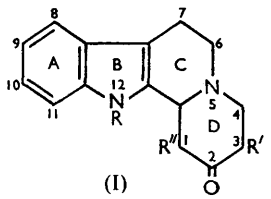
413. *The Constitution of Yohimbine and Related Alkaloids. Part XII.* Some Unsuccessful Synthetic Approaches to Yohimbine and Alstoniline.*

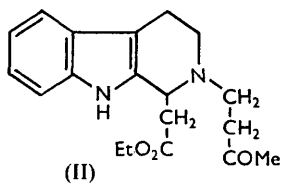
By K. B. Prasad and G. A. Swan.

Dieckmann cyclisation of diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate has been shown to yield mainly the ester (I; R = R′ = H, R″ = CO_2Et) and is therefore not of value for synthetic work in the yohimbine field. The ketone (III) was synthesised, but did not prove a useful intermediate. β-*o*-(Methoxymethyl)phenylalanine (VI) has also been synthesised.

Groves and Swan [1] synthesised the ketone (I; R = R′ = R″ = H), but were unable to introduce into position 3 a substituent suitable for building up of ring E of yohimbine and related alkaloids. This ketone was obtained by a Dieckmann reaction on diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate, followed by hydrolysis and decarboxylation of the crude reaction product, which probably contained both isomeric β-keto-esters (I; R = R′ = H, R″ = CO_2Et, and R = R″ = H, R′ = CO_2Et). We have now fractionated the product at the β-keto-ester stage, though the homogeneity of our crystalline material is uncertain and attempts to build up ring E by treating this material with 4-diethylaminobutan-2-one methiodide were unsuccessful. We therefore repeated the synthesis of the diesters, using ethyl [*carboxy*-^{14}C]acrylate, and isolated two radioactive fractions of the β-keto-ester formed by its cyclisation. If the material consisted of (I; R = R″ = H, R′ = CO_2Et) then on hydrolysis it should yield inactive ketone, with the



(I)



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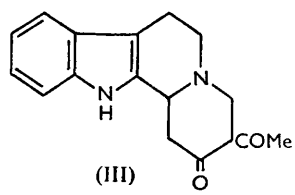


(III)

evolution of strongly radioactive carbon dioxide; if it were (I; R = R′ = H, R″ = CO_2Et), the ketone formed should be active and the evolved carbon dioxide inactive. The measured relative activities of the products from the two fractions of β-keto-ester were comparable and suggest that the reaction product contained only about 15% of the desired (I; R = R″ = H, R′ = CO_2Et). It was thought that this unfavourable ratio might be improved by introducing a benzyl substituent (R) (which might be removable at a later stage). Some intermediates towards the possible synthesis of 1-benzyltryptamine by extension of Speeter and Anthony's method [2] are described in the Experimental section; but the base used was prepared by a different method.[3] However, this base failed to condense satisfactorily with 1-ethyl 4-hydrogen 2-oxosuccinate and this approach was abandoned.

Ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate underwent a Mannich reaction with acetone and formaldehyde to give the ester (II), which by Dieckmann reaction gave the pyridocoline (III). Here again we were unsuccessful in our attempts to build up ring E by the use of 4-diethylaminobutan-2-one methiodide, as ring D opened very readily. In other work we synthesised the amine (IV) but we were unable to isolate the pyridone (V) after an attempted Dieckmann reaction. We had also thought that the pyridocoline (III) (or the enol-ether formed by methylating it) might condense with ethyl cyanoacetate to

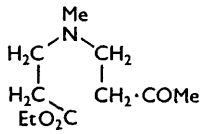
* Part XI, preceding paper.

[1] Groves and Swan, *J.*, 1952, 650.
[2] Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208.
[3] U.S.P. 2,642,438.

give a product containing a pyranone ring (E), which could be used for the synthesis of alkaloids of the alstonine type. However, our attempts to condense 2-acetyl*cyclo*hexanone with ethyl cyanoacetate in the presence of sodium ethoxide apparently gave ethyl 6-oxoheptane-1-carboxylate.

Mild alkaline hydrolysis of the condensation product of 3-methylenepentan-2-one with ethyl oxalate gave 5-methylene-2 : 4-dioxoheptanoic acid; but we were unable to condense this with tryptamine to yield the ketone (I; R = R'' = H, R' = Et).

Our main interest in these experiments had been the hope that they might open the way to the synthesis of compounds containing the methoxycarbonyl group of yohimbine and alstoniline. After their failure, we turned to the synthesis of β-*o*-(methoxymethyl)phenylalanine (VI), hoping that this might condense with formaldehyde to give the quinoline (VII), which could be subjected to a series of reactions previously carried out on 1 : 2 : 3 : 4-



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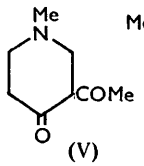

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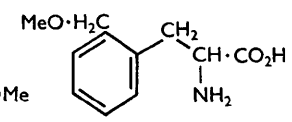
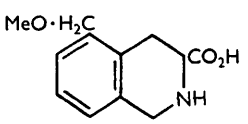


(VI)



(VII)

tetrahydro*iso*quinoline-3-carboxylic acid,[4] [5] with subsequent conversion of the methoxymethyl group into a methoxycarbonyl group.[6] *o*-Methoxymethylbenzyl chloride was condensed with ethyl acetamidomalonate and the product was hydrolysed to β-*o*-methoxymethylphenylalanine. Attempts to condense this with formaldehyde in the presence of hydrochloric acid, however, led to 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid. The mechanism of this reaction is not clear. During the reaction, the amino-group would be present as a salt and therefore unlikely to undergo cyclisation. Perhaps the methoxymethyl group is converted into a chloromethyl group so that cyclisation occurs on subsequent evaporation. The product of attempted esterification of the amino-acid with ethanolic hydrogen chloride is likewise ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate.

o-(Methoxymethyl)benzyl chloride condensed with diethyl malonate, and hydrolysis and decarboxylation of the product yielded β-(*o*-methoxymethyl)phenylpropionic acid. Attempts to cyclise the acid gave non-ketonic products.

Experimental

Dieckmann Cyclisation of Diethyl 1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetate*-2-*propionate*.—The reaction was carried out on the diester (1·2 g.) as described by Groves and Swan,[1] except that the hydrolysis was omitted and at the end of the reaction the cooled mixture was treated with water and the benzene layer was shaken with 10% sodium hydroxide solution. The combined aqueous layers were extracted with benzene, then neutralised with acetic acid and the resulting gum was taken up in chloroform. The solvent was removed from the dried (Na_2SO_4) extract and a solution of the residue in benzene and light petroleum was poured through a column of alumina. Development was begun with benzene containing 1% of ethanol and the residue from the eluate, when recrystallised from light petroleum, gave a pale yellow solid (90 mg.), m. p. 126—128°, after sintering at 120°. This was dissolved in hot, light petroleum. On cooling, clusters of almost colourless needles separated; but when the solution was then placed in a refrigerator, deep yellow prisms also separated. On subsequent attempts to obtain only the colourless needles, the deep yellow prisms always separated and the *product* had m. p. 128—129° (Found: C, 69·65; H, 6·65. $C_{18}H_{20}O_3N_2$ requires C, 69·25; H, 6·4%). Development of the chromatogram was continued with benzene containing 4% of ethanol, yielding a bright yellow solid (170 mg.), m. p. 115—117°, after sintering at 110°.

A similar experiment in which the product was crystallised from benzene–light petroleum,

[4] Clemo and Swan, *J.*, 1946, 617.
[5] Swan, *J.*, 1949, 1720.
[6] Cf. Elderfield and Wythe, *J. Org. Chem.*, 1954, **19**, 683.

without chromatography, yielded a bright yellow substance, m. p. 115—116° (Found: C, 69·2; H, 6·8%).

An attempt to alkylate the keto-ester with 4-diethylaminobutan-2-one methiodide in the presence of methanolic sodium methoxide [7] gave, as the only pure products 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-octahydro-2-ketoindolo[2 : 3-*a*]pyridocoline and *dimethyl* 1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate*-2-*propionate*, colourless prisms, m. p. 140° (from benzene–light petroleum) (Found: C, 66·1; H, 6·85. $C_{18}H_{22}O_4N_2$ requires C, 65·45; H, 6·65%). The latter compound (mixed m. p. not depressed) was also obtained by refluxing the diethyl ester for a few hours with anhydrous methanol containing a trace of sodium methoxide.

Experiment using Ethyl [carboxy-^{14}C]*Acrylate*.—Potassium [^{14}C]cyanide, prepared from barium [^{14}C]carbonate (5 μc) by McCarter's method,[8] was diluted with inactive sodium cyanide (2·7 g.) and gradually added to a refluxing solution of ethylene chlorohydrin (5 g.) in ethanol (15 ml.), being washed in with further ethanol (12 ml.). The mixture was refluxed for 8 hr., kept overnight at room temperature, diluted with ether (20 ml.), and filtered and the filter cake was washed with ethyl acetate. On distillation the fraction (3·23 g.) of b. p. 110°/15 mm. was collected and redistilled, with a little inactive hydracrylonitrile as " chaser ".

Copper bronze (0·17 g.) and absolute ethanol (5·3 g.) were mixed, cooled with water, and treated gradually with a mixture of concentrated sulphuric acid (3·6 ml.) and water (0·75 ml.). The above nitrile (3·58 g.) was then added and the mixture was stirred and its temperature was raised to 130° during 35 min.; distillation began, and the temperature was then raised to 150° during a further 1 hr. The residue was allowed to cool and diluted with ethanol (3·6 ml.) and its temperature was again raised to 130°, then to 170° during 100 min. The combined distillates were shaken with 6 vols. of saturated brine, dried ($CaCl_2$), and distilled, giving ethyl [*carboxy*-^{14}C]-acrylate (1·78 g.), b. p. 98—100°. The low-boiling fraction of the distillate, when shaken with 6 vols. of saturated brine, dried, and distilled, yielded a further amount (0·07 g.) of ester. The combined product was redistilled, with the addition of inactive ethyl acrylate (1·3 g.), giving 2·78 g. of product, b. p. 98—100°.

This ester was heated in a sealed tube for 15 hr. at 134° with ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate (2·2 g.). The product was evaporated to dryness (water-bath/reduced pressure), and the residue was dissolved in ether, treated with ethanolic hydrogen chloride, and stirred until crystallisation occurred. The resulting precipitate was collected, washed with ether, and recrystallised from ethanol, giving a hydrochloride (2·48 g.; m. p. 147—148°) which yielded a base, m. p. 76—78° (0·5 g.) (from benzene–light petroleum). This, diluted with inactive diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate (0·7 g.), in dry benzene was added to alcohol-free sodium ethoxide (from sodium, 0·11 g.) and the mixture was refluxed for 4·5 hr. in nitrogen. After cooling, the mixture was treated with water and the benzene layer extracted with dilute sodium hydroxide solution. The combined aqueous extracts were extracted with ether, adjusted to pH 5 with acetic acid, and extracted with chloroform. The dried (Na_2SO_4) chloroform extract yielded a gum (0·67 g.) which was extracted with boiling light petroleum (b. p. 60—80°) (70 ml.), leaving a gum A (0·34 g.). The petroleum solution was kept overnight at room temperature, decanted from a small amount of bright yellow solid, concentrated to 10 ml., and kept overnight at 0°. The resulting pale yellow crystals (0·28 g.; m. p. 102—119°) were recrystallised twice from light petroleum (b. p. 60—80°), giving B (0·17 g.; m. p. 123—125°). The residue A was extracted further with boiling light petroleum, and the resulting extracts were combined with the mother-liquor from which the crystals (0·28 g.; m. p. 102—119°) had been filtered and the mixture was concentrated to 10 ml. On cooling, further crystals C (0·1 g.; m. p. 117—118°) separated.

The crystals C (50 mg.) were refluxed with N-hydrochloric acid (8 ml.) for 4 hr., during which nitrogen was passed first through the refluxing solution, then through three bubblers containing carbonate-free sodium hydroxide solution. The carbonate collected was precipitated in the usual manner as barium carbonate (34·5 mg.). The acidic, hydrolysed solution was evaporated to dryness (water-bath/reduced pressure), and the residue dissolved in water, basified with sodium hydroxide solution, and extracted with chloroform. The residue from the extract was recrystallised from benzene, affording the ketone, m. p. 178—180°. When material B (51·0 mg.) was similarly hydrolysed, barium carbonate (33·6 mg.) was obtained. The samples B and C and the ketones obtained by hydrolysis of them were burnt and the specific activities of the

[7] du Feu, McQuillin, and Robinson, *J.*, 1937, 53.
[8] McCarter, *J. Amer. Chem. Soc.*, 1951, **73**, 483.

resulting carbon dioxide, as well as that liberated by acidification of the barium carbonate samples, were measured by the gas-counting method [9] for $^{14}CO_2$.

Ethyl 1 : 2 : 3 : 4-*Tetrahydro*-2-3′-*oxobutyl*-β-*carboline*-1-*acetate* (II).—Ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate hydrochloride (2·4 g.), paraformaldehyde (0·4 g.), acetone (8 ml.), and ethanol (8 ml.) were refluxed for 5 hr., then evaporated to give a gum, which was dissolved in water and basified with aqueous sodium hydroxide. The base was collected, washed with water, dried in a vacuum-desiccator, and recrystallised from benzene–light petroleum, giving the *keto-ester* (2·12 g.), prisms, m. p. 143—144° (Found: C, 69·15; H, 7·5. $C_{19}H_{24}O_3N_2$ requires C, 69·5; H, 7·3%).

3-*Acetyl*-1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*octahydro*-2-*oxoindolo*[2 : 3-a]*pyridocoline* (III).—The above keto-ester (2·12 g.) was added to alcohol-free sodium ethoxide (0·7 g.) suspended in benzene (50 ml.), and the mixture was refluxed for 2·75 hr. in nitrogen, cooled, and treated with water. The organic layer was washed with dilute sodium hydroxide solution. The combined aqueous layers were extracted with ether, then exactly neutralised with dilute acetic acid, a pale buff precipitate being produced. This (1·62 g.) was collected, washed with water, dried, and recrystallised from benzene, giving the *diketone* (1·3 g.) as cream-coloured leaflets, m. p. 205—206° (Found: C, 72·5; H, 6·45. $C_{17}H_{18}O_2N_2$ requires C, 72·35; H, 6·4%).

Methylation of the Above Diketone.—Treatment of a solution of the diketone in N-sodium hydroxide with methyl sulphate yielded a precipitate which, after being washed with water, dried, and boiled first with methanol, then with benzene, had m. p. 192° (Found: C, 72·15, 72·25, 71·9, 71·65; H, 7·0, 7·35, 7·55, 7·35%). The same *product* (Found: C, 72·1; H, 6·9%) was obtained by treatment of the diketone with diazomethane.

N-2-*Cyanoethyl*-N-3-*oxobutylmethylamine.*—A mixture of *N*-2-cyanoethylmethylamine (12·1 g.), ethanol (30 ml.), concentrated hydrochloric acid (15 ml.), paraformaldehyde (7·5 g.), and acetone (30 ml.) was refluxed for 6 hr., the solvents were removed, and the residue was cooled and treated with water and saturated potassium carbonate solution and extracted with ether. The dried (K_2CO_3) extract on distillation gave the tertiary *base* (19·9 g.), b. p. 140—150°/12 mm. (Found: C, 62·5; H, 9·25. $C_8H_{14}ON_2$ requires C, 62·35; H, 9·1%).

Ethyl β-(N-*Methyl*-N-3-*oxobutylamino*)*propionate* (IV).—A solution of the above nitrile (25·25 g.) in absolute ethanol (100 ml.) was saturated with hydrogen chloride at 0°, kept overnight at room temperature, refluxed for 4 hr., and evaporated to a small volume. The *ester* (14 g.), b. p. 130°/14 mm., was isolated by extraction with ether, after basification with potassium carbonate (Found: C, 59·35; H, 9·55. $C_{10}H_{19}O_3N$ requires C, 59·7; H, 9·45%).

3-2′-*Phthalimidoethylindole.*—Tryptamine (0·5 g.) and phthalic anhydride (0·5 g.) were heated for 3 hr. at 180—190° and the *product* was recrystallised alternately from benzene and ethanol, giving plates, m. p. 164° (Found: C, 74·2; H, 5·3. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·85%).

1-*Benzylindol*-3-*ylglyoxylyl Chloride.*—This *chloride* was prepared from 1-benzylindole by Speeter and Anthony's method [2] and separated from benzene–light petroleum as yellow prisms, m. p. 105° (Found: C, 68·0; H, 4·35. $C_{17}H_{12}O_2NCl$ requires C, 68·55; H, 4·05%).

1-*Benzylindol*-3-*ylglyoxylamide.*—The above chloride with ethereal ammonia gave the *amide*, needles (from ethanol), m. p. 186° (for analysis dried for 5 hr. at 90°/0·1 mm.) (Found: C, 73·15; H, 5·25; N, 10·5. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·05; N, 10·05%).

1 : N : N-*Tribenzylindol*-3-*ylglyoxylamide.*—The chloride (0·1 g.) was treated with ethereal dibenzylamine (0·2 g.), and the *product* was extracted with dilute hydrochloric acid and crystallised from ethanol as needles, m. p. 143—144° (Found: C, 80·9; H, 5·85. $C_{31}H_{26}O_2N_2$ requires C, 81·2; H, 5·7%).

The *monobenzylamino-compound*, prepared similarly, separated from ethanol as needles, m. p. 172—173° (Found: C, 72·7, 72·6, 72·7; H, 5·05, 5·35, 5·2. $C_{17}H_{14}O_2N_2$,0·25C_2H_6O requires C, 72·5; H, 5·35%).

γ-*Formamidobutaldehyde* 1-*Benzyl*-1-*phenylhydrazone.*—This was prepared from 1-benzyl-1-phenylhydrazine and γ-formamidobutaldehyde diethyl acetal [11] and separated from light petroleum (b. p. 40—60°) as needles, m. p. 74—75° (Found: C, 73·35; H, 7·55. $C_{18}H_{21}ON_3$ requires C, 73·25; H, 7·1%).

[9] Swan, *J.*, 1955, 1039.
[10] Plieninger, *Chem. Ber.*, 1954, **87**, 127.
[11] Wohl, Schäfer, and Thiele, *Ber.*, 1905, **38**, 4159.

Attempted Condensation of 2-*Acetyl*cyclo*hexanone with Ethyl Cyanoacetate*.—Ethyl cyanoacetate (1·13 g.), followed by 2-acetyl*cyclo*hexanone [12] (1·4 g.) was added to a solution of sodium (0·23 g.) in absolute ethanol, and the solution was heated for 1·5 hr. on a water-bath, kept overnight at room temperature, treated with water containing concentrated hydrochloric acid (1·3 ml.) and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and distilled, yielding ethyl 6-oxoheptane-1-carboxylate, b. p. 120° (bath-temp.)/2 mm. (Found: C, 64·35; H, 9·9. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·7%).

Ethyl 2-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate*.—As the paragraph of this heading on p. 656 of the paper by Groves and Swan [1] is inaccurate, this paragraph is intended as a correction. A mixture of ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate (from the hydrochloride, 0·8 g.) and vinyl cyanide (2 ml.) was heated in a sealed tube for 22 hr. at 125°, the excess of vinyl cyanide was removed and the residue was stirred with ether, giving the *base* (0·5 g.), which when recrystallised from benzene containing a small proportion of light petroleum (b. p. 40—60°) had m. p. 130° (Found: C, 69·15; H, 6·7; N, 14·0. $C_{18}H_{21}O_2N_3$ requires C, 69·45; H, 6·75; N, 13·5%). When this was refluxed with ethanolic sodium hydroxide solution, the solution diluted with water, the ethanol removed, and the solution then acidified with acetic acid, it yielded 1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetic*-2-*propionic acid*, m. p. 219° (decomp.) (Found: C, 61·45; H, 6·05. $C_{16}H_{18}O_4N_2$,0·5H_2O requires C, 61·75; H, 6·1%). The same acid was obtained by saponification of diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate.

3-2′-(2-*Cyanoethylamino*)*ethylindole*.—Tryptamine (0·1 g.) was refluxed for 13 hr. with vinyl cyanide (1·5 ml.), the excess of the latter was removed, and a solution of the residue in ether was treated with ethanolic hydrogen chloride. The resulting precipitate was stirred with ether and recrystallised from ethanol–acetone–ether, giving the *indole*, m. p. 185° (Found: C, 62·4; H, 6·45; N, 16·95. $C_{13}H_{15}N_3$,HCl requires C, 62·5; H, 6·4; N, 16·8%).

5-*Methylene*-2 : 4-*dioxoheptanoic Acid*.—Ethyl oxalate (1·5 ml.) followed by 3-methylenepentan-2-one [13] (1 ml.) was added to sodium ethoxide (0·7 g.) in ether (20 ml.). The mixture became homogeneous and was kept for 3 days at room temperature before being diluted with water. The organic layer was extracted with dilute sodium hydroxide solution, and the combined alkaline layers were acidified and extracted with ether. The residue left on removal of the ether from the latter extract was kept in N-sodium hydroxide (5 ml.) for 1·5 hr. at room temperature, then acidified. The *acid* (0·2 g.) was precipitated; from carbon tetrachloride it formed cream-coloured crystals, m. p. 55—57°, giving an intense red colour with ferric chloride (Found: C, 56·2; H, 6·0. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%).

1-*Ethyl* 4-*Hydrogen* 2-*Oxosuccinate*.—Shaking diethyl sodio-oxaloacetate (20 g.) with water (150 ml.) and N-sodium hydroxide (150 ml.) for 10 min. and working up the whole as described by Groves and Swan [1] gave the acid in yields varying between 8 and 10 g.

α-*Ethoxycarbonyladiponitrile*.—Ethyl cyanoacetate (3·9 ml.) and γ-bromobutyronitrile (4·8 g.) were added to a solution of sodium (0·75 g.) in ethanol (20 ml.), the mixture refluxed for 6·5 hr., then cooled and filtered, and the ethanol removed from the filtrate. The residue was treated with water, acidified with acetic acid, and extracted with ether. Distillation of the dried (Na_2SO_4) extract gave the *nitrile* (2 g.), b. p. 170—175°/2 mm. (Found: C, 59·95; H, 6·8; N, 15·3. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·65; N, 15·55%).

Diethyl Acetamido-o-(*methoxymethyl*)*benzylmalonate*.—Diethyl acetamidomalonate [14] (29·7 g.) was added with stirring to a solution of sodium (3·2 g.) in absolute ethanol (175 ml.), followed by *o*-(methoxymethyl)benzyl chloride [15] (23·3 g.) in ethanol (25 ml.) during 10 min. The mixture was stirred and refluxed for 15 hr., then filtered, and the filter cake was washed with hot ethanol. The solvent was removed from the combined ethanolic solution (water-bath/reduced pressure), and the residue stirred with water until it crystallised. When recrystallised from water (1 l. per 10 g.) the *ester* (33·8 g.) formed needles, m. p. 73—74° (Found: C, 61·25; H, 7·1. $C_{18}H_{25}O_6N$ requires C, 61·55; H, 7·1%).

N-*Acetyl*-β-o-(*methoxymethyl*)*phenylalanine*.—The above ester (6 g.) was refluxed for 4 hr. with 10% aqueous sodium hydroxide (40 ml.). The solution was cooled, mixed with 3N-hydrochloric acid (40 ml.), refluxed for 1 hr., and filtered hot. The *acid* which separated on cooling

[12] Meerwein and Vossen, *J. prakt. Chem.*, 1934, **141**, 149.
[13] Colonge and Cumet, *Bull. Soc. chim. France*, 1947, 838.
[14] Vignau, *ibid.*, 1952, 638.
[15] Mann and Stewart, *J.*, 1954, 2819.

crystallised from aqueous ethanol and had m. p. 158° (3·5 g.) (Found: C, 61·85; H, 7·0. $C_{13}H_{17}O_4N$ requires C, 62·15; H, 6·75%).

β-(o-*Methoxymethyl*)*phenylalanine* (VI).—The above acetyl compound (3·5 g.) was refluxed for 10 hr. with water (42·5 ml.) and concentrated sulphuric acid (2·5 ml.). The cooled solution was treated with a slight excess of barium hydroxide solution and filtered. The filtrate was saturated with carbon dioxide, then heated on a water-bath, cooled, and filtered. The filtrate was passed through a column of Zeo-Karb 225 (previously washed successively with alkali, water, acid, and water) and washed through with distilled water until the eluate no longer left a residue on evaporation. 2N-Ammonia was then passed through the column until the eluate no longer gave a positive test with ninhydrin, and the collected ammoniacal extracts were then evaporated to a small volume and diluted with ethanol; the *amino-acid* (2·4 g.) separated as needles, m. p. 206—207° (decomp.) (Found: C, 63·45; H, 7·6; MeO, 12·4. $C_{11}H_{15}O_3N$ requires C, 63·15; H, 7·2; MeO, 14·8%). This (7·9 g.) was also obtained by direct hydrolysis of diethyl acetamido-*o*-(methoxymethyl)benzylmalonate (15 g.) with concentrated sulphuric acid (10 ml.) and water (170 ml.) for 48 hr.

The hydrolysis was also effected by heating the ester (1 g.) for 8 hr. on a water-bath with potassium hydroxide (2 g.) and water (2 ml.); acidification by acetic acid and evaporation (water-bath/reduced pressure) until the solution was neutral, gave the amino-acid (0·5 g.) after passage through a Zeo-Karb column.

A solution of the amino-acid (1·5 g.) in 2N-sodium hydroxide (5 ml.) was cooled in ice, with stirring, while 2N-sodium hydroxide (5 ml.) and acetic anhydride (0·5 ml.) were added. At intervals of 5 min. this addition of alkali followed by anhydride was repeated three times more. The mixture was kept at room temperature for 30 min., cooled in ice, and treated with 6N-sulphuric acid (9 ml.). The solid which separated had m. p. 158° and was identical with the *N*-acetyl-β-(*o*-methoxymethyl)phenylalanine above.

ω-*Ethoxy*-o-*toluic Acid*.—This was prepared as described for ω-methoxy-*o*-toluic acid by Clemo and Swan.[4] The ethyl ester formed needles, m. p. 22—23°, b. p. 165°/16 mm. (Found: C, 69·45; H, 8·05. Calc. for $C_{12}H_{16}O_3$: C, 69·25; H, 7·7%). The acid recrystallised from benzene–light petroleum, then sublimed at 70°/0·02 mm., forming needles, m. p. 82—83° (Found: C, 66·55; H, 6·75. Calc. for $C_{10}H_{12}O_3$: C, 66·65; H, 6·65%). Noyes and Coss,[16] using a different method of preparation, give b. p. 160°/20 mm. for the ester and m. p. 84—85° for the acid.

o-(*Ethoxymethyl*)*benzyl Alcohol*.—Reduction of the above ester, as described by Mann and Stewart [15] for the ω-methoxy-compound, gave the alcohol, b. p. 146—147°/18 mm. (Found: C, 72·6; H, 9·1. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·45%). This gave a 3 : 5-*dinitrobenzoate*, m. p. 52° (from ethanol) (Found: C, 56·2; H, 4·5. $C_{17}H_{16}O_7N_2$ requires C, 56·65; H, 4·45%). The *chloride* was lachrymatory (b. p. 133—134°/20 mm.) (Found: C, 64·55; H, 6·9. $C_{10}H_{13}OCl$ requires C, 65·05; H, 7·05%).

Attempted Reaction of β-(o-*Methoxymethyl*)*phenylalanine with Formaldehyde*.—When the amino-acid was treated with formaldehyde and hydrochloric acid as described by Archer [17] for the preparation of 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid from β-phenylalanine, it yielded a small amount of viscous material, which was removed, and the filtrate was concentrated to half its volume and kept overnight in a refrigerator, giving crystals of 1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylic acid hydrochloride*, m. p. 305° (decomp.) (Found: C, 56·2; H, 5·75. $C_{10}H_{11}O_2N$,HCl requires C, 56·2; H, 5·6%). Ammonia liberated the free amino-acid, m. p. 311—312°. With ethanol and concentrated sulphuric acid it gave the ester, b. p. 165° (bath-temp.)/2 mm. (Found: C, 70·75; H, 7·9. Calc. for $C_{12}H_{15}O_2N$: C, 70·25; H, 7·3%), which yielded a picrate, m. p. 195—196° (decomp.) (Found: C, 49·9; H, 4·05. Calc. for $C_{12}H_{15}O_2N$,$C_6H_3O_7N_3$: C, 49·75; H, 4·15%), and a *picrolonate*, m. p. 225° (decomp.) (Found: C, 56·0; H, 5·3. $C_{12}H_{15}O_2N$,$C_{10}H_8O_5N_4$ requires C, 56·3; H, 4·9%). Variation of the conditions gave the same product.

Diethyl o-(*Methoxymethyl*)*benzylmalonate*.—Diethyl malonate (14·4 g.), followed by *o*-(methoxymethyl)benzyl chloride (15 g.) during 20 min., was added with stirring to a cold solution of sodium (2·1 g.) in absolute ethanol (45 ml.). The mixture was refluxed for 6 hr., then filtered, and the filter cake was washed with hot ethanol. Distillation of the combined ethanolic solutions yielded the *ester* (23 g.), b. p. 220—250°/18 mm. (Found: C, 65·6; H, 7·7. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%).

[16] Noyes and Coss, *J. Amer. Chem. Soc.*, 1920, **42**, 1280.
[17] Archer, *J. Org. Chem.*, 1951, **16**, 430.

β-(o-*Methoxymethyl*)*phenylpropionic Acid*.—The above ester (23 g.) was heated for 24 hr. on a water-bath with potassium hydroxide (23 g.) in water (23 ml.). The cooled solution was extracted with ether, acidified with concentrated hydrochloric acid, and extracted again with ether. The residue left after removal of the ether from the latter extract was heated for 30 min. at 160°. On cooling, the residue (14·4 g.) solidified, and recrystallisation from light petroleum (b. p. 60—80°) gave the *acid* as needles, m. p. 75—76°, unchanged by sublimation at 60°/0·01 mm. (Found: C, 68·3; H, 7·6. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·2%).

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University of Durham, King's College,
Newcastle upon Tyne, 1.

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