SYNTHESIS OF ISATIN DERIVATIVES WITH POSSIBLE ANTIVIRAL OR ANTIMICROBIAL ACTION

1. ISATIN-3-THIOSEMICARBAZONE AND ITS CONVERSIONS

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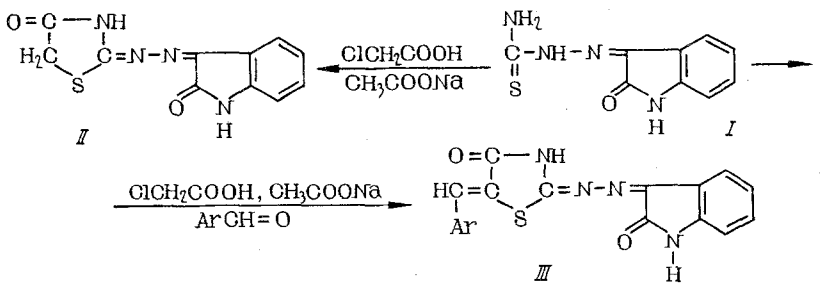
Among the chemotherapeutic media for treatment of virus illnesses the derivatives of thiosemicarbazide occupy a prominent place, for example, the anti-influenzal preparation kurtizon [1, 2]. Some of the thiosemicarbazones of isatin derivatives possess definite activity against the smallpox organism [3] (for example, 1-methylisatin thiosemicarbazone, known under the designation "marboran"). We have synthesized the thiosemicarbazone of unsubstituted isatin and have studied its properties and its conversion to pseudothiohydantoins.

Isatin-3-thiosemicarbazone (I) was prepared by the reaction of thiosemicarbazide with isatin in aqueous alcoholic solution; the mp of the product was 46° higher than that indicated in the literature [4].

The spectrum of isatin contains a high-intensity maximum at 245 mμ and a less intense one at 300 mμ. Transition to the thiosemicarbazone (I) leads to a lengthening of the conjugation chain, as a result of which a new high-intensity absorption maximum at 360 mμ arises, and both of the first two maxima are shifted hypsochromically:



Upon condensation of the thiosemicarbazone (I) with monochloroacetic acid in glacial acetic acid, the corresponding pseudothiohydantoin derivative was obtained—2,4-thiazolidinedione-2-(2',3'-dihydro-2'-indolone-3'-hydrazone) (II). Its 5-arylidene derivatives (III) were synthesized by condensation of monochloroacetic acid with the thiosemicarbazone (I) in the presence of an aromatic aldehyde. In this reaction we used benzaldehyde, salicylic and veratric aldehydes, p-chloro-, p-bromo-, p-nitro-, and p-dimethylaminobenzaldehydes, and also cinnamaldehyde and furfural.

The previously unknown thiazolidinedione (II) and its 5-arylidene derivatives (III) (see Table 1) are red-colored substances, which are very difficultly soluble in acetic acid, acetone, alcohol, or dioxane, and insoluble in ether, benzene, chloroform, or water.

When the thiazolidine ring is closed, the first and third absorption maxima are retained, but the weaker second maximum vanishes. Upon introduction of the arylidene residue, a new, extremely intense absorption maximum arises in the 393-475 mμ region. Other absorption maxima of the 5-arylidene derivatives (III), which are located in the short wave length region, are less strongly expressed.

EXPERIMENTAL

Isatin-3-thiosemicarbazone (I). A solution of 14.3 g of isatin in 65 ml of alcohol was poured into a boiling saturated aqueous solution of 9.1 g of thiosemicarbazide. The yellow crystals which precipitated were filtered off, and 22 g of product was obtained, mp 246° (from methanol).

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TABLE 1. Isatin-3-thiosemicarbazone (I), 2,4-Thiazolidinedione-2-(2',3'-dihydro-2'-indolone-3'-hydrazone) (II), and Its 5-Arylidene Derivatives (III)

Compound	Ar	Yield (in %)	Mp (in deg)	Found (in %)		Empirical formula	Calculated (in %)		Ultraviolet spectra	
				N	S		N	S	λmax	log ε (in moles/l.)
I	—	99,9	246	25,32	14,57	$C_9H_8N_4OS$	25,47	14,57	240 271 360	4,11 3,99 4,27
II	—	77,6	272	21,44	12,20	$C_{11}H_8N_4O_2S$	21,53	12,31	250 355	3,96 4,00
III	m-HO—C_6H_4	54,8	224	14,98	8,70	$C_{18}H_{12}N_4O_3S$	15,38	8,80	250 295 435	3,97 3,84 4,12
III	C_6H_5	51,6	264	16,46	9,44	$C_{18}H_{12}N_4O_2S$	16,09	9,20	250 345 440	4,11 4,07 4,23
III	p-Cl—C_6H_4	94,0	291	14,73	8,23	$C_{18}H_{11}ClN_4O_2S$	14,64	8,37	250 295 345 440	4,18 4,03 4,15 4,33
III	p-O_2N—C_6H_4	96,7	326	17,45	8,09	$C_{18}H_{11}N_5O_4S$	17,81	8,15	250 375 440	4,06 4,18 4,32
III	2,3=$(CH_3O)_2$ C_6H_3	97,9	272	13,47	7,66	$C_{20}H_{16}N_4O_4S$	13,73	7,85	250 285 349 475	4,28 3,88 4,35 4,43
III	p-$(CH_3)_2$ NC_6H_4	81,7	285	17,76	8,01	$C_{20}H_{17}N_5O_2S$	17,90	8,19	250 285 340 430	4,20 3,89 4,25 4,29
III	C_6H_5=CH=CH	80,7	260	14,97	8,86	$C_{20}H_{14}N_4O_2S$	14,97	8,56	250 365 445	4,25 4,39 4,42
III		88,6	283	16,41	9,43	$C_{16}H_{10}N_4O_3S$	16,57	9,47	255 330 445	4,09 4,21 4,38
III	p-Br=C_6H_4	93,6	174	12,95	7,49	$C_{18}H_{11}Br_2O_2$	12,99	7,50	249 290 320 393	4,42 4,28 4,36 4,58

2,4-Thiazolidinedione-2-(2',3'-dihydro-2'-indolone-3'-hydrazone) (III). A mixture of 2.2 g of isatin-3-thiosemicarbazone, 1.41 g of monochloroacetic acid, 0.82 g of anhydrous sodium acetate, and 30 ml of acetic acid was boiled for 3 h, and was then cooled; water was added, the precipitate was filtered off, and 2.02 g of red crystalline product was obtained, mp 272° (from alcohol).

5-Arylidine Derivatives of 2,4-Thiazolidinedione-2-(2',3'-dihydro-2'-indolone-3'-hydrazone) (III). A mixture of 2.2 g of isatin-3-thiosemicarbazone, 1.41 g of monochloroacetic acid, 0.82 g of anhydrous sodium acetate, the aldehyde, and 30 ml of glacial acetic acid was boiled for 3 h. After cooling, the precipitate was filtered off, and was washed with boiling acetic acid and with alcohol.

LITERATURE CITED

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