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A New Synthesis of Thiazolo[3,2-*a*]pyrimidinones

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5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones (V) have been prepared by *S*-alkylation of 6-methyl-2-thiouracil (Ib) with bromoacetone or bromoacetophenone followed by cyclization in sulfuric acid. By the same series of reactions, 2-thiouracil (Ia) gave rise to 7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones (VI). The properties and structures of the intermediates and products are discussed.

Previously, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones (V) (1) have been synthesized by reaction of 2-aminothiazoles with ethyl acetoacetate, ethyl β-aminocrotonate (2,3,4), or diketene (5). Apparently, 7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones (VI) have not been prepared hitherto, although certain dihydroderivatives are known (6,7). Also this structure was once (3a) mistakenly assigned to a compound which was later shown (2,3b) to have the 5-one structure. A convenient new synthesis of both 5-ones (V) and 7-ones (VI) is described in this paper. (Scheme I).

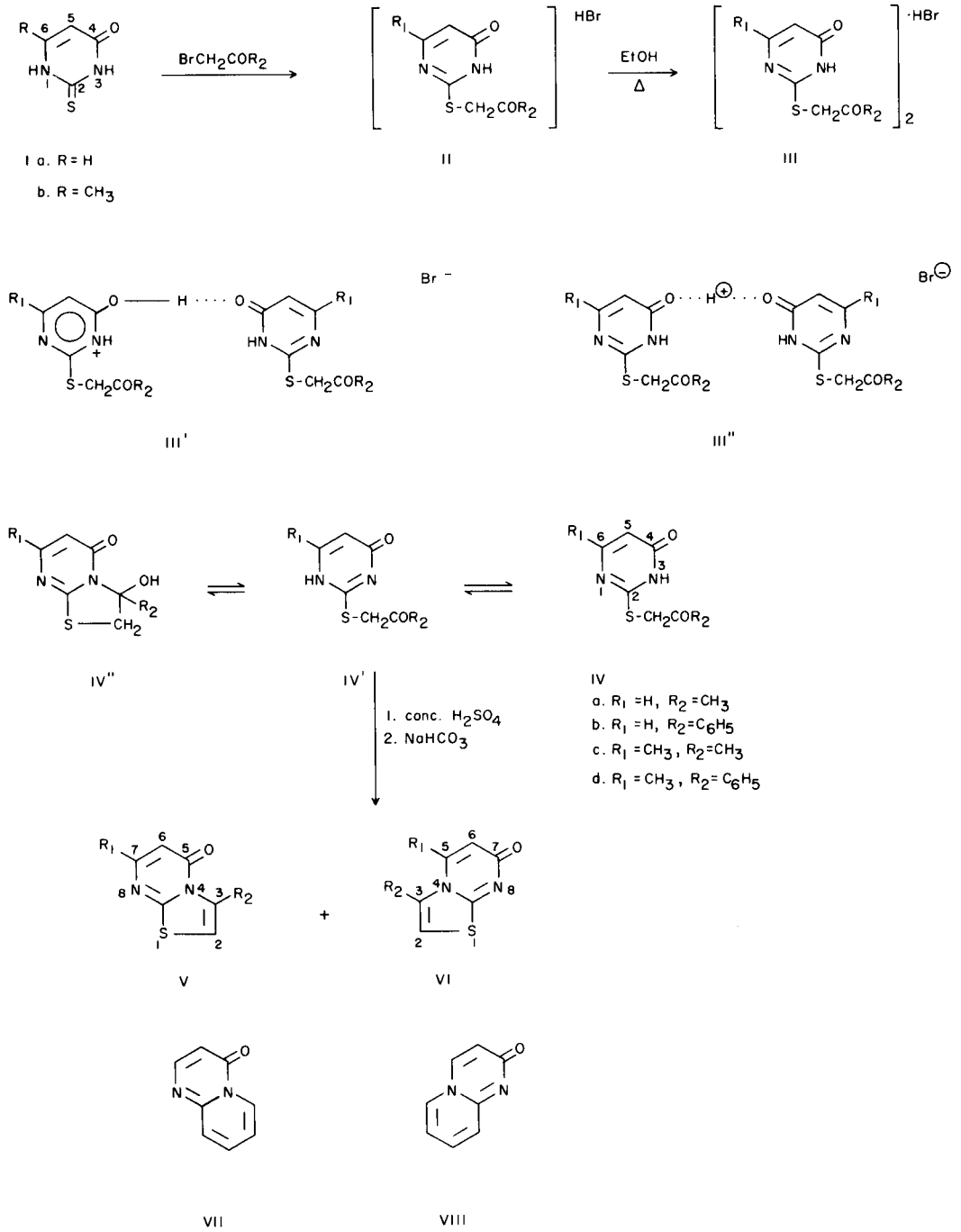
A heterogeneous reaction of 2-thiouracil (Ia) or 6-methyl-2-thiouracil (Ib) with bromoacetone or phenacyl bromide in acetone afforded the keto sulfide hydrobromides (II). Both 2-acetonylthio-4-pyrimidinone hydrobromide (IIa) and its 6-methyl analog (IIc) could be crystallized from ethanol-ether without change, but 2-phenacylthio-4-pyrimidinone hydrobromide (IIb) and its homolog (IId) were converted by this procedure into new compounds having quite different infrared spectra and different, though close, melting points. Elemental analysis showed that one molecule of hydrobromic acid was present for every two pyrimidinone moieties (III). A similar observation (8) made in the study of 5-hydroxythiazolo[3,2-*a*]isoquinolinium salts, suggested that analogous structures might be expected. In the present case, since the possibility of tautomerism is present, the resonance structures III′, III″ are only two of several which would describe the compounds.

The monomeric salt (II) and the dimeric salts (III) had ultraviolet spectra identical with those of their parent bases (IV) and were readily converted into the latter by weak base. With the keto sulfides (IV) the question of tautomerism again arises. Although they have been shown as 4(3*H*)-pyrimidinones, the possibility of their existing wholly or partly in the 4(1*H*)-pyrimidinone form (IV′) cannot be discounted. The former designation may be preferred since dipole moment studies (9) indicate that, in dioxan solution at least, 2-benzylthio-4-pyrimidinones are predominantly in the (3*H*) form. Inspection of the NMR spectra of the keto sulfides (IV) revealed a further complexity. The spectrum of IVc in deuteriochloroform unexpectedly had a pair of 1-proton doublets centered at δ 3.22 and 3.64 comprising an AB system (J = 11 cps), in addition to two 3-proton singlets at δ 1.91 and 2.23 due to the methyl groups, and a 1-proton singlet at δ 6.01 (ring proton at position 5) superimposed on a broad, 1-proton peak at δ 6.10. On the basis of structure IVc, the methylene group should appear as a 2-proton singlet. It appears that, in deuteriochloroform, the keto sulfide is entirely in the cyclic form IVc″ (10). Since the methylene protons in IVc″ are non-equivalent owing to the adjacent asymmetric center, an AB quartet results. The spectrum was unaffected by change in temperature. Curiously, the phenacyl analog IVd seems to exist only partially in the cyclic form in deuteriochloroform. An AB quartet (doublets centered at δ 3.35, 3.90, J = 11 cps) did not fully account for two methylene protons. Further, two methyl resonances occurred, at δ 2.08, 2.28, which together represented three protons, suggesting the presence of one of the two tautomeric forms, 4(3*H*)-pyrimidinone (IVd) or 4(1*H*)-pyrimidinone (IVd′). In dimethylsulfoxide-d_6 only one resonance for the methyl group, at δ 2.31, was observed. Tautomerism in these compounds is clearly solvent-dependent, and more work must be done before definite conclusions can be drawn concerning the structure of these compounds in solution. Unfortunately, keto sulfides IVa and IVb were insufficiently soluble in deuteriochloroform for comparisons to be made.

Concentrated sulfuric acid converted 6-methyl-2-acetonylthio-4-pyrimidinone (IVc) in high yield into 3,7-dimethylthiazolo[3,2-*a*]pyrimidin-5-one (Vc) which was shown to be identical (mixed melting point and infrared spectrum) with a sample prepared by the method of Ohta (3) from 2-amino-4-methylthiazole.

Similarly, 6-methyl-2-phenacylthio-4-pyrimidinone (IVd) on cyclization gave 7-methyl-3-phenylthiazolo[3,2-*a*]-

SCHEME I



pyrimidin-5-one (Vd), the identity of which was confirmed by elemental analysis, NMR spectrum and similarity of its ultraviolet spectrum with that of the methyl analog (Vc). This last observation indicated that the phenyl ring does not conjugate with the heterocyclic systems, an effect which has been previously noticed in the somewhat similar 5-hydroxy-3-phenylthiazolo[2,3-*a*]isoquinolinium salts (8). The 7-methyl-3-phenylthiazolo[3,2-*a*]pyrimidin-5-one (m.p. 203-204°) is not identical with the compound (m.p. 238-240°) assigned that structure by Allen *et al.*, (4) who report an ultraviolet spectrum quite different from that of the methyl analog (Vc) and a carbon analysis 1.1% too low.

TABLE I

Ultraviolet Spectra (a)

Keto Sulfides (IV).

IV	R_1	R_2	λ max, mμ (log ε)
a	H	CH_3	230 (4.25), 293sh (3.18)
b	H	C_6H_5	235 (4.23), 280sh (3.73)
c	CH_3	CH_3	234 (3.75), 287 (3.77)
d	CH_3	C_6H_5	240 (4.17), 281 (3.83)

5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones (V).

V	R_1	R_2	λ max, mμ (log ε)
a	H	CH_3	212 (3.75), 230 (3.85), 258 (3.68), 263sh (3.66), 330 (4.08), 346 (4.04)
b	CH_3	CH_3	212 (3.96), 230 (3.98), 257 (3.67), 264 (3.67), 325 (4.03), 338 (3.97) (b)
c	CH_3	C_6H_5	213sh (4.29), 266 (3.96), 325 (4.00), 336sh (3.94)

7*H*-Thiazolo[3,2-*a*]pyrimidin-7-ones (VI).

VI	R_1	R_2	λ max, mμ (log ε)
a	H	CH_3	225 (4.11), 276 (4.08)
b	H	C_6H_5	227 (4.38), 275 (4.17)

(a) In 95% ethanol. (b) Identical with the spectrum given by C. F. H. Allen *et al.*, ref. 4.

It is probably significant that Ohta (3) has reported that he was unable to prepare Vd by reaction of 2-amino-4-phenylthiazole with acetoacetic ester.

As would be expected from the isosteric nature of systems V and VII, the ultraviolet absorption spectra of the two systems are almost identical. In agreement with our assignment of the 7*H*-thiazolo[3,2-*a*]pyrimidin-7-one structure (VI) to the cyclization products obtained from thiouracil derivatives (IVa,b), these new products had a spectrum like that of the pyrido[1,2-*a*]pyridin-2-ones (VIII). Although NMR did not afford sufficient evidence for us to characterize the new cyclization products as 7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones (VIa,b) instead of 5-ones (Va,b), the spectrum of the methyl derivative (VIa) was consistent with the assigned structure.

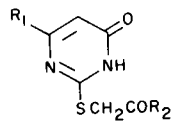
The remarkable change in the direction of cyclization caused by the introduction of a methyl group at position 6 of the keto sulfides (IV) is probably due to the steric repulsions to be expected if cyclization took place at N_3, bringing into juxtaposition alkyl or aryl groups at positions 3 and 5 (VIc,d). The transition state leading to the formation of such compounds would be expected to be less favorable than one leading to the isomeric structure (Vc,d). It appears that without the methyl group at position 6, the chief steric influence in the keto sulfides (IVa,b) is exerted by the carbonyl group. In the case of the phenacyl sulfide (IVb), cyclization appears to occur exclusively at the unhindered 1 position, while in that of the acetonyl sulfide (IVa) the same mode of cyclization is predominant, although a small amount of the more hindered (Va) is formed.

EXPERIMENTAL

Elemental analyses were by Janssen Pharmaceutica, Beerse, Belgium. Melting points, taken with a Thomas-Hoover apparatus, are corrected. Ultraviolet spectra were determined using 1 cm. matched quartz cells in a Cary Model 14 spectrophotometer, and infrared spectra as Nujol muls with a Perkin-Elmer Model 137 Infracord. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard.

TABLE II

Keto Sulfides



Hydrobromides (II)

Formula II	R_1	R_2	Yield %	M.p., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	H	Me	82	*ca.* 320 (a,b)	$C_7H_9BrN_2O_2S$	31.71	31.84	3.42	3.52	10.57	10.79
b	H	Ph	84	185-186 (a)	$C_{12}H_{11}BrN_2O_2S$	44.05	44.02	3.39	3.35	8.56	–
c	Me	Me	93	248-254 (a,b)	$C_8H_{11}BrN_2O_2S$	34.42	34.23	3.97	3.98	10.04	10.00
d	Me	Ph	96	212-213 (c)	$C_{13}H_{13}BrN_2O_2S$	45.76	45.69	3.84	3.84	8.21	8.27

Bases (IV) (d)

IV											
a	H	Me	82	161-162 (e,f)	$C_7H_8N_2O_2S$	45.64	45.71	4.38	4.55	15.21	15.38
b	H	Ph	93	168-169 (g,h)	$C_{12}H_{10}N_2O_2S$	58.52	58.94	4.09	4.23	11.38	11.23 (i)
c	Me	Me	85	144-145 (g,j)	$C_8H_{10}N_2O_2S$	48.47	48.32	5.08	5.30	14.13	14.21
d	Me	Ph	100	169-170 (g,h)	$C_{13}H_{12}N_2O_2S$	59.98	60.39	4.65	4.75	10.76	10.56

(a) Microcrystalline powder. (b) Melts with previous decomposition. (c) Microneedles. (d) The yields shown for the bases were obtained starting with the hydrobromides (II). (e) Needles. (f) From chloroform-ligroin. (g) Flakes. (h) From benzene. (i) S, Calcd.: 13.02, Found: 13.11. (j) From benzene-ligroin.

Hydrobromides (II) of *S*-Acetonyl-(or Phenacyl)-2-thiouracil.

Finely powdered 2-thiouracil of 6-methyl-2-thiouracil (Ia or b, 0.1 mole) and the α-bromo ketone (slight excess) were refluxed for 6 hours in reagent grade acetone (50 ml. per g. of I). The amorphous thiouracil, though almost insoluble in acetone, was eventually replaced by a suspension of the crystalline keto sulfide hydrobromide (II) which was collected, washed with acetone and dried. More product was obtained by concentrating the filtrates. Whereas the acetonyl hydrobromides (IIa and c) could be recrystallized from ethanol-ether, the phenacyl analogs (IIb and d) were completely converted to the corresponding dimeric compounds (IIIb and d) (see below). The crude products gave satisfactory analyses, however.

Dimeric Hydrobromide of *S*-Phenacyl-2-thiouracil (IIIb).

The bromide of *S*-phenacyl-2-thiouracil (IIb) was dissolved in hot ethanol and ether was added until the solution became turbid. On cooling needles of the dimeric hydrobromide (IIIb), m.p. 183-183.5°, separated out. There was no change in melting point or in composition on further recrystallization from ethanol-ether; yield quantitative.

Anal. Calcd. for $C_{24}H_{21}BrN_4O_4S_2$: C, 50.26; H, 3.69; N, 9.77. Found: C, 50.10; H, 3.76; N, 9.42.

Dimeric Hydrobromide of *S*-Phenacyl-6-methyl-2-thiouracil (IIId).

This preparation, carried out as in the case of (IIIb), afforded IIId in quantitative yield as needles, m.p. 201-202°.

Anal. Calcd. for $C_{26}H_{25}BrN_4O_4S_2$: C, 51.91; H, 4.19; N, 9.31. Found: C, 51.58; H, 4.15; N, 9.32.

Keto Sulfides (IV).

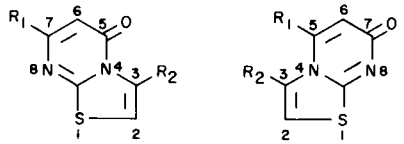
The monomeric (II) or dimeric (III) hydrobromide was shaken in chloroform carefully while adding sodium bicarbonate solution (10%) until all but a trace of solid had dissolved in the organic phase. The chloroform layer was dried and distilled to leave a solid, or an oil which solidified on standing. The crude keto sulfide (IV) was crystallized from an appropriate solvent (Table II), ν max 2,500-3,000 cm^{-1} (broad), 1710, 1660 cm^{-1}.

Thiazolo[3,2-*a*]pyrimidinones (V and VI).

The keto sulfide (1.0 g.) was dissolved in concentrated sulfuric acid (5 ml.), and after standing for 15 minutes at 30° the solution was added carefully to dry ether. The resulting solid was collected, washed with ether, and then stirred with sufficient sodium bicarbonate to make the solution just basic to litmus. Careful neutralization with dilute hydrochloric acid caused precipitation of a solid which was collected, dried, and combined with a chloroform

TABLE III

Thiazolo[3,2-*a*]pyrimidinones



V
5H-5-one

VI
7H-7-one

5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones (V)

Formula V	R_1	R_2	Yield, % (a)	M.p., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	H	Me	19 (b)	128-129 (c)	$C_7H_6N_2OS$	50.59	50.55	3.64	3.80	16.86	16.89
c	Me	Me	93	136.5-137.5 (d,e,f)							
d	Me	Ph	94	203-204 (d,g)	$C_{13}H_{10}N_2OS$	64.44	64.69	4.16	4.40	11.56	11.48

7*H*-Thiazolo[3,2-*a*]pyrimidin-7-ones (VI)

VI											
a	H	Me	70 (h)	282-284 (i, j)	$C_7H_6N_2OS$	50.59	50.43	3.64	3.66	16.86	16.49
b	H	Ph	86 (k)	239-240 (i)	$C_{12}H_8N_2OS$	63.14	63.23	3.53	3.79	12.27	12.32

(a) Yields are from keto sulfides (IV). (b) Obtained along with a 70% yield of the isomer (VIa). (c) Flakes. (d) Needles. (e) Lit. m.p. 137° (2, 3, 4). (f) NMR (deuteriochloroform) singlet δ 2.31 (3H) and doublet at 2.80 (3H), for methyl groups at positions 3 and 7; singlet 6.05 (1H) and quartet (1H) at 6.43 (J = 1.5 cps), ring protons at position 6 and 2, respectively. (g) NMR (deuteriochloroform), singlet at δ 7.34 (5H), phenyl group; singlet, 2.31 (3H), methyl group; singlets, δ 6.01 (1H) and 6.61 (1H) ring protons at positions 6 and 2. (h) Also afforded 19% of 5-one (Va). (i) Amorphous powder from water; sublimes as needles. (j) NMR (trifluoroacetic acid) singlet δ 2.78 (3H) methyl group; doublets, 7.31 (1H) and 8.82 (1H) ring protons at positions 6 and 5; singlet 7.55 (1H), ring proton at position 2. (k) In contrast to the methyl analog (IVa), the keto sulfide IVb gave no 5-one as a by-product.

extract of the filtrate. Thorough extraction of this solid with boiling ligroin (b.p. 60-90°) left a residue which was essentially 3-methyl-(or phenyl)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (VIa or b). It could be crystallized from a large volume of xylene or from water; or it could be sublimed *in vacuo* using a micro-sublimination apparatus, ν max 1600-1640 cm^{-1}. The ligroin-soluble material, consisting entirely of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (Va,c,d) was isolated by removal of the solvent and crystallized from a suitable benzene-ligroin mixture, ν max 1680-1700 cm^{-1}.

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(1) Chemical Abstracts nomenclature. These compounds have also been named pyrimido[2,1-*b*]thiazol-5-ones, 4-oxo-1-thia-3*a*, 7-diazaindenes and 4,9-dihydro-4-keto-7,9-diazathianaphthenes.

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