INDOLE DERIVATIVES

XCV.* SYNTHESIS OF MERCAPTO DERIVATIVES OF TRYPTOPHAN FROM α-NITRO-β-INDOLYLACRYLIC ACID ESTERS

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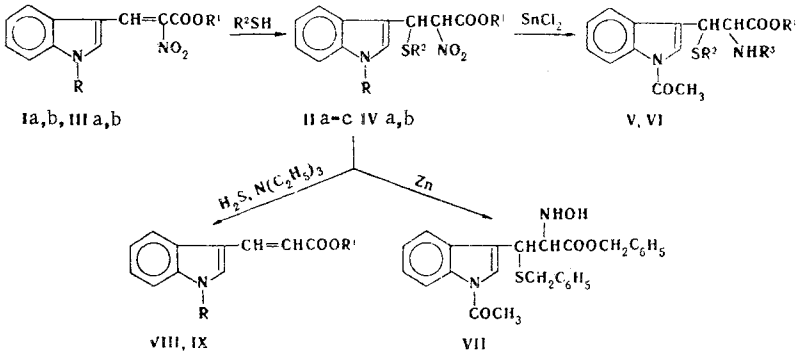
Derivatives of β-mercaptotryptophan and α-hydroxylamino-β-mercapto-β-indolylpropionic acid were obtained by addition of thiols and hydrogen sulfide to α-nitro-β-(3-indolyl)acrylic acid esters and subsequent reduction of the products.

Considering the difficulties that arise in the removal of protective groups from sulfur-containing N-acylated tryptophan derivatives [1], we synthesized indolylcysteine derivatives by reduction of the corresponding mercapto nitro compounds. For this, we used methods developed for the preparation of indolylcysteamine derivatives [2].



I, II, VIII R=H; III, IV, IX R=COCH₃; a R¹=CH₃, R²=COCH₃; b R¹=R²=CH₂C₆H₅; c R¹=CH₃, R²=H; V R¹=CH₃, R²=H, R³=COCH₃; VI R¹=R²=CH₂C₆H₅, R³=H

Starting esters I and III, which are mixtures of geometrical isomers, were obtained by known methods [3, 5].

The addition of thiylating agents such as benzyl mercaptans, thioacetic acid, and hydrogen sulfide to N-acetylated (IIIa,b) and nonacetylated esters (Ia,b) of α-nitro-β-(3-indolyl)acrylic acid proceeds readily, but the products of reaction with nonacetylated esters Ia,b are unstable, and only ester IIb could be isolated in analytically pure form. Adducts IIa,c are rapidly converted to trans-β-(3-indolyl)acrylic acid esters (VIII, IX). Compound IIb changes similarly but somewhat more slowly on storage. Considering the fact that many β-substituted propionic acids are completely stable, the lability of the α-nitro-β-(3-indolyl)propionic acid derivatives that we obtained should be ascribed to the electron-donor effect of the indole ring.

* See [1] for communication XCIV.

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Similar disintegration of α,β-substituted β-(3-indolyl)propionic acids was also observed in the synthesis of β-(3-indolyl)glyceric acid derivatives [6].

In accordance with the accepted mechanism of the addition of thiylating agents to olefins with an activated double bond [7], the rate-determining step is addition of thiolate ion to the β-carbon atom. In the case of trisubstituted ethylenes, the addition of a proton to the carbanion should lead to the formation of erythro and threo isomers. In fact, a double set of signals, close in chemical shifts, is observed in each case in the PMR spectra of IIb and IVa,b. This mixture of isomers is formed both from the individual starting olefins and from a mixture of their geometrical isomers, and this confirms a carbanion addition mechanism in this case.

One of the isomers of IVb was isolated from a mixture of the erythro and threo isomers by crystallization [1]. Thioester IVa could not be separated into isomers because of rapid isomerization. Partial conversion of the isomer can be observed in a study of the PMR spectra of a solution of IVa in benzene; this makes it possible to assign the signals. An individual isomer of IVb [1] also undergoes a similar transformation in solution.

Reduction of nitro compound IVb with zinc in acetic acid or with stannous chloride in acetic acid containing hydrogen chloride gives, respectively, hydroxylamine VII or amine VI. Transacylation occurs during the reduction of methyl α-nitro-β-acetylthio-β-(1-acetyl-3-indolyl)propionate (IVa), and methyl α-acetamido-β-mercapto-β-(1-acetyl-3-indolyl)propionate (V) is formed.

Only one geometrical isomer was detected by PMR spectroscopy in all of the products of the reduction of V-VII. The assignment of IIc, IVa,b, V, VI, and VII to the erythro and threo series is difficult, inasmuch as the spin–spin coupling constants of the protons attached to the α- and β-carbon atoms are close.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-10 spectrometer. Silufol plates were used for chromatography, and development was accomplished with a 10% solution of phosphomolybdic acid and heating to 110°. The amines were detected by reaction with ninhydrin.

Benzyl α-Nitro-β-benzylmercapto-β-(3-indolyl)propionate (IIb). A 1.13-ml (9.6 mmole) sample of benzyl mercaptan and 0.04 ml of triethylamine were added to a solution of 3 g (9.6 mmole) of ester Ib in 15 ml of methanol. After the yellow coloration had disappeared, the mixture was placed in a refrigerator to precipitate 2.48 g (59%) of colorless crystals with mp 147-149°. IR spectrum: 3400 (NH), 1750 (ester), and 1566 and 1340 cm^{-1} (NO_2). Found, %: C 67.1; H 5.0; N 6.1; S 7.1. $C_{25}H_{22}N_2O_4S$. Calculated, %: C 67.3; H 4.9; N 6.2; S 7.1.

Methyl α-Nitro-β-acetylthio-β-(1-acetyl-3-indolyl)propionate (IVa). A 2.9-ml (0.041 mole) sample of thioacetic acid and 0.01 g of triethylamine were added with stirring to 10.1 g (0.035 mole) of the trans isomer or a mixture of the cis and trans isomers of IIIa in 80 ml of benzene. After the yellow coloration had vanished (after 10-15 min), 20 ml of petroleum ether was added, and the mixture was placed in a refrigerator. After 16 h, workup of the mixture gave 12.1 g (94%) of colorless crystals with mp 122-123° (from absolute alcohol). According to the PMR data, the mixture contained two isomers (see Table 1). IR spectrum: 1750 ($COOCH_3$), 1715 ($SCOCH_3$), 1700 ($NCOCH_3$), and 1565 and 1350 cm^{-1} (NO_2). Found, %: C 52.9; H 4.5; N 7.8; S 8.9. $C_{16}H_{16}N_2O_6S$. Calculated, %: C 52.7; H 4.4; N 7.7; S 8.8.

Benzyl α-Nitro-β-benzylmercapto-β-(1-acetyl-3-indolyl)propionate (IVb). A 68.2-mg (10.5 mmole) sample of benzyl mercaptan and one drop of triethylamine were added to a solution of 0.2 g (0.55 mmole) of trans-IVb in 1 ml of methanol. After 10 min, the mixture was diluted with 10 ml of petroleum ether and worked up to give 0.23 g of an oily product, which, according to the PMR data, contained two isomers (see Table 1). Crystallization from methanol gave 0.12 g (45%) of colorless crystals of an isomer (1) of IVb with mp 111°. IR spectrum: 1732 (broad, ester), 1563 and 1340 cm^{-1} (NO_2). Found, %: C 66.4; H 5.0; N 5.7; S 6.5. $C_{27}H_{24}N_2O_5S$. Calculated, %: C 66.4; H 4.9; N 5.7; S 6.5.

Benzyl α-Hydroxylamino-β-benzylmercapto-β-(1-acetyl-3-indolyl)propionate (VII). Zinc dust (4.17 g) was added gradually in the course of 30 min at 3-4° to a solution of 4.17 g (8.5 mmole) of IVb in 150 ml of acetic acid and 13 ml of water. After 1 h, 150 ml of concentrated ammonium hydroxide and ice were added simultaneously up to pH 6 (the temperature was not allowed to exceed 10°); the mixture was extracted with methylene chloride, and the extract was dried with magnesium sulfate. The solvent was evap-

TABLE 1. PMR Spectra of the Synthesized Compounds[a]

Compound	Isomers	NCOCH₃	SCH₂, SCOCH₃ or NCOCH₃	OCH₂ or OCH₃	β-CH	α-CH	$J_{\alpha,\beta}$, Hz	2-H	Aromatic protons	Solvent
IIc	1	—	3,76 q[b]	4,93 m	4,99 m	5,60 d	11,0	—[c]	—[c]	C_5D_5N
	2	—	3,76 or	5,37 q[b]	4,99 m	5,53 d	12,0	—[c]	—[c]	C_5D_5N
IId	1	2,62 s	2,34 s	3,79 s	5,87 s	6,26 s	8,2	7,87 s	7,1—8,5 m	
	2	2,62 s	2,34 s	3,69 s	5,87 s	6,31 s	9,9	8,00 s	7,1—8,5 m	
IIe	1	2,44 s	3,75 m	5,02 s	5,02 e	6,21 e	10,8	7,70 s	6,8—8,4 m	CD_3COCD_3
	2	2,57 s	3,52 s	5,36 s	5,02 e	6,28 e	11,4	7,90 s	6,8—8,4 m	
IIIa	1	2,64 s	2,20 s	3,47 s	4,99 q[d]	5,78 e	11,0	7,85 s	7,15—7,80 m	
IIIb	1	2,41 s	3,75 q[e]	5,00 q[f]		4,58 q	8,9	7,48 s	6,7—8,4 m	CD_3OD
IIIb	1	2,36 s	3,48 q[g]	4,21 q[h]		4,93 q	13,0	—[c]	6,8—8,4 m	$CDCl_3$
IVb		—	—	5,25 s	7,94 e	6,49 e	15,5	—[c]	7,1—8,3 m	$CDCl_3$

[a]On the δ scale. The following abbreviations are used: s is singlet, d is doublet, q is quartet, and m is multiplet. [b]J = 13 Hz. [c]This region is covered by signals from the solvent. [d]$J_{\alpha\text{-H,NH}}$ = 6.5 Hz; the splitting vanishes when CD_3OD is added. [e]J = 14.2 Hz. [f]J = 11.4 Hz. [g]J = 14.0 Hz. [h]J = 8.5 Hz.

orated to give 2.73 g (65%) of colorless crystals with mp 157-159° (from chloroform–cyclohexane). According to the PMR data, the product was an individual isomer. IR spectrum: 1730 (broad, ester) and 3260 (NHOH) cm^{-1}. Found, %: C 68.5; H 5.5; N 5.8; S 6.7. $C_{27}H_{26}N_2O_4S$. Calculated, %: C 68.4; H 5.5; N 5.8; S 6.7.

Hydrochloride of Benzyl α-Amino-β-benzylmercapto-β-(1-acetyl-3-indolyl)propionate (VI). A 3.42-g (7.6 mmole) sample of ester IVb was added to a solution of 7.9 g (0.035 mole) of $SnCl_2 \cdot 2H_2O$ and 3.7 g (0.1 mole) of hydrogen chloride in 30 ml of acetic acid, and the mixture was placed in a refrigerator. After 2 days, the mixture was poured into ice water, the excess acid was neutralized with sodium peroxide, and tin was precipitated with hydrogen sulfide. The sulfides were removed by filtration, the filtrate was evaporated to dryness, and the residue was extracted with alcohol to give 1.08 g (27%) of colorless crystals of the hydrochloride of amine VI with mp 175-177° (from absolute alcohol). IR spectrum: 2600-3200 (NH_3^+) and 1730 cm^{-1} (ester). Found, %: C 65.7; H 5.5; Cl 7.3; N 5.8; S 6.3. $C_{27}H_{26}N_2O_3S \cdot HCl$. Calculated, %: C 65.5; H 5.5; Cl 7.2; N 5.6; S 6.4.

Methyl α-Acetamido-β-mercapto-β-(1-acetyl-3-indolyl)propionate (V). A 4.45-g sample (12 mmole) of ester IVa was added to a solution of 11.2 g (0.058 mole) of anhydrous stannous chloride and 8.3 g (0.23 mole) of hydrogen chloride in 52 ml of acetic acid, and the mixture was placed in a refrigerator. After 3 days the suspension was poured into water, and the precipitate was removed by filtration and suspended in water. The tin ions were precipitated with hydrogen sulfide, and the precipitated sulfides were removed by filtration. The filtrate was evaporated to dryness, and the residue was extracted with absolute alcohol. The extract was evaporated to give 1.98 g of colorless crystals with mp 165-166° (from water) and R_f 0.73 [the eluent was the upper layer of a butanol–acetic acid–water mixture (4:1:5)]. IR spectrum: 3120 and 1630 (amide), 1735 ($COOCH_3$), and 1710 cm^{-1} ($COCH_3$). Found, %: C 56.9; H 5.4; N 8.4; S 9.3. $C_{16}H_{18}N_2O_4S$. Calculated, %: C 57.1; H 5.4; N 8.4; S 9.4.

Reaction of Methyl α-Nitro-β-(3-indolyl)acrylate (Ia) and Thioacetic Acid. A 1.35-ml (0.18 mole) sample of thioacetic acid and 0.1 ml of triethylamine were added to a solution of 4.44 g (0.018 mole) of ester Ia in 30 ml of benzene, and the mixture was stirred for 30 min. The addition of petroleum ether precipitated methyl α-nitro-β-acetylthio-β-(3-indolylpropionate (IIa) as a yellowish oil with R_f 0.37 [benzene–ether (9:1)]. Attempts to crystallize the product or storage of it led to rapid conversion to methyl trans-β-(3-indolyl)acrylate (VIII) with mp 151-152° and R_f 0.15, which was identical to the compound obtained in [8].

Reaction of Ester Ia with Hydrogen Sulfide. A stream of hydrogen sulfide was bubbled for 1.5 h through an ice-cooled solution of 1 g (6.4 mmole) of ester Ia and 0.04 ml of triethylamine in 30 ml of benzene. Addition of petroleum ether gave methyl α-nitro-β-mercapto-β-(3-indolyl)propionate (IIc) or the corresponding disulfide as a yellow oil with R_f 0.43, which was rapidly converted to methyl ester VIII, which was identical to the product described above.

Reaction of Benzyl α-Nitro-β-(1-acetyl-3-indolyl)acrylate (IIIb) with Hydrogen Sulfide. A 0.5-ml (3.5 mmole) sample of triethylamine was added to a suspension of 1.8 g (5 mmole) of ester IIIb in 6 ml of methanol, and the flask was connected to a gasometer containing hydrogen sulfide. With periodic shaking, 450 ml of hydrogen sulfide was absorbed after 24 h, during which the yellow precipitate was converted to a colorless precipitate. It was removed by filtration to give 0.85 g (61%) of benzyl trans-β-(3-indolyl)acrylate (IX) with mp 148-149° (from chloroform). IR spectrum: 3390 (NH), 1710 (CO), and 1640 cm^{-1} (C=C). Found, %: C 78.1; H 5.4; N 5.0. $C_{18}H_{15}NO_2$. Calculated, %: C 78.0; H 5.4; N 5.0. Ester IX was also obtained in 71% yield by reaction of benzyl α-nitro-β-(3-indolyl)acrylate with hydrogen sulfide.

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