INDOLE DERIVATIVES

XXXI. Synthesis of β-Glycerides of 3-Indolyl Carboxylic Acids*

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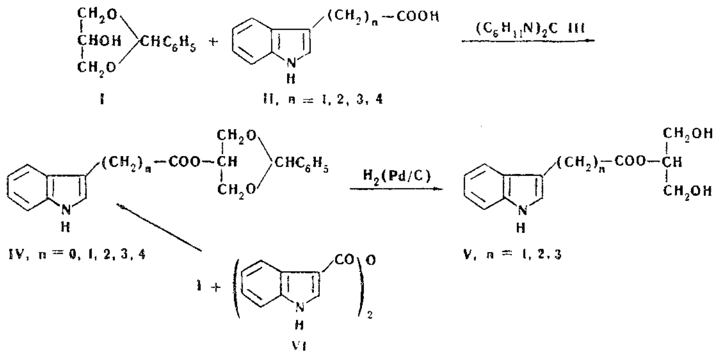
The synthesis of β-glycerides of 3-indolyl carboxylic acids has been effected by the reaction of 3-indolyl carboxylic acids with benzylideneglycerol in the presence of dicyclohexylcarbodiimide with the subsequent elimination of the benzylidene group by hydrogenolysis. The α- and β-glycerides have been separated by paper chromatography.

In a continuation of work on the synthesis and the study of the chemical properties and biological activity of glycerides of 3-indolyl carboxylic acids, by the interaction of α,α'-benzylideneglycerol (I) with 3-indolyl carboxylic acids (II, n = 1, 2, 3, 4) in the presence of N,N'-dicyclohexylcarbodiimide (III) we have obtained benzylidene derivatives of glycerides of the acids IV, n = 1, 2, 3, 4, which were converted into the corresponding glycerides (V, n = 1, 2, 3) through the elimination of the benzylidene group by hydrogenolysis. The benzylidene derivative of the glyceride of indole-3-carboxylic acid (IV, n = 0) was obtained by acylating I with the acid anhydride VI.



The successful completion of the synthesis depends on the elimination of the benzylidene group blocking positions 1 and 3 of the glycerol. We tried acid hydrolysis with boric acid under the conditions for obtaining β-glycerides of higher aliphatic acids [2]. However, we were unable to isolate the free β-glycerides because of the considerable resinification of the reaction mixture. The reductive debenzylideneation of (IV, n = 0, 1, 2, 3, 4) requires a very active catalyst, the method for the preparation of which we give below. Other catalysts [3] were also tested (some even at high pressures), but they all proved less reliable. We did not succeed in debenzylideneating the benzylidene derivatives of the glycerides of indole-3-carboxylic acid (IV, n = 0), and δ-(3-indolyl)-valeric acid (IV, n = 4).

The IR spectra of the benzylidene derivatives of the glycerides IV (n = 0, 1, 2, 3, 4) contained intense narrow bands at 3350–3440 cm^{-1}, which are characteristic for the stretching vibrations of the NH bond of an indole ring. The presence of an ester group was shown by intense narrow bands in the 1720 cm^{-1} region. In the derivative of indole-3-carboxylic acid (IV, n = 0) this frequency was displaced to the long-wave region of the spectrum and was present in the 1685–1687 cm^{-1} region, which may be explained by the polarization of the C═O bond through the conjugation of the carbonyl group with the π-electron system of electrons of the indole ring [4]. The spectra also had bands in the 1175–1178 cm^{-1} region (C—O in COOR), the 1620, 1590, and 1450 cm^{-1} regions (aromatic system attached to the indole ring [5]), and the 745 and 760 cm^{-1} regions (C—H bonds of the four adjacent hydrogen atoms of the indole ring and the five adjacent hydrogen atoms of the benzylidene group). All the benzylideneglycerols IV (n = 0, 1, 2, 3, 4) were purified by chromatography on hydrated silica with subsequent recrystallization.

Table 1

R_f Values of β- and α-Glycerides of 3-Indolyl Carboxylic Acids in Paper Chromatography

Compound	R_f	R_f of the α-isomer	Color in ultraviolet light
V, n=1	0.48	0.57	Violet
V, n=2	0.41	0.32	Violet
V, n=3	0.21	0.28	Pink-violet

The IR spectra of the β-glycerides V (n = 1, 2, 3) obtained include characteristic absorption bands:

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*For communication XXX, see [1].

Table 2

α,α'-Benzylideneglycerides of 3-Indolylcarboxylic acids

Compound	Benzylideneglycerides of the acids	Mp, °C	R_f*	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IV, $n=1$	3-Indolylacetic	103—105	0.63	$C_{20}H_{19}NO_4$	71.52	5.94	4.44	71.21	5.64	4.16	25.5
IV, $n=2$	β-(3-Indolyl)-propionic	129—131	0.58	$C_{21}H_{21}NO_4$	71.87	6.21	4.04	71.80	5.98	3.99	30.0
IV, $n=3$	γ-(3-Indolyl)-butyric	84—85	0.60	$C_{22}H_{23}NO_4$	72.20	6.50	3.89	72.34	6.30	3.84	33.0
IV, $n=4$	δ-(3-Indolyl)-valeric	119—121	0.65	$C_{23}H_{25}NO_4$	72.49	6.82	3.61	72.84	6.60	3.69	57.0

*Thin-layer chromatography on silica (fixed layer, 3% of gypsum) in the ether–benzene (7 : 3) system.

strong broad bands in the 3390–3420 cm^{-1} region as a result of the superposition of the stretching vibrations of the NH and OH groups, and very strong bands in the 1710–1740 cm^{-1} region together with absorption at 1160–1180 cm^{-1}, which clearly shows the presence of an ester group. These spectra are similar to those of the α-monoglycerides [6] with the exception of the less sharp and less intense appearance of the characteristic bands of the structure: the C—O stretching vibrations of the hydroxyl derivatives (1045–1050 cm^{-1}) and the stretching vibrations of the C—O in COOR (the latter are shifted to the long-wave region of the spectrum, 1150–1180 cm^{-1}).

The β-glycerides were purified by adsorption chromatography on silica. In view of the instability of the β-monoglycerides due to the ease of migration of a β-acyl group into the α position [1], the necessity arose for showing the absence of migration in the hydrogenolysis of α,α'-benzylidene-β-acylglycerides (IV) and in the chromatographic purification of the β-monoglycerides on silica. The purity of the β-glycerides V (n = = 1, 2, 3) and of the corresponding α-isomers was checked by paper chromatography. Table 1 gives the R_f values of the α- and β-glycerides on chromatography on acetylated paper [7] in water saturated with n-butanol.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument in the form of mulls in paraffin oil for IV (n = 0, 1, 2, 3, 4) or liquid films for V (n = = 1, 2, 3). For the chromatographic separation of the α- and β-glycerides, British chromatographic paper No. 42 was used.

α,α'-Benzylideneglyceride of indole-3-carboxylic acid (IV, n = 0). 3.04 g (0.01 mole) of indole-3-carboxylic acid anhydride [6] and 0.05 g of anhydrous sodium acetate were added to 12.6 g (0.07 mole) of α,α'-benzylideneglycerol (I, mp 82–83° C) [8] at 90–95° C. The mixture was stirred at the given temperature for 50 hr and was then dissolved in ether and the ethereal solution was washed with cold saturated $NaHCO_3$ solution and dried. The ether was distilled off in vacuum and the residual oil was chromatographed on hydrated silica. The reaction product was eluted with ether. Yield 1.05 g (32.7%), mp 202–203° C (from benzene). Found, %: C 70.25; H 5.39; N 4.60%. Calculated for $C_{19}H_{17}NO_4$, %: C 70.58; H 5.26; N 4.34%.

α,α'-Benzylideneglyceride of 3-indolylacetic acid (IV, n = 1). A cooled solution of 10.3 g (0.05 mole) of dicyclohexylcarbodiimide (III) [9] in 25 ml of absolute acetone was added to a solution of 9 g (0.05 mole) of α,α'-benzylideneglycerol (I) and 8.8 g (0.05 mole) of 3-indolylacetic acid (II, n = 1) in 40 ml of absolute acetone cooled to −30° C. When the formation of a precipitate began, 2 ml of dry pyridine was added and the mixture was left at −30° to −40° C for 72 hr with periodic shaking. The precipitated N, N'-dicyclohexylurea was filtered off, the acetone was evaporated off in vacuum, the residual oil was dissolved in ether, and the solution was washed with 5% acetic acid, $NaHCO_3$ solution, and water, and was dried. The ether was evaporated off in vacuum and the residue was chromatographed on hydrated silica with benzene, the fraction with R_f 0.39 (in the ether–benzene (7:3) system) being collected. This gave 4.3 g of a white crystalline powder [from benzene–n-heptane (8:2)]. The results of the elementary analysis and the properties of these compounds and their homologs (IV, n = 2, 3, 4) obtained by an analogous procedure, are given in Table 2.

β-Glyceride of 3-indolylacetic acid (V, n = 1). A hot solution of 0.2 g of $PdCl_2$ in 16 ml of 0.25 N hydrochloric acid was added to a hydrogenation flask already containing 1.14 g of activated carbon in an atmosphere of hydrogen. Then a hot solution of 7 g of sodium acetate (pure for analysis) in 20 ml of water was added and the mixture was stirred at 80–90° C until the absorption of hydrogen ceased (about 2 hr). After cooling in an atmosphere of hydrogen, the catalyst was filtered off on a glass filter and, with continuous stirring, washed with cold water until the wash waters no longer contained chloride ions. Then air was passed through the catalyst for 5–10 min in order to activate it, and it was washed with absolute tetrahydrofuran, with care being taken to reduce contact of the catalyst with air in order to avoid

Table 3

β-Glycerides of 3-Indolyl Carboxylic Acids

Compound	β-Glycerides of the acids	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
V, $n=1$	3-Indolylacetic	1.5525	$C_{13}H_{15}NO_4$	62.54	5.68	5.28	62.65	6.02	5.62	78.0
V, $n=2$	β-(3-Indolyl)-propionic	1.5725	$C_{14}H_{17}NO_4$	64.15	6.49	5.25	63.87	6.47	5.32	81.0
V, $n=3$	γ-(3-Indolyl)-butyric	1.5820	$C_{15}H_{19}NO_4$	64.84	6.62	4.90	64.98	6.86	5.05	72.0

inflammation. It was then rapidly transferred to the hydrogenation flask.

A solution of 1.68 g (0.005 mole) of the benzylideneglyceride IV (n = 1) in 30 ml of absolute tetrahydrofuran was stirred with 1.2 g of the catalyst prepared as described above in an atmosphere of hydrogen at room temperature and a pressure of 40–50 cm of water until the absorption of hydrogen ceased. If no hydrogen was absorbed, the catalyst was activated by vigorous shaking in the air for 2–3 min. Hydrogenation took 6 hr and 240 ml of hydrogen was absorbed (theoretical amount 224 ml). The catalyst was filtered off and washed with tetrahydrofuran, and the solution was evaporated in vacuum. The residue was dissolved in a mixture of ether and ethanol (9:1) and passed through a column of silica. The product was eluted with the above-mentioned mixture of solvents, the solvents were distilled off in vacuum, with the last traces being eliminated in a vacuum of 10^{-3} mm (room temperature), and the residual dark brown oil was dried over phosphorus pentoxide in a vacuum desiccator. The results of elementary analysis and the properties of this compound and its homologs (V, n = 2, 3), which were obtained similarly, are given in Table 3.

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