88. *Syntheses in the Indole Series. Part II. Derivatives of β-Keto-β-3-indolylpropionic Acid.*

By JOHN W. BAKER.

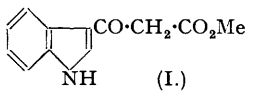
Indolylmagnesium iodide reacts with the acid chloride of the appropriate alkyl hydrogen malonate to give *methyl* (I) and *ethyl β-keto-β-3-indolylpropionate*, hydrolysis of which affords 3-indolyl methyl ketone (II). With nitrosyl chloride (I) affords its *oximino*-derivative, whilst with hydroxylamine it is converted into 3-3'-*indolyl*iso*oxazolid*-5-*one*.

The complex action of phenyl *iso*cyanate on (I) and (II) has been investigated.

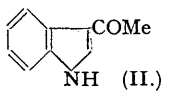
IN continuation of the experimental study of possible intermediates in the enzymic breakdown of tryptophan to indole and verification of the tentative mechanism proposed by Baker and Happold (*Biochem. J.*, 1940, **36**, 657; Baker, Happold, and Walker, to be published in *Biochem. J.*, 1946) it became desirable to investigate

possible routes for the synthesis of tryptophan derivatives containing a β-keto-group. Condensation of suitable ester-acid chlorides with indolylmagnesium iodide (Baker, *J.*, 1940, 458) seemed to promise a suitable starting point for such syntheses.

Condensation of indolylmagnesium iodide with the acid chloride of methyl hydrogen malonate affords, mainly, *methyl β-keto-β-3-indolylpropionate* (I), m. p. 120°, together with a small quantity of a *substance* $(C_{10}H_9ON)_x$, m. p. 204°, which is not identical with 3-indolyl methyl ketone since it is devoid of ketonic properties, and for which a molecular weight determination suggests the value $x = 2$. The structure of this by-product has not been ascertained. *Ethyl β-keto-β-3-indolylpropionate*, m. p. 121°, is similarly prepared from the acid chloride of ethyl hydrogen malonate. Hydrolysis of (I) either with boiling hydrochloric acid or with cold, aqueous sodium hydroxide followed by acidification at 0°, converts it into the genuine 3-indolyl methyl ketone (II), identical with a specimen synthesised by the action of indolylmagnesium iodide on acetyl chloride. The ketonic character of (I) is confirmed by the formation of a 2 : 4-*dinitrophenylhydrazone*, but an attempt to obtain an enolic derivative with phenyl *iso*cyanate led to complex products. No condensation occurred when the two substances were kept sealed together at room temperature for 24 hours. Addition of a few drops of triethylamine * to a hot solution of (I) and phenyl *iso*cyanate in dry benzene gave a *product*, m. p. 143° (decomp.), of composition approximating to the addition of two molecules of the *iso*cyanate to (I). In most solvents it formed a gel, attempts to purify which, gave a new *substance*, m. p. 170° (decomp.), containing only one molecule of phenyl *iso*cyanate per molecule of (I) and which may be (III; R = CO_2Me), since it was converted by dilute aqueous sodium hydroxide into a *derivative*, m. p. 237°, possibly (III; R = H), by hydrolysis of the β-keto-ester grouping.



(I.)



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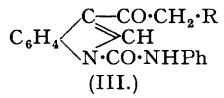

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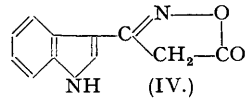

(IV.)

The triethylamine-catalysed action of phenyl *iso*cyanate on (II), however, gave a compound, m. p. 152°, isomeric but not identical with (III; R = H), which may be the phenylurethane of the enolic form of (II). In view of the main object of this series of investigations, these derivatives have not so far been examined further.

Two routes for the introduction of an amino-group into (I) have been explored. Both give crude products which show slight positive results with tryptophanase but no pure product has yet been isolated. The action of nitrosyl chloride on an ethereal solution of (I) at 0° affords its β-iso*nitroso-derivative*, m. p. 155°, and an *isomeride*, m. p. 125—126° (decomp.). Reduction of the β-*iso*nitroso-derivative has, so far, yielded no pure product.

Ethyl β-keto-β-3-indolylpropionate is converted by one molecular proportion of bromine in dry ether into its α-*bromo-ester*, m. p. 132°, which reacts with a solution of ammonia in dry methyl alcohol, saturated at 0°, to give a bromine-free product, the structure of which has not yet been established.

With hydroxylamine hydrochloride and barium carbonate in boiling methyl alcohol (I) affords 3-3′-*indolyl*-iso*oxazolid*-5-*one* (IV), m. p. 192° (decomp.), a possible intermediate for the synthesis of β-amino-β-3-indolylpropionic acid.

Experimental.

Methyl β-Keto-β-3-indolylpropionate.—Indole (17·4 g.) dissolved in dry ether (100 c.c.) was added to the Grignard compound prepared from 3·6 g. of magnesium and 24 g. of ethyl iodide in 30 c.c. of dry ether and the mixture was refluxed on a steam-bath until the evolution of ethane ceased. The decanted solution of the indolylmagnesium iodide was added dropwise, with vigorous mechanical stirring, to a dry ethereal solution of 20·4 g. of the acid chloride of methyl hydrogen malonate, cooled in an ice-salt freezing mixture. After addition was complete the red reaction mixture was immediately decomposed with ice and ammonium chloride and was repeatedly extracted with ether.

Washing this orange-red solution with sodium carbonate solution removed most of the colour, and the resulting pale yellow ethereal solution was dried (Na_2SO_4) and the ether was distilled off through a Widmer column. The residue (23 g.) partly crystallised after keeping at room temperature for 48 hours, after which dilution with cold ether and filtration at the pump gave 5—7 g. of a clean, cream-coloured powder. This was repeatedly extracted (Soxhlet) with boiling benzene which left a small amount of insoluble material, m. p. 204°, after crystallisation from methyl alcohol (Found: C, 75·3; H, 5·85; N, 8·8; *M*, 375. $(C_{10}H_9ON)_2$ requires C, 75·5; H, 5·7; N, 8·8%; *M*, 312).

Concentration of the benzene solution gave *methyl β-keto-β-3-indolylpropionate*, m. p. 120° after recrystallisation from the same solvent (Found: C, 66·5; H, 5·2; N, 6·55. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·45%).

Its dark red 2 : 4-*dinitrophenylhydrazone*, crystallised from acetone, had m. p. 262° (decomp.) (Found: C, 54·1; H, 3·9. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8%).

Ethyl β-keto-β-3-indolylpropionate, m. p. 121°, was similarly prepared (Found: C, 67·9; H, 6·1. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 255°, after crystallisation from acetone (Found: C, 55·55; H, 4·14; N, 17·1. $C_{19}H_{17}O_6N_5$ requires C, 55·45; H, 4·2; N, 17·0%).

A mixture of the methyl keto-ester (I) (0·55 g.) and phenyl *iso*cyanate (2 mols., 0·6 g.) was warmed in 5—10 c.c. of dry benzene until an almost homogeneous solution was obtained, and then a few drops of triethylamine were added. The solution was again warmed on a steam-bath for a few minutes and seeded with the product. Crystallisation began on keeping at room temperature, but the whole mass soon set to a gel. After 24 hours the mass was drained on porous porcelain in a desiccator and the powdered *product* was triturated with ether. A specimen, m. p. 143° (decomp.), was analysed (Found: C, 69·1; H, 5·4; N, 9·5. $C_{26}H_{21}O_5N_3$ requires C, 68·6; H, 4·6; N, 9·2%). Attempts to purify this specimen further by " crystallisation " from acetone gave a *product* which, after washing with a warm mixture of acetone–

* The efficacy of base catalysis in the condensation of phenyl *iso*cyanate with alcohols has been demonstrated in a series of kinetic investigations, the results of which will be published later.

ether, had m. p. 170° (decomp.) (Found: C, 67·4; H, 5·1; N, 8·9. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%). This was warmed with a few c.c. of 2N-sodium hydroxide and then kept for 24 hours at room temperature. The white crystalline material was filtered, washed, and crystallised from methyl alcohol. The product, m. p. 237°, depressed the m. p. of carbanilide (m. p. 240°) to 210—220°, and analysis suggests that it is the N-*phenylcarbamido*-derivative (III; R = H) of 3-indolyl methyl ketone (Found: C, 73·1; H, 4·9. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·0%).

Hydrolysis of the Keto-ester.—The keto-ester (0·22 g.) was kept, with frequent shaking, with 3 c.c. of cold, 0·5N-sodium hydroxide, filtered from a trace of undissolved material, and then added slowly to 3 c.c. of ice-cold 0·5N-sulphuric acid. The heavy white precipitate was filtered off and washed with water. The filtrate gave a pale purple colour with ferric chloride. Crystallisation of the dried precipitate from methyl alcohol gave 3-indolyl methyl ketone, m. p. 194°, not depressed by admixture with a synthetic specimen prepared (below) by the action of indolylmagnesium iodide on acetyl chloride (Found: C, 75·15; H, 5·8. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7%). The same ketone was obtained by ether extraction of the product resulting from hydrolysis of the keto-ester with boiling, concentrated hydrochloric acid under reflux for 1—2 hours, but much tar formation also occurs under these conditions. The ketone, m. p. 194°, depresses the m. p. of the compound $(C_{10}H_9ON)_2$, m. p. 204° (obtained in the original preparation of the keto-ester), to 167°. Moreover, the latter compound gives no precipitate with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid solution.

3-3′-*Indolyl*iso*oxazolid-5-one.* The keto-ester (I) (0·5 g.) was refluxed with hydroxylamine hydrochloride (0·2 g.) and pure barium carbonate (0·25 g.) in dry methyl alcohol (10 c.c.) for 24 hours. After cooling and filtering, the solution was concentrated to small bulk and allowed to crystallise. After twice recrystallising from methyl alcohol the iso*oxazolidone* was obtained in long slender prisms, m. p. 192° (decomp.) after darkening at *ca.* 182° (Found: 65·7; H, 4·10; N, 13·7. $C_{11}H_8O_2N_2$ requires C, 66·0; H, 4·0; N, 14·0%).

Methyl α-Oximino-β-keto-β-3-indolylpropionate.—Methyl β-keto-β-3-indolylpropionate (0·55 g.) was suspended in 10—15 c.c. of dry ether, the suspension was cooled in ice, and a stream of nitrosyl chloride (from nitrosylsulphuric acid and sodium chloride) was passed in for 10—15 minutes with frequent stirring. The insoluble cream coloured powder was separated by filtration from the orange-red solution. The powder was washed with dry ether; it was insoluble in most solvents. A specimen, m. p. 125—126° (decomp.), was analysed (Found: C, 57·3; H, 4·1. $C_{12}H_{10}O_4N_2$ requires C, 58·5; H, 4·1%). It is thus probably isomeric with the *oximino* compound which was obtained by evaporation of the ethereal filtrate under reduced pressure at room temperature. This crystallised from ether in felted masses of fine needles, m. p. 155° (Found: N, 11·2. $C_{12}H_{10}O_4N_2$ requires N, 11·4%).

Synthesis of 3-*Indolyl Methyl Ketone.*—The Grignard reagent prepared from 0·8 g. of magnesium and 5·4 g. of ethyl iodide was warmed with 3·9 g. of indole in dry ether solution until evolution of ethane ceased. The product was added dropwise to a solution of 2·6 g. of acetyl chloride in dry ether, cooled in a freezing mixture, with constant stirring. The product was decomposed with ice and ammonium chloride and extracted with ether. The residue from the dried ethereal solution was repeatedly extracted with boiling ligroin (b. p. 40—60°) to remove any unchanged indole, and the insoluble residue was extracted with ether. The portion undissolved by the ether was crystallised from benzene containing a little ethyl alcohol. 3-Indolyl methyl ketone, m. p. 194°, separated. The portion extracted with ether was evaporated, and the residue, after several crystallisations from benzene, gave 1 : 3-diacetylindole, m. p. 152° (Found: C, 71·7; H, 5·8; N, 7·4. Calc. for $C_{12}H_{11}O_2N$: C, 71·6; H, 5·5; N, 7·0%) (cf. Oddo and Sessa, *Gazzetta*, 1911, **41**, i, 239).

Action of Phenyl iso*Cyanate on* 3-*Indolyl Methyl Ketone.*—A few drops of triethylamine were added to a hot solution of 0·3 g. of the ketone and 0·4 g. of phenyl *iso*cyanate in 10 c.c. of dry benzene and the mixture was kept sealed at room temperature for 18 hours. The solid product was separated and crystallised from dry benzene. Carbanilide separated first, and from the mother liquor by repeated recrystallisation from benzene was obtained a *substance*, m. p. 154° with previous softening (Found: C, 73·5; H, 5·2; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·0; N, 10·1%).

Bromination of Ethyl β-Keto-β-3-indolylpropionate.—A solution of dry bromine (1·2 g.) in ether was added dropwise to a cold suspension of 1·74 g. of the keto-ester in the same solvent with constant stirring. The solution was evaporated over potassium hydroxide in a vacuum desiccator at room temperature until the residue was free from hydrogen bromide. The *bromo-ester* had m. p. 133° after several crystallisations from ether (Found: C, 50·3; H, 4·2; Br, 25·85. $C_{13}H_{12}O_3NBr$ requires C, 50·3; H, 3·9; Br, 25·8%).

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

THE UNIVERSITY, LEEDS. [*Received, December 7th*, 1945.]