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INDOLE DERIVATIVES.

127.* INVESTIGATION OF THE ALKYLATION OF INDOLE BY POLYESTERS

B. Ya. Eryshev, Yu. I. Smushkevich,   UDC 547.757.07:542.953
and N. N. Suvorov

The alkylation of indole by polyesters of ω-hydroxyalkanoic acids was studied.
The optimum conditions and ratios of the reacting substances were found, and a
number of ω-(3-indolyl)alkanoic acids were obtained.

3-Indolylacetic acid (heteroauxin) is a plant-growth stimulator [2]. However, the known methods for the preparation of heteroauxin have substantial drawbacks, and this compels one to search for new methods for its synthesis. Thus the preparation of heteroauxin from gramine [3, 4] is carried out with the aid of cyanide salts, and the alkylation of indole by chloroacetic acid [5] is accompanied by pronounced corrosion of the apparatus because of the presence of the Cl⁻ ion in the reaction mixture.

The task of the present research was to find an alkylating agent that would exclude the indicated drawbacks. We initially attempted to use sodium acetoxyacetate as the alkylating agent, but the low yields obtained in its preparation from chloroacetic acid and sodium acetate [6] did not meet with our requirements. It is known that the formation of products of alkylation at both the lactone oxygen atom and at the ether bond was observed in the alkylation of indole by oxalactones [7]. We therefore decided to investigate polyglycolide, obtained by the method in [8] in 80-90% yield, as the alkylating agent.

Fusion of indole with polyglycolide under the conditions of the method in [9] showed that alkylation does take place but is accompanied by decarboxylation, which was detected from the formation of skatole and the vigorous evolution of CO_2 upon neutralization. Similar results were obtained both in the presence of air and in a nitrogen atmosphere. In accordance with the method used to prepare heteroauxin in [10] by the reaction of indole with chloroacetic acid in an alkaline medium (at an initial nitrogen pressure of 5 atm), we obtained heteroauxin in 70-85% yield when we replaced chloroacetic acid with polyglycolide. A search for the optimum ratios of the reacting substances and the optimum conditions showed that decreasing the temperature to 200°C lowers the yield to 42% and that a decrease in the concentration of the reacting substances by a factor of two also leads to a decrease in the yield of heteroauxin to 56%. A decrease in the alkali concentration also led to a decrease in the yield of heteroauxin to 13-25%. The optimum molar ratios and reaction conditions were as follows: an indole–polyglycolide–alkali ratio of 3:4:15, a reaction temperature of 250°C, and a reaction time of 6 h with an initial nitrogen pressure of 5 atm and an overall reaction pressure of 45-50 atm. The yield of heteroauxin in this case reaches 85-95%.

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*See [1] for communication 126.

TABLE 1. ω-(3-Indolyl)alkanoic Acids

| Acid (R = 3-indolyl)	mp, °C	Empirical formula	Yield, %
3-Indolylacetic	166—168 (167—168 [2])	$C_{10}H_9NO_2$	88—95
ω-(3-Indolyl)valeric	102—104 (103—105 [6])	$C_{13}H_{15}NO_2$	33—40
ω-(3-Indolyl)enanthic	91—93 (92—93 [6])	$C_{15}H_{19}NO_2$	61—66
ω-(3-Indolyl)pelargonic	101—103	$C_{17}H_{23}NO_2$*	40—49

*Found %: C 74.6, H 8.4, N 5.2. Calculated, %: C 74.7, H 8.5, N 5.1.

Under similar conditions, when the reaction time was 12 h and the molar ratio of the starting substances was 4:4:15, we obtained ω-(3-indolyl)valeric, ω-(3-indolyl)enanthic, and ω-(3-indolyl)pelargonic acids. Polyesters of ω-hydroxyvaleric, ω-hydroxyenanthic, and ω-hydroxypelargonic acids were synthesized by the method in [8].

On the basis of the concepts expressed by Jonson and Crosbi [11] regarding the mechanism of the alkylation of indole by glyoxylic acid under similar conditions,
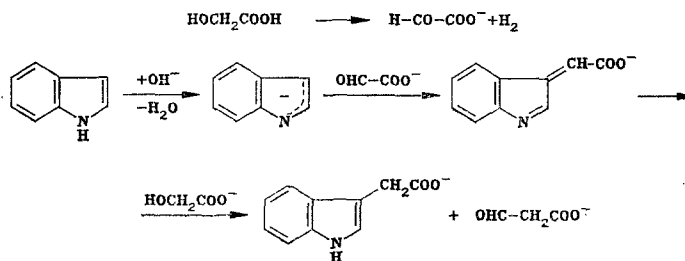
it may be concluded that chloroacetic acid, with a chlorine atom in its composition, is readily converted to glyoxylic acid via the scheme:
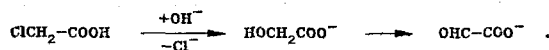
It is formed even more readily and rapidly and under milder conditions from polyglycolide:
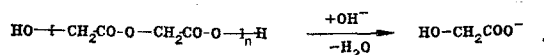
EXPERIMENTAL

A 100-ml steel autoclave was charged with 5.0 g (30 mmole) of indole, 8.55 g (150 mmole) of KOH, 40 mmole of the polyester, and 30 ml of distilled water, after which the autoclave was sealed and a nitrogen pressure of 5 atm was created. The autoclave was then placed in an oscillating heater and heated to 250°C, at which temperature it was maintained for 6-12 h, depending on the nature of the polyester. The pressure during the reaction rose to 45-50 atm. At the end of the reaction, heating and stirring were ceased, and the autoclave was cooled. The reaction mass was removed from the autoclave and filtered through a fluted filter to remove the resinous formations, and the filtrate was neutralized with respect to Congo Red with hydrochloric acid (1:1). The precipitated ω-(3-indolyl)alkanoic acid was removed by filtration and dried to constant weight in a vacuum desiccator. The results are presented in Table 1.

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STERIC EFFECTS IN THE SYNTHESIS OF INDOLES
FROM PYRIDINIUM SALTS

S. P. Gromov, M. M. Bkhaumik,
and Yu. G. Bundel'

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In the synthesis of indoles from pyridinium salts the degree of transamination depends on the character of the alkyl group attached to the nitrogen atom of the amine and its nucleophilicity. The yields of indoles decrease as the steric hindrance becomes greater.

We have previously proposed a fundamentally new approach to the synthesis of the indole two-ring system based on the transformation of the pyridine ring under the influence of substituted ketones in the presence of bases [1].

It is known that pyridinium salts tend to undergo transamination in the step involving an acyclic intermediate, which leads to other pyridinium salts or products of their recyclization to give anilines [2, 3]. 1,2,4,6-Tetramethyl-3-nitropyridinium iodide (I) is a convenient model for a detailed study of transamination in the synthesis of indoles. In this case, under the influence of methylamine and acetone, we observed the maximum yield (60%) of 1,2,5,7-tetramethylindole (II); this evidently indicates the small amount of steric hindrance created by the methylamino group in the formation of the indole two-ring system.

N-Alkylindoles are formed in 23-26% yields by the action of solutions of n-butylamine, n-nonylamine, and n-cetylamine in acetone on nitropyridinium iodide I; this indicates the low degree of sensitivity of the reaction to a change in the length of the hydrocarbon chain in the starting aliphatic amine. However, the presence of indole II (4-7%) in the last two cases is evidently explained only by an incomplete exchange reaction because of the greater preferability of the smaller methylamine residue in the type A intermediate.

The yields of the corresponding indoles IIId and IIIe increase to 35-41% when the reaction is carried out in an acetone solution of isopropylamine or sec-butylamine (branching at the α-carbon atom). In this case, despite the greater degree of branching of the hydrocarbon chains attached to the nitrogen atom of the amine, the greater nucleophilicity of these amines in the reaction is probably the decisive factor.

Finally, indole derivatives IIIf and IIIg are formed in 3 and 10% yields, respectively, by the action of tert-butylamine and α-phenylethylamine in acetone on nitropyridinium iodide I; one should have expected this, considering the steric volumes of the substituents in these amines.

Thus, in the synthesis of indoles from pyridinium salts, the degree of transamination depends on the character of the alkyl group attached to the nitrogen atom of the amine and its nucleophilicity. The yields of indoles decrease as the steric hindrance becomes greater.