SYNTHESIS AND ALKYLATION OF 6,7-DIMETHYL-5H-1,2,4-TRIAZINO[5,6-b]INDOLE-3(2H)-THIONE

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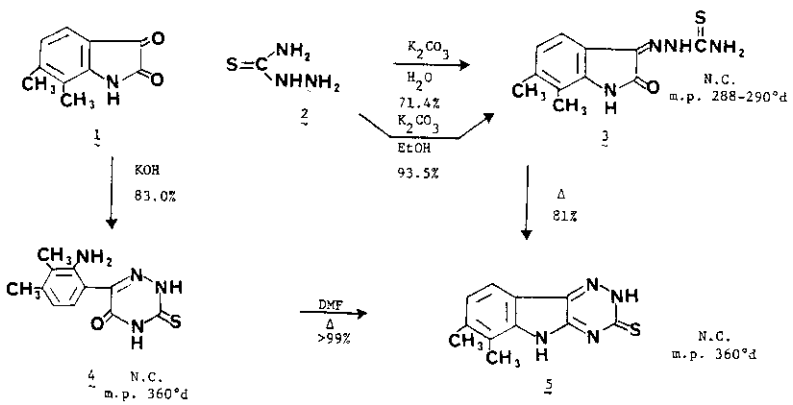
Abstract - The synthesis and alkylation of 6,7-dimethyl-5H-1,2,4-triazino[5,6-b]indole-3(2H)-thione (5) are described.

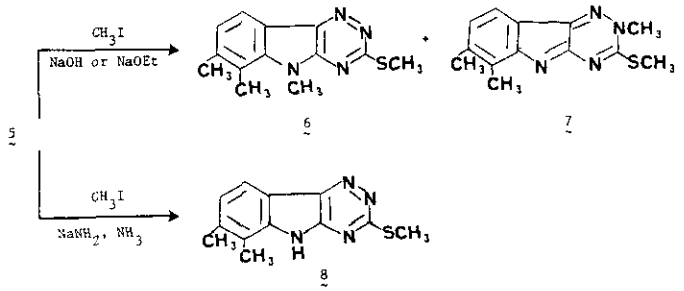
The broad range of antiviral activity exhibited by some triazinoindoles[1] led us to investigate the synthesis of the title compound (5) and its alkylation. The condensation of isatin with thiosemicarbazide and subsequent cyclization of the resulting thiosemicarbazone to the corresponding 1,2,4-triazino[5,6-b]indole has been reported by several investigators.[2-4] We prepared 5 (N.C., 81%Y, m.p. 360°d) by refluxing 6,7-dimethylisatin (1) with thiosemicarbazide (2) in an aqueous potassium carbonate solution. The intermediate thiosemicarbazone[5](3)(N.C., 93.5%Y, m.p. 288-290°d) could be obtained either by shortening the reflux period or by performing the condensation in absolute ethanol, using a catalytic amount of potassium carbonate. When 1 and 2 were condensed in aqueous potassium hydroxide, 6-(2-amino-3,4-dimethylphenyl)-3-thio-1,2,4-triazine-3,5(2H,4H)dione[6](4) was obtained (N.C., 83.0%Y, m.p. 360°d). Compound 5 could also be synthesized by refluxing 4 in dimethylformamide (Scheme 1).



Scheme 1

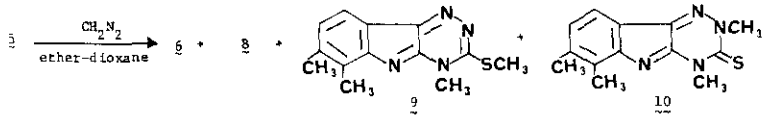
6,7-Dimethyl-5H-1,2,4-triazino[5,6-b]indole-3(2H)-thione (5) possesses four possible sites for alkylation. Therefore, it was of interest to vary the alkylation conditions to examine the possibility of controlling nitrogen and sulfur alkylation.

Methylation of 5 with methyl iodide in either aqueous sodium hydroxide or sodium ethoxide in ethanol led to the formation of two isomers (6 and 7) while the action of methyl iodide in sodamide in liquid ammonia afforded 8 exclusively (Scheme 2).



Scheme 2

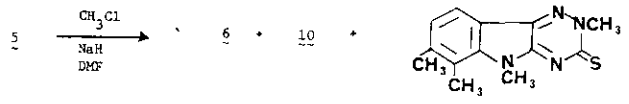
The reaction of 5 with diazomethane in ether-dioxane resulted in the formation of four products: 6, 8, 9, and 10 (Scheme 3).



Scheme 3

Compounds 6, 8 and 9 had been previously synthesized by other methods and therefore were easily characterized by comparison of their spectral data and melting points with those of authentic samples.[5] The ^{1}HNMR spectrum of 10 exhibited two resonances attributable to N-methyl groups which supported the structure shown.

The alkylation of 5 with methyl chloride and sodium hydride in dimethylformamide also afforded a mixture of products: 6, 10, and 11 (Scheme 4).

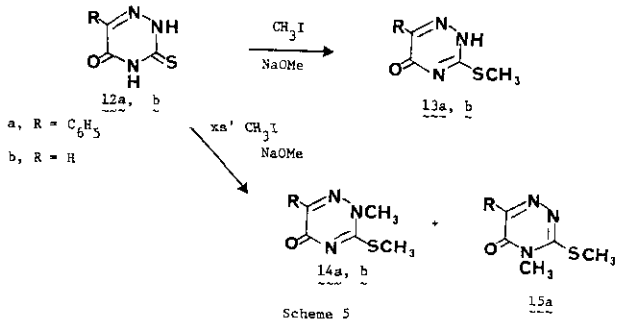


Scheme 4

Compound 6 was the major product in this reaction. Alkylation of 5 with methyl iodide in a dimethyl sulfoxide-water mixture in the presence of a phase transfer catalyst, benzyltrimethylammonium bromide also gave 6 as the main product along with smaller amounts of 9 and 11. Methylation of 5 with methyl iodide and silver oxide in dimethylformamide yielded a mixture of five compounds:

6, 7, 9, 10 and 11. The ratios of the methylated products obtained in these reactions are shown in Table I.

The results obtained when 5 was alkylated with methyl iodide and either sodium hydroxide or sodium ethoxide agree with the findings of other investigators for the methylation of 1,2,4-triazines. Daunis studied the alkylation of 12a with methyl iodide in the presence of sodium methoxide (Scheme 5).[7]



Scheme 5

Only sulfur methylation was observed when one mole of methyl iodide was used (13a). With an excess of alkylating reagent, two isomers, 14a and 15a, were obtained in a 4:1 ratio. Therefore, methylation at the 2-nitrogen was favored. Similar results were found by Gut et al. who reported that in the presence of an excess of methyl iodide alkylation of 12b occurred first on sulfur, and then on the 2-nitrogen (14b).[8] Alkylation on the 4-nitrogen was not reported. These results are consistent with the preferential alkylation at the 2-nitrogen of 5.

The hard-soft acid base (HSAB) concept may be used to rationalize all of these observations. Sulfur is the preferred site of alkylation in S_N2 reactions because of its greater polarizability. Once sulfur has been methylated, the softest nitrogen is alkylated next. Examination of the three possible anions formed after proton removal from 5 shows that the anion at the 5-position may extend its delocalization into either the benzene ring or triazine ring and might be considered the softer nitrogen. The preferential alkylation of the 2-nitrogen may be explained by the extra stability of the corresponding anion in the para-quinoid form.

The exclusive alkylation of sulfur with methyl iodide-sodamide in liquid ammonia was unexpected but could be attributed to the solubility of the product under the conditions used.

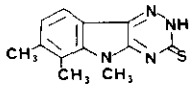
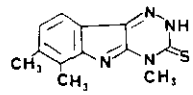
The products isolated from the reaction of 5 with diazomethane are in full agreement with those reported by Daunis et al.[9] Methylation of 16 with diazomethane resulted in initial methylation at the 4-nitrogen followed by the competitive methylation of the 2-nitrogen (17) and sulfur (18)

Table I. Methylation of 5

Conditions	Product Mixture (%)					
	8	6	7	9	10	11
NaOEt CH_3I	---	52.5	33.8	---	---	---
$NaOH/CH_3I$	0.8	45.5	18.7	---	---	---
$NaNH_2/NH_3$ CH_3I	99.9	---	---	---	---	---
CH_2N_2 Ether/Dioxane	23.46	25.97	---	28.88	21.69	---
NaH/CH_3Cl DMF	---	77.4	---	---	5.8	8.6
Benzyltrimethylammonium bromide CH_3I/NaOH/DMSO	---	79.5	---	9.6	---	2.7
Ag_2O CH_3I/DMF	---	27.3	35.0	2.2	1.9	1.4

Table II. Melting points, infrared, and ultraviolet data

COMPOUND	m.p., °C	INFRARED Major (KBr, cm^{-1}) Peaks	ULTRAVIOLET λmax (log ε) 95% EtOH	95% EtOH 1N KOH	95% EtOH 5% HCl
5	360 d	3300, 3050-2800 1610, 1575, 1160	236 (3.52) 260 (3.48) 306 (4.22)	290 (4.09) 370 (3.36)	260 (3.44) 306 (4.25)
8	316 d	3180, 1605, 1580 1410, 1180, 1110	230 (4.17) 270 (4.47) 352 (3.93)	230 (4.19) 282 (4.47) 350 (3.88)	
6	217-218	2880, 1565, 1350 1170	232 (4.15) 272 (4.43) 354 (3.89)		
7	243-244	1540, 1410	232 (4.03) 278 (4.56) 336 (3.70)		236 (4.01) 284 (4.55) 354 (3.71)
9	223-225	1580, 1440	266 (4.37) 364 (4.06)		228 (4.05) 270 (4.35) 370 (4.03)

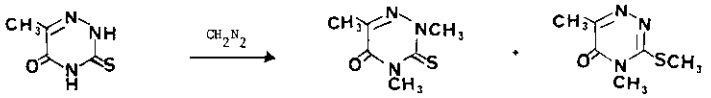
COMPOUND	m.p.	INFRARED	UV	
10	252-254	1610, 1570, 1115, 810	248 (3.83) 262 (4.09) 290 (4.49) 382 (3.92)	
11	282.5-283	1590, 1555, 1365, 1235 1210, 1050, 1015	242 (4.19) 268 (4.24) 306 (4.92) 370 (3.73)	
 19[a]	322-326 d	3080, 1595, 1561, 1552 1352, 1269, 1189, 1140 1124, 1058, 652	236 (3.31) 264 (3.31) 308 (3.77)	238 (3.47) 256 (3.36) 292 (3.73)
 20[a]	324-325	3050, 2900, 1610, 1580 1280, 1205, 1010	247 (3.98) 259 (4.11) 294 (4.56) 382 (3.96)	240 (4.08) 282 (4.39)

[a] Prepared by unequivocal methods, see ref. 5.

Table III. ^{1}H NMR data

Compound	Aromatic Methyl	SCH_3	NCH_3	Aromatic Protons	Solvent
5	2.1 (6H,s)			7.00 + 7.13 (1H,d) 7.58 + 7.71 (1H,d)	CF_3COOH
8	2.33 (6H,s)	2.67 (3H,s)		7.25 + 7.38 (1H,d) 7.85 + 7.98 (1H,d)	CF_3COOH
6	2.40 (3H,s) 2.54 (3H,s)	2,69 (3H,s)	3.89 (3H,s)	7.04 + 7.17 (1H,d) 7.93 + 8.06 (1H,d)	$CDCl_3$
7	2.45 (3H,s) 2.62 (3H,s)	2.75 (3H,s)	4.04 (3H,s)	7.04 + 7.17 (1H,d) 7.72 + 7.85 (1H,d)	$CDCl_3$
9	2.45 (3H,s) 2.53 (3H,s)	2.84 (3H,s)	3.98 (3H,s)	7.09 + 7.22 (1H,d) 7.92 + 8.05 (1H,d)	$CDCl_3$
10	2.30 (6H,s)		4.10 (3H,s) 4.22 (3H,s)	7.25 + 7.38 (1H,d) 7.73 + 7.86 (1H,d)	CF_3COOH
11	2.07 (3H,s) 2.26 (3H,s)		3.75 (3H,s) 3.92 (3H,s)	6.98 + 7.11 (1H,d) 7.58 + 7.71 (1H,d)	CF_3COOH
19	2.62 (3H,s) 2.83 (3H,s)		4.30 (3H,s)	7.44 + 7.56 (1H,d) 8.06 + 8.14 (1H,d)	CF_3COOH
20	2.30 (3H,s) 2.39 (3H,s)		3.89 (3H,s)	7.00 + 7.13 (1H,d) 7.52 + 7.65 (1H,d)	DMSO-d_6

(Scheme 6).



16 17 18

Scheme 6

A small amount of O-alkylation was also observed. Protonation of diazomethane results in a hard methylating species (CH_3^+) which is expected to attack nitrogen in preference to sulfur. The predominance of methylation at the 4-nitrogen supports the hard character of this center, and is consistent with the fact that the 4-nitrogen was not alkylated with a soft methylating agent such as methyl iodide. Methyl chloride, a harder methylating agent than methyl iodide afforded more nitrogen alkylation. Phase transfer catalysis gave 6 as the major product although some alkylation of the harder nitrogens was observed to a small extent.

Methylation in the presence of silver oxide in dimethylformamide afforded a complex mixture of five products, the predominant product showing preferential alkylation at the 2-nitrogen as well as at sulfur.

The melting points, infrared and ultraviolet data of the alkylated products are summarized in Table II, and the nuclear magnetic resonance data for these compounds are contained in Table III.

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