100. *Syntheses in the Indole Series. Part I. Synthesis of Indolyl-3-glyoxylic Acid and of* r-3-*Indolylglycine.*

By John W. Baker.

The lower homologue of tryptophan, 3-indolylglycine, is important in mechanistic studies of the degradation of *l*-tryptophan to indole by *E. Coli*.

The Grignard compound of indole condenses with the acid chloride of methyl hydrogen oxalate to give *methyl indolyl-3-glyoxylate* (I), the *oxime* of which, isolated in two forms, is readily reduced to *methyl α-aminoindolyl-3-acetate*, from which r-3-*indolylglycine* is obtained on hydrolysis.

The prototropic system present in (I) has also been examined.

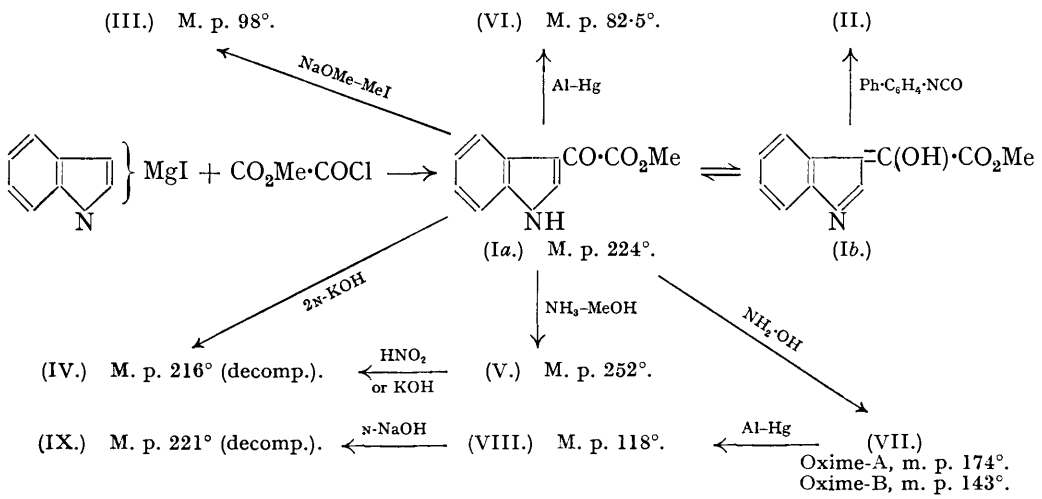
In connection with a systematic study of the mechanism of the breakdown of tryptophan with tryptophanase (Happold and Hoyle, *Biochem. J.*, 1935, **29**, 1918; Baker and Happold, to be published in *Biochem. J.*, 1940) the synthesis of a series of indole derivatives with amino-acid and keto-acid side chains in the 3-position has been commenced. Although several methods are available for the synthesis of indole derivatives which contain an alanine type of side chain, 3-indolylglycine, the lower homologue of tryptophan, has not hitherto been prepared. Repeated attempts to obtain this compound from the cyanohydrin of indole-3-aldehyde by the method of Cocker and Lapworth (J., 1931, 1391) proved unsuccessful, as also did various methods using indolyl-3-acetic acid as a starting material. Attention was then turned to the use of the Grignard compound of indole itself. Condensation of equimolecular quantities of the acid chloride of methyl hydrogen oxalate with indolylmagnesium iodide, the former reagent being in excess throughout the reaction, affords a good yield of *methyl indolyl-3-glyoxylate* (I). As anticipated, this contains a prototropic pentad system. It affords an *acetyl* derivative (? *O*- or *N*-) and with xenylcarbimide it affords the *xenylurethane* (II) of the enolic form (I*b*). Methylation of (I) with sodium methoxide and methyl iodide readily converts it into *methyl* 1-*methylindolyl-3-glyoxylate* (III). Hydrolysis of (I) with 2N-potassium hydroxide gives *indolyl-3-glyoxylic acid* (IV), which gives almost colourless solutions in benzene and ethyl acetate, although the crystals themselves are yellow. The same acid is obtained from the *amide* (V) either by hydrolysis or by the action of nitrous acid. A substance thought to be this acid was obtained in small yield by Sanna (*Rend. Seminario facolta Sci. Univ. Cagliari*, 1934, **4**, 28 : cf. *Chem. Abstr.*, 1936, 6363) by boiling 3-trichloroacetylindole with aqueous potassium carbonate, but all attempts to obtain a copy of this paper have been unsuccessful, so a comparison of the properties of the two specimens has not been possible. Reduction of (I) with aluminium amalgam in moist ether converts it into *methyl indolyl-3-glycollate* (VI). Sanna (*loc. cit.*) claims to have obtained the corresponding indolyl-3-glycollic acid, m. p. 174°, by hydrolysis of 3-dichloroacetylindole with boiling 5% potassium hydroxide solution, followed by acidification with dilute hydrochloric acid. Hydrolysis of (VI) with N-sodium hydroxide at about 50°, followed by addition of a very slight excess of 0·5N-hydrochloric acid, gives an immediate white precipitate of an acid, which, however, rapidly turns violet, presumably owing to atmospheric oxidation, since the colour is destroyed by reduction with a little zinc and hydrochloric acid. This rapid oxidation militates against purification. The acid can be isolated as a dark violet powder which with ether affords an almost colourless solution, leaving the coloured material insoluble. Addition of light petroleum to the ethereal solution gives a white precipitate, which immediately turns violet again. Although only an abstract of Sanna's paper is available, it appears doubtful whether the acid he describes was actually indolyl-3-glycollic acid.

Methyl indolyl-3-glyoxylate affords a convenient material from which to synthesise 3-indolylglycine. When refluxed with hydroxylamine hydrochloride and barium carbonate in dry methyl alcohol, it is converted into a mixture of oximes (VII); *oxime-A* is the major product, and a small amount of *oxime-B* can be isolated with difficulty from the mother-liquor. Reduction of oxime-A with aluminium amalgam in moist ether converts

it into *methyl α-aminoindolyl-3-acetate* (VIII), from which r-3-*indolylglycine* (IX) is readily obtained by hydrolysis with warm N-sodium hydroxide.

The condensation of ester acid chlorides of dibasic acids with indolylmagnesium iodide thus appears to open up a fertile field of synthesis in the indole series, but since the investigation is likely to be interrupted by present conditions it was decided to place these preliminary results on record. They are summarised in Table I.

TABLE I.



EXPERIMENTAL.

Methyl Indolyl-3-glyoxylate.—A solution of 17·4 g. of indole in 100 c.c. of dry ether was added to a cold solution of the Grignard compound prepared from 3·6 g. of magnesium turnings and 24 g. of ethyl iodide in about 30 c.c. of dry ether. The mixture was refluxed until the evolution of ethane ceased. The resulting solution of the Grignard compound of indole was added dropwise with vigorous mechanical stirring to a solution of 18·3 g. of the acid chloride of methyl hydrogen oxalate (Scholl and Egerer, *Annalen*, **1913**, **397**, 326) cooled in ice–salt. The product, containing a thick, dark brown mass, was immediately decomposed with ice and ammonium chloride, the liquid filtered, and the residual ester washed with ether–acetone to remove colouring matter. Crystallisation of the almost colourless ester (16 g.) from absolute alcohol and then from acetone gave *methyl indolyl-3-glyoxylate* (I) in fine needles, m. p. 224° after sintering at about 210° (Found : C, 64·6; H, 4·4; N, 6·9. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4; N, 6·9%). A further quantity of the ester, obtained by concentration of the ethereal layer together with ethereal extracts of the aqueous liquor after washing with sodium bicarbonate solution and drying over sodium sulphate, was purified by decolorisation with charcoal and crystallisation from acetone.

The ester (I) was warmed on the steam-bath with a little acetyl chloride and a few drops of pyridine, and the product washed with water and repeatedly crystallised from absolute alcohol; the *acetyl* derivative had m. p. 130° (Found : C, 63·65; H, 4·5; N, 5·9. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

A mixture of 0·05 g. of (I) and 0·05 g. of xenylcarbimide was gently warmed until it fused and was then kept at 100° for 48 hours. The product extracted by hot benzene was repeatedly crystallised from benzene or benzene–ligroin (b. p. 60—80°), giving the *xenylurethane* (II), which shrank suddenly at 167° but did not clear (to a brown liquid) until 200° (Found : C, 70·5; H, 4·65. $C_{24}H_{18}O_4N_2$ requires C, 70·8; H, 4·8%).

A little of the ester (I) was added to a few c.c. of aqueous ammonia (*d* 0·880) and an equal volume of absolute alcohol. The resulting pale yellow solution was kept at room temperature for 24 hours and then evaporated to dryness on the steam-bath. Crystallisation (twice) of the colourless crystalline residue from hot aqueous alcohol gave slightly impure *indolyl-3-glyoxylamide* (V), m. p. 252° (slight decomp.) (Found : C, 62·9; H, 4·2; N, 14·1. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%). When boiled with concentrated aqueous potassium hydroxide,

the amide evolved ammonia and gave a yellow solution, acidification of which gave the acid (IV) (below). The same acid was obtained, together with much unchanged material, when the amide was warmed (50—60°) with sodium nitrite in aqueous-alcoholic hydrogen chloride. After cooling, much unchanged amide crystallised. The mother-liquor was evaporated to dryness on the steam-bath, and the residue extracted with boiling benzene. A small amount of the acid crystallised from the yellow solution so obtained.

Indolyl-3-glyoxylic Acid (IV).—A little of the ester (I) was warmed with 10 c.c. of 2N-sodium hydroxide at 40—50° and the yellow solution, after being kept at room temperature for 2 hours, was filtered into ice-cold hydrochloric acid. The precipitated acid was filtered off, washed with water, drained on porous tile, and repeatedly crystallised from ethyl acetate–benzene. The *acid*, m. p. 216° (decomp.) after darkening at 196°, was obtained in fan-like clusters of small yellow needles (Found: C, 64·1; H, 3·7; N, 7·35. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7; N, 7·4%).

Methylation of (I).—The ester (I) (1·0 g.), dissolved in dry methyl alcohol, was added to a solution of 0·11 g. of sodium in 20 c.c. of dry methyl alcohol, and the yellow solution refluxed for 10 minutes. An excess of methyl iodide (3 c.c.) was added, and the solution refluxed for 1·5—2 hours. After evaporation of most of the methyl alcohol the residue was dissolved in ether, washed with water and aqueous sodium carbonate, and dried over calcium chloride. When the ethereal solution was concentrated, some unchanged (I) (m. p. and mixed m. p. 222°) separated; the residue from the mother-liquor slowly crystallised in a vacuum desiccator. After draining on porous tile, crystallisation from ether containing a little methyl alcohol afforded *methyl 1-methylindolyl-3-glyoxylate* (III), m. p. 98°, in well-formed prisms (Found: C, 66·3; H, 5·3. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1%).

Reduction of (I).—The ester (I) (1·0 g.) was reduced, in suspension in moist ether containing a little methyl alcohol, with aluminium amalgam (Vogel, J., 1927, 597). After 2—3 hours the liquid was filtered, and the residual aluminium hydroxide repeatedly extracted with dry ether. The residue from the combined ethereal extracts after drying over sodium sulphate was a non-homogeneous liquid, which slowly crystallised in a vacuum desiccator. After draining on porous porcelain the ester was repeatedly crystallised from benzene and then from ether–ligroin. *Methyl indolyl-3-glycollate*, m. p. 82·5°, was obtained in hard compact masses (Found: C, 64·4; H, 5·55; N, 6·9. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%). It had a great tendency to separate as an oil from solvents.

Synthesis of r-3-*Indolylglycine.—Oximes of* (I). A mixture of 4 g. of the keto-ester, 1·75 g. of hydroxylamine hydrochloride, and 2·5 g. of pure barium carbonate in 200 c.c. of dry methyl alcohol was refluxed for 36 hours. After filtration from barium chloride the solution was evaporated to dryness on a steam-bath, and the residue repeatedly extracted with boiling ether. Addition of ligroin (b. p. 40—60°) to the concentrated ethereal solution gave *oxime-A* (VII), which, after repeated crystallisation from dry ether, had m. p. 174° to an orange-red liquid (Found: C, 60·7; H, 4·9; N, 12·5. $C_{11}H_{10}O_3N_2$ requires C, 60·6; H, 4·6; N, 12·8%). From the accumulated mother-liquors the much more soluble *oxime-B* was isolated in small yield; after crystallisation from ether–ligroin (b. p. 40—60°) it was obtained in stellate clusters of fine prisms, m. p. 143° (Found: C, 61·0; H, 4·8%). A mixture with oxime-A softened at 140° and melted indefinitely between 143° and 165°.

Reduction of the oxime. Oxime-A (1 g.), containing a little of oxime-B, (m. p. 166°) was reduced with aluminium amalgam made from 1·5 g. of thin aluminium foil in 100 c.c. of moist ether. Evaporation of a small portion of the dried ethereal extract after working up as above gave a residue which quickly crystallised. The main bulk of the ethereal solution was concentrated, seeded, and allowed to crystallise. Crystallisation first from benzene–ligroin (b. p. 80—100°) and finally from benzene gave *methyl α-aminoindolyl-3-acetate* (VIII), m. p. 118° (Found: C, 64·8; H, 6·1. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

Hydrolysis of the glycine ester. The ester (VIII) (0·2 g.) and a little water were warmed with 1 c.c. of N-sodium hydroxide (theoretical quantity). It went rapidly into solution. Immediate acidification with 2·0 c.c. of 0·5N-hydrochloric acid precipitated the free acid. After draining on porous porcelain crystallisation from a concentrated aqueous solution gave r-3-*indolylglycine* (IX), m. p. 221° (decomp.) (Found: C, 62·4; H, 5·4. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3%). The acid is insoluble in acetone and most organic solvents.

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