966. *A Modified Proline Synthesis.*

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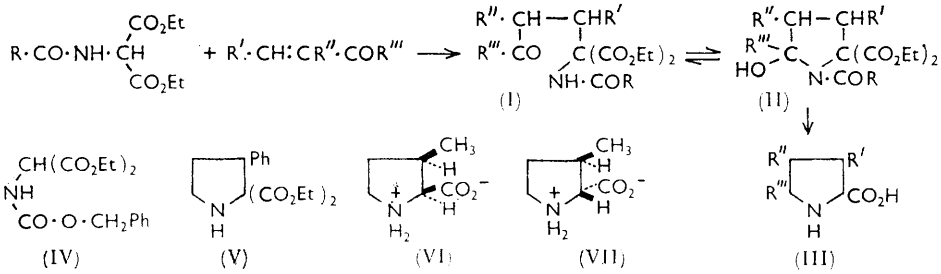
The Michael addition of diethyl *N*-acylaminomalonates and particularly diethyl *N*-benzyloxycarbonylaminomalonate to αβ-unsaturated aldehydes yields 5-hydroxy-*N*-acylpyrrolidines which can be converted easily by reduction and hydrolysis into mixtures of the diastereoisomeric 3- or 4-substituted DL-prolines. The mixture of 3-methylprolines obtained in this manner was separated into the *erythro*- and *threo*-DL-isomers.

The Michael addition of diethyl *N*-acylaminomalonates to αβ-unsaturated aldehydes,[1] ketones,[2] esters,[3,4] amides, or nitriles [4] is now well established as the primary step in syntheses of a variety of α-amino-acids. The use of αβ-unsaturated carbonyl compounds in the reaction is particularly suitable for the preparation of proline analogues,[1,4,5] the biochemical importance of which becomes increasingly evident as they continue to be isolated from natural products.[6-10] The addition of the amino-group of aminomalonic acid to the carbon–carbon double bond of acrolein, with a subsequent aldol condensation, leads to the formation of isomers of 3-hydroxyproline.[11]

We have used the Michael addition of diethyl *N*-acylaminomalonates to αβ-unsaturated aldehydes on several occasions, and like Dalby, Kenner, and Sheppard,[5] have found that the intermediate products (I) tend to exist largely in the cyclic form (II). For example, the crystalline product (II; R = Me, R′ = Ph, R″ = R‴ = H) from cinnamaldehyde and diethyl acetamidomalonate, contained no absorption maxima in the infrared spectrum corresponding either to an aldehyde group or to an amide (II band, present for example in diethyl acetamidomalonate at 1540 cm.$^{-1}$). The nuclear magnetic resonance (n.m.r.) spectrum confirmed the cyclic nature of the product. The hydroxyl proton appeared as a singlet at τ 8·02 (1 proton) and the adjacent C-5 proton appeared (in $CDCl_3$) as a doublet



(IV) (V) (VI) (VII) (III)

at τ 4·19 (J = 4·2 c./sec.), coupled to one of the C-4 protons, the second having an unfavourable dihedral angle, as revealed by a Dreiding model. The signal at τ 8·02 was absent in the spectrum of the corresponding phenylurethane and the doublet corresponding to the C-5 proton was shifted downfield to τ 3·16 (J = 4·2 c./sec.). On the other hand, the

[1] Moe and Warner, (*a*) *J. Amer. Chem. Soc.*, 1948, **70**, 2763; (*b*) 1949, **71**, 2586; (*c*) U.S.P., 2,523,743—6; Sanno, *J. Pharm. Soc. Japan*, 1958, **78**, 1113.
[2] Sanno, *J. Pharm. Soc. Japan*, 1958, **78**, 1113; Gershon and Scala, *J. Org. Chem.*, 1961, **26**, 2347.
[3] Cocolas and Hartung, *J. Amer. Chem. Soc.*, 1957, **79**, 5203.
[4] Shimo and Wakamatsu, *J. Org. Chem.*, 1961, **26**, 3788.
[5] Dalby, Kenner, and Sheppard, *J.*, 1962, 4387.
[6] Hulme and Arthington, *Nature*, 1952, **170**, 659; 1954, **173**, 588.
[7] Kenner and Sheppard, *Nature*, 1958, **181**, 48; Burroughs, Dalby, Kenner, and Sheppard, *ibid.*, 1961, **189**, 394.
[8] Biemann, Deffner, and Steward, *Nature*, 1961, **191**, 380.
[9] Gray and Fowden, *Nature*, 1962, **193**, 1285.
[10] Irreverre, Morita, Ishii, and Witkop, *Biochem. Biophys. Res. Comm.*, 1962, **9**, 69; Irreverre, Morita, Robertson, and Witkop, *J. Amer. Chem. Soc.*, 1963, **85**, 2824.
[11] Morita, Irreverre, Sakiyama, and Witkop, *J. Amer. Chem. Soc.*, 1963, **85**, 2832.

cinnamaldehyde adduct readily formed a semicarbazone and analogues of (II) have been reported to form 2,4-dinitrophenylhydrazones,[1] suggesting that a certain amount of the keto-amide (I) is also present. A similar equilibrium mixture existed in the adduct obtained from cinnamaldehyde and diethyl formamidomalonate and also in that from *m*-nitrocinnamaldehyde and diethyl acetamidomalonate.

The conversion of the adducts (II) into prolines (III) involves reduction, hydrolysis, and decarboxylation.[1,2,12] In order to facilitate the conversion, we have investigated the use of diethyl benzyloxycarbonylaminomalonate[13] (IV), which permits the removal of the *N*-acyl protecting group under milder conditions. With cinnamaldehyde at room temperature, compound (IV) gave an oil, formulated as (II; R = OCH_2Ph, R′ = Ph, R″ = R‴ = H) on the grounds of infrared spectrum (absence of amide II band). Hydrogenolysis gave the corresponding pyrrolidine (V), which formed a crystalline hydrochloride and which, by acid hydrolysis and decarboxylation, gave 3-phenylproline, characterised as the N-toluene-*p*-sulphonyl derivative. 2,2-Diethoxycarbonylpyrrolidine[14] and the 3- and 4-methyl derivatives were obtained similarly from diethyl benzyloxycarbonylaminomalonate with acrolein, crotonaldehyde, and α-methylacrolein, respectively, and each was characterised as the corresponding picrolonate. The yields of the methylpyrrolidines, obtained using carefully dried ethanol as solvent, exceeded 80%. Hydrolysis of the diesters with 6N-hydrochloric acid gave 3-methylproline (61%) and 4-methylproline (66%) both of which gave single yellow spots[15] on paper chromatograms after development with ninhydrin and were characterised as their respective toluene-*p*-sulphonates. This relatively simple procedure for the synthesis of 3- and 4-substituted DL-prolines, and resulting in reasonable yields of the products, represents an improvement on earlier reported syntheses of 3-methyl-[16] and 4-methyl-proline.[5,16,17]

In the conversion of monosubstituted pyrrolidine-2,2-dicarboxylic esters into the corresponding prolines, the product is a mixture of diastereoisomers. The n.m.r. spectrum of a solution of the 3-methylproline obtained in this manner in deuterium oxide showed the presence of two doublets at τ 9·0 and 9·24 corresponding to the nuclear methyl groups on each of the diastereoisomers (VI) and (VII). The doublets were of equal intensity suggesting an approximate 1 : 1 isomeric ratio. Repeated crystallisation of the mixture was found to concentrate one isomer and after six or seven crystallisations it was obtained in a pure state as indicated by the disappearance of the higher-field methyl doublet in the n.m.r. spectrum of the product. The toluene-*p*-sulphonyl derivative of this isomer gave colourless laths, m. p. 114·5—115·5 (from ether). However, the derivative prepared from the mixed isomers, when crystallised four times from ethanol, gave colourless rhombs, m. p. 183—185°, and the two derivatives possessed quite different infrared and n.m.r. spectra. Hydrolysis of the latter derivative gave the second diastereoisomer of 3-methylproline, which showed the higher-field methyl doublet in its n.m.r. spectrum.

The assignment of configuration to the two isomers is not possible at the present time. The n.m.r. evidence initially suggests the *erythro*-configuration (VI) for the isomer obtained by repeated crystallisation of the mixture, because the methyl group of (VI) would be expected to be more deshielded by the α-carboxyl group than the one in the *threo*-structure (VII). However, the relative positions of the methyl doublets is reversed in the spectra of the toluene-*p*-sulphonyl derivatives of the two isomers. Also, the second isomer, obtained by hydrolysis of the toluene-*p*-sulphonate, m. p. 183—185°, shows a larger coupling constant (τ 5·91; J = 7·2 c./sec.) for the C-2 proton than that of the first isomer, the C-2 proton doublet of which is well defined in the spectrum of its toluene-*p*-sulphonate at τ 6·05, J = 4·6 c./sec. By analogy with the spectral properties of the diastereoisomeric forms of

[12] Vogel and Davis, *J. Amer. Chem. Soc.*, 1952, **74**, 109.
[13] Frankel, Harnik, and Levin, *J. Amer. Chem. Soc.*, 1952, **74**, 3873.
[14] Heyningen, *J. Amer. Chem. Soc.*, 1954, **76**, 3043.
[15] Johnson and McCaldin, *J.*, 1958, 817.
[16] Takahashi and Kariyone, *J. Pharm. Soc. Japan*, 1959, **79**, 711.
[17] Dakin, *J. Biol. Chem.*, 1946, **164**, 615.

3-hydroxyproline,[10] this evidence might favour the *erythro*-configuration for the second isomer. This problem is still under consideration.

Examination of the crystallised, mixed 3-methylprolines by the automatic amino-acid analyser [18] also revealed the presence of the two isomers in the approximate ratio 45 : 55 but with the 3-phenylprolines the ratio was 72 : 28. We are grateful to Dr. H. Irreverre for these determinations. The 3-phenylproline was repeatedly crystallised and the change in composition followed by infrared spectroscopy. No further change in the spectrum was observed after the product had been crystallised twice, but the configuration of the isomer so obtained has not yet been determined with certainty. The separation and identification of the *erythro*- and *threo*-forms of 4-methylproline through the copper salts has been reported by Kenner and his co-workers.[5]

Dr. E. Katz (Department of Microbiology, Georgetown University, Washington, D.C). has observed that 3-methylproline, prepared by the present method, is a potent inhibitor of actinomycin production by *Streptomyces antibioticus*. Inhibition was total at 0·5—1·0 μg./ml. and 50% at 0·1 μg./ml. 4-Methylproline was less inhibitory (50% at 7·5 μg./ml.) and was incorporated into the peptides of actinomycin in place of proline. We are grateful to Dr. Katz for permission to mention these results.

Experimental

Infrared spectra were measured with a Unicam S.P. 100 instrument and n.m.r. spectra with an AEI RS2 instrument operating at 60 Mc/sec. Spectra were determined either in deutero-chloroform using tetramethylsilane as internal reference or in deuterium oxide using dioxan as internal reference. Light petroleum refers, except where otherwise stated, to the fraction b. p. 60—80°. The solvent system used for the determination of R_F values was t-butyl alcohol–acetic acid–water (2 : 1 : 1).

Diethyl 1-*Acetyl*-5-*hydroxy*-3-*phenylpyrrolidine*-2,2-*dicarboxylate*.—Sodium (0·12 g., 0·005 mole) was dissolved in a stirred solution of diethyl acetamidomalonate (10·8 g., 0·05 mole) in ethanol (55 ml.), and the solution was stirred and cooled in ice whilst cinnamaldehyde (7·2 g. 0·055 mole) was added dropwise. After 2 hr. at room temperature acetic acid (1·0 ml.) was added and the ethanol removed. The residue was dissolved in benzene (35 ml.) and filtered. Addition of light petroleum (b. p. 40—60°) precipitated a gum, which crystallised after trituration. The *product* (14·8 g.) crystallised from benzene–ether as needles, m. p. 93—94° (Found: C, 61·8; H, 6·5; N, 3·7. $C_{18}H_{23}NO_6$ requires C, 61·9; H, 6·9; N, 4·0%), $\nu_{max.}$ (Nujol) 3300 (OH), 1740 (ester C:O), and 1620 (amide C:O) cm.$^{-1}$.

The *semicarbazone* of the acyclic tautomer formed minute rhombs, m. p. 92—93° (from benzene) (Found: C, 56·9; H, 6·2; N, 13·7. $C_{19}H_{26}N_4O_6$ requires C, 56·1; H, 6·45; N, 13·8%).

The corresponding *phenylurethane* formed prisms, m. p. 130—132° (from ethyl acetate–light petroleum) (Found: C, 64·1; H, 5·9; N, 5·6. $C_{25}H_{28}N_2O_7$ requires C, 64·1; H, 6·0; N, 6·0%), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$ (urethane C:O).

Diethyl 1-*Formyl*-5-*hydroxy*-3-*phenylpyrrolidine*-2,2-*dicarboxylate*.—Sodium (0·1 g., 0·004 mole) was dissolved in a stirred solution of diethyl formamidomalonate (7·6 g., 0·037 mole) in ethanol (35 ml.), which was cooled in ice whilst cinnamaldehyde (5·5 g., 0·04 mole) was added dropwise. After 2 hr. at 25—30°, acetic acid (1·0 ml.) was added and the *product* was worked up as before to yield prisms (10·1 g.), m. p. 115—116° (from benzene–ether) (Found: C, 60·8; H, 6·2; N, 4·2. $C_{17}H_{21}NO_6$ requires C, 60·9; H, 6·3; N, 4·2%), $\nu_{max.}$ 1664 (amide C:O), 1736 (ester C:O), and 3400 cm.$^{-1}$ (OH).

Diethyl 1-*Formyl*-5-*hydroxy*-3-m-*nitrophenylpyrrolidine*-2,2-*dicarboxylate*.—Sodium (0·1 g.) was dissolved in a stirred solution of diethyl formamidomalonate (4·06 g.) in ethanol (35 ml.), which was kept at 40° whilst *m*-nitrocinnamaldehyde (3·6 g.) was added. After 2 hr. at 40°, acetic acid (1·0 ml.) was added, and the product was worked up as before, affording needles (5·20 g.), m. p. 111—112° (from ether) (Found: C, 53·6; H, 5·4; N, 7·0. $C_{17}H_{20}N_2O_8$ requires C, 53·7; H, 5·3; N, 7·4%), $\nu_{max.}$ 1358 and 1542 (C–NO_2), 1667 (amide C:O), 1738 (ester C:O), and 3350 cm.$^{-1}$ (OH).

Diethyl Benzyloxycarbonylaminomalonate.[12]—Sodium hydrogen carbonate (50 g.), water (250

[18] Spackman, Stein, and Moore, *Analyt. Chem.*, 1958, **30**, 1190.

ml.), ethyl acetate (250 ml.), and benzyl chloroformate (50 g.) were stirred briskly, whilst diethyl aminomalonate hydrochloride (43·8 g.) was added in portions over 10 min., with ice-cooling. After stirring for 1 hr., the layers were separated and the aqueous phase was washed with ethyl acetate (100 ml.). The combined ethyl acetate extracts were washed with N-hydrochloric acid (250 ml.) and water (200 ml.), and dried. The solvent was removed and the residual oil distilled at 0·45 mm. The fraction b. p. 187—190° was collected (5·37 g.) and crystallised on cooling, m. p. 32—33° (lit.,[12] 32—33°).

Diethyl 3-*Phenylpyrrolidine*-2,2-*dicarboxylate Hydrochloride*.—Diethyl benzyloxycarbonylaminomalonate (51·5 g., 0·17 mole) was dissolved in a solution of sodium (1·0 g., 0·04 mole) in ethanol (200 ml.), cinnamaldehyde (24·0 g., 0·18 mole) was added, and the mixture stirred at room temperature for 2 hr. Acetic acid (10 ml.) was added, the ethanol was removed, and the residue dissolved in ethyl acetate (200 ml.), washed with aqueous sodium hydrogen carbonate (200 ml.) and water (200 ml.), and dried. Removal of the solvent gave a syrup (78 g.) which had no amide II band in the infrared spectrum, and which did not crystallise. The syrup was dissolved in ethanol (300 ml.), 5% palladium–charcoal (5 g.) was added and the mixture hydrogenated at atmospheric pressure until the absorption of hydrogen ceased. The solvent was removed from the filtrate, and the residual oil was dissolved in dry ether (250 ml.). Hydrogen chloride was passed through the solution, when a crystalline precipitate of the product (33·6 g.) separated and formed needles, m. p. 155° (from ethanol–ether) (Found: C, 58·2; H, 6·6; Cl, 11·0; N, 4·5. $C_{16}H_{22}ClNO_4$ requires C, 58·6; H, 6·8; Cl, 10·8; N, 4·3%).

3-*Phenylproline*.—Diethyl 3-phenylpyrrolidine-2,2-dicarboxylate hydrochloride (0·53 g.) in 6N-hydrochloric acid (10 ml.) was heated under reflux for 3 hr., then evaporated to dryness under reduced pressure. A solution of the residue in water was adjusted to pH 7 by agitation with Amberlite IR-45, filtered, and the water removed under reduced pressure, leaving a crystalline *residue* (0·22 g.) which formed needles, m. p. 275—277° (decomp.) (from water) (Found: C, 69·0; H, 6·9; N, 7·2. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·9; N, 7·3%), $\nu_{max.}$ (KBr disc) 1600 (CO_2H) and 3453 cm.$^{-1}$ (NH), R_F, 0·88.

The N-*toluene*-p-*sulphonyl derivative* of the amino-acid formed colourless rhombs, m. p. 185—188° (from ethanol) (Found: C, 63·0; H, 5·6; N, 4·1; S, 9·2. $C_{18}H_{19}NO_4S$ requires: C, 62·6; H, 5·5; N, 4·1; S, 9·3%).

Diethyl Pyrrolidine-2,2-*dicarboxylate*.—Diethyl benzyloxycarbonylaminomalonate (5·15 g., 0·017 mole) was dissolved in absolute ethanol (25 ml.), and a solution of sodium (0·075 g., 0·0036 mole) in ethanol (5·0 ml.) was added. Acrolein (1·25 ml., 0·019 mole; twice distilled over calcium oxide), in ethanol (10 ml.), was added dropwise over 5 min., with magnetic stirring, and exclusion of moisture. The mixture rapidly became warm, then slowly cooled, and after 30 min. glacial acetic acid (0·143 ml.) in ethanol (0·5 ml.) was added, and the solvent removed. The residue was hydrogenated in ethanol (50 ml.) at atmospheric pressure over 10% palladium–charcoal (0·5 g.) until hydrogen uptake ceased. The filtered solution was evaporated, and the residue was dissolved in ether (40 ml.), and extracted with N-hydrochloric acid (30 ml.). The acid extract was immediately treated with an excess of sodium hydrogen carbonate, and extracted with ether (2 × 25 ml.). The ether extracts were washed and dried, and the solvent was removed. The residual oil was distilled and a colourless liquid, b. p. 76—80°/0·2 mm., n_D^{22} 1·4490 (1·6 g., 45%), was collected, $\nu_{max.}$ 1735 (ester C:O) and 3360 cm.$^{-1}$ (NH). The *picrolonate* formed yellow plates m. p. 168—169° (from ethanol) (Found: C, 49·9; H, 5·3; N, 14·4. $C_{20}H_{25}N_5O_9$ requires C, 50·1; H, 5·3; N, 14·6%).

Diethyl 3-*Methylpyrrolidine*-2,2-*dicarboxylate*.—The procedure of the preceding experiment was followed using crotonaldehyde (1·7 ml., 0·021 mole), freshly distilled over calcium oxide. The product was distilled as a colourless liquid (3·04 g., 80%), b. p. 77—80°/0·17 mm., n_D^{24} 1·4475, $\nu_{max.}$ (film) 1734 and 3335 cm.$^{-1}$. The *picrolonate* formed yellow needles, m. p. 107—108° (from ethanol) (Found: C, 51·0; H, 5·3; N, 13·7. $C_{21}H_{27}N_5O_9$ requires C, 51·1; H, 5·5; N, 14·2%).

Diethyl 4-*Methylpyrrolidine*-2,2-*dicarboxylate*.—Prepared as above from methacrolein (2·0 ml.) freshly distilled over calcium oxide, the product was distilled as a colourless liquid (3·11 g., 82%), b. p. 78—81°/0·15 mm., n_D^{24} 1·4434, $\nu_{max.}$ (film) 1736 and 3360 cm.$^{-1}$. The *picrolonate* formed plates, m. p. 161° (from ethanol) (Found: C, 51·6; H, 5·8; N, 14·1. $C_{21}H_{27}N_5O_9$ requires C, 51·1; H, 5·5; N, 14·2%).

3-*Methylproline*.—Diethyl 3-methylpyrrolidine-2,2-dicarboxylate (3·0 g.) was heated under reflux with 6N-hydrochloric acid (60 ml.) for 3 hr. The solution was evaporated to a colourless

gum, which slowly crystallised on standing. This material was dissolved in water (65 ml.), and stirred with Amberlite IR-45 resin (17 g.) until the solution was neutral (*ca.* 18 hr.). Filtration, followed by evaporation of the solution under reduced pressure, yielded a solid (1·84 g.) which crystallised from ethanol–ether as small, rhombic crystals (1·28 g., 76%, overall 61%), m. p. 201—205°. Above 100° the crystalline form disappeared, reappearing as needles at *ca.* 160° (Found, on a sample dried for 8 hr. *in vacuo* over P_2O_5: C, 55·5; H, 8·4; N, 10·7. Calc. for $C_6H_{11}NO_2$: C, 55·8; H, 8·6; N, 10·85%). The product, R_F 0·81, gave a yellow coloration with ninhydrin and a blue coloration with isatin. It had $\nu_{max.}$ (KBr disc) 1615 (CO_2H) and 3450 cm.$^{-1}$ (NH). The *toluene*-p-*sulphonate* formed rhombs, m. p. 183—185° (from ethanol) (Found: C, 55·1; H, 6·0; N, 4·7. $C_{13}H_{17}NO_4S$ requires C, 55·1; H, 6·05; N, 4·9%), $\nu_{max.}$ (KBr disc) 1174 and 1347 (SO_2), 1713 (carboxyl C:O) and broad absorption between 2500—3100 cm.$^{-1}$ (CO_2H). The n.m.r. spectrum (in $CDCl_3$ containing a few drops of trifluoroacetic acid) showed a single methyl doublet (τ 8·91, J = 6·6 c./sec.), and a doublet (τ 5·60, J = 8·4 c./sec.) assigned to the C-2 proton.

The n.m.r. spectrum (in D_2O) of the 3-methylproline after one crystallisation showed two doublets of almost equal intensity at τ 9·24 (J = 7·2 c./sec.) and τ 9·0 (J = 6·6 c./sec.), assigned to the methyl groups in each of the diastereoisomers present in approximately equal amounts. The absorption at lowest field was a well-defined doublet at τ 6·14 (J = 7·2 c./sec.), assignable to the C-2 proton of one of the isomers, the proton being deshielded by both the α-nitrogen atom and the adjacent carboxyl group. After six crystallisations, small colourless rhombs, m. p. 218—219°, were obtained. The *toluene*-p-*sulphonate* crystallised as laths, m. p. 114·5—115·5° (from ether) (Found: C, 55·2; H, 5·8; N, 4·9. $C_{13}H_{17}NO_4S$ requires C, 55·1; H, 6·05; N, 4·9%), $\nu_{max.}$ (KBr disc) 1150 and 1347 (SO_2), 1720 (carboxyl C:O), and broad absorption between 2500—3100 cm.$^{-1}$ (CO_2H), and it was not superimposable upon the spectrum of the toluene-*p*-sulphonate obtained from the diastereoisomeric mixture. The n.m.r. spectrum in $CDCl_3$ showed a single methyl doublet (τ 9·03, J = 6·5 c./sec.), and a doublet (τ 6·05, J = 4·6 c./sec.) assigned to the C-2 proton. In the n.m.r. spectrum of the six-times-crystallised amino-acid, both the high-field methyl doublet and the doublet at τ 6·14 were absent, indicating that the product consisted of only one isomer. The spectrum showed a methyl doublet at τ 8·97 (J = 5·4 c./sec.), a complex series of absorptions between τ 7·53 and 8·70, assigned to the three protons attached to C-3, and C-4, and six peaks at τ 6·50, 6·63, 6·65, 6·74, 6·80, and 6·88, assigned to the three protons at C-2 and C-5.

The four-times-crystallised toluene-*p*-sulphonyl derivative (m. p. 183—185°) (150 mg.) obtained from the mixture of 3-methylproline diastereoisomers, was heated with a 1 : 1 (w/w) mixture of hydrobromic acid–acetic acid (30 ml.) in a sealed tube at 100° for 2 hr. The product was diluted with water and filtered, and the filtrate was evaporated to a brown gum, which crystallised from ethanol–ether as colourless needles (64 mg.). This material was dissolved in water (3·0 ml.) and stirred with Amberlite IR-45 resin until the solution was neutral. Filtration, followed by evaporation of the solution, gave a solid residue, which crystallised from ethanol–ether in clusters of needles (30 mg.), m. p. 210—211° (Found: C, 55·9; H, 8·6; N, 10·95. $C_6H_{11}NO_2$ requires: C, 55·8; H, 8·6; N, 10·85%). The infrared spectrum (KBr disc) was not identical with that of the previously described diastereoisomer, and showed bands at 1620 (carboxyl C:O), broad absorption between 2500—3100 (CO_2H), and 3450 cm.$^{-1}$ (NH). The n.m.r. spectrum in D_2O, using sodium 3-(trimethylsilyl)propane-1-sulphonate as internal reference, showed a doublet (τ 5·91, J = 7·2 c./sec.) due to the proton at C-2, a complex series of signals (τ 6·32—8·54) arising from the five protons at C-3, C-4, and C-5, and a doublet (τ 9·04, J = 10·2 c./sec.) assigned to the protons of the C-3 methyl group.

4-*Methylproline*.[5]—Diethyl 4-methylpyrrolidine-2,2-dicarboxylate (2·2 g.) was heated under reflux with 6N-hydrochloric acid (40 ml.) for 3 hr. The solution was evaporated to dryness under reduced pressure, and the solid residue was dissolved in water (50 ml.) and stirred with Amberlite IR-45 resin (12 g.) until neutral. The resin was separated, and the water removed under reduced pressure leaving a residue (1·43 g.) which crystallised from ethanol–ether as laths (0·99 g., 80%; overall, 66%), m. p. 218—225° (decomp.) (Found, on a sample dried to constant weight *in vacuo* over P_2O_5: C, 55·7; H, 8·3; N, 10·85%), R_F 0·82, $\nu_{max.}$ (KBr disc) 1622 (CO_2H) and 3425 cm.$^{-1}$ (NH). The *toluene*-p-*sulphonate* formed needles m. p. 132—134° (from ethanol) (Found: 55·2; H, 5·8; N, 4·65. $C_{13}H_{17}NO_4S$ requires C, 55·1; H, 6·05; N, 4·9%), $\nu_{max.}$ (KBr disc) 1160 and 1355 (SO_2), 1705 and 1722 (CO_2H doublet) and broad absorption at 2500—3300 cm.$^{-1}$ (CO_2H).

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