# INDOLE DERIVATIVES

## XCIV.* SYNTHESIS OF MERCAPTO DERIVATIVES OF TRYPTOPHAN FROM ACETAMIDOINDOLYLACRYLIC ACID ESTERS

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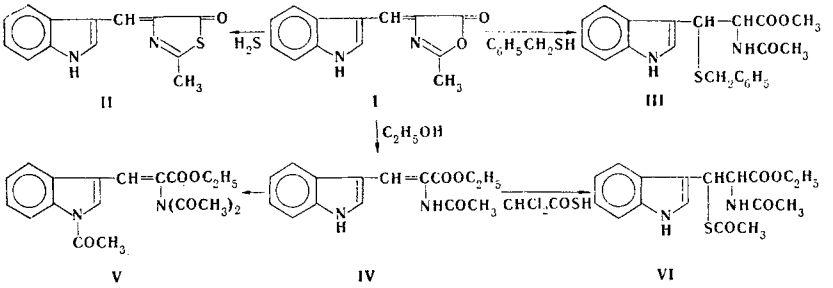
Reactions of α-acetamido-β-(3-indolyl)acrylic acid derivatives with some sulfur-containing compounds were carried out. Benzyl and acetyl derivatives of β-mercaptotryptophan esters were obtained.

A previous attempt to synthesize β-mercaptotryptophan (indolylcysteine) from the corresponding thiothiazolidone was unsuccessful [2]. In order to obtain β-mercaptotryptophan derivatives we started from the corresponding azlactones and acetamidoindolylacrylic acid esters using methods similar to those used for the synthesis of penicillamine and similar substances [3]. It was found that only thiazolidone II is formed in the reaction of azlactone I with hydrogen sulfide. At the same time, benzyl mercaptan adds to the C=C bond with simultaneous opening of the azlactone ring to give, according to the PMR data, a mixture of diastereomeric esters III. Ester III was acetylated thoroughly and converted to the amide. A single individual isomer was isolated in both cases from the mixtures of diastereomers by crystallization. Removal of the protective groups in ester III, its acetyl derivatives, and amide by hydrolysis in the presence of acids or bases under mild conditions and also by the action of sodium in liquid ammonia leads in all cases primarily to splitting out of benzyl mercaptan and the production of compounds that do not contain sulfur.



Further investigations were made with ester IV, which was obtained by gentle alcoholysis of azlactone I. Acetylation of ester IV gives triacetate V. As can be concluded from the chromatograms, the addition of thioacetic acid at room temperature takes place to a barely appreciable degree. An increase in the temperature and the use of triethylamine as a catalyst lead to resinification. Dichlorothioacetic acid, which is recommended for such reactions [4], reacts more vigorously in ethyl acetate. Transacylation apparently occurs during the reaction, and the product isolated is a mixture of diastereomeric esters of α-acetamido-β-acetylthio-β-(3-indolyl)propionic acid (VI). Attempts to remove the protective acetyl groups in ester VI also lead to splitting out of a sulfur-containing residue. Thioacetic acid adds readily to 1-

* See [1] for communication XCIII [1].

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acetyl-3-nitrovinylindole [5] but does not react with ester IV, while dichlorothioacetic acid adds to ester IV but does not react with 1-acetyl-3-nitrovinylindole. Research in this area will be continued.

## 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. The UV spectra of alcohol solutions were recorded with an EPS-3 spectrophotometer. Chromotography was carried out on plates with a fixed layer of silica gel and with a loose layer of activity II (Brockmann scale) aluminum oxide; the chromatograms were developed with a solution of p-dimethylaminobenzaldehyde in alcohol containing hydrochloric acid and by means of an ultrachemiscope.

2-Methyl-4-[(3-indolyl)methylene]-5-thiazolone (II). Hydrogen sulfide was bubbled for 6 h through a solution of 1 g (4.42 mmole) of azlactone I and 4 ml of triethylamine in 20 ml of ethyl acetate, after which 20 ml of water was added, and the aqueous layer was separated and acidified with hydrochloric acid. The acidic mixture was filtered to give 0.35 g (33%) of bright-orange crystals with mp 201-202° (from benzene). IR spectrum: 3190 (NH), 1690 (CO), 1660, and 1640 $cm^{-1}$ (C=C, C=N). UV spectrum, $\lambda_{max}$, nm (log ε): 224 (4.00), 256 (3.57), 227 (3.61), 285 (3.63), and 426 (4.13). PMR spectrum* (deuterodimethylformamide), δ: 2.69 (s, $CH_3$), 7.20-8.17 (m, indole-ring protons), and 7.60 and 8.65 ppm (two s, indole =CH and 2-H). Found, %: C 64.4; H 4.4; N 11.3; S 13.1. $C_{13}H_{10}N_2OS$. Calculated, %: C 64.4; H 4.4; N 11.5; S 13.2.

Methyl α-Acetamido-β-benzylmercapto-β-(3-indolyl)propionate (III). A 4.52-g (0.02 mole) sample of azlactone I and 3.7 g (0.03 mole) of benzyl mercaptan were added to a solution of 0.004 mole of sodium methoxide in 15 ml of methanol, after which the mixture was heated at 60-61° in a stream of nitrogen for 14 h. Acetic acid (0.6 ml) was added, and 12 ml of methanol was removed by distillation. The residue was chromatographed on 500 g of aluminum oxide, which was first calcined thoroughly at 500° for 1 h. The substances were eluted successively with benzene, ethyl acetate, and acetone to give, respectively, benyl mercaptan (1.52 g, $R_f$ 0.92, $Al_2O_3$, ethyl acetate), 4.21 g of a light-yellow oil, and 0.62 g of methyl α-acetamido-β-(3-indolyl)acrylate with mp 190-191° (from ethyl acetate). IR spectrum: 3450, 3400 (NH), 1690 (ester), 1665 (amide), and 1638 $cm^{-1}$ (C=C). UV spectrum, $\lambda_{max}$, nm (log ε): 227 (4.45), 262 (3.93), 277 (3.94), and 340 (4.34). PMR spectrum ($CD_3OD$), δ: 2.15 (s, $CCH_3$), 3.78 (s, $OCH_3$), 7.73 and 7.90 (two s, indole β-CH and 2-H), and 7.0-7.6 ppm (m, indole-ring protons). Found, %: C 65.0; H 5.5; N 10.7. $C_{14}H_{14}N_2O_3$. Calculated, %: C 64.8; H 5.5; N 10.8.

Trituration of the light-yellow oil with isooctane gave 2.43 g (32%) of ester III as a yellowish electrifiable powder with mp 65-70° and $R_f$ 0.63. IR spectrum (film): 3420, 3320 (NH), 1742 (ester), and 1670 $cm^{-1}$ (broad, amide). PMR spectrum ($CDCl_3$), δ: 1.88 (s, $CCH_3$), 1.92 (s, $CCH_3$), 3.51 (s, $OCH_3$), 3.53 (s, $OCH_3$), 3.65 (d, $CH_2$), 4.53 (d, α-CH), 5.20 (q, β-CH), and 7.2-8.3 ppm (m, aromatic ring protons). Found, %: C 65.9; H 6.0; N 7.1; S 8.1. $C_{21}H_{22}N_2O_3S$. Calculated, %: C 66.0; H 5.8; N 7.3; S 8.3.

α-Acetamido-β-benzylmercapto-β-(3-indolyl)propionamide. Ester III [0.92 g (2.4 mmole)] was mixed with 5 ml of concentrated ammonium hydroxide, and the precipitate that formed after 3 months was washed with water to give 0.8 g (91%) of colorless crystals with mp 216° (after several crystallizations from alcohol). IR spectrum: 3400, 3340, 3300 (NH) and 1685 and 1620 $cm^{-1}$ (CO). PMR spectrum (deutero-DMFA), δ: 2.02 (s, $CH_3$), 3.66 (q, $CH_2$), 5.15 (q, β-CH), and 7.2-8.2 ppm (m, aromatic ring protons). The α-CH signals at ~4.7-4.8 ppm are covered by the signal of the water present in the solvent. Found, %: C 65.2; H 5.6; N 11.3; S 9.0. $C_{20}H_{21}N_2O_3S$. Calculated, %: C 65.3; H 5.8; N 11.4; S 8.8.

Methyl α-Acetamido-β-benzylmercapto-β-(1-acetyl-3-indolyl)propionate. A total of 0.2 ml of 57% perchloric acid was added to a solution of 0.97 g (2.54 mmole) of ester III in 3 ml of acetic anhydride, and the mixture was heated at 80° for 1 h, after which it was poured into water. The aqueous mixture was extracted with benzene, and the benzene extract was chromatographed ($Al_2O_3$, benzene) to give 0.9 g (84%) of colorless crystals with mp 172-173° (from methanol). IR spectrum: 3280 (NH), 1725, 1709, and 1655 $cm^{-1}$ (CO). PMR spectrum ($CDCl_3$), δ: 1.96 (s, $CCH_3$), 2.55 (s, $NCOCH_3$), 3.65 (s, $COOCH_3$), 3.69 (d, $CH_2$), 4.52 (d, α-CH), 5.13 (q, β-CH), and 7.2-8.3 ppm (m, aromatic ring protons). Found, %: C 65.1; H 5.7; N 6.7; S 7.4. $C_{23}H_{24}N_2O_4S$. Calculated, %: C 65.1; H 5.7; N 6.6; S 7.5.

* The following abbreviations are used here and subsequently: s is singlet, d is doublet, q is quartet, t is triplet, and m is multiplet.

Ethyl α-Acetamido-β-(3-indolyl)acrylate (IV). A total of 5 ml of a 2 N solution of sodium ethoxide in ethanol was added to a solution of 2.26 g (0.01 mole) of azlactone I in a mixture of 5 ml of alcohol and 10 ml of benzene. After 5 min, 9 ml of dilute (1:1) hydrochloric acid was added to the warm mixture, and the benzene was evaporated on a rotary evaporator. The precipitate was removed by filtration to give 1.8 g (65%) of colorless crystals with mp 171-172° (from 70% alcohol). IR spectrum: 3300, 3284 (NH), 1690, 1645, and 1625 $cm^{-1}$ (CO, C=C). UV spectrum, $\lambda_{max}$, nm (log ε): 227 (4.44), 262 (3.93), 277 (3.94), and 339 (3.33). PMR spectrum (deutero-DMF), δ: 1.27 (t, $CCH_3$), 2.14 (s, $NCOCH_3$), 4.20 (q, $CH_2$), 7.1-8.1 (indole-ring protons), and 7.73 and 8.02 ppm (two s, indole β-CH and 2-H). Found, %: C 65.9; H 6.0; N 10.6. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.2; H 5.9; N 10.3.

Ethyl α-Diacetylamino-β-(1-acetyl-3-indolyl)acrylate (V). A mixture of 4.24 g (15.6 mmole) of ester IV, 17 ml of acetic anhydride, and 4 ml of pyridine was heated at 100° for 2 h, after which it was poured over ice and worked up to give 3.3 g (59%) of colorless crystals with mp 139-140° (from ethyl acetate). IR spectrum: 1715, 1705 (broad, CO), and 1640 $cm^{-1}$ (C=C). UV spectrum, $\lambda_{max}$, nm (log ε): 224 (4.30), 241 (3.95), 256 (3.92), 334 (3.87). PMR spectrum ($CD_3COCD_3$), δ: 1.32 (t, $CH_3$), 2.32 [s, $N(COCH_3)_2$], 2.68 (s, $1\text{-}COCH_3$), 4.30 (q, $CH_2$), and 7.83 and 8.06 (two s, indole β-CH and 2-H), and 7.2-8.4 ppm (indole-ring protons). Found, %: C 64.2; H 5.5; N 7.8. $C_{19}H_{20}N_2O_5$. Calculated, %: C 64.0; H 5.6; N 7.8.

Ethyl α-Acetamido-β-acetylthio-β-(3-indolyl)propionate (VI). A mixture of 2.7 g (0.01 mole) of ester IV and 2.5 ml of dichlorothioacetic acid in 20 ml of ethyl acetate was refluxed for 2 h in a stream of nitrogen, after which it was vacuum evaporated, and the residual dark oil was chromatographed [$Al_2O_3$ thoroughly calcined at 500° for 6 h, benzene–alcohol (9:1)]. A substance with $R_f$ 0.5 (yellow spots) was extracted with ethyl acetate to give 1.7 g (49%) of a light-yellow caramel-like mass (mixture of isomers). IR spectrum: 3200-3400 (broad, NH), and 1735 and 1670 $cm^{-1}$ (CO). PMR spectrum (deutero-DMFA), δ: 1.08 (m, $CH_3$), 1.94 (m, $SCOCH_3$, $NCOCH_3$), ~4.2 (m, $CH_2$ and α-CH), 5.20 (m, β-CH), and 7.2-8.3 ppm (indole-ring protons). Found, %: C 58.3; H 5.7; Cl 0.2; N 8.0; S 9.4. $C_{17}H_{20}N_2O_4S$. Calculated, %: C 58.3; H 5.7; Cl 0.0; N 8.0; S 9.2.

## LITERATURE CITED


1. N. N. Suvorov, V. S. Velezheva, and V. V. Vampilova, Khim. Geterotsikl. Soedin., 646 (1974).
2. D. O. Holland and J. N. C. Nagler, J. Chem. Soc., 285 (1953).
3. The Chemistry of Penicillin, Princeton University Press (1949).
4. J. Sicher, M. Svoboda, and J. Farkaš, Coll. Czech. Chem. Commun., 20, 1439 (1955).
5. L. Kh. Vinograd, O. D. Shalygina, N. N. Bulatova, N. P. Kostyuchenko, T. N. Zykova, A. L. Mikerina, G. S. Arutyunyan, and N. N. Suvorov, Khim.-Farmats. Zh., No. 12, 15 (1971).