INDOLE DERIVATIVES. V. SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF ω-(3-INDOLYL)-ALKANOIC ACIDS

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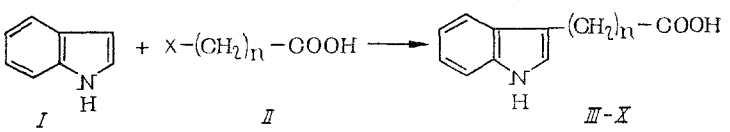
Indolylalkanoic acids have already been, for a long time, the subject of numerous and many-sided studies, both from the chemical and from the biological aspect. However, most of these works have been devoted to the lower members of the indolylalkanoic acid series: 3-indolylacetic acid, β-(3-indolyl)-propionic acid, and γ-(3-indolyl)-butyric acid. Data on succeeding members, and especially on the higher homologs of this series, are either few or nonexistent. Meanwhile, it may be expected that among the indicated compounds there will be substances which possess biological activity. In particular, ω-(3-indolyl)-undecanoic acid, which is an indole analog of hydnocarpic acid, seems of interest in this respect.

One of the reasons for the insufficient study of the higher indolyl-alkanoic acids consists of the fact that previously there was no convenient method of synthesizing such compounds. The most general one, apparently, should be considered the method of alkylating indole with lactones; however, it was limited to the synthesis of δ-(3-indolyl)-valeric acid and ε-(3-indolyl)-caproic acid [1]. Halogenated alkanoic acids should be considered more promising alkylating agents. Several years ago two of us worked out a simple and convenient method of synthesizing heteroauxin from indole and chloroacetic acid [2]. Moreover, in recent years ω-chloroalkanoic acids with an odd number of carbon atoms, obtainable from tetrachloroalkanes, have become rather available compounds. Therefore, in further work, using various halogenated alkanoic acids and introducing some improvements into our method, we were able to synthesize some other ω-(3-indolyl)-alkanoic acids [3]:



I *II* *III-X*

The alkylation of indole (I) with ω-haloalkanoic acids (II) was conducted in strongly alkaline medium, with heating in an autoclave. As our experiments showed, the optimum reaction conditions are a temperature of 240-250°, a pressure of 18-20 atm, and a 1:2 ratio of indole to haloalkanoic acid. Yields of ω-(3-indolyl)-alkanoic acids (III-X) thereupon were 42-90% (Table 1).

Heteroauxin is prepared under somewhat different conditions. First of all, the reaction takes place better under a nitrogen atmosphere, while this circumstance does not play an important role in the case of the other ω-(3-indolyl)-alkanoic acids. On the other hand, the synthesis of heteroauxin requires a higher pressure, 40-45 atm. The yield of it under such conditions is quantitative. Further elevation of reaction temperature to 280-290° or of pressure to 80-90 atm leads to a reduction in yield to 50%.

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TABLE 1. ω-(3-Indolyl)-alkanoic Acids and Their Derivatives

Compound	Name of compound	Found (in %)			Empirical formula	Calcd. (in %)			Mp (in deg)	Yield (in %)
		C	H	N		C	H	N		
III	Indolyl-3-acetic acid [5]	—	—	—		—	—	—	167—8	98
IV	β-(3-Indolyl)-propionic acid [1]	—	—	—		—	—	—	136—8	65
V	γ-(3-Indolyl)-butyric acid [1]	—	—	—		—	—	—	126—7	57
VI	δ-(3-Indolyl)-valeric acid [1]	71.97	7.09	6.46	$C_{13}H_{15}NO_2$	71.89	6.95	6.45	103—5	92
	Ethyl ester	73.34	7.99	5.49	$C_{15}H_{19}NO_2$	73.47	7.76	5.71	49—50	96
	Hydrazide	—	—	18.05	$C_{13}O_{17}N_3O$	—	—	18.18	108—10	93
VII	ε-(3-Indolyl)-caproic acid [1]	72.24	7.50	6.03	$C_{14}H_{17}NO_2$	72.72	7.32	6.06	140—2	42
	Ethyl ester	74.12	8.45	5.34	$C_{16}H_{21}NO_2$	74.13	8.11	5.41	43—5	85
	Hydrazide	—	—	17.31	$C_{14}H_{19}N_3O$	—	—	17.14	108—9	85
VIII	ω-(3-Indolyl)-enanthic acid [6]	72.82	8.30	5.71	$C_{15}H_{19}NO_2$	73.47	7.75	5.71	92—3	90
	Ethyl ester	75.19	8.11	5.12	$C_{17}H_{23}NO_2$	74.73	8.42	5.13	40—1	81
	Hydrazide	—	—	17.02	$C_{15}H_{21}N_3O$	—	—	16.21	105—7	80
IX	ω-(3-Indolyl)-pelargonic acid	74.83	8.43	5.18	$C_{17}H_{23}NO_2$	74.73	8.42	5.13	103—114	90
	Ethyl ester	75.68	9.35	4.48	$C_{19}H_{27}NO_2$	75.75	8.97	4.65	35— 6	74
	Hydrazide	—	—	14.48	$C_{17}H_{25}N_3O$	—	—	14.63	100—1	93
X	ω-(3-Indolyl)-undecanoic acid	74.87	9.19	4.69	$C_{19}H_{27}NO_2$	75.75	8.97	4.65	89—90	85
	Ethyl ester	76.58	9.57	4.34	$C_{21}H_{31}NO_2$	76.59	9.42	4.26	38—9	92
	Hydrazide	—	—	13.37	$C_{19}H_{29}N_3O$	—	—	13.33	98—100	76

The character of the halogen does not show up noticeably in the course of alkylation of indole with chloro- or bromoalkanoic acids, except for the fact that the yield of indolylalkanoic acids is 5-7% greater with the latter. However, upon alkylation of indole with iodoacetic acid under the same conditions, much resinification of the reaction mixture occurs, and the yield of heteroauxin is sharply diminished.

We have also prepared a number of derivatives of ω-(3-indolyl)-alkanoic acids: sodium salts, which were used in further work as water-soluble forms of the acids, esters, and hydrazides. We had proposed to use the latter for synthesis of higher indolylalkylamines; but, besides this, the hydrazides of the higher indolylalkanoic acids also present interest from the chemotherapeutic angle, since it is known that some hydrazides have definite antitubercular activity.

To identify the compounds prepared, we took their infrared spectra, in which the following characteristic absorption bands were observed: NH frequency of pyrrole ring, 3460-3420 cm^{-1}; carbonyl frequency of carboxyl group, 1715-1695 cm^{-1}; δ_{OH} of carboxyl group, 935-910 cm^{-1}; carbonyl frequency of ester group 1740-1720 cm^{-1}; carbonyl frequency of hydrazides 1640-1630 cm^{-1} (for the hydrazides of 3-indolylacetic acid and β-(3-indolyl)-propionic acid, the carbonyl frequency is 1670 cm^{-1}).

Tuberculostatic activity was studied in vitro in a Soton growth medium without serum and in the presence of 10% horse blood serum. We investigated tuberculosis mycobacteria of the human type, strains Academia and H37Rv. It was observed that the compounds described possess tuberculostatic activity, which decreases somewhat in the presence of blood serum. The most effective were the higher indolyl-substituted fatty acids (enanthic, pelargonic, or undecanoic). Indolylacetic, -propionic, and -butyric acids are weakly active. The hydrazides of the acids are weakly active in vitro. Data on the tuberculostatic activity of the ω-(3-indolyl)-alkanoic acids and their hydrazides are given in Table 2.

For the synthesis of ω-(3-indolyl)-alkanoic acids we used δ-chlorovaleric, ω-chloroenanthic, and ω-chloropelargonic acids produced by the Kaluzhskii Combine of Synthetic and Natural Perfume Materials pilot plant and ω-bromo-undecanoic acid produced by the Moscow ester plant. The technical products were purified by repeated recrystallization. ε-Bromocaproic acid was prepared from ε-caprolactone and hydrobromic acid by the method described in [4]. γ-Chloro- and γ-bromobutyric acids were prepared by this same method from γ-butyrolactone and the appropriate hydrogen halide acids.

TABLE 2. Tuberculostatic Activity of ω-(3-Indolyl)-alkanoic Hydrazides

Compound	Tuberculostatic activity (in μg/ml)		
	strain		
	Academia		H37Rv with serum
	without serum	with serum	
III	4000	–	–
Hydrazide	250	250	250
IV	62.5		–
Hydrazide	125	250	250
V	1000	–	–
Hydrazide	125	250	250
VI, Hydrazide	125	125	125
VII, Hydrazide	62.5	125	125
VIII	7.8	62.5	31.2
Hydrazide	62.5	125	500
IX	3.9	62.5	15.6
Hydrazide	125	250	> 125
X	7.8	62.5	15.6
Hydrazide	62.5	125	250

ω-(3-Indolyl)-alkanoic Acids (III-X). Into a rocking autoclave of 250 ml capacity was charged 0.05 mole of indole, 0.1 mole of the chloro- or bromoalkanoic acid, 0.4 mole of potassium hydroxide, and 50 ml of water. Then, over a period of 2-2.5 h the temperature was raised to 240-250°, and heating of the reaction mixture at this temperature was continued for 12 h. The pressure in the autoclave was 18-20 atm. In the case of heteroauxin synthesis, after the components had been charged to the autoclave, nitrogen was pressured in, raising the pressure to 5 atm, and heating was started after this. During the reaction the pressure in the autoclave rose to 40-45 atm.

At the end of the reaction the autoclave was washed out with water, the wash water was combined with the reaction mixture, and the solution obtained was filtered from a small amount of suspended indole which had not reacted. The filtrate was acidified with dilute (1:3) hydrochloric acid to an acid reaction to Congo red, or with formic acid to pH 3.0. The precipitate which fell, or the oil which crystallized upon standing, was separated by filtration, dried, and purified by two- or three-fold recrystallization from aqueous alcohol. Benzene may also be used as a recrystallization solvent. Purer products were obtained upon recrystallization with addition of a small amount of silica gel or "carbolen" activated charcoal.

Sodium Salts of ω-(3-Indolyl)-alkanoic Acids. The purified ω-(3-indolyl)-alkanoic acid (10 g) was dissolved in 100 ml of absolute alcohol with warming and stirring, and then a hot solution of sodium ethoxide prepared from 1.1 g of sodium and 15 ml of absolute ethanol was added rapidly; the mixture was stirred and warmed for 10-15 min; and then it was cooled to room temperature, without interrupting the stirring. The precipitate which fell was filtered off, washed with a cold mixture of ethanol and ether, and was dried. The sodium salts of ω-indolyl-3-alkanoic acids were crystallized from a mixture of absolute ethanol and dry ether.

Ethyl Esters of ω-(3-Indolyl)-alkanoic Acids. The ω-(3-indolyl)-alkanoic acid (0.05 mole) was dissolved in 50 ml of absolute ethanol, 2.5 ml of sulfuric acid (d. 1.84) was added, and the mixture was heated for 4 h on a boiling water bath. At the end of the reaction, the mixture was poured into 500 ml of water, the mixture was extracted with ether, and after the usual work-up and drying, the ether solution was shaken for 4 h with activated charcoal. The ether was then distilled off and the residue was recrystallized from aqueous alcohol. A purer product was obtained after distillation under vacuum at a pressure of $2 \cdot 10^{-3}$ mm Hg.

Hydrazides of ω-(3-Indolyl)-alkanoic Acids. The ester of the ω-(3-indolyl)-alkanoic acid (0.05 mole), 0.05 mole of hydrazine hydrate, and a three-fold amount (by weight) of absolute ethanol were heated for 3 h on a boiling water bath; then the alcohol was distilled off, reducing the volume of the solution remaining to 5-7 ml; then 5-10 ml of hot water was added to this solution dropwise. The precipitate of hydrazide which fell was filtered off and recrystallized from aqueous alcohol.

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