INDOLE DERIVATIVES

XCIII.* SYNTHESIS OF 5-(3-INDOLYLMETHYL)BARBITURIC AND 5-(3-INDOLYLMETHYL)THIOBARBITURIC ACIDS

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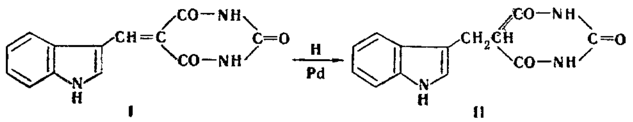
5-(3-Indolylmethyl)barbituric and 5-(3-indolylmethyl)thiobarbituric acids were obtained by condensation of 3-indolylmethylmalonic ester with urea and thiourea in monoglyme (1,2-dimethoxyethane) in the presence of lithium methoxide. The first of the two acids was also obtained by catalytic hydrogenation of 5-(3-indolylmethylene)barbituric acid.

Sekija and co-workers [2] have shown that the reduction of 5-(3-indolylmethylene)barbituric acid (I) by means of triethylammonium formate gives the triethylammonium salt of 5-methylbarbituric acid, indole, and di(3-indolyl)methane rather than 3-indolylmethylbarbituric acid (II). A dialkylation product is formed exclusively instead of acid II in the alkylation of barbituric acid (III) with gramine [1].

We have accomplished the synthesis of acid II by several methods. One of them involved the hydrogenation of chalcone II over palladium or Raney nickel.



Because of the low solubility of chalcone I, the reduction was carried out either in 10% NaOH (method A) or in highly polar aprotic solvents – dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (method B). Reduction via method A is accompanied by cleavage of chalcone I to starting barbituric acid III and 3-formylindole (IV), in which case the yield of acid II is 48%. A better yield (65%) is obtained by reduction by method B, but in this case high-melting unidentified products are formed along with acid II.

We were able to isolate acid II in the crystalline state only in the form of complexes with the solvents (chloroform or methylene chloride). The complex could not be decomposed by drying. Acid II decomposed after vacuum drying at 80° for 50 h. The formation of stable complexes of barbituric acid derivatives with such solvents as alcohol, acids, toluene, dimethylacetamide, DMSO, and DMF has been previously observed [3, 4].

The absorption bands of $C=O$ groups in the IR spectrum of acid II lie at 1680, 1701, and 1750 cm^{-1}, while the absorption bands of the NH groups lie at 3200 (broad), 3390, and 3450 cm^{-1}. The absorption bands of the $C=O$ groups in the IR spectrum of the complex of two molecules of acid I with one molecule of chloroform are found at 1700 and 1730 cm^{-1}, while those of the NH groups are at 3150, 3220, 3280, 3420, and 3450 cm^{-1}.

A quartet at 3.9 ppm, which is affiliated with 5-CH of barbituric acid, and an unsymmetrical doublet at 3.2 ppm from the protons of the CH_2 group of the 3-indolylmethyl grouping are observed in the PMR

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*See [1] for communication XCII.

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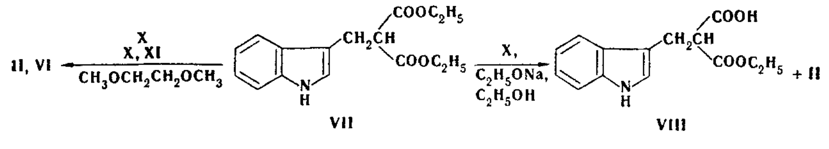
spectrum of the complex of acid II in $(CD_3)_2CO$. The signals of the indole ring protons are observed as a multiplet at 6.9-7.5 ppm, while the signals of the three NH protons are observed as a singlet at 10 ppm. The absence of a 3-H indole signal at 6.4 ppm [5] confirms the 3-indolylmethyl-substituted structure of acid II. Chalcones I and V were obtained in high yields via a modified method [6] by heating 3-formylindole with barbituric and thiobarbituric acids in acetic acid.

We were unable to convert thiochalcone V to 5-(3-indolylmethyl)-2-thiobarbituric acid VI by catalytic hydrogenation over Raney nickel and palladium, by indirect electroreduction, by reduction with sodium in liquid ammonia, or by reduction with sodium borohydride.

We also tried another route to obtain acid II by condensation of 3-indolylmethylmalonic ester (VII) with urea (X). When the condensation is carried out in alcohol in the presence of sodium hydroxide, 3-indolylmethylmalonic acid ester (VIII) is formed along with acid II. The former is apparently obtained as a result of partial hydrolysis of ester VII in the presence of sodium ethoxide. Monoester VIII is obtained in 53% yield in the condensation of ester VII with thiourea (XI). In fact, heating of ester VII in alcohol with sodium ethoxide gives monoester VIII in 62% yield.



II, X X=O; VI, XI X=S

The best yield of acid II (75%) was obtained when the condensation of ester VII with urea in 1,2-dimethoxyethane (monoglyme) was carried out with a twofold excess of lithium methoxide (method C). Only by this method were we able to obtain thio acid VI (in 89% yield).

The PMR spectrum of thio acid VI is similar to the spectrum of its oxygen analog. The structure of thio acid VI was also confirmed by conversion of its lithium salt to 3-indolylmethylmalonic acid diamide (IX) on heating in water with Raney nickel. The PMR spectrum of diamide IX is similar to the spectra of acids II and VI.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard (s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet).

Chromatography was carried out on plates with a fixed layer of Silufol UV-254 silica gel. Acetone–chloroform (1 : 1) was the eluent.

5-(3-Indolylmethylene)barbituric Acid (I). A 2.6-g (20.0 mmole) sample of barbituric acid was dissolved by heating in 30 ml of acetic acid, and the resulting solution was mixed with a hot solution of 2.9 g (20 mmole) of 3-formylindole in 10 ml of acetic acid. The resulting mixture was heated for another 15 min, after which it was cooled. The precipitate was removed by filtration and washed with hot acetic acid and ethanol to give 4.2 g (82%) of chalcone I. Found %: C 61.4; H 3.8; N 16.4. $C_{13}H_9N_3O_3$. Calculated %: C 61.1; H 3.5; N 16.5. IR spectrum: 1550, 1650, and 1690 [CH=C(CO)$_2$], 1730 (CO), and 3170, 3290, and 3380 cm^{-1} (NH).

5-(3-Indolylmethylene)-2-thiobarbituric Acid (V). This compound was obtained from 0.7 g (5 mmole) of thiobarbituric acid in 11 ml of acetic acid and 0.7 g (5 mmole) of 3-formylindole in 6 ml of acetic acid in analogy with the synthesis of acid I. The yield was 1.2 g (85.5%). Found %: C 57.3; H 3.2; N 15.2; S 11.5. $C_{13}H_9N_3O_2S$. Calculated %: C 57.5; H 3.3; N 15.5; S 11.8. IR spectrum: 1540, 1620, 1640 [CH=C(CO)$_2$], 1690 (CO), and 3100-3200, 3450 cm^{-1} (NH).

5-(3-Indolylmethyl)-2-thiobarbituric Acid (VI). A solution of 2.89 g (10 mmole) of ester VII, 0.76 g (10 mmole) of thiourea, and dry lithium methoxide [from 0.14 g (20 mmole) of lithium] in 30 ml of monoglyme was heated with stirring at 80-90° in a stream of N_2 for 3 h. It was then cooled, and the precipitate was removed by filtration to give 2.6 g of the lithium salt of acid VI. The salt was dissolved in the minimum amount of water, and 5% HCl was added to the solution with stirring. The precipitate [2.5 g (89.5%)] was removed by filtration and washed with water. Reprecipitation from methanol by the addition of water gave a product with mp 134–135° (dec.). Found %: C 57.4; H 4.2; N 14.9; S 11.3. $C_{13}H_{11}N_3O_2S$. Calculated %: C 57.1; H 4.1; N 15.3; S 11.7. IR spectrum: 1590–1630, 1670 (CO); 3220–3240, 3380, and 3420 (NH); 2500–2700 (SH); and 3580 (OH) cm^{-1}. PMR spectrum in $(CD_3)_2CO$: 3.2 ppm (unsym., d, 3-CH_2), 3.5 ppm (q, CH), 6.8–7.4 ppm (m, aromatic protons).

5-(3-Indolylmethyl)barbituric Acid (II). A) A 0.85-g (3.3 mmole) sample of chalcone I was hydrogenated in 20 ml of 5% NaOH at 50° over Raney Ni. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the filtrate was extracted with ether and ethyl acetate to remove the 3-formylindole. The residue was acidified with 5% HCl and extracted with ether. The ether extracts were washed with water and dried with $MgSO_4$. The ether was evaporated, and the resulting oil was crystallized by the addition of ether to give 0.5 g (48%) of a product with mp 130° (dec.). Recrystallization from acetone–chloroform gave a product with R_f 0.45. A sample was prepared for analysis by drying in vacuo (0.5 mm) at 80° for 1 h and at room temperature for 48 h. Found %: C 51.6; H 3.7; Cl 16.2; N 13.5. $C_{27}H_{23}Cl_3N_6O_6$. Calculated %: C 51.2; H 3.6; Cl 16.8; N 13.3.

B) A 2-g (7.8 mmole) sample of chalcone I was heated in 150 ml of DMF to 80°, and the resulting suspension was hydrogenated over freshly reduced palladium (0.4 g of $PdO/CaCO_3$). The hydrogenation was carried out at 60°. After the theoretical amount of hydrogen had been absorbed, the precipitate was removed by filtration and washed with ether. The ether and DMF were evaporated, and the residual oil crystallized after the addition of chloroform to give 1.53 g (62%) of acid II with an initial decomposition temperature of 125° and R_f 0.45.

C) This compound was also obtained in analogy with the synthesis of thioacid VI from 2.89 g (10 mmole) of ester VII, 0.6 g (10 mmole) of urea, and lithium methoxide [from 0.14 g (20 mmole) of lithium] in 30 ml of monoglyme at 80–90° for 10 h. The yield of the lithium salt of acid II was 2.5 g (82%). Acid II was isolated from its lithium salt in 75% yield by the method used to isolate thioacid VI.

Ethyl 3-Indolylmethylmalonate (VIII). A) A 0.76-g (20 mmole) sample of thiourea and 2.89 g (10 mmole) of ester VII were added to sodium ethoxide obtained from 0.23 g (20 mmole) of Na and 15 ml of absolute ethanol, and the mixture was heated with stirring in a stream of N_2 for 9 h. It was then cooled, diluted with water, and extracted with ether and ethyl acetate. The aqueous solution was acidified with 10% HCl and extracted with ether. The ether extracts were washed with water and dried with $MgSO_4$. The ether was evaporated, and the residual oil crystallized on standing to give 1.7 g (53%) of a product with mp 106–108° (from water). Found %: C 64.1; H 5.9; N 5.3. $C_{14}H_{15}NO_4$. Calculated %: C 64.4; H 5.8; N 5.4. IR spectrum: 1710, 1740 (CO), 2500–2700 (associated OH), 3400 (NH) cm^{-1}. PMR spectrum [in $(CD_3)S{=}O{-}CCl_4$, (1 : 7)]: 1.2 and 4.0 ppm (t and q, C_2H_5), 3.3 ppm (unsym., d, 3-CH_2), 3.6 ppm (q, CH), 6.9–7.3 ppm (m, aromatic protons), intensity ratio 3 : 2 : 2 : 1 : 5.

B) A 1-g (3.5 mmole) sample of ester VII and 0.2 g (3.5 mmole) of urea were added to sodium ethoxide obtained from 0.08 g (3.4 mmole) of Na and 10 ml of absolute alcohol in a stream of N_2, and the mixture was heated at 90° for 12 h. The precipitate was removed by filtration, and washed with absolute alcohol and ether to give 1.2 g of the salt of acid II, from which acid II was obtained in analogy with the synthesis of thio acid VI from its lithium salt. The mother liquor from the filtration of the precipitate was evaporated, and the residue was dissolved in water, extracted with 5% HCl, and extracted with ether. The ether extracts were washed with water and dried with $MgSO_4$. The ether was removed by distillation to give 0.4 g (44.5%) of ester VIII with mp 106–108°.

C) A 0.58-g (2 mmole) sample of ester VII was added to sodium ethoxide obtained from 0.09 g (4 mmole) of Na and 3 ml of absolute alcohol, and the mixture was heated for 8 h. The alcohol was evaporated, and the residue was diluted with water and extracted with ether. The aqueous alkaline solution was acidified with 5% HCl and extracted with ether. The ether extracts were washed with water and dried with $MgSO_4$. The ether was removed by distillation to give 0.2 g (62.5%) of ester VIII with mp 106–108°. The product did not depress the melting point of the compound obtained by method A.

3-Indolylmethylmalonic Acid Diamide (IX). A mixture of 0.8 g (2.9 mmole) of the lithium salt of acid VI, 5 g of Raney Ni, 5 ml of methanol, and 15 ml of water was refluxed for 10 h, after which the catalyst was removed by filtration and washed with hot methanol. The filtrate was evaporated to half its volume, acidified with 10% HCl, cooled, and filtered to give 0.5 g (71.2%) of diamide IX with mp 206–208° (from water). Found %: C 62.9; H 5.3; N 18.2. $C_{12}H_{13}N_3O_2$. Calculated %: C 62.4; H 5.6; N 18.2. IR spectrum: 1620, 1670–1680 (CO); 3200, 3370, 3400, and 3480 cm^{-1} (NH). PMR spectrum [in $(CD_3)_2S{=}O{-}CCl_4$ (2 : 3)]: 3.3 ppm (unsym. d, 3-CH_2), 3.6 ppm (q, CH), 6.9–7.3 ppm (m, aromatic protons).

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