Di[2-oxo-2-(1-adamantyl)ethyl] Sulfate (XXII). Concentrated sulfuric acid was added to a solution of 2.0 g of diazoketone [15] in 15 ml of chloroform while vigorously stirring and cooling to 0-5°, until nitrogen evolution ceased. The mixture was kept at room temperature for 1 h and the solvent distilled off. The residue was recrystallized from acetone or hexane to given 1.0 g of XXII.

Compounds XXIII and XXIV were prepared analogously.

2-Chloro-2-nitrosoadamantane (VII). A stirred solution of 3 g of oxime VI in 100 ml of dry carbon tetrachloride was treated at −10 to −15° with 2.0 g of N,N'-dichloro-N,N'-dinitro-ethylenediamine [4]. The precipitated N,N'-dinitro-ethylenediamine was filtered off, the solvent distilled off, and the residue recrystallized from aqueous methanol to give 3.2 g (88%) of VII, mp 152-153°. A mixed melting point determination with an authentic sample [5] showed no melting point depression.

LITERATURE CITED

1. A. L. Fridman, I. K. Moiseev, N. A. Kolobov, et al., Khim. Farm. Zh., No. 7, 6 (1974).
2. R. Black and G. Gill, J. Chem. Soc. (C), 671 (1970).
3. H. Geluk and J. Schlatmann, Tetrahedron, 14, 5361 (1968).
4. V. P. Ivshin, A. L. Fridman, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim., 640 (1970).
5. A. Kayen et al., Rec. Trav. Chim. Pays Bas, 90, 866 (1971).
6. H. Stetter and H. Stark, Chem. Ber., 95, 574 (1962).
7. H. Stetter and J. Meyer, Chem. Ber., 95, 667 (1962).
8. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495 (1961).
9. V. S. Zaselov, Farmakol. Toksikol. No. 4, 418 (1963).
10. V. S. Zaselov, Antispasmodic Properties of Benzilamide and Its Derivatives, Candidate's Dissertation, Perm (1964).
11. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959), p. 71.
12. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1959), p. 456.
13. H. Stetter, J. Garther, and P. Tacke, Chem. Ber., 98, 3888 (1965).
14. H. Stetter, J. Meyer, M. Schwarz, et al., Chem. Ber., 93, 226 (1960).
15. T. Sasaki, S. Egucki, and T. Toru, Bull. Chem. Soc. Jap., 42, 1617 (1969).

INDOLYLALKANOIC ACID THIOAMIDES

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No systematic study of the biological activity of indolylalkanoic acid thioamides has been carried out hitherto. The first representative of this series of compounds has been prepared by the action of hydrogen sulfide on 3-indolylcarbonitrile under pressure at high temperature [1]. We have succeeded in showing that this and other indolylalkanoic acid thioamides can be prepared much more conveniently from the preparative point of view by reacting the corresponding nitriles with thioacetic acid at room temperature. This method can be used directly for the synthesis of thioamides from the readily available nitriles of indolylcarboxylic acid, indolylacetic acid and indolylpropionic acid. If, however, the nitrile is obtained by dehydration of the corresponding amide, it is naturally simpler to convert the amide directly into the thioamide by treatment with phosphorus pentasulfide. It should be borne in mind, however, that this leads to the dehydration of a large proportion of

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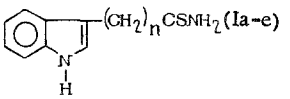
TABLE 1. 3-Indolylalkanoic Acid Thioamides  (Ia-e)

Compound	n	Thioamide yield (%)	Melting point (deg)	Found (%)			Empirical formula
				C	H	S	
Ia	0	96	154—5	61,1	4,6	18,2	$C_9H_8N_2S$
Ib	1	63	159—60	63,3	5,4	16,8	$C_{10}H_{10}N_2S$
Ic	2	73	159—60	65,0	5,7	15,8	$C_{11}H_{12}N_2S$
Id	3	40	117—8	66,1	6,5	14,6	$C_{12}H_{14}N_2S$
Ie	4	76	103—4	67,3	6,9	13,9	$C_{13}H_{16}N_2S$

Compound	Calculated (%)			R_f		Tuberculostatic activity (μg/ml)
	C	H	S	nitrile	thioamide	
Ia	61,3	4,6	18,0	0,40	0,13	31*
Ib	63,1	5,3	16,8	0,52 [3]	0,26	4
Ic	64,7	5,9	15,7	0,53 [4]	0,24	0,12
Id	66,0	6,5	14,7	0,59	0,27	0,5
Ie	67,3	6,9	13,8	0,62	0,30	0,5

*Low antitubercular activity in [1].

the amide into the nitrile by reaction with the phosphorus pentoxide formed. It is also useful to treat this mixture of thioamide and nitrile with thioacetic acid so that the mixture is converted into the thioamide alone.

The thioamides obtained are colorless, readily crystallizing substances which are practically insoluble in water. Only the thioamide of 3-indolylcarboxylic acid is colored (bright orange) owing to the conjugation of the indole nucleus with the thioamide group, which shows up in the UV spectrum as a maximum at 308 nm. This and the other thioamides also have absorption maxima at 218-220 and 269-271 nm and a shoulder at 290 nm. All the thioamides investigated have similar IR spectra. In the 3400 and 3350-3150 cm^{-1} regions there are four sharp maxima connected with the vibrations of the NH bonds in the indole and NH_2 groups. The intense "amide" bands of the primary thioamide grouping are located at ~1625 cm^{-1} and in the vicinity of 1460-1410, ~1300, and 990 cm^{-1} [2].

In a study of the antimicrobial activity of the synthesized thioamides in vitro against nine pathogens causing acute bacterial infections, against Mycobacterium tuberculosis, and against five types of pathogenic fungus, we showed that they inhibit the growth of Gram-positive bacteria, Mycobacterium tuberculosis and pathogenic fungi. The greatest activity was observed against the tuberculosis bacillus (H-37-R_V strain, see Table 1), a distinct activity maximum of 0.12 μg/ml being observed for the thioamide of 3-indolylpropionic acid (Ic). We also studied the chemotherapeutic activity of the thioamides with the highest in vitro activity against experimental tuberculosis in white mice. We found that compounds Ic-Ie have no effect on the development of the tubercular process even at the maximum tolerable doses (0.62, 0.31 and 0.16 mg for mice weighing 15-16 g).

EXPERIMENTAL

The IR spectra were recorded with UR-10 and Perkin-Elmer instruments, and the UV spectra were recorded with an EPS-3 spectrophotometer. Chromatography was carried out on Silufol with a mixture of benzene and acetone (4:1), the substances being detected by means of an ultrachemiscope and by their color reaction with p-dimethylaminobenzaldehyde.

3-Indolylcarboxylic Acid Thioamide (Ia). A mixture of 4.26 g (0.03 mole) of 3-indolylcarbonitrile, 6.83 g (0.09 mole) of thioacetic acid and 0.9 g (0.015 mole) of glacial acetic acid was placed in a flask at a temperature of about 20°. After 1 month, the mixture was heated at 60° for 2 h, diluted with benzene, and the product recrystallized from toluene to give orange crystals of Ia. Compounds Ib-Id were prepared analogously (see Table 1).

3-Indolylvaleric Acid Thioamide (Ie). A mixture of 3.7 g (0.017 mole) of indolylvaleramide (mp 126-128°), 0.83 g of phosphorus pentasulfide and 15 ml of pyridine was heated on a boiling-water bath for 1 h, diluted with

water, and the mixture of nitrile and thioamide extracted with methylene chloride. The evaporated extract was treated with 1.3 g (0.017 mole) of thioacetic acid and, after 1 month, treated analogously to Ia, to give colorless crystals of Ie (see Table 1).

LITERATURE CITED

1. E. P. Doyle, W. Ferrier, D. O. Holland, et al., J. Chem. Soc., 2853-2857 (1956).
2. K. A. Jensen and P. H. Nielsen, Acta Chem. Scand., 20, 597-629 (1966).
3. É. A. Markaryan and A. E. Kalaidzhyan, Sint. Geterotsikl. Soedin. (Akad. Nauk Armyansk. SSR, Inst. Tonkoi Organich. Khim.), No. 7, 33-34 (1966).
4. A. P. Terent'ev, A. N. Kost, and V. A. Smit, Zh. Obshch. Khim., 26, 557-559 (1956).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SPIRO[CYCLOALKANE-2-THIOBARBITURIC] ACIDS

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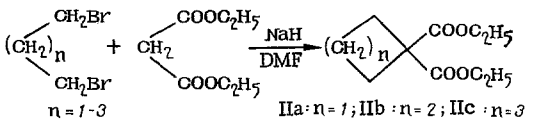
The object of the present work has been to synthesize potentially biologically active spiro[cycloalkane-2-thiobarbituric] acids (I). Attempts to synthesize these compounds by condensing 1,1-cyclopropane- and 1,1-cyclobutanedicarboxylic acid esters with thiourea in boiling ethyl alcohol in the presence of sodium ethoxide as condensing agent have been unsuccessful [1].

We have synthesized compounds I from 1,1-cycloalkanedicarboxylic acid esters (II) and thiourea in dimethyl sulfoxide (DMSO). The starting esters II were prepared by reacting dibromoalkanes with malonic ester and sodium hydride in dimethylformamide (DMF) according to the following scheme:



The purity of the resulting esters IIa-IIc was confirmed by gas–liquid chromatography, and the physical constants of these products agreed with the literature data [1].

The cycloalkanedicarboxylic acid esters IIa-IIc were reacted with thiourea in the presence of sodium methoxide at 20° in DMSO. In each case the product isolated was a white crystalline substance shown to be pure by thin-layer chromatography. The IR spectrum of the compound obtained from IIa had absorption bands in the 3090 and 3170 cm^{-1} regions characteristic of NH and OH stretching vibrations and bands in the vicinity of 1675 and 1715 cm^{-1}, which we assigned to vibrations of the carbonyl groups, as well as NH bending bands in the 1535 cm^{-1} region and a C=S band in the 1170 cm^{-1} absorption region.

On the basis of these data, the product was assigned the structure of spirocyclobutane-2-thiobartituric acid. The structure of this compound was also confirmed by elementary-analysis data.

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