

758. *The Structure of Certain Polyazaindenes. Part XI.* The Preparation of 2- and 3-Alkylsulphonyl- and -Hydroxy-tetra-azaindenes.*

By L. A. WILLIAMS.

2- and 3-Alkylthiotetra-azaindenes give rise to sulphones on oxidation with hydrogen peroxide in acetic acid. These sulphones are converted into the hydroxy- or alkoxy-derivatives by hot aqueous sodium hydroxide or alcoholic sodium alkoxides.

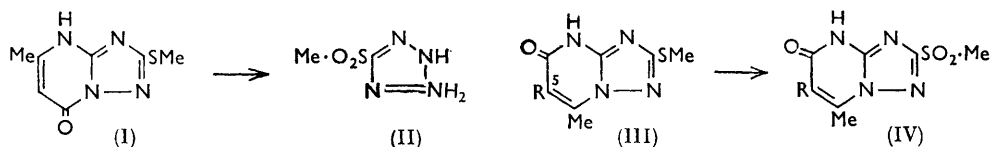
NOELL and ROBINS¹ showed that the reaction of chlorine with alkylthiopurines can proceed in two directions, depending on whether anhydrous or aqueous methanol is used as solvent. In the former 6- and 8-alkylthio-groups were replaced by chlorine, but a 2-alkylthio-group was oxidized to an alkylsulphonyl group: in aqueous methanol, all the

* Part X, *J.*, 1962, 2222.

¹ Noell and Robins, *J. Amer. Chem. Soc.*, 1959, **81**, 5997.

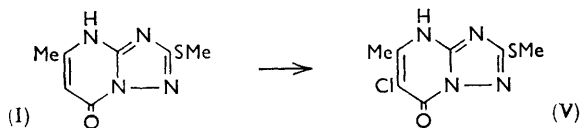
methylthio-groups were oxidized to methylsulphonyl groups. Andrews *et al.*² showed that, in aqueous conditions, chlorine oxidizes 2-methylthioadenine to 2-methylsulphonyladenine, and more recently Goerdeler and Rachwalsky³ showed that, under similar conditions, 3-alkylthio-5-amino-1,2,4-thiadiazole is oxidized to the corresponding alkylsulphonyl derivative.

Attempts, however, to oxidize 4,7-dihydro-6-methyl-2-methylthio-4-oxo-⁴ (I) or 6,7-dihydro-4-methyl-2-methylthio-6-oxo-1,3,3a,7-tetra-azaindene⁵ with chlorine in methanol did not yield the expected 2-alkylsulphonyltetra-azaindene, but instead ruptured the six-membered ring and 3-amino-5-methylsulphonyl-1,2,4-triazole (II) was isolated.



The presence of a 5-substituent in the azaindene (III; R = CO₂Et or CO₂H) allowed the oxidation of the alkylthio-group to the alkylsulphonyl group. Conditions, however, were critical in the case of the acid and decarboxylation occurred to give the sulphone (IV; R = H). However, the ester (III; R = CO₂Et) under similar conditions gave the expected sulphone (IV; R = CO₂Et).

The rupture of the ring mentioned above indicated the presence of water in the methanol, and the reaction of the azaindene (I) was repeated in methanol previously dried with magnesium methoxide. In this series the alkylthio-group was neither oxidized nor replaced by chlorine, in contrast to the reactivity of the same group in the purine series;¹ instead substitution by chlorine in the 5-position resulted, giving compound (V).



2-Methylthioadenine can also be oxidized to a sulphone with hydrogen peroxide in acetic acid.² In the tetra-azaindene series this reagent gave, in each case, the required alkylsulphonyl compound. By this means, the isomeric sulphones (VI—IX; R = SO₂·Me) amongst others, have been prepared.

Unsuccessful attempts were made to replace the methylsulphonyl by an amino-group by treating the sulphones (VI and VII; R = SO₂·Me) with primary or secondary amines (including morpholine and piperidine), liquid ammonia, or sodamide in liquid ammonia, the only products being the amine salts of the starting materials.

Postovskii and Alekseeva⁶ prepared 6-nitrobenzothiazolinone by hydrolytic attack on aryl- or alkyl-sulphonyl-6-nitrobenzothiazoles in acidic or alkaline solutions. In aqueous alkali the sulphones (VI—IX) gave smoothly the hydroxytetra-azaindenes (VI—IX; R = OH); infrared measurements in potassium bromide discs or paraffin indicate a carbonyl rather than hydroxyl group in these compounds. By the use of sodium alkoxides in alcohol the alkoxy-derivatives (VI and VII; R = OAlk) have been prepared.

The structures of these compounds (VI—IX; R = SO₂·Me, OH, or OAlk) follow from that of the parent alkylthio-compounds, all of which have previously been described and

² Andrews, Anand, Todd, and Topham, *J.*, 1949, 2490.

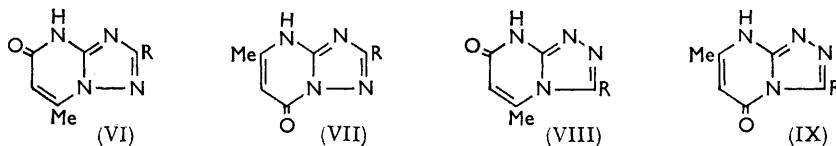
³ Goerdeler and Rachwalsky, *Chem. Ber.*, 1960, **93**, 2190.

⁴ Fry, B.P. 648,185.

⁵ Williams, *J.*, 1961, 3046.

⁶ Postovskii and Alekseeva, *Zhur. obshchei Khim.*, 1953, **23**, 1905; *Chem. Abs.*, 1955, **49**, 1011.

had structures assigned to them.^{4,5,7,8} The hydroxytetra-azaindene (VII; R = OH) is identical with the compound * obtained by condensation of 3-amino-5-hydroxy-1,2,4-triazole⁹ with ethyl acetoacetate, from which it can be concluded that in this amino-triazole also, it is the N₍₂₎-atom of the ring which is involved in cyclization; this is in keeping with earlier findings in which other aminotriazoles were used.^{5,7}



It was shown by the present author⁵ that 4,7-dihydro-4-oxotetra-azaindenes can be distinguished from the 6,7-dihydro-6-oxo-isomers by the presence of three strong infrared absorption peaks in the region 1725—1550 cm.⁻¹, the 6-oxo-isomers showing only two major absorption peaks in this region. This distinction is again shown in the isomeric sulphones (VI—IX) (see Table 1), from which it is confirmed that no re-arrangement in

TABLE 1.

Infrared absorption frequencies (cm.⁻¹) of methyl sulphones (VI—IX; R = SO₂·Me).

Compound	$\lambda_{\max.}$	Compound	$\lambda_{\max.}$	Compound	$\lambda_{\max.}$	Compound	$\lambda_{\max.}$
VI	1667s	VII	1667s	VIII	1709s	IX	1724s
	1575s		1613s		1600s		1639s
	—		1547s		—		1587s
	1351m		—		—		1333s
	1322s		1325s		1316s		1316m
	1143s		1154s		1156s		1149s

the position of the oxo-group occurs during oxidation of the parent alkylthio-compound. It is also possible to distinguish 1,2,3a,7-tetra-azaindenes from the 1,3,3a,7-isomers by the presence of an absorption peak at 1325 cm.⁻¹ in the latter.⁵ With the sulphones (VI—IX) this peak is obscured by strong absorption in the same region due to the sulphone group, which absorbs strongly in the regions 1350—1300 and 1175—1100 cm.⁻¹.¹⁰

In the ultraviolet region the long-wavelength absorption of the 6-oxo-isomers is found, in keeping with earlier results,⁵ at lower extinction values than for the isomeric 4-oxo-compound.

EXPERIMENTAL

Microanalyses are by Mr. C. B. Dennis; ultraviolet absorptions are for methanol solutions, and the infrared measurements were made on potassium bromide discs.

3-Amino-5-methylsulphonyl-1,2,4-triazole (II).—4,7-Dihydro-6-methyl-2-methylthio-4-oxo-1,3,3a,7-tetra-azaindene⁴ (10 g.) was suspended in methanol (150 c.c.). Into this cooled suspension chlorine was passed at such a rate that the temperature remained below 10°. In $\frac{1}{2}$ hr. all the solid had dissolved and the exothermic reaction had ceased. The solvent was removed by drawing dry air through the solution until the volume was reduced to 30 c.c. After chilling, the *product* was collected and recrystallized from alcohol-benzene, to give crystals (4 g.) which, recrystallized from water, had m. p. 243—245° (Found: C, 22.1; H, 4.3; N, 34.4; S, 18.7. C₃H₆N₄O₂S requires C, 22.2; H, 3.7; N, 34.5; S, 19.7%).

Ethyl 6,7-Dihydro-4-methyl-2-methylsulphonyl-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate (IV; R = CO₂Et).—Ethyl 6,7-dihydro-4-methyl-2-methylthio-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylate⁵ (6 g.) was suspended in methanol (140 c.c.) and the suspension cooled to 6°.

* The author thanks his colleague Dr. C. Holstead for the preparation of this compound.

⁷ Williams, *J.*, 1960, 1829.

⁸ Allen, Reynolds, Tinker, Williams, and VanAllan, *J. Org. Chem.*, 1960, 25, 361.

⁹ Godfrey and Kurzer, *J.*, 1960, 3437.

¹⁰ Braude and Nachod, "Determination of Organic Structure by Physical Methods," Academic Press Inc., New York, 1955, p. 213.

Chlorine was passed in at such a rate that the temperature remained below 10° until a clear solution resulted (*ca.* 1 min.). On further stirring, a solid separated and was collected to give the *product* (6 g.) which recrystallized from aqueous acetic acid as needles, m. p. 264° (Found: C, 40.2; H, 4.5; N, 18.7; S, 10.8. C₁₀H₁₂N₄O₅S requires C, 40.0; H, 4.0; N, 18.7; S, 10.7%).

5-Chloro-4,7-dihydro-6-methyl-2-methylthio-4-oxo-1,3,3a,7-tetra-azaindene (V).—4,7-Dihydro-6-methyl-2-methylthio-4-oxo-1,3,3a,7-tetra-azaindene (10 g.), dried at 100° overnight, was suspended in methanol dried with magnesium methoxide (150 c.c.). Dry chlorine was passed in, the temperature being kept below 10°. After 50 min. all the solid had dissolved and after a further 5 min. a colourless precipitate separated. The *product* (6 g.) was collected and recrystallized from benzene-methanol as colourless prisms, m. p. 259° (Found: C, 34.4; H, 3.8; Cl, 15.0; N, 22.7; S, 12.6. C₇H₇ClN₄OS.H₂O requires C, 33.9; H, 3.6; Cl, 14.3; N, 22.6; S, 12.9%).

6,7-Dihydro-4-methyl-2-methylsulphonyl-6-oxo-1,3,3a,7-tetra-azaindene (IV; R = H).—*Method I.* 6,7-Dihydro-4-methyl-2-methylthio-6-oxo-1,3,3a,7-tetra-azaindene-5-carboxylic acid⁵ (III; R = CO₂H) (3.4 g.) was suspended in methanol (70 c.c.) and chilled to 5°. Chlorine was passed in for 5 sec., during which the temperature rose to 22°. The green suspension soon dissolved to give a colourless solution from which a solid separated as the temperature again fell. The *product* (2.4 g.) was collected and washed with a little methanol and recrystallized from water as colourless needles, m. p. 290–291° (Found: C, 36.3; H, 3.9; N, 24.5%, cf. below).

Method II. The azaindene⁵ (VI; R = SMe) (4.5 g.) was dissolved in glacial acetic acid (100 c.c.) at 80° and the solution added to 30% hydrogen peroxide (14.2 g.) in acetic acid (100 c.c.) also at 80°. The temperature was kept at 80–85° for 4 hr., then the mixture was concentrated to half volume and cooled, and ether was added. The solid which separated (5.1 g.) was collected and twice recrystallized from aqueous acetic acid to give colourless needles (3.6 g.), m. p. 290–291°, identical with the product obtained by method I (Found: C, 37.1; H, 3.9; N, 24.4; S, 14.0. C₇H₈N₄O₃S requires C, 36.9; H, 3.5; N, 24.6; S, 14.0%), λ_{max} 287 mμ (log ε 3.659).

Other sulphones prepared by method II are given in Table 2.

TABLE 2.

2- and 3-Alkylsulphonylazaindenes.

No.	Formula	5-Subst.	R	Yield (%)	M. p.	Cryst. from	λ _{max} . (mμ) & (log ε)
1	VII	H	SO ₂ ·Me	70	246°	Aq. EtOH	285 (4.13)
2	VIII	H	SO ₂ ·Me	48	305	H ₂ O	230 (3.99), 290* (3.36)
3	IX	H	SO ₂ ·Me	29	223	Aq. EtOH	295 (4.10)
4	VII	H	SO ₂ ·Et	46.5	242–243	EtOH-C ₆ H ₆	—
5	VII †	CO ₂ Et	SO ₂ ·Me	65	297–302	1:1 Aq. AcOH	—

* Shoulder. † H at position 6.

No.	Found (%)				Formula	Required (%)			
	C	H	N	S		C	H	N	S
1	37.1	4.0	24.3	14.2	C ₇ H ₈ N ₄ O ₃ S	36.9	3.5	24.6	14.0
2	37.0	3.9	24.2	14.5	"	"	"	"	"
3	36.9	3.9	24.2	13.9	"	"	"	"	"
4	39.8	4.5	22.7	13.1	C ₈ H ₁₀ N ₄ O ₃ S	39.7	4.1	23.2	13.1
5	37.7	3.2	19.9	11.0	C ₉ H ₁₀ N ₄ O ₅ S	37.8	3.5	19.6	11.2

4,7-Dihydro-2-hydroxy-6-methyl-4-oxo-1,3,3a,7-tetra-azaindene.—*Method A.* The sulphone (VII; R = SO₂·Me) (1 g.) was refluxed for 1 hr. in 10% sodium hydroxide solution (10 c.c.). After cooling, the solution was acidified with concentrated hydrochloric acid, and the solid which separated recrystallized from water, to give the *product*, m. p. 363° (Found: C, 43.4; H, 3.8; N, 33.4. C₆H₈N₄O₂ requires C, 43.3; H, 3.6; N, 33.8%), λ_{max} 223 (log ε 4.43), 283 mμ (log ε 3.88).

Method B. Sodium (0.92 g.) was dissolved in ethanol (100 c.c.), and 3-amino-5-hydroxy-1,2,4-triazole (4 g.) was added together with ethyl acetoacetate (5.2 g.). The mixture was refluxed for 20 hr. after which the precipitated sodium salt was collected and dissolved in water.

The solution was filtered and acidified with hydrochloric acid to give 4.5 g. of product, m. p. 350° (Found: C, 43.0; H, 4.0; N, 33.9%).

Other 2- and 3-hydroxy-azaindenes prepared by Method A above are given in Table 3.

TABLE 3.
2- and 3-Hydroxyazaindenes.

Formula	5-Subst.	Yield (%)	M. p.	Found (%)			Formula	Required (%)			$\lambda_{\max.}$ (m μ) & (log ϵ)
				C	H	N		C	H	N	
VI	H	75.5	360°*	43.3	3.9	33.8	C ₈ H ₈ N ₄ O ₂	43.3	3.6	33.8	253 (3.76) 300 (3.76)
VIII	H	42.0	315*	42.8	4.0	34.2	"	"	"	"	225 (4.31) 256 (3.75) ¶
IX	H	64.0	364*	43.0	4.0	33.8	"	"	"	"	—
VII §	CO ₂ H	73.0	325 †	36.7	2.9	—	C ₈ H ₄ N ₄ O ₄	36.7	2.0	—	—
VIII	CO ₂ H	27.8	270 ‡	36.7	3.8	24.0	C ₇ H ₆ N ₄ O ₄ ·H ₂ O	36.9	3.5	24.6	—

* From 1 : 1 aq. AcOH. † From AcOH. ‡ From H₂O; for m. p., sample placed in bath 5° below m. p. § H at position 6. ¶ Shoulder.

2-Ethoxy-4,7-dihydro-6-methyl-4-oxo-1,3,3a,7-tetra-azaindene (VII; R = OEt).—Sodium (0.46 g.) was dissolved in ethanol (10 c.c.), 4,7-dihydro-6-methyl-2-methylsulphonyl-4-oxo-1,3,3a,7-tetra-azaindene (2.28 g.) was added, and the mixture was refluxed for 3 hr. Water (10 c.c.) was then added and the solution acidified with concentrated hydrochloric acid and chilled. The *product* was collected and recrystallized from water; it had m. p. 280° (Found: C, 49.9; H, 5.2; N, 29.2. C₈H₁₀N₄O₂ requires C, 49.5; H, 5.2; N, 28.9%).

2-Ethoxy-6,7-dihydro-4-methyl-6-oxo-1,3,3a,7-tetra-azaindene (VI; R = OEt).—6,7-Dihydro-4-methyl-2-methylsulphonyl-6-oxo-1,3,3a,7-tetra-azaindene (0.7 g.) was refluxed as above with sodium (0.14 g.). After cooling, the solution was acidified with hydrochloric acid, and ether (15 c.c.) was added. The *product* was collected; recrystallized from water it (0.15 g.) had m. p. 200—202° (Found: C, 49.1; H, 5.2; N, 28.9%).

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