INDOLE DERIVATIVES.

XCIX.* REACTION OF INDOLES WITH CHLOROACETIC ACIDS

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Indole and 2- and 5-substituted indoles react with both chloroacetic and dichlorolacetic acids to give 3-indolylacetic acids. Substitution of the pyrrole ring in the 1 and 3 positions hinders the reaction. The pathways of formation of heteroauxin from indole and chloroacetic acid are discussed.

The reaction of indole with chloroacetic and other ω-haloalkanoic acids gives heteroauxin and its homologs [2]. Substituted indoles (Ia-e) also react with chloroacetic acid to give the corresponding 3-indolyl acetic acids but in lower yields than in the case of heteroauxin. The alkylation of 5-methoxyindole is accompanied by demethylation, so that a mixture of 5-hydroxy-3-indolyl- and 5-methoxy-3-indolylacetic acids is obtained. When 5-nitroindole is treated with chloroacetic acid, the reaction mass resinifies and indole compounds of acidic character cannot be isolated. 1-Methyl-2,3-dimethyl-, and 3-phenylindoles do not react with chloroacetic acid under our conditions.

Unexpectedly, it was found that heteroauxin is formed in almost quantitative yields when indole is heated with dichloroacetic acid in alkaline solution (under pressure). 2-Substituted indoles (Ib,c) behave similarly. Indole does not react with trichloroacetic acid under these conditions.

Thus substitution in the 1 and 3 positions of the pyrrole ring interferes with alkylation of indole with halo acids, whereas in other respects the reaction apparently is general in character, although it is complicated in some cases by side processes.

Whereas alkylation of indole with haloalkanoic acids is a convenient method in a preparative respect for the synthesis of 3-indolylalkanoic acids, the problem of the possible pathways of their formation is rather complex. An analogous reaction — alkylation of indole with hydroxy acids, in particular, glycolic acids [3] — is considered to be a process in which the decisive point is the reaction of indole in the active indolenine form with the glyoxylic acid formed due to dehydrogenation of glycolic acid. Dehydrogenation of alcohols, which is one of the steps in the Guerbet reaction [4], was observed during the benzylation of indole with benzyl alcohol [5] and may be due to the catalytic action of the walls of the apparatus during operation under pressure. Subsequent reduction of the alkylidene derivative (III) with hydrogen under the reaction conditions (~40 atm absolute) is somewhat doubtful.

In addition, in our case it was not possible to make allowance for the alternative possibility of electrophilic substitution in the 3 position or rearrangement of the initially formed 1-indolylacetic acid to heteroauxin [a similar reaction — iso-

*See [1] for communication XCVIII.

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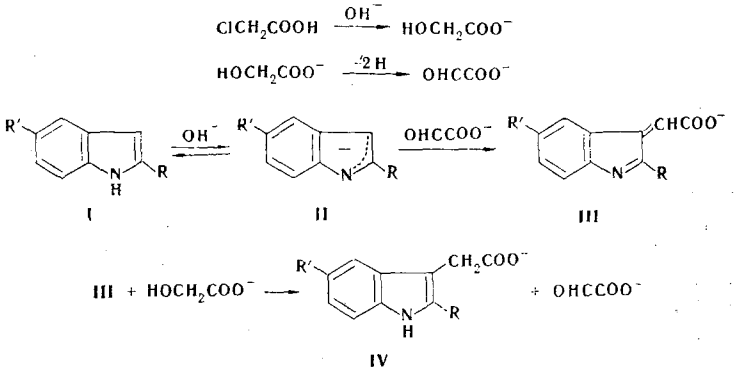
merization of 3-(1-indolyl)propionic acid to 3-(3-indolyl)propionic acid — was described in [6]].

However, this assumption was not confirmed. 1-Substituted indoles, which are incapable of conversion to anion II, do not react with chloroacetic acid, and quaternization of the structure here is apparently inadequate. This reagent, like benzyl chloride under these conditions, does alkylate indole, but the product is benzoic acid, i.e., the reaction proceeds via the known benzylation scheme. Finally, 1-indolyl acetic acid is not isomerized to heteroauxin.

At the same time the quantitative yield of heteroauxin in the reaction of indole with dichloroacetic acid in alkaline solution provided a basis to assume that, strictly speaking, the alkylating reagent is glyoxylic acid. This was confirmed by alternative synthesis of heteroauxin from indole and glyoxylic acid ester. The yield of heteroauxin increased as the amount of glyoxylic acid was increased, and this indicated the equilibrium character of the reaction.

All of this with allowance for data on base-catalyzed carbinol—carbonyl equilibrium reactions [7, 8], makes it possible to present the possible scheme of the alkylation of indole with chloroacetic acid.



I a R=R′=H; b R=CH_3, R′=H; c R=C_6H_5, R′=H; d R=H, R′=Cl; e R=H, R′=CH_3O;
IV a R=R′=H; b R=CH_3, R′=H; c R=C_6H_5, R′=H; d R=H, R′=Cl; e R=H, R′=CH_3O;
f R=H, R′=OH

The role of glyoxylic acid is still not completely clear. It itself may reduce intermediate III. In addition, under the reaction conditions, it may undergo disproportionation [9] and conversion to glycolic acid (oxalic and formic acids were detected in the reaction products). The latter seems more likely to us, inasmuch as both the alkylation of indole with dichloroacetic acid and yet another variant of the reaction — alkylation by lactones [6] — are explained in this case.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-20 spectrometer.

3-Indolylacetic Acids (IV). A 100-ml steel rotating autoclave was charged with 1.3 g (11 mmole) of indole I, 1.4 g (15 mmole) of monochloroacetic acid, 5.6 g (0.1 mole) of potassium hydroxide, and 30 ml of water. The autoclave was filled with nitrogen (~5 atm absolute) and heated at 240-250° for 10-12 h. The reaction mixture was then cooled to 5-10°, and a small amount of unchanged indole was removed by filtration. The filtrate was extracted with ether and acidified to pH 2-3 with dilute hydrochloric acid. The resulting precipitate was separated, washed to neutrality with water, and dried. The filtrate was extracted twice with ether, and the residue obtained after the usual workup from the ether extract was combined with the material isolated previously. The data are presented in Table 1.

Practically quantitative amounts of starting indoles were isolated from the reaction mixtures after treatment of 1-methyl- 2,3-dimethyl-, and 3-phenylindoles with monochloroacetic acid under these conditions.

TABLE 1. 3-Indolylacetic Acids

Compound	Indole (I) R	Indole (I) R′	mp, °C*	IR spectra cm^{-1} ν_{CO}	IR spectra cm^{-1} ν_{NH}	Empirical formula	N, % found,	N, % calc.	Yield %
IVa[3]	H	H	165	1700	3400	—	—	—	95
IVb[10]	CH_3	H	197	1720	3420	$C_{11}H_{11}NO_2$	7,3	7,4	57
IVc[11]	C_6H_5	H	173—174	1720	3420	$C_{16}H_{13}NO_2$	5,8	5,6	30
IVd[12]	H	Cl	156—157	1700	3420	$C_{10}H_8ClNO_2$	7,0	6,7	24
IVe[13]	H	CH_3O	142	1700	3380	$C_{11}H_{11}NO_3$	7,2	6,8	3
IVf[14]	H	OH	141—144	1700—1720	3420 ν_{OH} 3520	$C_{10}H_9NO_3$	7,3	7,5	70

*Compounds IVa,b,d were crystallized from aqueous alcohol, IVc,e were crystallized from benzene, and IVf was crystallized from chloroform—petroleum ether.

Reaction of Indoles with Dichloroacetic Acid. The reaction was carried out via the method described above but with equimolar amounts (with respect to indole) of dichloroacetic acid in place of monochloroacetic acid. The yield of heteroauxin with mp 165° was 91.5% (based on the converted indole). 2-Methyl-3-indolylacetic (72%) and 2-phenyl-3-indolylacetic (66%) acids were similarly obtained.

Treatment of Indole and 2-Methyl- and 2-Phenylindoles with Trichloroacetic Acid. An autoclave was charged with 11 mmole of indole (2-methyl- or 3-phenyl), 1.15 mmole of trichloroacetic acid, 0.1 mole of potassium hydroxide and 30 ml of water. The reaction was carried out as in the preceding case, and the starting indole was isolated from the reaction mixtures in all cases.

3-Benzylindole. A mixture of 1.2 g (10.3 mmole) of indole, 2.0 g (15.8 mmole) of benzyl chloride, 6.15 g (0.11 mmole) of potassium hydroxide, and 30 ml of water was heated in an autoclave at 240-250° for 11 h. The mixture was then cooled and extracted with ether, and the extracts were washed with water and dried with magnesium sulfate. The ether was removed by distillation, and the residual oil was chromatographed with a column filled with activity II Al_2O_3 with elution by petroleum ether to give 0.37 g (21%) of 3-benzylindole with mp 100-101° (103-105° [5]). The IR spectra were identical. The second fraction yielded 0.12 g of unchanged indole.

The aqueous solution remaining after extraction was evaporated to one third of its original volume and acidified with dilute hydrochloric acid to give 0.9 g of benzoic acid with mp 122°.

Reaction of Indole with Ethyl Glyoxylate. A total of 0.7 g (46.3%) of heteroauxin with mp 164° was obtained from 1 g (8.5 mmole) of indole and 2.6 g (25.5 nmole) of ethyl glyoxylate in a solution of 5 g (0.09 mole) of potassium hydroxide in 25 ml of water under the conditions presented in the general method for the synthesis of 3-indolylacetic acids. When 1.3 g (12.8 mmole) of ester was used, 0.3 g (23.7%) of heteroauxin was obtained.

Oxalic and formic acids with R_f 0.07 and 0.78 were detected by TLC of the mother liquor on Silufol in an ethanol—ammonia—water system (20:2:8).

1-Indolylacetic Acid. A mixture of 0.8 g (4.3 nmole) of 1-indolylacetic acid [15] (mp 172°) and 4.2 g (0.08 mole) of potassium hydroxide in 20 ml of water was heated in an autoclave at 250° for 10 h. The mixture was then cooled and acidified with dilute hydrochloric acid to give 0.6 g of a substance that was identical to the starting acid with respect to its IR spectrum and melting point.

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