INDOLE DERIVATIVES

XCII.* ALKYLATION OF BARBITURIC ACIDS WITH MANNICH BASES

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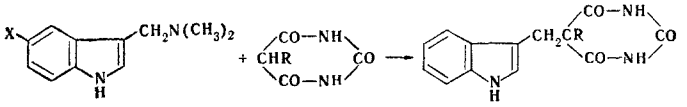
5-Substituted(butyl, phenyl)-5-skatyl(5-methoxyskatyl)barbituric acids were obtained by alkylation of the corresponding barbituric acids with gramine and 5-methoxygramine in dimethylformamide and dimethyl sulfoxide. 5,5-Dialkylation products were obtained in the alkylation of barbituric and thiobarbituric acids with gramine.

Alkylation with Mannich bases is widely used for the synthesis of derivatives of β-keto, malonic, and nitroacetic esters, β-diketones, and nitro compounds. We have developed a method for the alkylation of 2-thiobarbituric acid (I) and barbituric acid (II) and its derivatives by the action of gramine (III) or 5-methoxygramine (IV). The reaction in alcohol, dioxane, and pyridine is complicated by the fact that both components are only slightly soluble in these solvents. Judging from the literature data [2], dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) cannot be used, inasmuch as they condense with acids I and II on heating and even at room temperature.

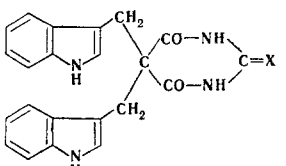
5-Butyl(phenyl)-5-skatylbarbituric acids (VIII-IX) were obtained in 70-75% yields in the alkylation of sodium salts of 5-butyl(phenyl)barbituric acids (VI, VII) by gramine methiodide (V) by the method previously used for the introduction of the skatyl group into malonic esters [3].

Considering that the more acidic [than malonic esters ($pK_a \sim 13$)] β-diketones (pK 5-6) are alkylated directly by gramine (and not in the form of sodium salts) without a catalyst or in the presence of catalytic amounts of KOH [4], we applied this method for the alkylation of barbituric acids (pK 4-5).

Barbituric acids VIII and X were obtained in yields of 95 and 80% when a catalytic amount of KOH was used:



III, IV VI, VII VIII-X



XIII, XIV

III X=H; IV X=OCH_3; VI R=C_4H_9;
VII R=C_6H_5; VIII X=H, R=C_4H_9;
IX X=H, R=C_6H_5; X X=OCH_3, R=C_4H_9;
XI, XIII X=O; XII, XIV X=S

The yield of acid IX was 86% during alkylation with gramine of acid VII in the presence of 0.5-1 mole of KOH.

*See [1] for communication XCI.

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TABLE 1

Compound	mp, °C	Empirical formula	Found, %				Calc., %				IR spectra, cm^{-1}		
			C	H	N	S	C	H	N	S	C=O	barbituric acid NH	indole NH
XIII	234—235 (alcohol)	$C_{22}H_{18}N_4O_3$	68,1	4,6	14,7	—	68,4	4,7	14,5	—	1700 s, 1710 s, 1760 s	3080, 3150, 3180, 3220, 3220	3420
XV	141, 210—212 (ethyl acetate, alcohol)	$C_{28}H_{30}N_4O_5S_2$	57,3	5,7	10,3	11,6	57,6	5,6	10,3	11,8	1630 w, 1700—1740 br, s	3230 br, 3470 br, 3530 br,	3400 w, m
XIV	200—201	$C_{28}H_{30}N_4O_2S$	65,2	4,3	13,9	7,5	65,6	4,5	13,9	7,9	1530 s, 1680 s C=S 1725 s	3100—3190 br 3220 br,	3400
XVI	140—142, 169—170 (alcohol)	$C_{30}H_{42}N_4O_4S_3$	55,4	5,7	10,4	16,8	55,9	5,4	10,0	17,2	1620 s, 1690 m, 1709 c	3190, 3220	3400
VIII	200—203 (alcohol)	$C_{17}H_{19}N_3O_3$	65,6	5,9	13,8	—	65,2	6,1	13,4	—	1645—1680 br, 1690— 1725 br, 1750 m	3080—3120 br, 3220 m	3450
X	165—168 (aqueous alcohol)	$C_{18}H_{21}N_3O_4$	62,6	6,2	11,9	—	62,9	6,2	12,2	—	1680—1720 br, 1745 m	3080—3100 br,	3410 s, 3450 c, 3610 s
IX	214—216 dec. (aqueous methanol)	$C_{19}H_{15}N_3O_3$	68,3	4,7	12,9	—	68,5	4,5	12,6		1650, 1680—1710 c, br, br, m 1740 m	3080—3100 br	3480

Dialkylation products – 5,5-diskatylbarbituric and thiobarbituric acids (XII and XIV) – are formed in the alkylation of sodium salts XI and XII of barbituric and thiobarbituric acids with gramine methiodide. Under these conditions, the formation of condensation products of acids I and II was not observed in DMSO.

Diskatylbarbituric acids XIII and XIV are obtained in the best yields (80-85%) by the reaction of an equimolar amount of salts XI and XII with methiodide V. A complex mixture of products is formed in the case of a twofold excess of methiodide V as compared with salts XI and XII.

Dialkylation products XIII and XIV are also the principal reaction products in the alkylation of barbituric and thiobarbituric acids with gramine in equimolar ratios. The monoalkylation products cannot be obtained in the alkylation of a fivefold to tenfold excess of acids I and II. The same principle was also observed in the alkylation of dimedone and dihydroresorcinol (pK_a ~5.2-5.6 [4]) with gramine.

Diskatylbarbituric acids XIII and XIV are obtained as a result of the reaction in the form of stable complexes XV and XVI containing two DMSO molecules.

The formation of side complexes due to hydrogen bonds of the NH groups of phenobarbital was previously observed with compounds that are electron donors – DMSO and N,N-dimethylacetamide (DMA) [5]. Complex XV of acid XIII is stable in water and also on prolonged heating (for greater than 40 h) but decomposes in alkaline media at 100°. Complex XVI of thioacid XIV is less stable and gradually decomposes on repeated recrystallizations from alcohol. Thioacid XIV is resinified on storage and on heating in water and in most organic solvents and is purified only by rapid reprecipitation from methanol by the addition of water. The skatylbarbituric acids do not complex with DMF.

The absorption bands of carbonyl groups lie at 1680, 1700-1720, and 1740-1760 cm^{-1} [6] in the IR spectra of acids VIII-X and XIII. There are several bands apparently due to different forms of intermolecular hydrogen bonds with participation of NH groups of the barbituric acids at 3060-3300 cm^{-1}, and bands involving the NH groups of indoles are found at 3400-3480 cm^{-1}. In addition to absorption bands of two carbonyl groups, the IR spectrum of thioacid XIV contains a C=S absorption band at 1530 cm^{-1} [7].

The aliphatic portion of the PMR spectra of acids XIII and XIV contains only one singlet at 3.5 ppm with an intensity of four proton units. The spectra of acids VIII and IX contain the same signal with an intensity of two proton units; this excludes isomeric structures of the products of N- or O-alkylation of the starting barbituric acids.

The signals of aromatic ring protons in the form of a multiplet lie at 6.8-7.3 ppm. The absence of indole 3-H signals at 6.4 ppm [8] and the presence of an indole 2-H doublet at 6.7 ppm confirms the 5-(3-indolylmethyl)barbituric acid structure (VIII-IX, XIII-XIV).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The melting points of the compounds, the results of analyses, and the IR spectral data are presented in Table 1.

5,5-Diskatylbarbituric Acid (XIII). A mixture of 0.64 g (5 mmole) of acid II, 1.74 g (10 mmole) of gramine, and 0.01 g of KOH in 10 ml of DMSO was heated at 80-100° in a stream of nitrogen for 6 h. The reaction mixture was cooled and diluted with water, and the resulting precipitate was removed by filtration to give 2.4 g (88.6%) of complex XV with mp 135-137° and 208-210°.

Acid XIII [1.2 g (62%)] with mp 221-223° was obtained when this reaction was carried out in DMF with the same amounts of starting materials.

A 2.4-g sample of complex XV was dissolved in saturated sodium carbonate solution and extracted three times with ether. The sodium carbonate solution was acidified with 5% HCl and extracted with ether and ethyl acetate. The extract was dried with $MgSO_4$, and the solvents were removed by distillation to give 1.5 g (78%) of acid XIII.

A) Gramine methiodide (V). A 3.69-g (2.5 mmole) sample of methyl iodide was added dropwise to a solution of 4.52 g (2.5 mmole) of gramine in 10 ml of DMSO, and the mixture was allowed to stand for 10-12 h.

B) Alkylation with methiodide V. A 3.8-g (30 mmole) sample of acid II was added to sodium ethoxide, prepared from 0.57 g of Na (2.5 mmole) and 30 ml of absolute methanol, and the mixture was refluxed for 15 min, after which the alcohol was evaporated to dryness. A total of 45 ml of DMSO and the earlier prepared methiodide V were added to salt XI, and the mixture was heated at 90-100° for 6 h in a stream of nitrogen. The unchanged salt XI was removed by filtration, and the filtrate was diluted with water. The resulting precipitate was removed by filtration and washed with water to give 6.15 g (90.7%) of complex XV.

5,5-Diskatyl-2-thiobarbituric Acid (XIV). A mixture of 1.1 g (7.5 mmole) of acid I, 2.6 g (15 mmole) of gramine, and 0.01 g of KOH in 10 ml of DMSO was heated at 80-100° in a stream of nitrogen for 6 h. It was then diluted with water and acidified with 5% HCl. The resulting precipitate was removed by filtration and washed with water to give 3.8 g (92%) of complex XVI with mp 130-134°. To free the complex of DMSO, 3.8 g of complex XVI was passed through a column containing silicon dioxide (pure for luminophores) with elution by acetone–chloroform (1 : 3) to give 2.4 g (80%) of acid XIV with mp 192-195°.

Acid XIV was obtained in 75% yield when this reaction was carried out in DMF with the same amounts of starting materials.

5-Butyl-5-skatylbarbituric Acid (VIII). This compound was obtained from 2.3 g (12.5 mmole) of acid VI, 2.17 g (12.5 mmole) of gramine, and 0.01 g of KOH in 20 ml of DMSO in analogy with the synthesis of acid XIII. The alkylation time at 80-100° was 5 h. The yield of product with mp 208-210° was 3.7 g (95.9%).

5-Butyl-5-(5-methoxyskatyl)barbituric Acid (I). This compound was obtained from 1.84 g (10 mmole) of acid VI, 2.04 g (10 mmole) of gramine IV, and 0.01 g of KOH in 10 ml of DMSO in analogy with the synthesis of acid VIII. The yield was 2.6 g (75.8%).

5-Phenyl-5-skatylbarbituric Acid (IX). This compound was obtained from 1.3 g (6.2 mmole) of acid VII, 1.09 g (6.2 mmole) of gramine, and 0.35 g (6.2 mmole) of KOH in 10 ml of DMSO in analogy with the synthesis of acid XIV. The yield was 1.8 g (86.5%).

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