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THE CHEMISTRY OF INDOLE

III. Some Special Features of the Reactivity of 3-Carboxyacylindoles*

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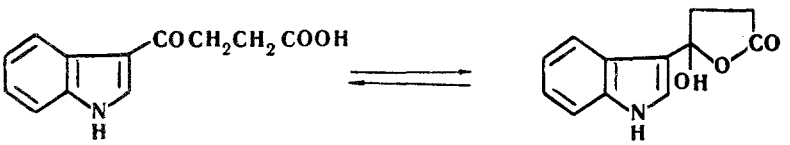
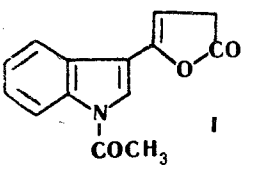
A number of amides of indole ketoacids are synthesized. 3-Carboxyacylindoles can be converted to the corresponding enol-lactones by treatment with acetic anhydride or acetyl chloride. Reaction of the lactones with ammonia or amines involves lactone ring opening, and this makes it possible to prepare some N-substituted or unsubstituted ketoacid amides. Deacylation can occur in the action of strong bases or high temperatures on indoleketoacids. Reaction of 2-(indolyl-3') benzoic acid with dimethyl sulfate proceeds in two ways: the NH group is methylated, and there is conversion to the corresponding indolenine, with subsequent methylation of the enol.

In preceding papers [1-3], we offered a method of synthesizing γ- and δ-ketoacids of the indole series, as well as their functional derivatives of the keto group. It was shown that a carboxyl group in the γ-position makes for certain difficulties in effecting substitution and reduction. To a considerable extent the structures and reactivities of the 3-carboxyacylindoles are conditioned by two factors: firstly, special features of the conjugation of the carbonyl group with the indole ring π-electrons and secondly, the possible occurrence of the γ- and δ-ketoacids in the cyclic hydroxylactone forms. Investigation of the IR spectra of these acids in the solid state [2] made it possible to decide unequivocally in favor of an open structure. But a number of chemical reactions indicate possible formation in solution of cyclic compounds by, for example, intramolecular cyclization of acyl-cations, arising from an open form [4, 5].



Thus under the action of acetyl chloride, γ-(indolyl-3)-γ-ketobutyric acid and δ-(indolyl-3)-δ-ketovaleric acid, rather readily enolize to give 40% yields of the enols, acetylation occurring at the nitrogen.



I

If, however, acetic anhydride in the presence of sodium acetate is used, the yield of enol-lactone I is only 18%.

It can be assumed that partial formation of lactol form also occurs under the action of such acid reagents as hydrochloric acid or phosphorus pentachloride. Apparently, it was for that reason that we cound not obtain γ-(indolyl-3)-γ-ketobutyryl chloride and effect Clemmensen reduction of it [3].

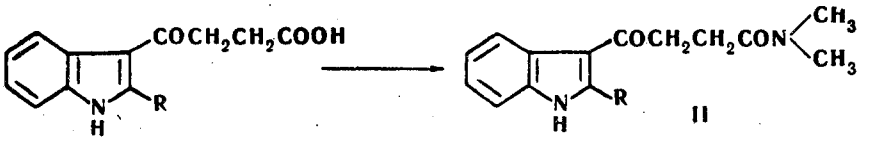
In alkali the ketoacids studied exist only in the open form. Thus an attempt to convert the above-described enol-lactones to enol lactams by treatment with ammonia leads to lactone ring opening and formation of the corresponding amides of the ketoacids, the structures of these being confirmed by retro-synthesis. Both unsubstituted amides and dimethylamides II of ketobutyric and ketovaleric acids of the indole series were obtained, the best yields (50–70%) being secured by use of the method of mixed anhydrides.

Such ketoamides are of independent interest as intermediates in the synthesis of dihomotryptamines. Actually, lithium aluminum hydride reduction of N, N-dimethyl γ-(indolyl-3)-γ-ketobutyramide (II, R = H) leads to formation of 3-(4-dimethylaminobutyl) indole, but the exceptionally low solubility of the starting compound in ether offers considerable experimental difficulty (after 15 hr it was possible to isolate only traces of compound which the IR spectrum showed not to contain carbonyl groups). There is practically no reduction of γ-(indolyl-3)-γ-ketobutyric acid itself under the same conditions. The compound isolated in traces was the corresponding alcohol (lack of absorption bands in the region of carbonyl group vibrations).

The action of lithium aluminum hydride on 2-(indoyl-3')-benzoic acid leads not only to reduction of the keto

*For Part II see [1].

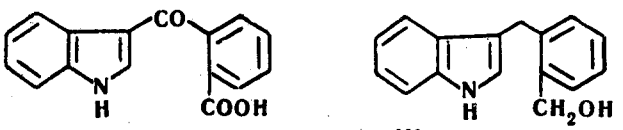
group to methylene, but also of the carboxyl group to an alcohol one.



II

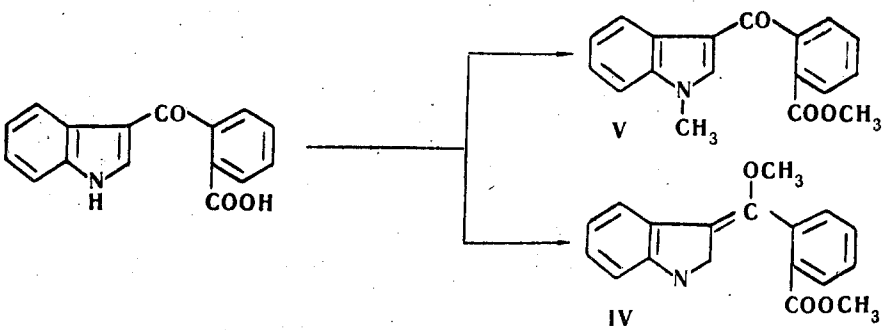
Amides of Indole Ketoacids

Name	Mp, °C	Formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
δ-(indolyl-3)-ε-keto-valeramide	150—151	$C_{13}H_{14}N_2O_2$	67,46 67,55	6,12 6.10	—	67,80	6.13	—	55
γ-(2-Methylindolyl-3)-γ-ketobutyramide	198	$C_{13}H_{14}N_2O_2$	67,59	5.92	—	67,80	6.13	—	54
γ-(2-Phenylindolyl-3)-γ-ketobutyramide	222	$C_{18}H_{16}N_2O_2$	—	—	9.54 9.36	—	—	9,58	70
N, N-Dimethyl γ-(indolyl-3)-γ-ketobutyramide	180—181	$C_{14}H_{16}N_2O_2$	68,42 68,34	6.71 6,71	—	68.81	6.61	—	46
N, N-Dimethyl δ-(indolyl-3)-δ-ketovaleramide	187—188	$C_{15}H_{18}N_2O_2$	69.78 69.88	7.01 7.13	—	69.76	7.01	—	65
N, N-Dimethyl γ-(2-phenyl-indolyl-3)-γ-ketobutyramide	190—191	$C_{20}H_{20}N_2O_2$	74.64 74.58	6.10 6.07		74.98	6.29	—	57



III

The action of diazomethane on the keto acids which we have previously described [2] gave almost quantitative yields of the corresponding methyl esters. It is proved that methylation of the nitrogen of the indole ring does not occur. We obtained 1-methyl keto acids by use of dimethyl sulfate in alkali. In some cases simultaneous esterification of the carboxyl group was observed. Alkali facilitates formation of an indolenine structure. When 2-(indoyl-3') benzoic acid is methylated, compound IV is isolated as a side reaction product (frequencies 1640 cm^{-1} (C=N) and 1722 cm^{-1} ($COOCH_3$)).



Acid hydrolysis of IV leads not only to formation of the keto form, but to simultaneous alkylation of the nitrogen atom, i.e., to structure V (shown chromatographically, and also by comparison of melting points).

Peculiarities of the keto group at the β-position in the indole ring are further exhibited in the comparative ease of deacylation. It is known that when 3-acylindoles are heated at 200–220° in the presence of alkoxides of alkali metals, the corresponding indole homologs are formed [6]. Actually we isolated 3-ethylindole when γ-(indolyl-3)-γ-keto-

butyric acid was refluxed with sodium ethoxide in toluene. Further, thin-layer chromatography on alumina showed that similar deacylation occurs when γ-(2-phenylindolyl-3)-γ-ketobutyric acid is reduced with Raney alloy in alkaline solution under the conditions previously described. 2-Phenylindole [R_f 0.64 (Al_2O_3; benzene); 0.43 (Al_2O_3; benzene-n-heptane 3:1)] was detected among the reaction products. The side chain is also split off when the ketoacid is heated above its melting point in a vacuum. Thus 2-(indoyl-3') benzoic acid is decomposed into phthalic anhydride and indole (shown chromatographically), which latter immediately dimerizes under the conditions used.

Experimental

γ-(1-Acetylindolyl)-$\Delta^{\beta,\gamma}$-butenolide (I). a) A mixture of 2.2 g (10 mmole) γ-(indolyl-3-)-γ-ketobutyric acid and 60 ml freshly-distilled acetyl chloride was refluxed for 5 hr, and after distilling under reduced pressure, the product was recrystallized from petrol ether (bp 70–80°), yield 0.9 g (40%), of a yellow amorphous product, mp 152°.

b) A mixture of 1 g (4.6 mmole) γ-(indolyl-3)-γ-ketobutyric acid, 50 ml Ac_2O, and 2 g NaOAc, was refluxed for 2 hr in a current of dry N_2. Then the Ac_2O was distilled off under vacuum, and the residue repeatedly extracted with hot petrol ether (bp 80–90°), and on cooling the extracts gave 0.17 g (18%) lactone, mp 153° (ex petrol ether) [5]. IR spectrum 1654, 1714, 1782 cm^{-1}.

6-(1'-Acetylindolyl-3')-3,4-dihydropyr-2-one. 2.3 g (10 mmole) δ-(indolyl-3)-δ-ketovaleric acid was cyclized by treating it with 60 ml AcCl. After working up in the usual way, there was obtained 1 g (40%) dihydropyrone, mp 154° (ex benzene). IR spectrum: 1652, 1714, 1764 cm^{-1}. UV spectrum: λ_{max} (lg ε) 235 (4.69), 300 (4.51), 365 mμ (2.20) (in MeOH). Found: C 70.25, 70.09; H 5.18, 5.36%. Calculated for $C_{15}H_{13}NO_3$: C 70.57; H 5.13%.

γ-(Indolyl-3)-γ-ketobutyramide. a) A solution of 1 g (4.6 mmole) γ-(indolyl-3)-γ-ketobutyric acid in 40 ml EtOH was placed in a pressure tube, strongly cooled, and saturated with NH_3. After sealing it was heated at 115° for 20 hr, the EtOH distilled off under reduced pressure, and the residue recrystallized from 33% aqueous MeOH, to give 0.4 g amide, mp 210° [5], R_f 0.85 (Al_2O_3; isopropanol-ammonia-water = 8:1:1).

b) A mixture of 2.17 g (10 mmole) γ-(indolyl-3)-γ-ketobutyric acid and 0.8 g (13 mmole) urea was heated for 2 hr 30 min on an oil bath at 135–145°. The melt obtained was treated with a small quantity of MeOH, and the insoluble precipitate filtered off. It was then recrystallized (boiled with active charcoal) from 33% MeOH. Yield 0.62 g (29%), mp 204–205°. IR spectrum (in vaseline); 1618, 1626 (CO), 1671 (amide carbonyl); 3200, 3292, 3380 (NH, NH_2) cm^{-1}.

c) 2.2 g (20 mmole) $ClCO_2Et$, is rapidly added to a mixture of 4.3 g (20 mmole) γ-(indolyl-3)-γ-ketobutyric acid, 2.05 g (20 mmole) Et_3N, and 70 ml $CHCl_3$ at −5°, the mixture stirred for 15 min, then dry NH_3 passed in for 5 min, and the whole left for 1 hr at room temperature. The $Et_3N \cdot HCl$ precipitate was dissolved in water (0.7 g starting ketoacid, mp 230°, was recovered by acidifying the water layer), when a precipitate separated from the $CHCl_3$ layer, and this was filtered off, washed with water, and dried, yield 0.8 g amide, mp 209° (ex MeOH-H_2O). The chloroform extract was washed with a saturated aqueous solution of $NaHCO_3$, and then dried over anhydrous $MgSO_4$. After distilling off the solvent, there was obtained a further 0.6 g amide, mp 210–212°, total yield 1.4 g (39%, calculated on the reacted acid).

Method c was used to synthesize the other ketoacids. Dry NH_3 (or Me_2NH) was passed into a mixture of 5 mmole of the appropriate ketoacid, 0.26 g (2.6 mmole) Et_3N, and 0.26 g (2.4 mmole) $ClCO_2Et$. The table gives yields, melting points, and elementary analytical data for the amides, which were recrystallized from 33% MeOH.

2-(Skatyl) benzyl alcohol (III). 1.32 g (5 mmole) 2-(indolyl-3) benzoic acid was reduced in a Soxhlet apparatus, over 14–15 hr, with 1 g (26 mmole) $LiAlH_4$. The resultant yellow complex was carefully decomposed with moist ether and dilute HCl. The aqueous layer was extracted a few times with ether. The total ether extracts were dried over calcium chloride. After distilling off the solvent there remained an oil which was then dissolved in $CHCl_3$, and chromatographed on neutral Al_2O_3. Elution was with $CHCl_3$, and the eluate had a blue opalescence. The solvent was evaporated off, and the residue recrystallized from petrol ether, mp 78–80°, yield 0.3 g, R_f 0.45 (Al_2O_3; benzene-MeOH = = 9:1); 0.14 (Al_2O_3; CH_2Cl_2). λ_{max} (lg ε) 267 (4.16) hump 338 (3.49 mμ (in MeOH). Found: C 80.52, 80.51; H 6.53, 6.42%. Calculated for $C_{16}H_{15}NO$: C 80.95; H 6.37%.

Methyl cis-2-(indoyl-3) cyclohexene-4-carboxylate. An ethereal solution of diazomethane was prepared by treating 17 g N-nitrosomethylurea with a saturated solution of KOH, and 2.7 g (10 mmole) cis-2-(indoyl-3)-cyclohexene-4-carboxylic acid added to it. After standing for 10 hr at room temperature, the solvent was distilled off, and the residue (2.6 g, 93%) recrystallized from benzene-cyclohexane (1:1), mp 132°. IR spectrum (in vaseline): 3320 (NH), 1724 ($COOCH_3$), 1630, 1614 (CO) cm^{-1}. UV spectrum: λ_{max} (lg ε) 240–243 (4.13), 295 (4.14) mμ (in MeOH). Found: C 71.90, 71.88; H 6.48, 6.52%. Calculated for $C_{17}H_{17}NO_3$: C 72.06; H 6.06%.

Methyl cis-2-(indoyl-3)-bicyclo [2, 2, 1] hept-5-ene-3-carboxylate. Similarly, diazomethane esterification of 2.5 g (9 mmole) cis-2-(indoyl-3)-bicyclo [2, 2, 1] hept-5-ene-3-carboxylic acid gave 2.4 g (91%) of the Me

ester, mp 195° (ex benzene + little MeOH). R_f 0.25 (Al_2O_3; benzene-MeOH = 9:1). UV spectrum: λ_{max} mμ (lg ε) 240-243 (4.26), 296 (4.12) (in MeOH). Found: C 73.03, 73.31; H 5.85, 5.76%. Calculated for $C_{18}H_{17}NO_3$: C 73.20; H 5.80%.

Methyl-2-(indoyl-3) benzoate. 1 g (3.8 mmole) 2-(indoyl-3) benzoic acid similarly gave 1 g (96%) of the Me ester, mp 199-199.5° (ex MeOH); R_f 0.27 (Al_2O_3; benzene-MeOH = 9:1). Found: C 72.91, 72.81; H 4.86, 4.96%. Calculated for $C_{17}H_{13}NO_3$: C 73.11; H 4.69%.

0.3 g Me ester was refluxed for 1 hr 30 min with 2 N NaOH, the products allowed to cool, and made acid with dilute HCl, when 0.28 g 2-(indoyl-3) benzoic acid was obtained, mp 193-194° (ex aqueous MeOH).

Dimethyl sulfate methylation of 2-(indoyl-3) benzoic acid. 8 ml Me_2SO_4 was added over 30 min to a boiling solution of 1.32 g (5 mmole) 2-(indoyl-3) benzoic acid in 100 ml Me_2CO containing 5.6 g KOH and 25 ml H_2O. A white crystalline precipitate formed as the addition proceeded. After heating for 15 min longer the solvent was distilled off under reduced pressure and the precipitate which separated filtered off, 1.25 g, mp 100-103°. Recrystallization from aqueous MeOH gave 0.65 g 3-(α-methoxy-o-carboethoxybenzylidene) indolenine (IV) mp 112-113°; R_f 0.80 (Al_2O_3; benzene-MeOH = 9:1). UV spectrum: λ_{max}, mμ (lg ε) 257 (4.37), 283-286 (4.39) (in MeOH). Found: C 73.90, 74.07; H 5.54, 5.53%. Calculated for $C_{18}H_{15}NO_3$: C 73.70; H 5.16%.

Compound IV was refluxed for 15 hr with 2 N NaOH, and the reaction products acidified with dilute HCl to give 3-(α-methoxy-o-carboxybenzylidene) indolenine, mp 244° (ex MeOH).

The residue after recrystallizing from aqueous MeOH was crystallized from MeOH, to give 0.5 g compound V, mp 132°. R_f 0.80 (Al_2O_3; benzene-MeOH = 9:1). λ_{max}, mμ (lg ε) 250 (4.75), 312 (4.82) (in MeOH). Found: C 73.64, 73.73; H 5.24, 5.21%. Calculated for $C_{18}H_{15}NO_3$: C 73.70; H 5.16%.

Hydrolysis with NaOH solution gave 2-(1-methyl indoyl-3) benzoic acid, mp 233-234° (ex aqueous MeOH). R_f 0.47 (paper; BuOH saturated with 5% aqueous ammonia); 0.94 (paper; isopropanol-ammonia-water = 8:1:1). Found: C 68.88, 68.65; H 5.24, 5.15%. Calculated for $C_{17}H_{13}NO_3 \cdot H_2O$: C 68.68; H 5.09%.

Cis-2-(1-methylindoyl-3) cyclohexene-4-carboxylic acid. In the way described above, 1.35 g (5 mmole) cis-2-(indolyl-3) cyclohexene-4-carboxylic acid gave 1.27 g (85%) of the Me ester of the N-methylated ester, mp 182-183° (ex aqueous MeOH) Found: C 72.45, 72.56; H 6.56, 6.38%. Calculated for $C_{18}H_{19}NO_3$: C 72.70; H 6.44%.

Acidification of an alkaline solution gave 0.1 g cis-2-(1-methylindoyl-3) cyclohexene-4-carboxylic acid, mp 194-195° (ex aqueous MeOH). Found: C 72.46, 72.49; H 6.26, 6.38%. Calculated for $C_{17}H_{17}NO_3$: C 72.06; H 6.06%. 0.5 g of the Me ester of the acid was heated for 1 hr 30 min with 2 N NaOH; acidification then gave a compound mp 194-195°, identical with that described above.

γ-(2-Phenylindolyl-3) butyric acid. 4 g powdered Raney alloys was added in small portions, over 60-90 min, to a solution of 1.46 g (5 mmole) γ-(2-phenylindolyl-3)-γ-ketobutyric acid in 40 ml 10% NaOH at 90°, and then a further 20 ml alkali solution and 2 g Raney alloy were added. After that the reaction mixture was heated for 1 hr, the hot solution carefully filtered, cooled, and dilute HCl added slowly, dropwise, until the products were acid. Yield 0.45 g γ-(2-phenylindolyl-3) butyric acid, mp 138-139° (ex aqueous EtOH) [7].

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