INDOLE DERIVATIVES

LXXXV.* WILLGERODT–KINDLER REACTION WITH 3-ACYLINDOLES

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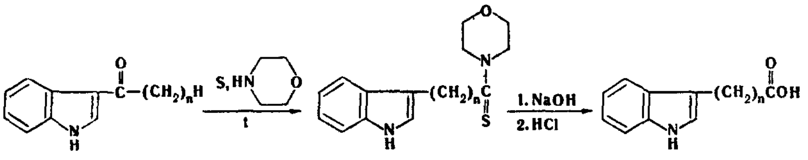
3-Indolylalkanoic acids (III) were obtained from 3-acylindoles (I) under the conditions of the Willgerodt–Kindler reaction. The reactivity of I falls as the chain lengthens and 3-caproylindole does not undergo reaction. Removal of the carbonyl group away from the indole ring promotes the conversion of the ketones to III. Sulfur-containing compounds, the structure of which was studied, were isolated along with the intermediate products – thiomorpholides of indolylalkanoic acids (II).

The literature contains contradictory data on the Willgerodt–Kindler reaction in the indole series. There are data [2, 3] indicating that ketones of the I type cannot be converted to acids either under the conditions of the Willgerodt reaction or under those of the Kindler modification, although N-substituted ketones react normally. Substituents in the 2 position of the indole ring do not interfere with the reaction [4]. Recently, when we were unable to obtain preliminary positive results in experiments with 3-acetylindole, there appeared a report regarding the synthesis of heteroauxin from 3-acetylindole via the Willgerodt–Kindler reaction [5].

We carried out the reaction under various conditions. Pronounced resinification occurred at elevated temperatures (180-200°) and on prolonged heating, and the acids were obtained in very low yields. The reaction proceeds considerably better at the boiling point of morpholine and when the ratio of ketone to sulfur to morpholine is 1 : 2 : 2. Acids III (n = 1-4) were obtained in yields of 30, 21, 14, and 1%, respectively, from the corresponding ketones. In the case of 3-caproylindole, we isolated only the starting ketone from the mixture at the end of the reaction. Thus the known principle for the Willgerodt reaction – that the degree of conversion of ketones to acids decreases as the chain lengthens – is also observed in the indole series.



I II III

I, II, III n = 1-5

It was also of interest to ascertain how the position of the carbonyl group relative to the indole ring affects the reactivity of the ketone. We found that 4-(3-indolyl)butyric acid is obtained from skatylacetone (IV) in 40-48% yield, a yield that is three times that obtained in the case of the reaction I (n = 3)→III (n = 3), and even somewhat better than for heteroauxin. The removal of the carbonyl group away from the ring probably has a favorable effect on the conversion of 3-indolyl alkyl ketones to acids.

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* See [1] for communication LXXXIV.

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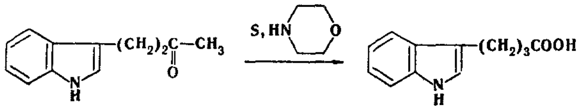

IV

Acids III were identified by determinations of the melting points of mixtures of the products with genuine samples of the acids and by comparison of their IR spectra.

Thin-layer chromatography (TLC) was used to establish that a mixture of products is formed in the reaction of the ketones with sulfur and morpholine. In a number of cases, the mixtures could be separated with columns filled with aluminum oxide. We isolated thiomorpholides II (n = 1-3), the starting ketones, and sulfur-containing compounds, the structures of which will be reported later.

In connection with the fact that there is a report regarding the tuberculostatic activity of 3-indolylcarboxylic acid thiomorpholide [6], tests of the thiomorpholides that we obtained were made in the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute in the Laboratory of G. N. Pershin by our old co-worker T. N. Zykova (whom we thank). However, it was found that they do not have appreciable tuberculostatic activity.

EXPERIMENTAL

3-Acetylindole was obtained by the Saxton method [7], 3-propionylindole and 3-butyryl-, 3-valeryl-, and 3-caproylindole were obtained by the Oddo method [8], and skatylacetone was obtained by the Holland method [9]. The Willgerodt–Kindler reaction and the isolation of the acid thiomorpholides were carried out by the methods described below. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrophotometer. Activity-II aluminum oxide was used for the chromatography, while Silufol plates with a fixed layer were used for TLC.

3-Indolylalkanoic Acids (III). A 0.02-g-atom sample of finely pulverized sulfur was added to a cooled suspension obtained from 0.01 mole of the ketone and 0.02 mole of dry freshly distilled morpholine, and the mixture was heated at the boiling point of morpholine (bath temperature 140-142°) for 4 h. It was then cooled to room temperature and extracted with chloroform (three 50-ml portions). The extract was washed with 50 ml of hydrochloric acid (1 : 5), water (50 ml), 10% NaOH solution, and water until it was neutral to universal paper. It was then dried over $CaCl_2$, and the solvent was removed at reduced pressure.

The dark-brown residue was mixed with 20 ml of 20% NaOH and 10 ml of ethanol, and the mixture was refluxed for 10-12 h. The ethanol was then removed by distillation, and 30 ml of water was added to the residue. The ice-cooled (1 : 1) solution was carefully acidified with hydrochloric acid to pH 2-3 and allowed to stand for several hours in the cold. The resulting precipitate was removed by filtration to give the following compounds: 3-indolylacetic acid with mp 163-164° (mp 164° [10]), 3-(3-indolyl)propionic acid with mp 132-133° (mp 134° [10]), 4-(3-indolyl)butyric acid with mp 122-123° (mp 124° [10]), and 5-(3-indolyl)-valeric acid with mp 103-105° (mp 105-107° [10]).

Indolylalkanoic Acid Thiomorpholides (II). The reaction mass remaining after carrying out the first step of the reaction and removal of the solvent by distillation was chromatographed with a column filled with aluminum oxide with an adsorbent–reaction product ratio of 30 : 1. Elution with heptane–benzene (4 : 1) or heptane gave a small amount of an oily substance followed by the thiomorpholides; the crude products were recrystallized from ethanol.

3-Indolylacetic Acid Thiomorpholide (II, n = 1). This compound, with mp 156-157° and R_f 0.47 [benzene–acetone (4 : 1)], was obtained in 25% yield. Found: C 64.6; H 6.2; N 11.1; S 12.8%. $C_{14}H_{16}N_2OS$. Calculated: C 64.6; H 6.1; N 10.7; S 12.3%.

3-(3-Indolyl)propionic Acid Thiomorpholide (II, n = 2). This compound, with mp 115-116° and R_f 0.53 [benzene–acetone (5 : 1)], was obtained in 22.2% yield. Found: C 65.7; H 6.3; N 10.7; S 11.9%. $C_{15}H_{18}N_2OS$. Calculated: C 65.7; H 6.7; N 10.1; S 11.6%.

4-(3-Indolyl)butyric Acid Thiomorpholide (II, n = 3). This compound, with mp 86-87° and R_f 0.47 [benzene–acetone (4 : 1)], was obtained in 9.7% yield. Found: C 66.7; H 6.9; N 9.2; S 11.1%. $C_{16}H_{20}N_2OS$. Calculated: C 66.6; H 6.9; N 9.7; S 11.1%.

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