170. *Studies in the Indole Series. Part II. Attempted Synthesis of Tryptophan from Substituted Malonic Esters.*

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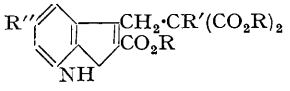
Some attempts to synthesise tryptophan from ethyl (2-carbethoxy-3-indolylmethyl)malonate and related compounds are described. Attempts to halogenate this ester in the α-position were unsuccessful; on bromination, substitution in the 5-position occurred, but sulphuryl chloride was without effect.

Bromination of ethyl methoxymethylmalonate led to ethyl αβ-dibromomethylmalonate, which reacted with potassium phthalimide to give ethyl α-bromo-β-phthalimidomethylmalonate. Condensation of ethyl α-phthalimido-β-methoxymethylmalonate, for which an improved synthesis is described, with 2-carbethoxyindole did not give the expected ethyl phthalimido(2-carbethoxy-3-indolylmethyl)malonate; with hydrogen bromide in acetic acid as condensing agent, ethyl α-phthalimido-β-acetoxymethylmalonate was obtained. This compound was also obtained from ethyl phthalimidomalonate and paraformaldehyde in acetic acid or anhydride.

Treatment of 2-carbethoxyskatole with sulphuryl chloride gave 1-hydroxy-2-carbethoxyskatole.

Maurer and Moser (*Z. physiol. Chem.*, 1926, **161**, 131) have described the preparation of ethyl (2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R′ = R″ = H) by the condensation of 2-carbethoxyindole and ethyl methoxymethylmalonate. They claimed to have prepared tryptophan from it, but did not give details either then or later. It therefore appeared desirable to investigate their claims, and attempts to synthesise tryptophan from this ester and related compounds are now described.

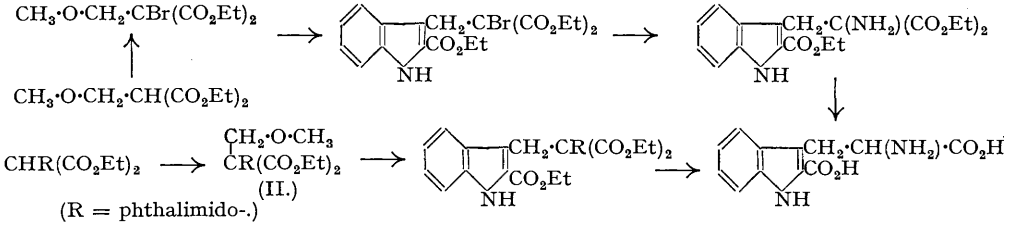


(I).

Some difficulties were encountered in the preparation of ethyl methoxymethylmalonate (Simonsen, J., 1908, **93**, 1780), an attempt to fractionate the product through a column at about 15 mm. pressure leading to its destruction and formation of a polymer of ethyl methylenemalonate. The mixture was separated by distillation through a column at a pressure of about 1 mm., but the yield was still less than that obtained by Simonsen. The use of benzene in place of ether in the reaction between sodiomalonic ester and chlorodimethyl ether, as described by Fischer and Nenitzescu (*Annalen*, 1925, **443**, 125), did not prove satisfactory in our hands and an attempt with magnesium replacing sodium (cf. Spassow, *Ber.*, 1937, **70**, 2381) failed completely.

All attempts to brominate (2-carboxy-3-indolylmethyl)malonic acid (I; R = R′ = R″ = H) (Maurer and Moser, *loc. cit.*) failed, probably because of the very low solubility of the acid in the usual solvents. Bromination of the corresponding triethyl ester gave a monobromo-compound which was not the expected ethyl bromo(2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R′ = Br R″ = H); prolonged alkaline hydrolysis converted it into a tricarboxylic *acid* still containing bromine. The compound was shown to be *ethyl (5-bromo-2-carbethoxy-3-indolylmethyl)malonate* (I; R = Et, R′ = H, R″ = Br) by comparison with a specimen prepared from 5-bromo-2-carbethoxyindole (Hughes *et al.*, *Proc. Roy. Soc. N.S.W.*, 1938, **71**, 475) and ethyl methoxymethylmalonate. Treatment of (I; R = Et, R′ = Br, R″ = H) with sulphuryl chloride in an attempt to obtain ethyl chloro(2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R″ = H, R′ = Cl) gave unchanged starting material as the only identifiable product.

Since the above reactions seemed to render the intended route to tryptophan impracticable, attention was turned to the preparation of suitably substituted malonic esters, which might be condensed with indole-2-carboxylic ester to give derivatives of tryptophan. The following scheme indicates the methods envisaged :



Bromination of ethyl methoxymethylmalonate yielded ethyl αβ-dibromomethylmalonate, even when the reaction medium was kept neutral by means of calcium carbonate. On reaction with potassium phthalimide, the dibromo-compound gave a phthalimidobromomethylmalonic ester, identical with the compound obtained from potassium phthalimide and an authentic specimen of ethyl αβ-dibromomethylmalonate (Haworth and Perkin, J., 1898, **73**, 330; Bachmann and Tanner, *J. Org. Chem.*, 1939, **4**, 493). The phthalimido-compound was shown to be *ethyl α-bromo-β-phthalimidomethylmalonate* by independent synthesis, as follows : Ethyl methoxymethylmalonate was converted into ethyl β-bromomethylmalonate (Simonsen, J., 1908, **93**, 1783), which reacted with potassium phthalimide to give *ethyl β-phthalimidomethylmalonate*; on bromination this gave ethyl α-bromo-β-phthalimidomethylmalonate, identical with the compound described above. An attempt to replace the bromine atom by a methoxy-group was unsuccessful; treatment with sodium methoxide gave phthalimide itself.

The preparation of ethyl phthalimidomethoxymethylmalonate (II) by Mitra's method (*J. Indian Chem. Soc.*, 1930, **7**, 800) was unsatisfactory, but the compound was obtained conveniently and in good yield

by the action of monochlorodimethyl ether upon sodiophthalimidomalonic ester (Dunn and Smart, *J. Biol. Chem.*, 1930, **89**, 46) in boiling benzene (cf. Maeda, Turumi, and Suzuki, *Bull. Inst. Phys. Chem. Res., Tokyo*, 1940, **19**, 267, who prepared the compound from the same reagents but in the absence of a solvent). Many attempts were made to condense the ester (II) with indole-2-carboxylic ester, but the presence of the phthalimido-group makes the condensation much more difficult. Alcoholic or acetic acid solutions of hydrogen chloride or bromide did not effect condensation, nor did sodium in benzene or toluene. Reaction in methyl-alcoholic sodium methoxide solution gave, in addition to unchanged materials, a very small quantity of a substance which, from its analysis, was not the expected compound and has not been identified.

When a solution of hydrogen bromide in acetic acid was used in the reaction, a compound which could also be obtained by the action of the same acid mixture upon ethyl phthalimidomethoxymethylmalonate was isolated. The same compound was prepared by the action of paraformaldehyde on ethyl phthalimidomalonate in acetic acid or anhydride solution in presence of zinc chloride. Analysis indicated the presence of three terminal methyl groups, and on hydrolysis the compound gave acetic acid, isolated and identified as the *p*-phenylphenacyl ester. These properties, together with the analytical figures, show that the compound is *ethyl phthalimidoacetoxymethylmalonate*. In view of the above results, this approach to the synthesis of tryptophan was abandoned.

It seemed possible that compounds related to tryptophan might be obtainable from ethyl skatole-2-carboxylate by condensation with suitable reactants. Several methods of preparing this ethyl ester are on record (Kermack, Perkin, and Robinson, J., 1921, **119**, 1634; Giua, *Atti Congr. Naz. Chim. Ind.*, 1924, 266; Wislicenus and Arnold, *Ber.*, 1887, **20**, 3395; *Annalen*, 1888, **246**, 334), and we found the Fischer cyclisation of ethyl propionylformate phenylhydrazone (cf. Wislicenus and Arnold, *loc. cit.*) to be convenient. This compound was prepared by the action of benzenediazonium chloride on ethyl ethylacetoacetate (Japp and Klingemann, *Ber.*, 1887, **20**, 2943; *Annalen*, 1888, **247**, 216).

Ethyl skatole-2-carboxylate could not be oxidised to 2-carbethoxyindole-3-aldehyde by means of selenium dioxide in benzene or acetic acid, only compounds of high m. p. being obtained, nor could it be condensed with ethyl oxalate, *p*-nitrosodimethylaniline, or ethyl mesoxalate, although a variety of conditions were used.

When ethyl skatole-2-carboxylate was treated with sulphuryl chloride in acetic acid, and the reaction mixture poured into water, a substance was isolated, the analysis of which agrees with that of 1-*hydroxy*-2-*carbethoxyskatole*. This formulation of the compound is supported by its solubility in alkali, in agreement with the properties of known *N*-hydroxy-indoles, and by the fact that two molecules of acetic acid are produced on oxidation with chromic acid, showing that the 3-methyl group has not been attacked.

Experimental.

Ethyl Methoxymethylmalonate.—Various modifications of Simonsen's method (*loc. cit.*) were used, of which the following gave the most satisfactory results. Sodium (11·5 g.) was powdered under toluene, the toluene decanted, and the sodium washed with ether by decantation. Dry ether (300 c.c.) was added, followed by ethyl malonate (80 g.). The mixture was stirred mechanically until all the sodium had reacted (2—3 hours). The flask was cooled in ice, and monochlorodimethyl ether (50 g.), dissolved in dry ether (50 c.c.), was added slowly with vigorous stirring, the mixture then being stirred for 2 hours at room temperature. Water was added, the ethereal layer separated, and the aqueous layer washed with ether. The combined ethereal extracts were washed with water and dried over calcium chloride; the ether was removed, and the residue distilled in a vacuum, a short fractionating column being used. Ethyl methoxymethylmalonate distilled at 79—83°/0·8 mm.; yield 40—45 g., 39—44%. The ester deteriorates on standing.

In another experiment on the same scale, the product was fractionally distilled at 15 mm. pressure. The liquid, b. p. 100—120°, partly polymerised to a white solid, which was filtered off after addition of petrol to the semi-solid mass. The solid (18 g.) melted at 153—154° after crystallisation from ethyl alcohol [Found: C, 55·6; H, 7·0. Calc. for $(C_8H_{12}O_4)_n$: C, 55·8; H, 7·0%]. Haworth and Perkin (*loc. cit.*) describe a polymer of ethyl methylenemalonate, m. p. 146—150°.

Ethyl (2-Carbethoxy-3-indolylmethyl)malonate.—This compound was prepared from 2-carbethoxyindole and freshly distilled ethyl methoxymethylmalonate as described by Maurer and Moser (*loc. cit.*), but their yield of 90% could not be obtained, our maximum being 60%.

Ethyl (5-Bromo-2-carbethoxy-3-indolylmethyl)malonate.—(a) *By bromination of ethyl (2-carbethoxy-3-indolylmethyl)-malonate.* Bromine (1 g.), dissolved in chloroform (10 c.c.), was added gradually at room temperature to a solution of the ester (2 g.) in chloroform (20 c.c.). After 3 hours the chloroform was distilled off; the residual oil rapidly solidified, melted at 159—160° after crystallisation from benzene–petrol (b. p. 60—80°) (Found: C, 51·8; H, 5·25; Br, 18·9. $C_{19}H_{22}O_6NBr$ requires C, 51·8; H, 5·0; Br, 18·2%); yield 1·9 g., 78%.

The *ester* (1 g.) was hydrolysed to the corresponding *acid* by refluxing for 2 hours with alcoholic sodium hydroxide (10%; 15 c.c.). The acid obtained by dilution with water, acidification, and ether extraction melted at 236—237° after crystallisation from acetone–petrol (b. p. 60—80°) (Found: C, 44·5; H, 3·9; N, 4·3. $C_{13}H_{10}O_6NBr$ requires C, 43·8; H, 2·8; N, 3·9%). The acid was converted into the *trimethyl* ester by refluxing for 6 hours with a 5% solution of hydrogen chloride in methyl alcohol. Crystals separated on standing overnight, and after recrystallisation from methyl alcohol had m. p. 179—180° (Found: C, 48·2; H, 3·9; Br, 20·3. $C_{16}H_{16}O_6NBr$ requires C, 48·3; H, 4·05; Br, 20·1%).

(b) *From 5-bromo-2-carbethoxyindole.* The method described by Hughes *et al.* (*loc. cit.*) for the preparation of 5-bromo-2-carbethoxyindole proved unsatisfactory, and the following modification was used. Ethyl pyruvate *p*-bromophenylhydrazone (20·4 g.), prepared as described by these authors, was added to a mixture of glacial acetic acid (75 c.c.) and concentrated sulphuric acid (5·4 c.c.). The mixture, after refluxing for 10 minutes, was poured into water (750 c.c.). The solid was filtered off and crystallised several times from ethyl alcohol (charcoal), giving 5-bromo-2-carbethoxyindole, m. p. 154—156° (Hughes *et al.* give m. p. 153°); yield 6·9 g., 36%. This compound (1·5 g.) was dissolved in ethyl alcohol (11 c.c.), ethyl methoxymethylmalonate (2 c.c.) and concentrated hydrochloric acid (2 c.c.) added, and the mixture refluxed for 2 hours. Dilution with water gave an oil which soon solidified. Crystallisation from benzene–petrol (b. p. 60—80°) gave a solid, m. p. 158—160°, not depressed on admixture with a specimen of the ester prepared

as in (a); yield 1·2 g., 49%. The corresponding acid and trimethyl ester were prepared, and shown by mixed m. p.'s to be identical with the corresponding derivatives described above.

Ethyl αβ-Dibromomethylmalonate.—(a) *From ethyl methoxymethylmalonate.* A solution of ethyl methoxymethylmalonate (20 g.) in carbon tetrachloride (20 c.c.) was warmed gently, and a solution of bromine (5·4 c.c.) in carbon tetrachloride (10 c.c.) added at such a rate that the solution boiled gently without external heating. The solution was then refluxed until it was almost colourless and no more hydrogen bromide was evolved. The cold solution was washed with 5% sodium carbonate solution, then with water, and dried over calcium chloride. The solvent was removed, and the residue distilled in a vacuum. Ethyl αβ-dibromomethylmalonate distilled at 124—126°/2 mm. A satisfactory analysis could not be obtained, the value for bromine always being considerably low, presumably owing to decomposition during distillation (Found: C, 34·3; H, 4·75; Br, 39·8; OEt, 30·1. Calc. for $C_8H_{12}O_4Br_2$: C, 28·9; H, 3·65; Br, 48·2; OEt, 27·2%). However, the analysis, together with the formation of ethyl α-bromo-β-phthalimidomethylmalonate on treatment with potassium phthalimide (see below), indicates that the product was mainly the dibromoester. A similar product was obtained when the reaction was carried out in presence of calcium carbonate (15 g.).

(b) *From ethyl methylenemalonate.* This ester was prepared from its polymer, described above (Haworth and Perkin, *loc. cit.*), or by Bachmann and Tanner's method (*loc. cit.*). A 20% solution of bromine in chloroform was added to an ice-cold solution of the ester (9·9 g.) in chloroform (50 c.c.) till a faint permanent colour remained in the solution. The chloroform was removed in a vacuum, leaving ethyl αβ-dibromomethylmalonate as a reddish oil (18 g.), which was used without further purification.

Ethyl Bromophthalimidomethylmalonate.—(a) *From ethyl αβ-dibromomethylmalonate.* This ester (3·3 g.) and potassium phthalimide (1·8 g.) were heated together at 150° for 2 hours, potassium bromide removed from the cooled product by trituration with water, and the residual solid filtered off and extracted with boiling ethyl alcohol. *Ethyl bromophthalimidomethylmalonate* formed white crystals, which, after further crystallisation from ethyl alcohol, melted at 137—138° (Found: C, 48·3; H, 3·9; N, 3·7; Br, 20·0; OEt, 21·9. $C_{16}H_{16}O_6NBr$ requires C, 48·2; H, 4·05; N, 3·5; Br, 20·1; OEt, 22·6%); yield 2·2 g., 55%.

(b) *Unambiguous synthesis.* Ethyl β-bromomethylmalonate (Simonsen, *loc. cit.*) (10 g.), potassium phthalimide (7·4 g.), and xylene (40 c.c.) were refluxed for 3 hours. After cooling, potassium bromide was filtered off, and xylene removed from the filtrate by distillation in a vacuum. The residual oil, which solidified slowly on standing, was crystallised from ether, giving *ethyl β-phthalimidomethylmalonate*, m. p. 91—92° (Found: C, 59·9; H, 5·9; N, 3·8. $C_{16}H_{17}O_6N$ requires C, 60·2; H, 5·4; N, 4·4%).

Uncrystallised phthalimido-ester, obtained as above from ethyl β-bromomethylmalonate (5 g.), was dissolved in chloroform (25 c.c.), and the solution refluxed while a solution of bromine (1·1 c.c.) in chloroform (5 c.c.) was added slowly, and then for a further hour. After distillation of the chloroform the residual oil soon solidified; after crystallisation from ethyl alcohol, ethyl α-bromo-β-phthalimidomethylmalonate was obtained as white crystals, m. p. 135—136°, not depressed on admixture with a specimen prepared as in (a); yield 2·7 g., 34% (based on ethyl β-bromomethylmalonate).

Ethyl Phthalimidomethoxymethylmalonate.—A suspension of finely powdered sodiophthalimidomalonic ester (Dunn and Smart, *loc. cit.*) (10 g.) in dry benzene (50 c.c.) was refluxed and stirred while a solution of monochlorodimethyl ether (5 g.) in benzene (10 c.c.) was added gradually. After a further hour's boiling, the solution was cooled, water added, the mixture filtered, and the benzene layer separated. The aqueous layer was washed with benzene, and the combined benzene solutions were washed with water and dried over sodium sulphate. The benzene was removed, and the residue of ethyl phthalimidomethoxymethylmalonate crystallised from ethyl alcohol, forming white crystals, m. p. 132—133° (Maeda, Turumi, and Suzuki, *loc. cit.*, give m. p. 133°); yield 7·8 g., 73%.

Ethyl Phthalimidoacetoxymethylmalonate.—(a) *From ethyl phthalimidomethoxymethylmalonate.* A mixture of the ester (2 g.) and hydrogen bromide in acetic acid (50%; 10 c.c.) was heated at 60° for 3 hours, and the clear solution cooled and poured into water. The resulting oil soon solidified and was crystallised from ethyl alcohol, giving *ethyl phthalimidoacetoxymethylmalonate* as colourless prisms, m. p. 110—111° (Found: C, 57·4; H, 5·0; N, 3·9; terminal CH_3, 14·9; *M*, 382. $C_{18}H_{19}O_8N$ requires C, 57·3; H, 5·1; N, 3·7; terminal CH_3, 12·0%; *M*, 377). The presence of an acetyl group in the molecule was established by hydrolysing the substance (0·98 g.) with boiling sulphuric acid (50%; 100 c.c.) for 1 hour. The solution was steam-distilled, the distillate neutralised with sodium hydroxide solution, evaporated in a vacuum to about 3 c.c., and boiled for 2 hours with *p*-phenylphenacyl bromide (0·65 g.) and ethyl alcohol (6 c.c.). The resulting solid, after crystallisation from ethyl alcohol, had m. p. 107—108° not depressed by authentic *p*-phenylphenacyl acetate (Found: C, 75·65; H, 5·7. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·55%).

The same malonate was obtained when ethyl phthalimidomethoxymethylmalonate and 2-carbethoxyindole and hydrogen bromide in acetic acid were boiled under reflux.

(b) *From ethyl phthalimidomalonate.* Ethyl phthalimidomalonate (5 g.), paraformaldehyde (1 g.), fused zinc chloride (1 g.), and acetic anhydride (10 c.c.) were refluxed for 6 hours. The excess of acetic anhydride was destroyed by boiling for a short time with water. The resulting oil solidified on standing, and after crystallisation from ethyl alcohol gave ethyl phthalimidoacetoxymethylmalonate, m. p. 110—111°, undepressed on admixture with a sample prepared as in (a); yield 1·35 g., 22%.

The following variations were tried in an effort to increase the yield: (i) omission of zinc chloride gave only 0·9 g. of product; (ii) omission of zinc chloride and doubling the amount of paraformaldehyde gave 0·65 g. of product; (iii) replacement of acetic anhydride by acetic acid did not alter the yield; (iv) use of hydrogen chloride in acetic acid at room temperature gave only unchanged ethyl phthalimidomalonate.

Ethyl Propionylformate Phenylhydrazone.—Ethyl ethylacetoacetate (32 g.) was dissolved in a mixture of ethyl alcohol (150 c.c.) and aqueous sodium hydroxide (20%; 150 c.c.) previously cooled to — 10°. The solution was kept below — 5° and stirred while a solution of benzenediazonium chloride, prepared from aniline (19·5 g.), hydrochloric acid (4N; 166 c.c.), and sodium nitrite (14·2 g.), was added gradually. After addition was complete, the mixture was kept at — 5° for 30 minutes, acidified with dilute hydrochloric acid, and diluted with 1 l. of water. The red solid was filtered off, washed with water, and dried (42 g.; 94%). It was used without further purification for the preparation of 2-carbethoxyskatole.

2-*Carbethoxyskatole.*—A solution of this crude phenylhydrazone (42 g.) in a mixture of ethyl alcohol (200 c.c.) and concentrated sulphuric acid (25 c.c.) was refluxed for 45 minutes, then poured into water, and the resulting solid filtered off, washed with water, and dried. After crystallisation from methanol, the 2-carbethoxyskatole melted at 134—136° (Wislicenus and Arnold, *Annalen*, 1888, **246**, 334, give m. p. 133—134°); yield 32 g., 83%.

1-*Hydroxy*-2-*carbethoxyskatole.*—2-Carbethoxyskatole (20 g.) and acetic acid (300 c.c.) were placed in a flask fitted with a mechanical stirrer, dropping-funnel, thermometer, and gas-outlet tube. The flask was warmed in a water-bath till all the solid had dissolved, and the solution was then stirred at 50—60° while a solution of sulphuryl chloride (9·6 c.c.) in acetic acid (20 c.c.) was added fairly rapidly from the dropping-funnel. When the addition was complete, the solution was heated to 70° and kept thereat for 30 minutes. The mixture was allowed to cool slowly with stirring, and then left overnight at room temperature. Most of the acetic acid was removed in a vacuum at a low temperature,

the residue poured into a large quantity of water, and the solution extracted thoroughly with ether. The ethereal solution was washed first with sodium hydrogen carbonate solution, then with water, and dried over calcium chloride. The ether was removed, leaving an oil, which solidified after long standing in the refrigerator. Crystallisation from ether–petrol (b. p. 40—60°) gave 1-*hydroxy*-2-*carbethoxyskatole* as colourless needles, m. p. 87—88° (Found: C, 65·8; H, 6·1; N, 6·7; terminal Me, 11·1. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4; terminal Me, 13·7%); yield 5·9 g., 27%. The compound was easily soluble in 2N-sodium hydroxide solution.

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