with concentrated hydrochloric acid produced an oil which was dissolved in ether, extracted with 10% potassium carbonate solution and regenerated by acidification. The crude acid was distilled, and yielded 109 g. (86%) of VI, b. p. 123–125° at 12 mm., $n^{25}\text{D}$ 1.4456.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.18; H, 10.32; neut. equiv., 156.2. Found: C, 69.15; H, 10.28; neut. equiv., 155.7.

This acid was shown to be homogeneous by conversion to the β-phenylethylamine salt which was fractionally crystallized from ethyl acetate. The first fraction (m. p. 83–84°) and the last fraction (m. p. 82.5–84°) gave no depression on admixture.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.40; H, 9.75; N, 5.16.

Hydrogenation of Methylisobutylvinylacetic Acid (VI).—A solution of 10.0 g. of VI in 20 ml. of ethanol was hydrogenated at 3–4 atm. pressure using 1 g. of "W-5" Raney nickel in four hours. The solution was filtered and distilled, 9.7 g. (96%) of methylethylisobutylacetic acid (I), b. p. 123–125° at 12 mm., $n^{25}\text{D}$ 1.4328, being collected. The β-phenylethylamine salt had a m. p. of 96.5–97.5°.

Ozonolysis of Ethyl Methylisobutylvinylacetate (IV).—A solution of 18.4 g. (0.1 m.) of IV in 180 ml. of chloroform was treated at 0° with 4% ozone at the rate of twenty liters per hour for three and one-half hours. The chloroform was evaporated at 20° under vacuum leaving a viscous oil which was dissolved in 300 ml. of dry ether. The solution was cooled in an ice-bath, and treated with 120 g. of zinc dust, followed by 60 ml. of glacial acetic acid added in small portions with good stirring. The ethereal solution was decanted, shaken for one hour with a slurry of 100 g. of precipitated chalk in 200 ml. of water and separated. The aqueous phase was extracted repeatedly with ether. The combined ethereal extracts were dried over anhydrous sodium sulfate and concentrated. Distillation of the residue gave one fraction (5.3 g.), b. p. 77–83° at 13 mm., (unchanged IV) and a second fraction (7.6 g.), b. p. 87–91° at 13 mm., presumably **ethyl methylisobutylformylacetate** (VII), which reduced Tollens reagent and gave a yellow 2,4-dinitrophenylhydrazone crystallizing from ethanol–water, m. p. 132°.

Anal. Calcd. for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05; N, 15.30. Found: C, 52.25; H, 6.11; N, 15.27.

VII was converted to the known methylisobutylmalonic acid[8] in almost quantitative yield by refluxing with an excess of silver oxide (Mallinckrodt, U. S. P.) in a water acetone (1:1) suspension for two hours, cooling, almost saturating with potassium carbonate, filtering, and separating the two layers which result. The upper (acetone) layer was diluted with an equal volume of water, boiled, made strongly basic with potassium hydroxide and refluxed for twelve hours. The cooled solution was strongly acidified and extracted several times with ether. On evaporating the ethereal solution and drying the residue in a vacuum desiccator over potassium hydroxide, crystals of methylisobutylmalonic acid (V) formed. Crystallization from benzene afforded pure V, m. p. 121–122° (reported[8] m. p. 122°). It gave no m. p. depression when mixed with a sample of V prepared from the corresponding ester.[8]

Oxidation of Methylisobutylvinylacetic Acid (VI) with Potassium Permanganate.—To a cooled (10°) solution of 15.6 g. (0.1 m.) of VI in 100 ml. of 10% potassium hydroxide solution, 1 l. of 1 *N* potassium permanganate solution was added dropwise at such a rate that the temperature did not exceed 20°. The solution was stirred at 20° until decolorized, filtered, and distilled giving 100 ml. of distillate which was extracted several times with ether. Evaporation of the ether extract gave a residue from which a 2,4-dinitrophenylhydrazone (0.8 g.), m. p. 93.5–94.5° after one crystallization from ethanol–water, was obtained. A mixed m. p. with an authentic sample of the **2,4-dinitrophenylhydrazone of methyl isobutyl ketone**, m. p. 93.5–94.5°, showed no depression.

The residual solution from the distillation was concentrated to 100 ml., cooled, acidified with concentrated hydrochloric acid and extracted several times with ether. Concentration of the dried ether extract gave material which was distilled almost to dryness. The yellow distillate was dissolved in 10% potassium carbonate solution, extracted with ether and acidified to give a colorless oil which was dissolved in benzene and dried over anhydrous sodium sulfate. Distillation yielded 4.0 g. (30%) of methylisobutylacetic acid, b. p. 204–208° (reported[8] b. p. 204–205°). Neut. equiv.: calcd. 130.2; found 132.1. The acid was converted to **methylisobutylacetamide**, m. p. 85.5–87° after crystallization from ethanol–water (reported[8] m. p. 90°). A mixed m. p. with authentic methylisobutylacetamide[8] showed no depression.

Resolution of Methylethylisobutylacetic Acid (I).—The brucine salt prepared from 158 g. of I was fractionally crystallized from ethyl acetate. The crystallization was inconvenient due to the viscous nature of the concentrated solutions, but other solvents appeared to be less satisfactory. One crystallization using a seed of highly resolved material gave 190 g. of salt which melted to a cloudy liquid at 77–78° and became clear at 102°, and which gave I, $[\alpha]^{29}\text{D}$ + 8.7° (c = 8.6, 95% ethanol). After thirteen recrystallizations, head fractions of the brucine salt (70 g.), m. p. 105–108° with clearing at 115° was obtained which gave I with an average rotation $[\alpha]\text{D}$ +15.3° (c = 9, 95% ethanol). Further fractional crystallization of 50 g. of this material from the same solvent gave 23 g. of the brucine salt, m. p. 114–115° with clearing at 117°, from which I, $[\alpha]^{24}\text{D}$ +21.55° (neat), $[\alpha]^{24}\text{D}$ +21.42° (c = 10.3, 95% ethanol), was obtained. This rotation could not be increased by further crystallization. (+) I has been shown to have the same infrared absorption curve as *dl*-I (Fig. 1) and has $n^{25}\text{D}$ 1.4322, and d^{25} 0.906; $M\text{D}$ calcd. 45.30; found, 45.29.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46; neut. equiv., 158.2. Found: C, 68.25; H, 11.46; neut. equiv., 158.3.

Anal. (brucine salt) Calcd. for $C_{32}H_{44}O_6N_2$: C, 69.54; H, 8.02; N, 5.07. Found: C, 68.95; H, 8.09; N, 5.20.

From the mother liquors and tail fractions there was obtained 36 g. of I, $[\alpha]^{25}\text{D}$ −5.30° (neat), and 55 g. of I, $[\alpha]^{23}\text{D}$ −2.89° (neat).

Resolution of Methylisobutylvinylacetic Acid (VI).—The α-phenylethylamine ($[\alpha]^{25}\text{D}$ +39.3°, neat) salt was prepared from 31 g. of VI, and fractionally crystallized from ethyl acetate. After five recrystallizations there was obtained 16 g. of salt, m. p. 93–96°, which on acidification gave 8 g. of VI, b. p. 123–125° at 12 mm., $[\alpha]^{25}\text{D}$ +13.79° (neat, d^{25} 0.927), $[\alpha]^{26}\text{D}$ +8.36° (c = 10.17, 95% ethanol); $M\text{D}$ calcd., 44.83; found, 44.94.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.49; H, 9.75; N, 5.21.

A solution of 7 g. of (+)VI was dissolved in 20 ml. of ethanol and hydrogenated at room temperature and 3–4 atm. pressure using 1 g. of "W-5" Raney nickel.[7] On distillation, 6.5 g. of methylethylisobutylacetic acid (I) was obtained, b. p. 123–125° (12 mm.), $[\alpha]^{25}\text{D}$ +6.02° (neat), $n^{25}\text{D}$ 1.4326. If optically pure I is assumed to have a rotation of 21.6°, the rotation of VI is calculated to be 49.4°.

Summary

The synthesis and resolution of the trialkyl substituted acetic acid, methylethylisobutylacetic acid, is reported.

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