INDOLE DERIVATIVES

138.* SYNTHESIS OF SOME NEW SULFUR-CONTAINING DERIVATIVES OF INDOLE

I. Sh. Chikvaidze, N. Sh. Megrelishvili, Sh. A. Samsoniya, and N. N. Suvorov

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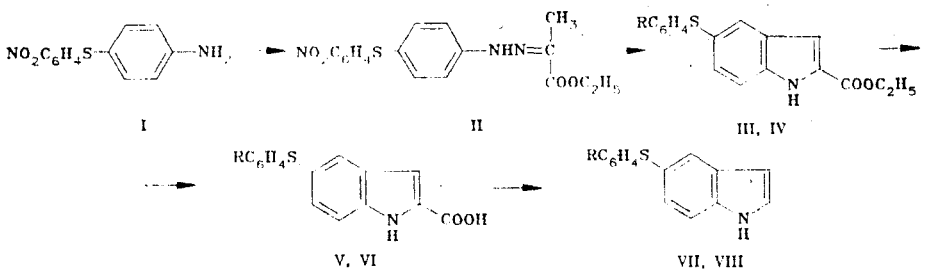
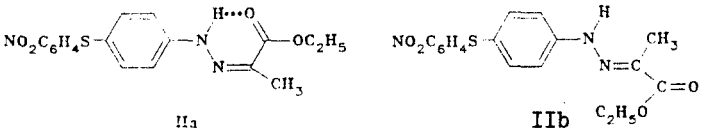
2-Ethoxycarbonyl-5-(p-nitrophenylthio)indole and the corresponding acid were obtained by the E. Fischer reaction. Decarboxylation of the acid gave 5-(p-nitrophenylthio)indole. The geometric isomers of the initial hydrazone of ethyl pyruvate were isolated and characterized.

The present communication is devoted to the synthesis of some new sulfur-containing amines of the indole series.



III, V, VII R=NO_2; IV, VI, VIII R=NH_2

The 4-p-nitrophenylthiophenylhydrazone of ethyl pyruvate (II) was obtained by the Japp—Klingemann method [2]. The hydrazone represents a mixture of two geometric isomers: syn (IIa) and anti (IIb). We were able to separate this mixture by column chromatography.



The presence of an intramolecular hydrogen bond, which is possible with the syn orientation of the substituents, makes it possible to distinguish between the syn and anti forms of the hydrazone on the basis of their spectra [3]. In the IR spectrum of the syn isomer (IIa) the absorption bands of the NH and CO groups are shifted toward lower frequencies by 85 and 25 cm^{-1} respectively compared with the analogous bands in the spectrum of the anti isomer (IIb); in the UV spectrum of the syn isomer (IIa) there is a bathochromic shift of the long-wave absorption band by 15 nm compared with the analogous band in the spectrum of the anti isomer (IIb) (Table 1); in the PMR spectrum of the syn isomer (IIa) the signal for the proton of the NH group appears in the downfield region compared with the signal of the analogous proton of the anti form (IIb).

2-Ethoxycarbonyl-5-(p-nitrophenylthio)indole (III) was obtained by the E. Fischer reaction. The best results were obtained during cyclization with polyphosphoric esters. Saponification of the ester (III) gave the acid (V), the decarboxylation of which was conducted in boiling quinoline in the presence of copper chromite [4].

Reduction of the nitro group gave 2-ethoxycarbonyl-5-(p-aminophenylthio)indole (IV), 2-carboxy-5-(p-aminophenylthio)indole (VI), and 5-(p-aminophenylthio)indole (VIII). The best yields were obtained with zinc dust in a water—alcohol suspension in the presence of calcium chloride by the method described in [5].

*For Communication 137, see [1].

I. Dzhavakhishvili Tbilisi State University, Tbilisi 380028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1508-1511, November, 1991. Original article submitted June 20, 1990.

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TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Molecular formula	mp, °C	R_f*	IR spectrum, cm^{-1}				UV spectrum, λ_{max}, nm (log ε)	M^+	Yield, %
				CO	NH	NO_2	NH_2			
IIa	$C_{17}H_{17}N_3O_4S$	111...112	0,96	1680	3280	1520, 1345	—	207 (4,44); 224 (4,21); 252 (4,15); 349 (4,56)	359	15,7
IIb	$C_{17}H_{17}N_3O_4S$	104...105	0,4	1705	3365	1520, 1345	—	207 (4,43); 223 (4,25); 245 (4,01); 334 (4,57)	359	48,6
III	$C_{17}H_{14}N_2O_4S$	193...194	0,67	1700	3320	1525, 1390	—	205 (4,25); 240 (4,45); 320 (4,15); 340 (4,11)	342	56,0
IV	$C_{17}H_{16}N_2O_2S$	115...116	0,18	1690	3310	—	3220	207 (4,60); 241 (4,59); 256 (4,53); 294 (4,36); 335 (3,64)	312	55,0
V	$C_{15}H_{10}N_2O_4S$	260(decomp)	0,18	1670	3330	1530, 1380	—	203 (4,43); 239 (4,56); 298 (4,14); 341 (4,15)	314	66,6
VI	$C_{15}H_{12}N_2O_2S$	239...240	0,6	1690	3425	—	3320	207 (4,48); 243 (4,43); 314 (4,28); 339 (3,59)	284	44,0
VII	$C_{14}H_{10}N_2O_2S$	153...154	0,48	—	3420	1510, 1345	—	202 (4,58); 240 (4,76); 251 (4,16); 287 (3,96); 344 (4,23)	270	40,0
VIII	$C_{14}H_{12}N_2S$	135...136	0,4	—	3385	—	3320	205 (4,51); 227 (4,39); 243 (4,22)	240	28,5

*Compounds (IIa, b, III, V) in a 1:2 mixture of hexane and ether; compound (IV) in a 4:1 mixture of chloroform and ether; compound (VI) in ether; compound (VII) in benzene; compound (VIII) in a 1:1 mixture of benzene and ether.

TABLE 2. PMR Spectra of Compounds (III-VIII)

Compound	1-H	Chemical shifts, ppm*										SSCC, J, Hz
		2-H, d.d	3-H	4-H, d	6-H, dd	7-H, d	A-H	B-H	CH_2—Et, q	CH_3—Et, t	NH_2	
III	12,28 s	—	7,24 d.d	8,02	7,41	7,62	7,18 d	8,09 d	4,37	1,36	—	$J_{13}=1,8$; $J_{37}=0,36$; $J_{46}=1,5$; $J_{67}=8,4$; $J_{Et}=7,3$; $J_{AB}=8,8$
IV	10,98 s	—	7,10 d.d	7,55	7,19	7,45	7,19 d.d	6,68 d.d	4,35	1,35	4,92 s	$J_{13}=2,2$; $J_{37}=1,0$; $J_{46}=2,2$; $J_{67}=8,8$; $J_{AB}=8,8$
V	11,29 s	—	7,30 d.d	8,07	7,47	7,73	7,24 d.d	8,12 d.d	—	—	—	$J_{13}=2,2$; $J_{37}=1,0$; $J_{46}=1,8$; $J_{67}=8,3$; $J_{AB}=8,8$
VI	9,90 s	—	7,06 d	7,52	7,20	7,41	7,20 d.d	6,63 d.d	—	—	6,08 b.m	$J_{13}=2,2$; $J_{46}=1,8$; $J_{67}=8,8$; $J_{AB}=8,4$
VII	11,49 s	7,49	6,53 br.s	7,87	7,26	7,57	7,15 d.d	8,08 d.d	—	—	—	$J_{12}=2,6$; $J_{13}=2$; $J_{23}=2,9$; $J_{46}=1,5$; $J_{67}=8,4$; $J_{AB}=8,8$
VIII	11,09br.s	7,31	6,35 m	7,41	6,98	7,31	7,09 d.d	6,54 d.d	—	—	5,26 s	$J_{12}=2,5$; $J_{13}=2,2$; $J_{23}=2,9$; $J_{46}=1,8$; $J_{67}=8,4$

*The PMR spectra of compounds (III, VII, VIII) were recorded in DMSO-d_6, the spectra of compounds (IV, V) were recorded in acetone-d_6, and the spectrum of (VI) was recorded in deuterochloroform.

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil and chloroform on a UR-20 instrument. The UV spectra were obtained on a Specord spectrophotometer in ethanol. The PMR spectra were obtained on a WP-200SY spectrometer with TMS as internal standard. The mass spectra were obtained on a Ribermag R10-10B spectrometer at 70 eV. The reactions and the individuality of the obtained compounds were monitored by TLC on Silufol UV-254 plates. Silica gel with a particle size of 100-250 μ was used for column chromatography.

The characteristics of the compounds are given in Tables 1 and 2. The elemental analysis of the obtained compounds agree with the calculated data.

4-p-Nitrophenylhydrazones of Ethyl Pyruvate (IIa, b). A mixture of 15 g (60 mmole) of compound (I), 48 ml of concentrated hydrochloric acid, and 600 ml of water was heated to 70°C and cooled to 35-40°C. A saturated solution of 4.8 g (66 mmole) of sodium nitrite was added, and the mixture was stirred for 1 h. To the obtained solution we added CH_3COONa to pH 5, and we kept the mixture for 12-15 h. The yellow crystals that separated were dissolved by heating to 35-40°C. The obtained solution was quickly added with vigorous stirring to a separately prepared mixture of 9.5 ml (66 mmole) of α-methylacetoacetic ester, 60 ml of ethanol, 3.7 g (66 mmole) of potassium hydroxide, and 5 ml of water. After a few minutes an oil and yellow crystals separated from the reaction mixture. The mixture was stirred for 4 h and left overnight, extracted with chloroform (4 × 120), dried over calcium chloride, and evaporated. The obtained oil was crystallized from ethanol. We obtained 14.2 g (66%) of a mixture of isomers. A 0.7-g sample of this mixture was separated in the 1:1 hexane—ether system; the first fraction (R_f 0.96, 1:2 hexane—ether) contained 0.11 g of the syn isomer (IIa); the second fraction (R_f 0.4, 1:2 hexane—ether) contained 0.34 g of the anti isomer (IIb).

Compound (IIa). PMR spectrum (acetone-d_6): 7.55 [2-H (6-H), s]; 7.41 [3-H (5-H), d]; 7.25 [2′-H (6′-H), d]; 8.12 [3′-H (5′-H),d]; 12.17 (NH, s); 4.34 (CH_2—Et, q); 1.36 (CH_3—Et, t); 2.17 (C—CH_3, s); $J_{23} = J_{56} = 8.4$; $J_{2'3'} = 8.8$ Hz. Compound (IIb). PMR spectrum (acetone-d_6): 7.45 [2-H (6-H), s]; 7.54 [3-H (5-H), d]; 7.24 [2′-H (6′-H), d]; 8.12 [3′-H (5′-H), d]; 9.55 (NH, s); 4.26 (CH_2—Et, q); 1.32 (CH_3—Et, t); 2.13 (C—CH_3, s); $J_{23} \approx J_{2'3'} = 8.4$ Hz.

2-Ethoxycarbonyl-5-(p-nitrophenylthio)indole (III). A mixture of 3.6 g (10 mmole) of the unpurified hydrazone (II) and 30 g of polyphosphoric esters was heated to 80°C and stirred for 30 min. The mixture was then cooled and poured into 400 ml of cold water. The precipitate was filtered off, washed to a neutral reaction with water, and dried. The product was purified on a column in the 1:2 hexane—ether system, and 1.9 g was obtained. For the further transformations the product was purified by boiling in small amounts of isopropyl alcohol. We obtained 2.35 g (69%) of the product.

2-Ethoxycarbonyl-5-(p-aminophenylthio)indole (IV). To a solution of 2 g (6 mmole) of compound (III) in 300 ml of ethanol we added a solution of 7 g of calcium chloride in 10 ml of water and 16 g of zinc dust. The mixture was boiled with vigorous stirring for 2 h, filtered, and poured into 500 ml of water. The colorless precipitate was filtered off and crystallized from octane. We obtained 1 g of compound (IV).

2-Carboxy-5-(p-nitrophenylthio)indole (V). To a solution of 0.34 g (1 mmole) of compound (III) in 10 ml of isopropyl alcohol we added 56 ml of a 10 % aqueous solution of sodium hydroxide. The mixture was boiled for 1 h, cooled, filtered, and acidified to pH 1 with hydrochloric acid. The precipitate was filtered off, washed with water, and dried. The product was purified by reprecipitation. We obtained 0.2 g of the indole (V).

2-Carboxy-5-(p-aminophenylthio)indole (VI). A. The product was obtained similarly to compound (V) from 0.3 g (1 mmole) of the indole (IV). The yield was 0.12 g (44%).

B. The compound was obtained similarly to compound (IV) from 0.15 g (0.5 mmole) of compound (V). The yield was 0.05 g (38%).

The indicated yields were obtained after purification on a column in the 1:1 chloroform—ether system.

5-(p-Nitrophenylthio)indole (VII). A mixture of 0.7 g (2 mmole) of the acid (V), 0.5 g of copper chromite, and 30 ml of quinoline was boiled with stirring for 20 min. The hot reaction mixture was filtered, poured into 100 ml of 10% hydrochloric acid, extracted with ether (4 × 50 ml), and dried over sodium sulfate. The product was purified on a column with benzene as eluant. We obtained 0.24 g of compound (VII).

5-(p-Aminophenylthio)indole (VIII). The compound was obtained similarly to compound (IV) from 0.24 g (0.8 mmole) of compound (VII). The product was crystallized from octane. We obtained 0.06 g of the indole (VIII).

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ACYLATION OF 3-SUBSTITUTED 1-AMINOTHIOHYDANTOINS

A. T. Ayupova and G. G. Galust'yan

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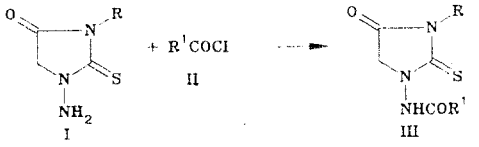
1-Monoacylamino-3-aryl(alkenyl)thiohydantoins were obtained by the acylation of 3-R-1-aminothiohydantoins by acid chlorides in various solvents and also under the conditions of phase-transfer catalysis.

Plant growth regulators [1,2], herbicides [3,4], and fungicides [5,6] have recently been found among derivatives of hydantoin, which have been the subject of searches for effective pesticides. The acylation of 3-substituted 1-aminothiohydantoins was investigated in order to find new physiologically active substances in the hydantoin series.

The synthesis of these compounds was realized comparatively recently, and their properties have been studied little with the single exception of the acylation of 1-amino-3-phenylthiohydantoin by acetic anhydride in the presence of anhydrous sodium acetate [7].

In the present work we investigated the acylation of 3-substituted 1-aminothiohydantoins (I) by carboxylic acid chlorides (II) (acetic, chloroacetic, benzoic) in aprotic (benzene) and protophilic (pyridine) solvents and also in a two-phase system (benzene—aqueous sodium hydroxide solution).



III a $R=C_6H_5$, $R^1=CH_3$; b $R=C_6H_5$, $R^1=CH_2Cl$; c $R=R^1=C_6H_5$; d $R=CH_2=CH-CH_2-$, $R^1=CH_3$; e $R=CH_2=CH-CH_2-$, $R^1=CH_2Cl$; f $R=CH_2=CH-CH_2-$, $R^1=C_6H_5$; g R=α-Naphthyl $R^1=CH_3$; h R=α-Naphthyl $R^1=CH_2Cl$; and R=α-Naphthyl $R^1=C_6H_5$

During acylation of the aminothiohydantoins (I) by acetyl chloride, chloroacetyl chloride, and benzoyl chloride in dry benzene in the presence of triethylamine (amine—acyl chloride—triethylamine ratios 1:1:1, method A [8]) we isolated the monoacylation products (III) with yields of 35-40% and also a large part of the initial compound (I). Increase in the amount of acyl chlorides did not change the yield of the product (III) and led to the formation of trace quantities of diacylation products. 3-Phenyl-1-diacetylaminothiohydantoin was synthesized for identification by the method in [7].

Realization of acylation in pyridine (method B [9]), which was at the same time solvent and hydrogen chloride acceptor, also did not help to increase the yields of compounds (III).

The acylation of the aminothiohydantoins (I) in the two-phase system, where the acyl chloride and aminothiohydantoin are present in the nonaqueous phase (benzene) while the sodium hydroxide is in the aqueous phase (method C [10]), increased the yield of the required products (III) to 70%. On account, clearly, of the fact that the amine hydrochloride formed in the reaction dissolves in the water and is converted into the amine by the action of alkali it then passes into the nonaqueous phase and reenters the reaction.

The nature of the substituents at position 3 of the aminothiohydantoins (I) does not substantially affect the yields of the final products (III).

The IR spectra of compounds (IIIa-i) contain absorption bands for the hydantoin ring at 1195 cm^{-1}, for the thiohydantoin carbonyl group at 1765 cm^{-1}, and for the carbonyl fragment of the acyl group at 1695-1700 cm^{-1}.

In the mass spectra of compounds (III) there are clearly defined peaks corresponding to the molecular ions (M^+), and there are also strong peaks formed as a result of the successive elimination of the acyl and aminoacyl fragments and the sulfur atom from the molecular ion. One of the main processes in the dissociation of the molecular ions is the elimination of the NR—C=S and O=C—NR—C=S fragments.

Institute of Chemistry of Vegetable Substances, Uzbek Academy of Sciences, Tashkent 700170. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1512-1514, November, 1991. Original article submitted February 2, 1990; revision submitted March 23, 1991.