INDOLE DERIVATIVES

XLIX. Synthesis of DL-α-Mercapto-β-(indol-3-yl) propionic Acid (Indol-3-ylthiolactic Acid)*

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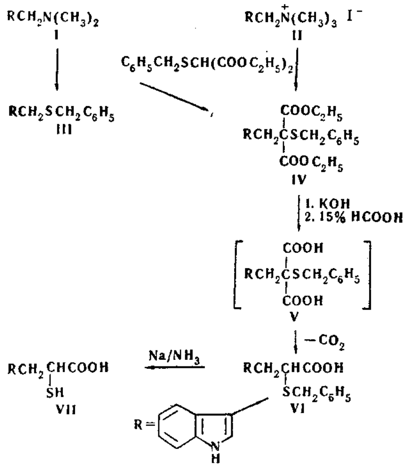
Benzylthio(skatyl)malonic ester has been synthesized by the condensation of gramine in toluene or its methiodide in ethanol with benzylthiomalonic ester, and this has been converted by monodecarboxylation and debenzylation with sodium in liquid ammonia into DL-α-mercapto-β-(indol-3-yl)propionic acid [β-(3-indol-yl)thiolactic acid]. DL-α-Benzylmercapto-β-(indol-3-yl)propionic acid has also been obtained from methyl DL-α-bromo-β-(indol-3-yl)propionate and benzyl mercaptan. Alkaline hydrolysis of S-[β-(indol-3-yl)-α-methoxycarbonylmethyl]thiouronium bromide has led to ring closure with the formation of 5-skatylthiazolidine-2,4-dione.

The study of the chemotherapeutic properties of some sulfur-containing indole derivatives [2, 3] has shown that many of them possess tuberculostatic activity. In view of this, it appeared of interest to synthesize DL-β-(indol-3-yl)-α-mercaptopropionic acid (indol-3-ylthiolactic acid) (VII).

The synthesis of VII was carried out by condensing gramine (I) or its methiodide (II) with benzylthiomalonic ester. The latter was obtained from bromomalonic ester and benzyl mercaptan in an alkaline medium.



When the condensation of I with benzylthiomalonic ester was carried out in absolute xylene, marked resinification of the reactants took place and the reaction mixture gave, in addition to the expected benzylthio(skatyl)malonic ester (IV), a 15% yield of benzyl skatyl sulfide (III). The reaction between I and benzylthiomalonic ester in absolute toluene led to the formation of IV with a yield of 24%. The reaction of II with benzylthiomalonic ester in absolute ethanol led to similar results.

The hydrolysis of the ester IV was effected with an aqueous ethanolic solution of caustic potash. It was necessary to acidify the alkaline solution with 15% formic acid using vigorous cooling. The use of mineral acids led to the splitting off of benzyl mercaptan and to the resinification of the reaction products. Even acidification with 15% formic acid was accompanied by the partial splitting off of benzyl mercaptan. The process of hydrolysis was accompanied by the simultaneous monodecarboxylation of the benzylthio(skatyl)malonic acid (V) with the formation of the acid VI. The latter was also obtained from methyl DL-α-bromo-β-(indol-3-yl)propionate (VIII) and benzyl mercaptan. The benzyl

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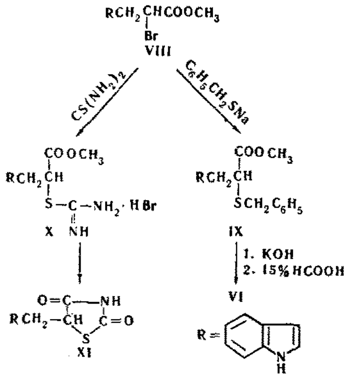
*For part XLVIII, see [1].

protection was removed by the action of sodium in liquid ammonia.



Attempts to obtain DL-α-mercapto-β-(indol-3-yl)propionic acid by the alkaline hydrolysis of the corresponding S-isothiourea (X) did not lead to the desired result, since in an alkaline medium, and also on boiling in aqueous solution, compound X is converted into 5-skatylthiazolidine-2,5-dione (XI).

EXPERIMENTAL

The IR spectra of the compounds obtained were recorded on a UR-10 instrument in the form of mulls in paraffin oil (for crystalline compounds) or in the form of liquid films (for compounds existing as oils).

Benzylthiomalonic ester. The sodium benzyl sulfide obtained from 18.7 g (0.151 mole) of benzyl mercaptan and 8.15 g (0.151 mole) of sodium methoxide in 80 ml of absolute methanol was added to 36 g (0.151 mole) of bromomalonic ester in 80 ml of methanol in a current of nitrogen which had been passed through a solution of pyrogallol. The mixture was boiled in a current of nitrogen for 6 hr, cooled, and poured into 400 ml of water, and the product was extracted with ether. The extracts were washed with water and dried with $MgSO_4$, the solvent was distilled off under reduced pressure, and the residue was distilled in vacuo. Yield 26 g (61%). Bp 148–153° C (1.5 mm). Mp 60–62° C (from ethanol). IR spectrum, cm^{-1}: 1745 (C=O); 1255 (C—O—C); 770, 700 (C—H bonds in a monosubstituted benzene ring). Found, %: C 59.71; H 6.29; S 11.21%. Calculated for $C_{14}H_{18}O_4S$, %: C 59.60; H 6.37; S 11.35%.

Benzyl skatyl sulfide (III). A mixture of 2.6 g (0.015 mole) of gramine, 4.23 g (0.015 mole) of benzylthiomalonic ester, 0.04 g of sodium, and 50 ml of absolute xylene was boiled in a current of nitrogen until the evolution of dimethylamine had completely ceased (20 hr). The precipitate was filtered off, and the solvent was distilled off in vacuo. The residual oil was chromatographed on a column of alumina, the product being eluted with an ether–petroleum ether mixture (1 : 1). Yield 0.5 g (15%). Mp 70–71° C (from hexane). According to the literature [4], mp 72° C. A mixture with an authentic sample obtained from gramine and benzyl mercaptan gave no depression of the melting point. IR spectra, cm^{-1}: 3350 (N—H); 1600, 1580 (aromatic system of bonds of the indole ring); 750 (C—H bonds in an ortho-disubstituted benzene ring); 705 (C—H bonds in a monosubstituted benzene ring).

Benzylthio(skatyl)malonic ester (IV). A) A mixture of 2.6 g (0.015 mole) of gramine, 4.23 g (0.015 mole) of benzylthiomalonic ester, 0.04 g of sodium, and 50 ml of absolute toluene was boiled in a current of nitrogen until the evolution of dimethylamine had ceased completely (20 hr). The solution was filtered, evaporated in vacuo to a volume of 10 ml, and passed through a column of alumina (1 : 30), the product being eluted with an ether–petroleum ether mixture (1 : 1). The yield of IV (vitreous mass) was 1.5 g (24%). IR spectrum, cm^{-1}: 3420 (N—H); 1730 (C=O); 1620, 1550 (aromatic system of bonds of indole ring); 1260 (C—O—C); 750 (C—H bonds in an ortho-disubstituted benzene ring); 710 (C—H bonds in a monosubstituted benzene ring). Found, %: C 67.21; H 6.18; N 3.85; S 7.38. Calculated for $C_{23}H_{25}NO_4S$, %: C 67.30; H 6.09; N 3.41; S 7.79.

B) A mixture of 5 g (0.017 mole) of gramine methiodide (II), 4.9 g (0.017 mole) of benzylthiomalonic ester, and the sodium ethoxide obtained from 0.4 g (0.017 g-at.) of sodium and 50 ml of absolute ethanol was boiled in a current of nitrogen for 18 hr. The mixture was cooled, poured into 150 ml of water, and extracted with ether. The ethereal extract was washed with water and dried with $MgSO_4$, and the solvent was evaporated to a volume of 4 ml and passed through a column of alumina (1 : 30), the product being eluted with an ether–petroleum ether mixture (1 : 1). Yield 1.7 g (25%). The IR spectrum and the elementary analysis were completely identical with those for the reaction product from experiment A.

Methyl DL-α-bromo-β-(indol-3-yl)propionate (VIII). With the ice-salt cooling and stirring, 1.86 g (0.0069 mole) of phosphorus tribromide in 70 ml of absolute ether was added to 4.5 g (0.02 mole) of methyl DL-β-(indol-3-yl)lactic acid [5, 6] in 200 ml of absolute ether, and the mixture was left at room temperature for 24 hr. Then the solution was poured off from the oil that had formed, and was washed with water, sodium bicarbonate, and water again, and was dried with $MgSO_4$. The solvent was evaporated in vacuo to a volume of 5 ml and the bromination product was chromatographed on a column of alumina (1 : 30) in an ether–petroleum ether mixture (10 : 1). Yield 1.4 g (31%). Mp 90–92° C (from benzene with heptane). Found, %: C 50.80; H 4.33; Br 27.98; N 5.08. Calculated for $C_{12}H_{12}BrNO_2$, %: C 51.06; H 4.23; Br 28.30; N 4.94.

Methyl DL-α-benzylthio-β-(indol-3-yl)propionate (IX). In a current of nitrogen, the sodium ethoxide obtained from 0.15 g (0.005 g-at.) of sodium and 20 ml of methanol was added to a mixture of 1.4 g (0.005 mole) of the ester VIII, 0.615 g (0.005 mole) of benzyl mercaptan, and 35 ml of methanol. The mixture was boiled in a current of nitrogen for 6 hr. After cooling, it was diluted with 200 ml of water, the reaction product was extracted with ether, and the extract was washed with water and dried with $MgSO_4$. After the solvent had been distilled off in vacuo, the residue was dissolved in 5 ml of ether and passed through a column of alumina (1 : 30), the product being eluted with a mixture of ether and petroleum ether (1 : 1). This gave 0.7 g (44%) of IX with mp 90–91° C (from benzene with petroleum ether). IR spectrum, cm^{-1}: 3410 (N—H); 1730 (C=O); 1620, 1555 (aromatic system of bonds of an indole ring); 750 (C—H bonds in an ortho-disubstituted benzene ring); 710 (C—H bonds in a monosubstituted benzene ring). Found, %: C 69.87; H 5.93; N 4.38; S 9.74. Calculated for $C_{19}H_{19}NO_2S$, %: C 70.02; H 5.85; N 4.41; S 9.82.

DL-α-Benzylthio-β-(indol-3-yl)propionic acid (VI). A) A mixture of 1.9 g (0.0046 mole) of the ester IV, 2.5 g of KOH, 25 ml of ethanol, and 30 ml of water was boiled in a current of nitrogen for 6 hr 30 min. The solution was cooled and diluted with 100 ml of water, and the hydrolysis product was extracted with ether. With cooling, the aqueous layer was acidified to pH 2 with chilled 15% formic acid and extracted with ethyl acetate. The extract was washed with water and dried with $MgSO_4$, and the solvent was distilled off in vacuo; the resulting oil was dissolved in 4 ml of dichloroethane and the solution was left in the refrigerator. This gave 0.5 g (34%) of VI with mp 125–127° C. IR spectrum, cm^{-1}: 3440 (N—H); 3000–2500 (O—H of the dimer of the acid); 1700 (C=O); 1620, 1590 (aromatic system of bonds of an indole ring); 710 (C—H bonds in a monosubstituted benzene ring); 740 (C—H bonds in an ortho-disubstituted benzene ring). Found, %: C 69.28; H 5.53; N 4.40; S 10.30. Calculated for $C_{18}H_{17}NO_2S$, %: C 69.51; H 5.46; N 4.50; S 10.28.

B) A mixture of 0.5 g (0.0015 mole) of the ester IX, 0.56 g (0.006 mole) of KOH, and 40 ml of ethanol was boiled in a current of nitrogen for 30 min, cooled to 0° C, and acidified with chilled 15% formic acid to pH 2, and the reaction product was extracted with ethyl acetate. The extract was washed with water and dried with $MgSO_4$, the solvent was distilled off in vacuo, the residual oil was dissolved in 2 ml of dichloroethane, and the solution was left in the refrigerator. This gave 0.31 g (65%) of the acid VI, mp 125–127° C. The IR spectrum and elementary analysis were completely identical with those of the substance from experiment A.

DL-β-(Indol-3-yl)-α-mercaptopropionic acid [β-(indol-3-yl)thiolactic acid] (VII). In a current of nitrogen, 0.02 g of sodium was gradually added to 0.3 g (0.001 mole) of the acid VI in 70 ml of ammonia (until the formation of a permanent blue color), and then the solution was stirred for 5–7 minutes and NH_4Cl was added to decolorize it. After evaporation of the ammonia, the residue was dissolved in 30 ml of water, and the solution was cooled to 0° C and acidified with chilled 15% formic acid to pH 2. The reaction product was extracted with ethyl acetate, the extract was washed with water and dried with $MgSO_4$, the solvent was distilled off in vacuo, and the residue was crystallized from dichloroethane. This gave 0.15 g (71%) of a substance with mp 160–161° C. IR spectrum, cm^{-1}: 3390 (N—H); 3100–2500 (O—H of a dimer of the acid); 1710 (C=O); 745 (C—H bonds in an ortho-disubstituted benzene ring). Found, %: C 59.78; H 4.88; N 6.36; S 13.99. Calculated for $C_{11}H_{11}NO_2S$, %: C 59.70; H 4.98; N 6.33; S 14.49.

S-[β-(Indol-3-yl)-α-methoxycarbonylethyl]thiouronium picrate (X). A solution of 0.6 g (0.002 mole) of the methyl ester VIII in 30 ml of ethanol was added to a boiling solution of 0.16 g (0.002 mole) of thiourea in 20 ml of ethanol, and the mixture was boiled for 4 hr. Then it was cooled, the solvent was distilled off in vacuo, and the noncrystallizable bromide of X was converted into the picrate. Mp 196–197° C (from ethanol). Found, %: C 45.30; H 3.67; N 16.30; S 6.36. Calculated for $C_{13}H_{15}NO_2S \cdot C_6H_3N_3O_7$, %: C 45.02; H 3.56; N 16.62; S 6.34.

5-Skatylthiazolidine-2,4-dione (XI). The oily bromide of X, 0.76 g (0.002 mole), was boiled in 50 ml of water for 20 min. The hot solution was filtered off and cooled, giving 0.2 g (49%) of XI with mp 251–252° C (from water). IR spectrum, cm^{-1}: 3442 (N—H); 1630, 1680 (C=O); 760 (C—H bonds in an ortho-disubstituted benzene ring). Found, %: C 58.28; H 4.30; N 11.66; S 12.68. Calculated for $C_{12}H_{10}N_2O_2S$, %: C 58.60; H 4.05; N 11.36; S 13.00.

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