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II. Reductive Amination of the Keto Group in 3-Carboxyacylindoles*

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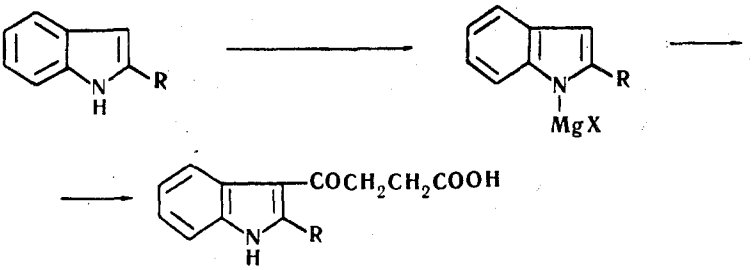
A number of indole keto acids are synthesized. It is shown that the keto group of these compounds can be transformed to an amino group, by treating the oximes with sodium in liquid ammonia.

Keto group structure and reactivity in 3-acylindoles are to a considerable extent determined by features of conjugation of the carbonyl link C=O with an electron pair of the nitrogen atom via a carbon-carbon bond of the pyrrole ring. Such conjugation is evidenced in the IR spectra by shift of the carbonyl group valence vibrations band towards lower frequencies, and by appearance of a new band in the 1550 cm^{-1} region, approximating closely to the valence vibrations of the amido group [1]. For this reason some authors [2] regard 3-acylindoles as vinyl amides. The nature of the carbonyl group is also indicated by a number of chemical properties of these compounds. Thus the action of hydrazine on 3-acylindole leads to pyrrole ring opening and formation of pyrazole derivatives [3]. Cases of deacylation on heating with alkalies have been noted [4]. N-unsubstituted 3-acylindoles are very readily reduced to the corresponding indole homologs by treatment with lithium aluminum hydride [5]. Hydroxyl derivatives where the hydroxyl group is on a carbon atom linked to the β-position in the indole, are unstable, and suffer hydrogenolysis on treatment with the same reagent [5]. The present work studies methods of reductive amination of 3-carboxyacylindoles, the latter being prepared by the action of the appropriate dicarboxylic acid anhydride on the magnesium derivative of the indole compound [6].



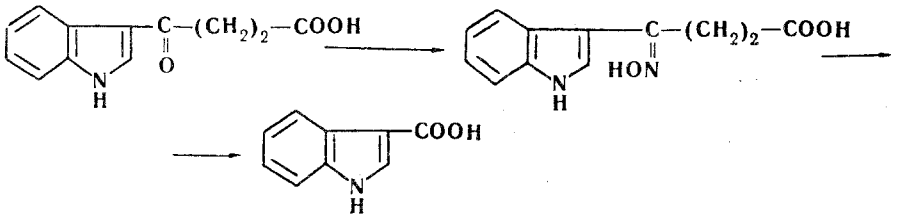
Independent of the character of the substituent in position 2 of the indole (R = H, Me, C_6H_5), the yields of the corresponding keto fatty acids vary within precisely the same limits, i.e., steric factors do not affect the reaction. It might be thought that acylation in that way does not proceed as a reaction involving transfer of the reaction center from position 1 to position 3 in the indole ring, but as an ordinary process of electrophilic acylation of the Friedel-Crafts reaction type, with magnesium iodide as the catalyst [7]. However, in our experiments, replacement of ethyl iodide by ethyl bromide was practically without effect on the reaction product yield, and indole acylation with β-carbomethoxypropionyl chloride in the presence of condensing agents such as $AlCl_3$ and $SnCl_4$ is accompanied by considerable resinification [6]. Even when benzene solutions of indole and chloride are mixed over a period of a few minutes, in the cold, an acylated indole trimer separates. If the indole is acylated using magnesium bromide as the catalyst, the yield of γ-(indolyl-3)-γ ketobutyric acid does not exceed 20%, the rest being converted to trimer and higher polymer. Under the same conditions 1-methyl indole is mainly recovered unchanged, only traces of γ-(N-methylindolyl-3)-γ-ketobutyric acid being isolated.

Attempted direct replacement of the keto group in γ-(indolyl-3)-γ-ketobutyric acid using the Leuckart reaction proved unsuccessful. When it was heated with formamide, with or without addition of formic acid, or with catalytic amounts of triethylamine and Raney nickel at 130-180°, the reaction mixtures resinified, and it did not prove possible to isolate individual compounds of indole character (failure to give a positive qualitative reaction with ninhydrin). Reductive oximination [8] was previously used in synthesizing γ-amino-γ-(indolyl-3) butyric acid, but difficulties in preparing the starting oximino acid and reducing it obliged the authors to first convert the oximino acid to the corresponding O-acetyl derivative. After a number of experiments, we began to carry out oximination of our keto acid in aqueous alkaline medium at 70-80°. The resultant oximes are quite stable compounds with sharp melting points.

*For Part I see [6].

When chromatographed on a thin layer of alumina or on paper, R_f is found to differ insignificantly from R_f for the starting keto acids (system isopropanol-ammonia-water = 8:1:1), but when the latter are present as impurities, they show themselves clearly, so that compound purity can be checked.

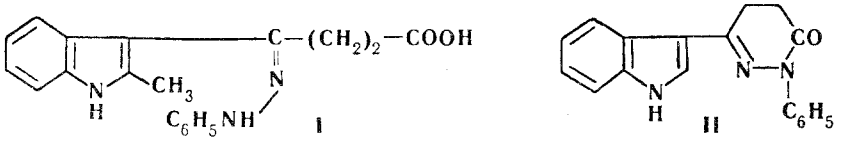
Oximination of γ-(indolyl-3)-γ-ketobutyric acid in aqueous ethanol in the presence of sodium acetate, is simultaneously accompanied by Beckmann rearrangement of the intermediate oxime. β-indolecarboxylic acid [9] can be detected in the reaction products by paper chromatography (R_f 0.35; "B" paper, isopropanol-ammonia-water = 8:1:1), indicating that the oximino group is syn to the indole ring. In acidic media the oximino group is readily hydrolyzed and simultnaeously strongly resinified.



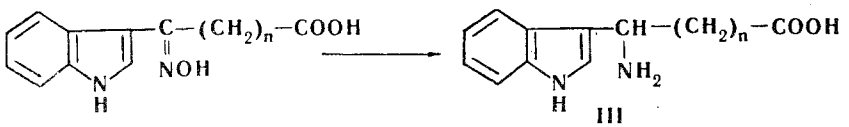
Decrease in amide character of the keto group in γ-(1-methylindolyl-3)-γ-ketobutyric acid on account of the electron-donor properties of the methyl group at the nitrogen atom somewhat facilitates formation of the corresponding oxime.

Sterically-hindered keto acids with a substituent at position 2 in the indole ring do not form oximes at all; though various conditions were used, none were obtained.

The steric hindrance factor was also encountered in the synthesis of phenylhydrazones. Thus γ-(2-methylindolyl-3)-γ-ketobutyric acid readily forms a stable, alkali-soluble phenylhydrazone (I), while under the same conditions a ketobutyric acid substituted at position 2 reacts faster, and the phenylhydrazone immediately cyclizes to give the alkali-insoluble 1-phenyl-3-(indolyl-3)- 1, 4, 5, 6-tetrahydropyridazin-6-one (II). The UV spectra of the two compounds, and also that of δ-(indolyl-3)-δ-ketovaleric acid phenylhydrazone, differ considerably, though with the first two there is distinct evidence of interaction between the C=N double bond and the indole system. In thin-layer chromatography on alumina (benzene-MeOH = 30:1) the phenylhydrazone I remains at the beginning, while the pyridazinone II has R_f 0.30.



The oximes prepared were reduced to the corresponding amino acids. It appeared to be most convenient to carry out the reduction with sodium in liquid ammonia.



The amino acids were isolated from the alkaline reaction mixture on Amberlite IRA-400 ion-exchange resin by eluting with 1-2% acetic acid. Ninhydrin (yellow color, changing to violet) and the Ehrlich reagent (rose, gradually turning brown) were used to check completeness of separation.

The indole γ- and δ-amino acids (III, n = 2, 3), obtained in 44-55% yields, are, because of their salt-forming properties, quite stable compounds. The yield of product on benzoylation reaches 90%.

Experimental

γ-(2-Methylindolyl-3)-γ-ketobutyric acid. A solution of 12.5 g (95 mmole) 2-methylindole in 25 ml anisole was added with cooling to EtMgI prepared from 2.4 g (0.1 g at) Mg turnings and 16.2 g (104 mmole) EtI in 50 ml anisole. After stirring for 20 min at room temperature, the products were held at 60–70° for 15–20 min, then a hot solution of 9.5 g (95 mmole) succinic anhydride in 50 ml anisole quickly added. The colored complex formed was heated for 2 hr on a boiling water bath, the products then decomposed with 75 ml 20% AcOH, the keto acid precipitated filtered off, washed with water, and dried in a drying oven. Yield 12 g (54%), mp 222–223° (ex MeOH). λ_{max}, mμ (lg ε): 268 (3.97), 328 (4.06) (10% aqueous NaOH). Found: C 67.34, 67.21; H 5.93, 5.88%. Calculated for $C_{13}H_{13}NO_3$: C 67.50; H 5.57%.

γ-(2-Phenylindolyl-3)-γ-ketobutyric acid. Produced in the way described above 0.85 g (0.035 g at) Mg, 5.76 g (37 mmole) EtI, and 7 g (36 mmole) 2-phenylindole in 100 ml anisole, and 3.4 g (34 mmole) succinic anhydride in 25 ml anisole gave a yellow complex, which became rose on further heating on a boiling water bath. Decomposition with AcOH, and precipitation from 10% alkali gave 4.2 g (40%) keto acid, mp 227–228° (ex MeOH), λ_{max}, mμ (lg ε) 270 (4.34), 335 (4.21) (10% aqueous NaOH). Found: C 73.44, 73.58; H 5.25, 5.28%. Calculated for $C_{18}H_{15}NO_3$: C 73.70; H 5.16%.

γ-(Indolyl-3)-γ-ketobutyric acid. A solution of 1.2 g (10 mmole) indole in 25 ml dry ether was added dropwise to a solution of $MgBr_2$ in ether prepared from 1.2 g (0.05 g at) Mg turnings and 2.5 ml bromine. The resultant oil was dissolved in a large volume of dry ether, and added dropwise, at −12 to −10° to a solution of 1.5 g (10 mmole) β-carbomethoxypropionyl chloride [10] in 15 ml dry ether. The yellow complex which separated was treated with ice and a solution of NH_4Cl. The ether layer was separated off, and the aqueous layer extracted thrice with ether. The total ether extracts were dried over $MgSO_4$, the solvent distilled off, and the residue heated for 2 hr with 2 N NaOH. The aqueous solution was acidified with dilute HCl, and the precipitate of β-(indolyl-3)-β-ketobutyric acid filtered off, yield 0.7 g (24%), mp 235° (ex AcOH) [6].

γ-(1-Methylindolyl-3)-γ-ketobutyric acid. a) Proceeding as above, a solution of 1.8 g (10 mmole) 1-methylindole in 25 ml dry ether was added to $MgBr_2$ prepared from 1.2 g (0.05 g at) Mg turnings and 2.5 ml bromine, the mixture heated on a boiling water bath for 20 min, and a solution of 1.5 g (10 mmole) β-carbomethoxypropionyl chloride in 20 ml dry ether added over 20–25 min. The products were worked up in the usual way to give 30 mg γ-(1-methyl-indolyl-3)-γ-ketobutyric acid, mp 175° (ex Me_2CO) [11].

b) 8 ml freshly-distilled Me_2SO_4 was dropped into a boiling solution of 1.1 g (5 mmole) γ-(indolyl-3)-γ-ketobutyric acid in 100 ml Me_2CO containing 5 g KOH and 25 ml water, the whole then heated 15 min on a water bath, the solvent evaporated off under reduced pressure, and the residue acidified with dilute HCl. The precipitate of γ-(1-methyl-indolyl-3)-γ-ketobutyric acid was filtered off, yield 1.1 g (93%), mp 175° (ex Me_2CO) [11].

N-Acetyl-o-[β, β-di(indolyl-3) ethyl] aniline. 0.8 g (10 mmole) AcOCl was added to a solution of 1.2 g (10 mmole) indole in 15 ml dry benzene, after some minutes a pinkish percipitate formed, it was filtered off, washed with benzene, and dried, yield 1.2 g, mp 199—201° (ex EtOH-H_2O), R_f 0.35 (Al_2O_3; benzene-MeOH = 9:1).

IR spectrum (in vaseline): 1680 (amide carbonyl); 3340, 3406 cm^{-1} (NH). UV spectrum λ_{max}, mμ (lg ε); 282 (4.92), 291 (4.86) (in MeOH). Found: C 79.41, 79.60; H 6.17, 6.19%; M 412. Calculated for $C_{26}H_{23}N_3O$: C 79.36; H 5.89%; M 3.93.

N-β-Carbomethoxypropionyl-o-[β, β-di(indolyl-3) ethyl] aniline. 1.6 g (11 mmole) β-carbomethoxypropionyl chloride was added to a solution of 1.2 g (10 mmole) indole in 15 ml dry benzene, and after some minutes 1.5 g white precipitate formed, mp 252–254° (ex MeOH). IR spectrum (in vaseline): 1654 (amide carbonyl), 1744 ($COOCH_3$), 3336 cm^{-1} (NH). UV spectrum: λ_{max} 224, 282 (hump), 289 mμ (in MeOH). Found: C 74.49, 74.25; H 6.01, 5.98%. M 437. Calculated for $C_{29}H_{27}N_3O_3$: C 74.81; H 5.85%; M 465.

γ-(Indolyl-3)-γ-oximinobutyric acid. 7.5 g (0.108 mole) hydroxylamine hydrochloride was added to a solution of 3.8 g (19 mmole) γ-(indolyl-3)-γ ketobutyric acid in 100 ml 10% NaOH, and the mixture heated on a water bath for 45–50 min at 70–80°. After cooling, the products were carefully acidified and brought to pH3 with 2 N HCl, when a yellow precipitate formed, which quickly formed a coagulum which was dispersed in powder form on trituration. Yield 3.5 g (88%) mp 145–146° (ex aqueous ethanol), R_f 0.50 ("B" paper, isopropanol-ammonia-water = 8:1:1), 0.52 ("B" paper; BuOH-AcOH-H_2O = 4:1:5). Found: C 61.78, 61.68; H 5.31, 5.19%. Calculated for $C_{12}H_{12}N_2O_3$: C 62.05; H 5.21%. The literature gives [8] mp 130–133° (decomp, ex benzene-MeOH).

δ-(Indolyl-3)-δ-oximinovaleric acid. A mixture of 3.9 g (0.018 mmole) δ-(indolyl-3)-δ-ketovaleric acid and 7.5 g (0.108 mole) hydroxylamine hydrochloride in 100 ml 10% NaOH was heated for 1 hr at 70–80°. After acidifying with dilute HCl, there was isolated 3.6 g (92%) oxime, mp 153–154° (ex MeOH-H_2O), R_f 0.55 ("B" paper, isopropanol-ammonia-water = 8:1:1). Found: C 63.71, 63.82; H 5.43, 5.47%. Calculated for $C_{13}H_{14}N_2O_3$: C 63.40; H 5.73%.

γ-(1-Methylindolyl-3)-γ-oximinobutyric acid. In a similar way 1.06 g (5 mmole) γ-(1-methylindolyl-3)-γ-ketobutyric acid, 2.1 g (26 mmole) hydroxylamine hydrochloride in 40 ml 10% NaOH gave, on working up in the usual way, 1.1 g (98%) a yellow oximino acid, mp 149–150° (ex MeOH-H_2O). Found: C 63.38, 63.28; H 6.10, 5.92%. Calculated for $C_{13}H_{14}N_2O_3$: C 63.40; H 5.73%.

γ-Amino-γ-(indolyl-3) butyric acid. About 80 ml liquid NH_3 was placed in a 3-necked flask fitted with a stirrer and air condenser carrying a soda-lime tube, and 3 g (13 mmole) γ-(indolyl-3)-γ-oximinobutyric acid added. Then 9 ml dry EtOH was added to the solution, and without removing the dry ice-Me_2CO cooling, 1.5 g Na metal added in small pieces, fresh Na being added only after complete decolorization of the solution. When the addition was finished, the reaction mixture was left at room temperature until the ammonia completely disappeared. The residue was dissolved in 30 ml water, and the amino acid precipitated on Amberlite-IRA-400 ion exchange resin (30 g). The amino acid was displaced with 1–2% AcOH. The resultant solution was evaporated to dryness under reduced pressure at a temperature not over 40°, and the oily residue treated with Me_2CO, to give 1.35 g (44%) of a white amorphous powder, mp 162–165° [8], R_f 0.67 ("B" paper, isopropanol-ammonia-water = 8:1:1); 0.54 ("B" paper, BuOH-AcOH-H_2O = =4:1:5).

γ-Benzamido-γ-(indolyl-3) butyric acid. 1 g (4.3 mmole) γ-(indolyl-3)-γ-oximinobutyric acid was reduced by the above method, using 0.5 g Na metal in 80 ml liquid NH_3, in the presence of 3 ml dry EtOH. After evaporating off the ammonia, the residue was dissolved in a small quantity of water, and benzoylated, by the Schotten-Baumann method, with 2 ml benzoyl chloride. After the odor of benzoyl chloride had vanished, the reaction mixture was acidified with 2N HCl, and the precipitate filtered off. Boiling with water removed benzoic acid, and the residue was recrystallized from MeOH, mp 226–227°, yield 1.2 g (89%), λ_{max} 270 mμ, lg ε 3.78 (10% aqueous NaOH). Found: C 70.81, 70.56; H 5.86, 5.97%. Calculated for $C_{19}H_{18}N_2O_3$: C 70.78; H 5.63%.

δ-Amino-δ-(indolyl-3) valeric acid. 1.05 g (4.3 mmole) δ-(indolyl-3)-δ-oximinovaleric acid was reduced, in the way described above, using 0.5 g Na, in liquid ammonia, and in the presence of EtOH. The amino acid was isolated, as described above, with Amberlite-IRA-400 anionite, to give 0.68 g (65%) colorless compound, mp 136–137°, R_f 0.79 ("B" paper; isopropanol-ammonia-water = 8:1:1). Schotten-Baumann benzoylation gave δ-(benzamido)-δ-(indolyl-3)-valeric acid, mp 196–197° (ex EtOH). Found: C 71.47, 71.30; H 5.81, 6.15%. Calculated for $C_{20}H_{20}N_2O_3$: C 71.41; H 5.99%.

1-Phenyl-3-(indolyl-3')-1,4,5,6-tetrahydropyridazin-6-one (II). A mixture of 1.4 g (6.5 mmole) γ-(indolyl-3)-γ-ketobutyric acid and 1.1 g (10 mmole) phenylhydrazine in 175 ml MeOH was refluxed in a flask for 30 hr, the solvent distilled off, to give an oil which was column chromatographed on grade 2 activity alumina. A fraction was taken having R_f 0.30 in thin-layer chromatography on alumina (benzene-MeOH = 25:1). The same solvent mixture was the eluant. Yield 1.1 g (53%) pale yellow compound mp 224° (ex benzene containing a small amount of MeOH). λ_{max}, mμ (lg ε): 263 (4.17), 313 (4.38) (in MeOH). Found: C 74.61, 74.80; H 5.50, 5.42%. Calculated for $C_{18}H_{15}N_3O$: C 74.71; H 5.23%.

δ-(Indolyl-3)-δ-ketovaleric acid phenylhydrazone. 1.5 g (6.5 mmole) ε-(indolyl-3)-δ-ketovaleric acid, 1.08 g (10 mmole) phenylhydrazine, and 150 ml MeOH were heated together for 35 hr, the solvent distilled off, and the residue recrystallized from benzene, to give 1 g (48%) phenylhydrazone, mp 174°; λ_{max} 335 mμ, lg ε 4.33 (in MeOH). Found: C 71.55, 71.55; H 6.12, 6.12%. Calculated for $C_{19}H_{19}N_3O_2$: C 71.02; H 5.96%.

γ-(2-Methylindolyl-3)-γ-ketobutyric acid phenylhydrazone (I). 1.2 g (5.2 mmole) γ-(2-methylindolyl-3)-γ-ketobutyric acid, 1.1. g phenylhydrazine, and 150 ml MeOH were heated together for 26 hr. The solid remaining after distilling off the solvent was recrystallized from benzene, yield 1.1 g (48%), mp 219–220°, λ_{max} (lg ε) 242 (4.25), 298 (4.14), 267 (4.14) mμ (in MeOH). Found: C 66.93, 66.96; H 5.90, 5.76%. Calculated for $C_{19}H_{19}N_3O_2 \cdot H_2O$: C 67.24; H 6.24%.

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