738. *Purines, Pyrimidines, and Imidazoles. Part XXII.*[1] *Some 5-(Alkylthio)uracils and Derived Sulphoxides and Sulphones*

By J. M. Carpenter and G. Shaw

Several 5-(alkylthio)uracils have been prepared by alkylation of 5-mercaptouracil. Their oxidation to corresponding sulphoxides and sulphones is described, and in some cases structures have been confirmed by alternative syntheses.

Uracils with negative substituents (especially halogens) in the 5-position are valuable antimetabolites and include the antiviral agent 5-iodo-2′-deoxyuridine which is highly effective against *Herpes simplex*. A previous Communication in this Series described the preparation for the first time of some 5-aryl(or alkyl)sulphonyluracils (I) by reaction of ammonia or primary amines with a linear ethoxymethylene derivative (II) and base-catalysed cyclisation of the aminomethylene derivative so formed.[2] Several of the sulphonyluracils have interesting physiological properties but are generally toxic. We have been interested in extending our work to include the preparation of analogous 5-(alkylthio)uracils (III) and related sulphoxides (IV) and to have an alternative route to the sulphonyl derivatives.

Although a few (arylthio)uracils (III; R = Ar) have been prepared recently by heating 5-bromouracil with a thiophenol and potassium carbonate in ethylene glycol[3] the only alkylthio-derivatives recorded are 5-(benzylthio)uracil (III; R = CH_2Ph) prepared by the condensation of the *C*-formyl ester (V; R = CH_2Ph, R′ = Et) with *S*-ethylthiouronium bromide and acid hydrolysis of the product,[4] and the bis-uracils (VI; $n = 2$—6) prepared from 5-mercaptouracil and corresponding dibromoalkanes.[5]

We now record the preparation of a series of 5-(alkylthio)uracils (III) by reaction of 5-mercaptouracil[6] with alkyl halides and sodium hydroxide in a nitrogen atmosphere. Oxidation of (III; R = Me, Et, or n-C_5H_{11}) with either fuming nitric acid or hydrogen peroxide in acetic acid gave in each case similar yields of the corresponding sulphoxides (IV;

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[2] M. R. Atkinson, G. Shaw, and G. Sugowdz, *J.*, 1957, 3207.
[3] B. Roth and G. H. Hitchings, *J. Org. Chem.*, 1961, **26**, 2770; B. Roth and L. A. Schloemer, *ibid.*, 1963, **28**, 2659.
[4] T. B. Johnson and H. H. Guest, *Amer. Chem. J.*, 1909, **42**, 271.
[5] J. Yun-feng and W. Yuen-yin, *Acta Pharmaceutica Sinica*, 1963, **10**, 298.
[6] R. R. Herr, T. Enkoji, and T. J. Bardos, *J. Amer. Chem. Soc.*, 1956, **78**, 401.

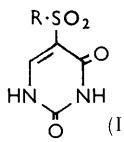
TABLE 1

Absorption spectra (λ in mμ) of 5-alkylthio-, 5-alkylsulphinyl-, and 5-alkylsulphonyl-uracils

Compound	Solvent	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{min.}$
(III; R = Me)	0·1N-HCl	212	8300	230—235 (infl.)	5850	—
	pH 7·2 *	212	8300	230—235 (infl.)	5850	—
	0·1N-NaOH	235	7150	294—295	6600	267
(III; R = Et)	0·1N-HCl	212	10,300	230 (infl.)	6600	—
	pH 7·2	211—212	10,300	230 (infl.)	6600	—
	0·1N-NaOH	235	8850	294	8600	264
(III; R = Pr^n)	0·1N-HCl	212	9450	228—230 (infl.)	6250	—
	pH 7·2	212	9450	228—230 (infl.)	6250	—
	0·1N-NaOH	235	8450	294	7600	264
(III; R = n-C_5H_{11}) ...	0·1N-HCl	212	8450	230—233 (infl.)	5550	—
	pH 7·2	212	8300	230—233 (infl.)	5550	—
	0·1N-NaOH	235	6900	294	5100	266
(III; R = $CH_2 \cdot CO_2Et$)	0·1N-HCl	205	6600	275—278	8050	215—235
	pH 7·2	205	8000	281—284	8550	235—245
	0·1N-NaOH	219—220	13,350	272—277	7100	245—255
(IV; R = Me)	0·1N-HCl	214	10,550	267	7500	239
	pH 7·2	217—218	9100	280	7450	252
	0·1N-NaOH	237	9450	284	9300	259
(IV; R = Et)	0·1N-HCl	214	9800	268	6850	242
	pH 7·2	219	8400	281	6850	253
	0·1N-NaOH	235	8650	285	8650	259
(IV; R = n-C_5H_{11})	0·1N-HCl	214	10,750	268	7200	242
	pH 7·2	217	9050	281	7650	254
	0·1N-NaOH	235	9850	286	8950	259
(I; R = Me)	0·1N-HCl	208	11,600	262	9650	229
	pH 7·2	223	11,650	281	11,700	254
	0·1N-NaOH	235—238	12,000	275—276	9600	249
(I; R = Et)	0·1N-HCl	207	10,150	262	11,400	227
	pH 7·2	223	9050	281—282	10,150	243—244
	0·1N-NaOH	231	10,050	275	9600	248
(I; R = n-C_5H_{11})	0·1N-HCl	208—209	12,100	261—262	10,900	230
	pH 7·2	223—224	11,750	281	12,850	242—244
	0·1N-NaOH	235	12,450	275	10,750	249

* M/30-Phosphate buffer.

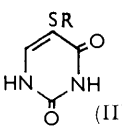
R = Me, Et, or n-C_5H_{11}) which have very similar and characteristic ultraviolet spectra (Table 1) and also the expected infrared absorption band at 1040 cm.$^{-1}$.



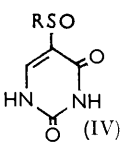
(I)

$R \cdot SO_2 \cdot C(:CH \cdot OEt) \cdot CO \cdot NH \cdot CO_2Et$

(II)



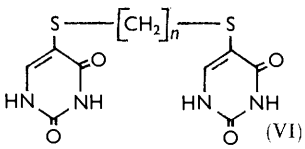
(III)



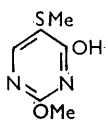
(IV)

$RS \cdot C(:CH \cdot OH)\ CO_2R'$

(V)



(VI)



(VII)

Oxidation of (III; R = Me, Et, or n-C_5H_{11}) with potassium permanganate in aqueous acetic acid gave the corresponding sulphones (I; R = Me, Et, or n-C_5H_{11}) ($\nu_{max.}$ 1145 cm.$^{-1}$, and a split band at 1340—1295 cm.$^{-1}$). The structure of the compound (I; R = Et) was further confirmed by its identity with the compound prepared by our earlier route [2] from the linear derivative (II; R = Et) and ammonia. Structural confirmation was also obtained for 5-(methylthio)uracil (III; R = Me). Acidic hydrolysis of the product (VII), obtained from the reactions between (V; R = R′ = Me) and *O*-methylisouronium hemisulphate yielded a small amount of a material having paper-chromatographic properties (in six solvent systems) identical with those of the 5-(methylthio)uracil described above.

Experimental

Ultraviolet spectra were measured on a Perkin-Elmer model 137 recording spectrophotometer.

5-(*Alkylthio*)*uracils*.—(*a*) A solution of 5-mercaptouracil [6] (1·44 g., 0·01 mole) in cooled boiled 1N-sodium hydroxide (11 ml., 0·011 mole) under nitrogen was shaken with the alkyl iodide (0·011 mole) (in the case of the n-pentyl derivative the bromide gave the same result) until it no longer gave a positive test for thiol with sodium nitroprusside solution. The time varied from about 15 min. with methyl and ethyl iodides to 1 hr. with the higher iodides. During the reaction period most of the product separated from solution but additional material was obtained by acidifying the solution with 10N-hydrochloric acid. The products, after recrystallisation to remove uracilyl disulphide which was always formed, were obtained in yields of 40—70%. Details are recorded in Table 2.

Table 2

5-Alkylthio-, 5-alkylsulphinyl-, and 5-alkylsulphonyluracils

Compound	M. p.	Yield (%)	Found (%)				Formula	Required (%)			
			C	N	N	S		C	H	N	S
(III; R = Me) [a]	300° (dec.)	59	38·05	3·8	17·65	20·15	$C_5H_6N_2O_2S$	38·0	3·8	17·7	20·3
(III; R = Et) [b]	258	70	41·3	4·5	16·0	18·25	$C_6H_8N_2O_2S$	41·85	4·7	16·3	18·65
(III; R = Pr^n) [c]	253	42	45·2	5·65	14·85	17·2	$C_7H_{10}N_2O_2S$	45·15	5·4	15·05	17·2
(III; R = n-C_5H_{11}) [d]	255	49	50·4	6·65	13·3	14·95	$C_9H_{14}N_2O_2S$	50·4	6·55	13·05	14·95
(III; R = $CH_2{\cdot}CO_2Et$) [e]	233	43	42·05	4·35	12·3	14·0	$C_8H_{10}N_2O_4S$	41·75	4·4	12·15	13·95
(IV; R = Me) [f]	228 (dec.)	59	34·5	3·6	16·05	18·7	$C_5H_6N_2O_3S$	34·5	3·45	16·1	18·4
(IV; R = Et) [g]	222 (dec.)	41	38·15	4·25	14·75	16·85	$C_6H_8N_2O_3S$	38·3	4·3	14·9	17·05
(IV; R = n-C_5H_{11}) [e]	207	56	47·05	6·0	12·0	14·1	$C_9H_{14}N_2O_3S$	46·95	6·15	12·15	13·9
(I; R = Me) [h]	342 (dec.)	45	31·7	3·35	14·95	16·7	$C_5H_6N_2O_4S$	31·6	3·2	14·75	16·85
(I; R = Et) [i]	284	54	35·05	4·25	13·45	15·35	$C_6H_8N_2O_4S$	35·3	3·95	13·75	15·7
(I; R = n-C_5H_{11} [d]	320 (dec.)	40	44·05	5·8	11·6	12·85	$C_9H_{14}N_2O_4S$	43·9	5·75	11·4	13·2

[a] Needles from acetic acid. [b] Needles from aqueous ethanol. [c] Plates from ethanol. [d] Plates from aqueous ethanol. [e] Needles from ethanol. [f] Prisms from aqueous ethanol. [g] Needles from ethanol–chloroform. [h] Needles from water. [i] Plates or prisms from water.

The yields of the methyl and ethyl derivatives were slightly improved by addition of 96% ethanol (10 ml.) to the reaction mixture.

(*b*) 5-Mercaptouracil (0·7 g., 0·005 mole) in water (10 ml.) containing sodium hydroxide (0·22 g., 0·0055 mole) under nitrogen was shaken with dimethyl sulphate (0·47 ml., 0·005 mole) for 5 min. and set aside overnight. The buff solid which separated was washed with water and recrystallised from acetic acid to give 5-(methylthio)uracil (0·22 g.), identical with that obtained under (*a*).

5-*Alkylsulphinyluracils*.—(*a*) The 5-(alkylthio)uracil (100 mg.) was treated at room temperature with fuming nitric acid (1 ml.). After the initial violent reaction the solution was evaporated *in vacuo* and the residue recrystallised.

(*b*) To a solution of the 5-(alkylthio)uracil (100 mg.) in acetic acid (15 ml.) was added one equivalent of 30% w/v hydrogen peroxide. The solution was set aside overnight, evaporated *in vacuo* (bath temperature $<40°$) to dryness, and the residue crystallised. The yields in each case were 50—60%, although in one case method (*a*) gave 89%. Further details are recorded in Table 2.

5-*Alkylsulphonyluracils*.—To a solution of the 5-(alkylthio)uracil (100 mg.) in warm acetic acid (15 ml.) was added a 40% excess of 3% aqueous potassium permanganate. After a few min. the solution was decolourised with sulphur dioxide and evaporated *in vacuo* at 40°. The product was separated from inorganic material by warming with water; if soluble it crystallised on cooling, if insoluble it was collected and crystallised fom aqueous ethanol. Yields of 40—55% were obtained, and further details are recorded in Table 2.

Methyl β-*Hydroxy*-α-(*methylthio*)*acrylate*.—To powdered sodium (1·3 g.) under ether was added dropwise a mixture of methyl (methylthio)acetate (6 g.) and ethyl formate (6 g.); a pale yellow solid was rapidly precipitated. The mixture was set aside overnight and the solid

(8·3 g.) washed with ether and dried *in vacuo* at room temperature. The *sodio-derivative* was obtained as a pale cream powder (Found: C, 35·45; H, 4·3; Na, 13·7; S, 18·75. $C_5H_7NaO_3S$ requires C, 35·3; H, 4·15; Na, 13·5; S, 18·85%). A portion of the sodio-derivative in water was acidified, and extracted with ether. Evaporation of the ether gave an oil which crystallised; the *product* crystallised from aqueous ethanol as needles, m. p. 75—76° (Found: S, 21·0. $C_5H_8O_3S$ requires S, 21·65%).

4-*Hydroxy*-2-*methoxy*-5-*methylthiopyrimidine* (VII).—Solutions of the foregoing sodio-derivative (0·85 g.) in water (5 ml.), *O*-methylisouronium hemisulphate (0·6 g.) in water (3 ml.), and sodium hydroxide (0·2 g.) in water (3 ml.) were mixed and heated on a water-bath for 6 hr. The cooled solution was acidified with 10N-hydrochloric acid, and set aside overnight, to give a crystalline precipitate. The *product* (0·05 g.) formed rectangular plates, m. p. 170—171° (from aqueous ethanol) (Found: C, 41·8; H, 4·75; N, 16·2; S, 18·8. $C_6H_8N_2O_2S$ requires requires C, 41·85; H, 4·7; N, 16·3; S, 18·6%); $\lambda_{max.}$ 206, 250—253, 290—295 mμ (ε 7650, 5850, 5050), $\lambda_{min.}$ 234, 275—277 mμ (in 0·1N-hydrochloric acid); $\lambda_{max.}$ 250—253, 285—290 mμ (ε 6150, 5600), $\lambda_{min.}$ 273 mμ (at pH 7·2); $\lambda_{max.}$ 245, 286 mμ (ε 5400, 5500), $\lambda_{min.}$ 268 mμ (in 0·1N-sodium hydroxide).

Hydrolysis of 4-*Hydroxy*-2-*methoxy*-5-*methylthiopyrimidine*.—The foregoing pyrimidine (several mg.) was heated on a water-bath with 10N-hydrochloric acid for 20 min.; the absorption spectra of the solution at pH 1, 7, and 13 were similar to those of 5-(alkylthio)uracils. The solution was chromatographed on paper in six different solvent systems (descending technique); a single major absorbing spot was observed corresponding in each case to 5-(methylthio)uracil which was run at the same time.

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