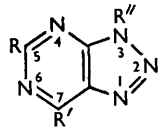
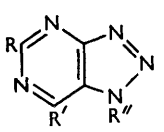
318. *The Synthesis of the* v-*Triazolo*[d]*pyrimidine Analogues of Adenosine, Inosine, Guanosine, and Xanthosine, and a New Synthesis of Guanosine.*

By J. Davoll.

The synthesis is described of the compounds named in the title, and of other glycosyl-*v*-triazolo[*d*]pyrimidines, from chloromercuri-derivatives of appropriate triazolopyrimidines. A new synthesis of guanosine (from 2-methylthio-9-β-D-ribofuranosyladenine) has been accomplished.

Derivatives of *v*-triazolo[*d*]pyrimidine, particularly the 5-amino-7-hydroxy-compound ("8-azaguanine") (I; R = NH_2, R′ = OH, R″ = H) have attracted considerable attention as purine antagonists in biological systems, including viruses [1] and cancers.[2] Since these compounds appear to function by incorporation as ribosyl derivatives, the synthesis, for biological testing, of derivatives analogous to the natural purine nucleosides was undertaken.


(I)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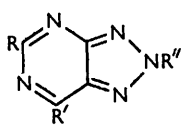
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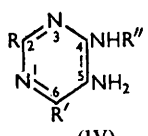
(IV)

Two synthetic routes were used. The first of these, treatment of 5-amino-4-glycosylaminopyrimidines (IV) with nitrous acid, like the analogous syntheses of purine nucleosides by Todd and his co-workers,[3] defines the point of attachment of the sugar to the base but is of little preparative value for furanose derivatives. This method was used to prepare 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine (I; R = H, R′ = NH_2, R″ = β-D-glucopyranosyl) from the glucosylaminopyrimidine [4] (IV; R = MeS, R′ = NH_2, R″ = D-glucosyl) by cyclisation and desulphurisation.

The second synthetic method involved the reaction of chloromercuri-derivatives of appropriate *v*-triazolo[*d*]pyrimidines with acylglycosyl halides; in the purine series this route affords the natural purine nucleosides in moderate yield.[5] A disadvantage is that two isomers (II) and (III) may be formed in addition to the required analogue (I), and in one case three products were in fact obtained. Since no unambiguous syntheses of 1- or 2-alkyl-*v*-triazolo[*d*]pyrimidines for spectroscopic comparison were available, structures could not be assigned with certainty to some of the compounds obtained.

The required *v*-triazolo[*d*]pyrimidines were prepared by standard methods (modified in some cases to avoid isolation of intermediates), acetylated, and converted into chloromercuri-compounds as described for the corresponding purines.[5,6] These were condensed with acylglycosyl halides in the usual way,[5,6] the ribofuranosyl derivatives being prepared from tri-*O*-benzoyl-D-ribofuranosyl chloride with the modifications introduced by Kissman *et al.*[7]

Deacetylation of the condensation product of 7-acetamido-*x*-chloromercuri-*v*-triazolo[*d*]-pyrimidine with tetra-*O*-acetyl-D-glucosyl bromide gave 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine, identical with material obtained by the first route, together with an

[1] Matthews and Smith, "Advances in Virus Research," Academic Press, New York, 1955, Vol. III, p. 49.
[2] Parks, "Antimetabolites and Cancer," Amer. Assoc. Advancement Science, Washington, D.C., 1955, p. 175.
[3] Kenner, Taylor, and Todd, *J.*, 1949, 1620, and other papers in this series.
[4] Holland, Lythgoe, and Todd, *J.*, 1948, 965.
[5] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650.
[6] *Idem*, *ibid.*, 1952, **74**, 1563.
[7] Kissman, Pidacks, and Baker, *ibid.*, 1955, **77**, 18.

isomeric compound. On the basis of a comparison of the ultraviolet spectrum of the latter compound with the 3-isomer, and with 7- and 9-methyladenine, this is considered to be the 1-glucopyranosyl derivative (II; R = H, R′ = NH_2, R″ = β-D-glucopyranosyl), but the alternative (III) cannot be definitely excluded. A similar condensation with use of tri-*O*-benzoyl-D-ribofuranosyl chloride gave only one crystalline product; this is the required 3-β-D-ribofuranosyl derivative (" 8-aza-adenosine ") (I; R = H, R′ = NH_2, R″ = β-D-ribofuranosyl) since its spectrum is virtually identical with that of the 3-glucopyranosyl derivative. On deamination it gave the 7-hydroxy-compound (" 8-azainosine ") (I; R = H, R′ = OH; R″ = β-D-ribofuranosyl).

The preparation of the triazolopyrimidine analogue of guanosine proved more difficult. In an attempt to apply the method used for the synthesis of guanosine [5] 5 : 7-diacetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine was condensed with tri-*O*-benzoyl-D-ribofuranosyl chloride and the product deacylated. The resulting crystalline compound had an indefinite melting point and a comparison of its spectrum with that of 5 : 7-diamino-3-methyl-*v*-triazolo[*d*]pyrimidine did not give any definite information as to structure. Conversion into a guanine analogue [5] gave (in 24% yield) a single product, possibly 5-amino-7-hydroxy-1-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (II; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl); it gave 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine on hydrolysis and had a spectrum differing from that of the 3-ribofuranosyl derivative prepared as described below. The same material was prepared (in 16% yield) directly from the crude condensation product.

The successful preparation [8] of N^2-alkylguanines from 2-methylthiohypoxanthine suggested an alternative route to the required compound, and in a model experiment 2-methylthio-9-β-D-ribofuranosylhypoxanthine (prepared from the adenine derivative [6]) gave a 24% yield of guanosine, identical with the natural nucleoside, on treatment with aqueous-ethanolic ammonia at 130°. When this route was applied in the triazolopyrimidine series two isomeric ribofuranosyl derivatives of 7-amino-5-methylthio-*v*-triazolo[*d*]pyrimidine were obtained. One of these was shown to be the required 3-β-D-ribofuranosyl derivative (I; R = MeS, R′ = NH_2, R″ = β-D-ribofuranosyl) by desulphurisation, and the other compound is provisionally assumed to be the 1-β-D-ribofuranosyl derivative (II). Both compounds were deaminated with nitrous acid, and the resulting 7-hydroxy-derivatives were heated with aqueous-ethanolic ammonia. No crystalline riboside was isolated from the second compound, but the 3-β-D-ribofuranosyl derivative gave the required 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (" 8-azaguanosine ") (I; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl), spectroscopically identical with the biosynthetic product.[9] The yield (8%) on the amination, however, was much lower than in the purine series, and a more satisfactory preparative method was sought.

It has been recently shown [10] that the chloromercuri-route may give *N*-glycosyl derivatives even in compounds where lactam–lactim tautomerism is possible, and it was found that deacylation of the condensation product of 5-acetamido-*x*-chloromercuri-7-hydroxy-*v*-triazolo[*d*]pyrimidine with tri-*O*-benzoyl-D-ribofuranosyl chloride in fact gave the required analogue of guanosine in 39% yield, together with an approximately equal amount of an isomeric compound which differed also from the (?) 1-ribofuranosyl derivative described above; it is tentatively regarded as 5-amino-7-hydroxy-2-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (III; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl).

5 : 7-Dihydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (" 8-azaxanthosine ") (I; R = R′ = OH; R″ = β-D-ribofuranosyl) was prepared by deamination of the above guanosine analogue.

Some spectral characteristics of our products are given in the annexed Table.

[8] Elion, Lange, and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 217.
[9] Friedkin, *J. Biol. Chem.*, 1954, **209**, 295.
[10] Fox, Yung, Davoll, and Brown, *J. Amer. Chem. Soc.*, 1956, **78**, 2117.

v-Triazolo[d]pyrimidine deriv.	$\lambda_{max.}$ (mμ) ($10^{-3}\varepsilon$ in parentheses) In HCl	At pH 6·8	In NaOH
(?) 7-Amino-1-β-D-glucopyranosyl-	244 (5·3), 286 (11·6) [a]	246 (5·5), 299 (10·3)	245 (5·3), 299 (9·8) [a]
7-Amino-3-β-D-glucopyranosyl-	263 (12·5) [a]	280 (11·7)	280 (11·2) [a]
7-Amino-3-β-D-ribofuranosyl-	260 (12·4) [a]	279 (12·0)	278 (12·4) [a]
7-Hydroxy-3-β-D-ribofuranosyl-	255 (9·4) [a]	256 (8·8)	277 (10·5) [a]
(?) 5 : 7-Diamino-β-D-ribofuranosyl-	260 (11·5), 286 (10·0) [a]	222 (21·7), 291 (7·2)	293 (7·4) [a]
5 : 7-Diamino-3-methyl-	254 (9·1), 284 (6·7) [a]	258 (5·1), 287 (8·8)	259 (5·1), 287 (8·8) [a]
(?) 7-Amino-5-methylthio-1-β-D-ribofuranosyl-	230 (12·3), 285 (13·3), 303 (12·6) [b]	223 (15·9), 248 (13·3), 279 (10·5), 308 (9·8)	248 (14·4), 279 (10·3), 310 (10·1) [b]
7-Amino-5-methylthio-3-β-D-ribofuranosyl-	245 (13·7), 280 (14·7) [b]	248 (19·4), 289 (13·5)	247 (18·9), 289 (12·9) [b]
(?) 7-Hydroxy-5-methylthio-1-β-D-ribofuranosyl-	222 (14·0), 238 (14·8), 287 (9·9) [b]	219 (15·0), 242 (14·3), 288 (9·8)	244 (15·0), 276 (9·8), 300 (10·8) [b]
7-Hydroxy-5-methylthio-3-β-D-ribofuranosyl-	232 (9·5), 273 (18·0) [b]	242 (12·5), 276 (15·1)	242 (16·8), 283 (14·8) [b]
(?) 5-Amino-7-hydroxy-1-β-D-ribofuranosyl-	285 (6·3) [c]	238 (sh) (8·4), 297 (7·1)	254 (5·6), 256 (5·6), 304 (8·8) [d]
(?) 5-Amino-7-hydroxy-2-β-D-ribofuranosyl-	238 (sh) (7·5), 296 (4·7) [c]	237 (sh) (8·4), 301 (5·6) [c]	303 (6·3) [d]
5-Amino-7-hydroxy-3-β-D-ribo-ribofuranosyl- [f]	255 (13·6), 269 (sh) (10·3) [c]	—	221 (23·0), 279 (11·6) [d]
,, ,, [g]	256 (13·7), 275 (sh) (9·5) [c]	256 (13·7), 275 (sh) (9·5)	222 (24·6), 279 (11·9) [d]
,, ,, [h]	254 (12·9), 270 (sh) [c]	256 (10·9), 270 (sh)	277 (11·2) [d]
5 : 7-Dihydroxy-3-β-D-ribofuranosyl-	240 (sh) (5·9), 256 (9·5) [a]	252 (9·7), 277 (8·8)	251 (7·1), 280 (9·5) [a]
2-Methylthio-9-β-D-ribofuranosylhypoxanthine	265 (15·1) [b]	262 (14·8)	225 (19·2), 271 (14·8) [b]

[a] 0·1N. [b] 0·05N. [c] 0·01N. [d] 0·03N. [e] In H_2O. [f] From 5-methylthio-compound. [g] From 5-acetamido-7-hydroxy-*v*-triazolo[*d*]pyrimidine. [h] Biosynthetic (ref. 9). pH 7·5.

Experimental

7-Amino-3-β-D-glucopyranosyl-v-triazolo[d]*pyrimidine.*—An aqueous solution (200 c.c.) of 5 : 6-diamino-4-D-glucosylamino-2-methylthiopyrimidine, prepared [4] from 6-amino-4-D-glucosylamino-2-methylthiopyrimidine (6·5 g.), was treated with glacial acetic acid (22 c.c.), followed by sodium nitrite (1·43 g.) in water (20 c.c.), added dropwise with stirring. After 2 hr. at room temperature, the solution was evaporated to dryness below 40°, the residue acetylated with acetic anhydride–pyridine at room temperature, and the product (3·64 g.) isolated with chloroform as an amorphous powder. A solution of this material in ethanol (250 c.c.) was boiled under reflux for 2 hr. with Raney nickel [11] (from 28 g. of alloy) and filtered hot. The residue (1·77 g.) obtained by evaporation of the combined filtrate and washings was deacetylated with methanolic ammonia at 0°, and the product converted into the *picrate* (1·41 g., 13% overall yield), plates, m. p. 187—191° (decomp.), raised to 201° (decomp.) by four recrystallisations from water (Found: C, 35·9; H, 3·4; N, 23·8. $C_{10}H_{14}O_5N_6,C_6H_3O_7N_3$ requires C, 36·4; H, 3·3; N, 23·9%).

Treatment of the picrate with Dowex No. 1 anion-exchange resin [5] gave *7-amino-3-β-D-glucopyranosyl-v-triazolo*[d]*pyrimidine* as blades (from water), m. p. 241° (decomp.), $[\alpha]_D^{20}$ −22° (*c* 1 in H_2O) (Found: C, 40·2; H, 4·8; N, 27·9. $C_{10}H_{14}O_5N_6$ requires C, 40·3; H, 4·7; N, 28·2%).

Chloromercuri-derivatives.—The triazolopyrimidine was dissolved in cold water (10 vols.) by addition of N-sodium hydroxide (2 equivs. for the diacetyl derivatives of 7-amino-5-methylthio- and 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine; 1 equiv. in the other cases). To the filtered solution was added mercuric chloride (1 mol.) in hot ethanol (8 c.c. per g.) followed by water (20 vols.) and Hyflo Supercel (1·5 times the weight of triazolopyrimidine). The product was collected after cooling, washed with water, dried, and powdered. Yields were 80—90%.

Reaction of Chloromercuri-derivatives with O-Acylglycosyl Halides.—In the reaction using tetra-*O*-acetylglucosyl bromide the procedure of Davoll and Lowy [5] was followed; those using tri-*O*-benzoyl-D-ribofuranosyl chloride were carried out as described by Kissman *et al.*,[7] except that the final extraction of the crude condensation product with ether was omitted.

[11] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

7-*Amino*-v-*triazolo*[d]*pyrimidine*.—4 : 6-Diamino-2-mercaptopyrimidine (35 g.) was nitrosated [12] and the crude wet product then boiled under reflux with stirring for 1 hr. with water (3 l.), ammonia (*d* 0·88; 120 c.c.), and Raney nickel [11] (from 180 g. of alloy). The mixture was filtered hot, and the filtrate evaporated under reduced pressure to 1·2 l., shaken with charcoal, and again filtered. To the filtrate was added glacial acetic acid (75 c.c.) followed by sodium nitrite (13 g.) in water (100 c.c.), added dropwise with stirring. The triazolopyrimidine (13·5 g., 40%) was collected after 1 hr. as an almost white powder.

7-*Acetamido*-v-*triazolo*[d]*pyrimidine*.—The above compound (2 g.) and acetic anhydride (20 c.c.) were boiled together under reflux for 4 hr. Collected after cooling and washed with ethanol, the *acetamido-compound* (2·06 g., 79%) had m. p. 294° (decomp.) and was sufficiently pure for further use. It formed prisms (from 50% aqueous 2-ethoxyethanol), m. p. 293—294° (decomp.) (Found: C, 40·3; H, 3·7; N, 47·2. $C_6H_6ON_6$ requires C, 40·5; H, 3·4; N, 47·2%).

7-*Acetamido*-x-*chloromercuri*-v-*triazolo*[d]*pyrimidine and Tetra*-O-*acetyl*-D-*glucopyranosyl Bromide*.—The reaction between the chloromercuri-compound (9·05 g.) and the bromide (10 g., 1·1 mol.) gave a syrupy product (8·5 g., 77%), which crystallised from ethanol (150 c.c.) to give a compound (0·5 g.) as needles, m. p. 270° after recrystallisation from ethanol (Found: C, 48·1; H, 5·0; N, 11·3, 11·4%). It did not give a crystalline product on deacetylation with methanolic ammonia. The ethanolic filtrate was evaporated, the residue deacetylated with methanolic ammonia at 0°, and the product crystallised from water (25 c.c.), with charcoal, to give (?) 7-*amino*-1-β-D-*glucopyranosyl*-v-*triazolo*[d]*pyrimidine* (0·85 g., 13%), m. p. 250—251° (decomp.), $[\alpha]_D^{23}$ −16° (*c* 0·2 in H_2O) (Found: C, 40·0; H, 4·9; N, 27·7. $C_{10}H_{14}O_5N_6$ requires C, 40·3; H, 4·7; N, 28·2%). The *picrate* formed solvated needles (from 50% ethanol), m. p. 160° (effervescence) (Found: C, 37·5; H, 4·1; N, 22·3. $C_{10}H_{14}O_5N_6,C_6H_3O_7N_3,C_2H_6O$ requires C, 37·7; H, 4·0; N, 22·0%).

Addition of picric acid to the filtrate from the 1-glucosyl compound gave 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine picrate (1·53 g., 13%), m. p. 183° (decomp.), raised to 202° (decomp.) by several recrystallisations from water (Found: C, 36·3; H, 3·4; N, 24·0%). Removal of picric acid gave the 3-glucosyl derivative, m. p. 241° (decomp.), $[\alpha]_D^{20}$ −24° (*c* 0·93 in H_2O) (Found: C, 40·1; H, 4·8; N, 27·8%). This compound and its picrate did not depress the m. p.s of samples prepared as described above, and the ultraviolet absorption spectrum of the free compound was virtually identical with that of the previous sample.

7-*Amino*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Aza-adenosine* ").—Condensation of 7-acetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine (16·7 g.) with tri-*O*-benzoyl-D-ribofuranosyl chloride (1·09 mol.; from 22·1 g. of the 1-acetate) gave a syrupy product (24·5 g., 97%). This was deacylated with sodium methoxide (ref. 7, note 26), and after neutralisation with carbon dioxide the mixture was evaporated and the residue triturated with dry ether to remove methyl benzoate, and dried. Crystallisation from water (125 c.c.) with charcoal, followed by evaporation to 30 c.c. to obtain a second crop, gave a total of 1·69 g. (16%) of the 3-β-D-*ribofuranosyl compound* as needles, m. p. 209—218°, raised to 218—219° by recrystallisation from water, $[\alpha]_D^{23}$ −79° (*c* 0·46 in H_2O) (Found: C, 40·5; H, 4·9; N, 31·4. $C_9H_{12}O_4N_6$ requires C, 40·3; H, 4·5; N, 31·3%). The *picrate* separated from water in needles, m. p. 184° (decomp., previous darkening) (Found: C, 36·1; H, 3·2; N, 25·6. $C_9H_{12}O_4N_6,C_6H_3O_7N_3$ requires C, 36·2; H, 3·0; N, 25·4%).

Addition of picric acid to the mother-liquor from the above riboside gave a picrate (7·25 g.) which could not be purified; removal of picric acid gave a product which formed gelatinous solutions in water and did not crystallise. Its ultraviolet absorption spectrum showed maxima at 273 mμ (in 0·1N-hydrochloric acid) and 287 mμ (in 0·1N-NaOH).

7-*Hydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Azainosine* ").—A solution of 7-amino-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (2 g.) and sodium nitrite (5 g.) in hot water (25 c.c.) was cooled rapidly and treated with glacial acetic acid (5 c.c.). After 1 hr. water (25 c.c.) was added, and after 18 hr. the product (1·87 g.) was isolated by precipitation with excess of aqueous lead acetate and ammonia, treatment of the lead salt in 20% acetic acid with hydrogen sulphide, and evaporation of the lead sulphide filtrate. The 7-*hydroxy-compound* (1·38 g., 69%) separated from 80% ethanol (60 c.c.) as prisms or needles, m. p. 196—197°, raised to 199—200° by recrystallisation, $[\alpha]_D^{21}$ −54° (*c* 1·78 in H_2O) (Found: C, 40·2; H, 4·4; N, 26·3. $C_9H_{11}O_5N_5$ C, 40·2; H, 4·1; N, 26·0%).

[12] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3109.

5 : 7-*Diamino*-v-*triazolo*[d]*pyrimidine*.—To a solution of 2 : 4 : 6-triaminopyrimidine [13] (8·5 g.) in 10% acetic acid (220 c.c.) was added sodium nitrite (4·85 g.) in water (30 c.c.), dropwise, with stirring. After 1 hr. glacial acetic acid (115 c.c.) and 5% palladised charcoal were added, and the mixture was shaken in hydrogen, 2 mols. being absorbed in 1 hr. After removal of catalyst the almost colourless filtrate was treated with sodium nitrite (4·85 g.) in water (30 c.c.) added dropwise with stirring. The separated product was treated with charcoal in hot dilute aqueous ammonia, and the hot filtrate acidified with acetic acid, giving the *diamino-compound* (7·55 g., 73%) as a white powder (Found: N, 64·3. $C_4H_5N_7$ requires N, 64·9%).

5 : 7-*Diacetamido*-v-*triazolo*[d]*pyrimidine*.—The above diamino-compound (9·76 g.) and acetic anhydride (98 c.c.) were boiled together under reflux for 30 min. The *triacetyl compound* (13·3 g., 75%), m. p. 210° (decomp.) (Found: N, 35·4. $C_{10}H_{11}O_3N_7$ requires N, 35·4%), was collected after cooling and washed with ethanol. When this was heated to the b. p. with 2-ethoxyethanol (200 c.c.) containing a little water the *diacetamido-derivative* (9·94 g., 61% overall yield), m. p. 280° (decomp.), separated from the hot solution and was collected after cooling and washed with ethanol. It separated from 2-ethoxyethanol as hydrated needles of unchanged m. p. (Found: C, 38·7; H, 4·5; N, 38·6. $C_8H_9O_2N_7,H_2O$ requires C, 37·9; H, 4·4; N, 38·7%).

5 : 7-*Diacetamido*-x-*chloromercuri*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride*.—Condensation between the chloromercuri-compound (8 g.) and tri-*O*-benzoyl-D-ribofuranosyl chloride (1 mol.; from 8·56 g. of the 1-acetate) gave a pale yellow glass (11·4 g., 98%). Deacylation with sodium methoxide [7] and crystallisation of the product from water (15 c.c.) gave the 5 : 7-*diamino*-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*(s) (2·03 g., 42%), m. p. 127—150°, unchanged by further recrystallisation from water (Found: C, 37·8; H, 5·0; N, 34·5. $C_9H_{13}O_4N_7$ requires C, 38·2; H, 4·6; N, 34·6%).

5 : 7-*Diamino*-3-*methyl*-v-*triazolo*[d]*pyrimidine*.—2 : 4-Diamino-6-chloropyrimidine (3 g.) and benzylmethylamine (9 c.c.) were boiled together under reflux for 1 hr. The cooled mixture was extracted with boiling ethyl acetate (60 c.c.), the extract washed with 5% acetic acid, dried (Na_2SO_4), and evaporated, and the residue crystallised from ethyl acetate, to give 2 : 4-*diamino*-6-(N-*methylbenzylamino*)*pyrimidine acetate* (2·15 g., 36%), m. p. 146—148° (Found: C, 58·0; H, 6·9; N, 24·6. $C_{12}H_{15}N_5,C_2H_4O_2$ requires C, 58·1; H, 6·6; N, 24·2%). This material was nitrosated in the usual way in 20% acetic acid, and the product suspended in 50% acetic acid and hydrogenated in presence of 10% palladised charcoal. Three mols. of hydrogen were absorbed, and addition of 1 mol. of aqueous sodium nitrite to the filtered solution gave 5 : 7-*diamino*-3-*methyl*-v-*triazolo*[d]*pyrimidine* (84%) as laths (from water), m. p. 294—295° (Found: C, 36·1; H, 4·5; N, 59·4. $C_5H_7N_7$ requires, C, 36·4; H, 4·3; N, 59·4%). The compound was insoluble in alkali, excluding the possible structure 5-amino-7-methylamino-*v*-triazolo[*d*]-pyrimidine.

(?) 5-*Amino*-7-*hydroxy*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*.—(*a*) The crude condensation product (18·9 g.) from 5 : 7-diacetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine and tri-*O*-benzoyl-D-ribofuranosyl chloride was deacylated with methanolic ammonia, treated with nitrous acid, and finally deacylated with sodium methoxide, according to the general procedure for guanine derivatives,[5] without crystallisation of intermediates. The 5-*amino*-7-*hydroxy-compound* (1·26 g., 16%) crystallised without purification through the lead salt; it formed needles (from water), which decomposed without melting above 200° and had $[\alpha]_D^{20}$ −75° (*c* 0·9 in H_2O) (Found: C, 37·7; H, 4·6; N, 29·4. $C_9H_{12}O_5N_6$ requires C, 38·0; H, 4·3; N, 29·6%). Hydrolysis for 2 hr. with boiling N-hydrochloric acid gave material with the spectrum of 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine.

(*b*) The crystalline 5 : 7-diamino-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine(s) described above (0·45 g.) was boiled under reflux for 45 min. with acetic anhydride (5 c.c.). Evaporation and treatment as described in (*a*) gave the same 5-amino-7-hydroxy-compound (0·11 g., 24%), identified by its ultraviolet absorption spectrum in acid and alkali.

2-*Methylthio*-9-β-D-*ribofuranosylhypoxanthine*.—2-Methylthio-9-β-D-ribofuranosyladenine [6] (0·5 g.) in 0·4N-sulphuric acid (100 c.c.) was treated with sodium nitrite (1·2 g.). After 18 hr. the solution was neutralised with ammonia and evaporated to 15 c.c., to give the *hypoxanthine derivative* (0·46 g., 92%) as needles (from water), m. p. 246° (decomp., with darkening above 210°) (Found: C, 41·7; H, 4·5; N, 17·4. $C_{11}H_{14}O_5N_4S$ requires C, 42·0; H, 4·5; N, 17·8%).

[13] Sato, Nakajima, and Tanaka, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1951, **72**, 866 (*Chem. Abs.*, 1953, **47**, 5946e).

Guanosine.—The above compound (0·5 g.), aqueous ammonia (*d* 0·88; 4 c.c.), and ethanolic ammonia (4 c.c., saturated at 0°) were heated together in a sealed tube for 18 hr. at 130—132°. Evaporation of the cooled mixture and four crystallisations of the residue from water (charcoal) gave guanosine (0·12 g., 24%) as colourless needles which charred above 230° alone or in admixture with the natural nucleoside and had $[\alpha]_D^{24}$ −72° (*c* 0·96 in 0·1N-NaOH) {reported [5] for natural guanosine: $[\alpha]_D^{23}$ −70° (*c* 1·15 in 0·1N-NaOH)} (Found: C, 42·1; H, 4·6; N, 25·1. Calc. for $C_{10}H_{13}O_5N_5$: C, 42·4; H, 4·6; N, 24·7%). The infrared spectra of samples of the natural and synthetic compounds (as dihydrates, in Nujol mull), and their ultraviolet absorption spectra, were indistinguishable.

7-*Amino*-5-*methylthio*-v-*triazolo*[d]*pyrimidine.*—4 : 5 : 6-Triamino-2-methylthiopyrimidine (1·71 g.) in 10% acetic acid (55 c.c.) was treated with sodium nitrite (0·69 g.) in a little water. The precipitate was treated with charcoal in hot dilute aqueous ammonia and acidified with acetic acid, to give the *triazolopyrimidine* (1·55 g., 81%) as a hydrated powder, m. p. 282° (decomp.) (Found: C, 31·7; H, 3·6; N, 44·3. $C_5H_6N_6S,\frac{1}{2}H_2O$ requires C, 31·4; H, 3·7; N, 44·0%).

Acetyl Derivatives of 7-*Amino*-5-*methylthio*-v-*triazolo*[d]*pyrimidine.*—The above material (1 g.) and acetic anhydride (5 c.c.) were boiled together under reflux for 2 hr. Addition of dry ether (10 c.c.) to the cooled mixture gave the slightly impure *diacetyl compound* (1·06 g., 76%) as pale yellow crystals, m. p. 153—155° (Found: C, 41·3; H, 4·5; N, 30·5. $C_9H_{10}O_2N_6S$ requires C, 40·6; H, 3·8; N, 31·6%).

During several months in air one acetyl group was lost with formation of 7-*acetamido*-5-*methylthio*-v-*triazolo*[d]*pyrimidine*, m. p. 215—217° (Found: C, 38·1; H, 4·1. $C_7H_8ON_6S$ requires C, 37·5; H, 4·6%), which separated as solvated needles, m. p. 219—220°, from 70% ethanol (Found: C, 39·0; H, 5·1; N, 31·5. $C_7H_8ON_6S,C_2H_6O$ requires C, 40·0; H, 5·2; N, 31·1%).

7-*Acetamido*-x-*chloromercuri*-5-*methylthio*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride.*—The syrupy condensation product (31 g., 96%) obtained from the chloromercuri-compound (23 g.) and tri-*O*-benzoyl-D-ribofuranosyl chloride (1 mol.; from 25·4 g. of the 1-acetate) was deacylated with sodium methoxide,[7] and the product dissolved in hot water (175 c.c.) and treated with charcoal. A first crop (3·79 g., 24%), m. p. 193—197°, was collected after 1½ hr. at room temperature and a second crop (2·8 g., 18%), m. p. 142—150°, after a further 20 hr. at 3°.

Recrystallisation of the first crop from water gave 7-*amino*-5-*methylthio*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* as needles, m. p. 200—201° (Found: C, 37·7; H, 4·6; N, 26·7. $C_{10}H_{14}O_4N_6S$ requires C, 38·2; H, 4·5; N, 26·7%).

The second crop on recrystallisation from water gave (?) 7-*amino*-5-*methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* as needles, m. p. 156—158° (Found: C, 38·0; H, 4·8; N, 26·8%).

7-*Amino*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine from its* 5-*Methylthio-derivative.*—The above 5-methylthio-compound of m. p. 200—201° with acetic anhydride–pyridine at room temperature gave 7-*amino*-3-*tri*-O-*acetyl*-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (84%), as prisms (from ethanol), m. p. 152—153° (Found: C, 43·7; H, 4·8. $C_{16}H_{20}O_7N_6S$ requires C, 43·6; H, 4·6%). The triacetyl derivative (0·14 g.) was boiled for 2 hr. in ethanol (10 c.c.) with Raney nickel [11] (*ca.* 1 g.), and the product deacetylated with methanolic ammonia and crystallised from water, to give 7-amino-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (18 mg., 21%), m. p. and mixed m. p. 216—217° (Found: N, 31·3%). The ultraviolet absorption spectrum in acid and alkali was virtually identical with that of authentic material.

Desulphurisation of (?)7-*Amino*-5-*methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine.*—The above procedure yielded an amorphous product, which gave gelatinous solutions in water and showed ultraviolet absorption maxima at 285 mμ (in 0·1N-HCl) and 292 mμ (in 0·1N-NaOH).

7-*Hydroxy*-5-*methylthio*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine.*—A solution of 7-amino-5-methylthio-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (0·5 g.) in N-nitric acid (100 c.c.) was treated with sodium nitrite (1·2 g.). After 20 hr. at room temperature the 7-*hydroxy-compound* (0·43 g., 86%) was collected; it formed leaflets (from water), m. p. 181—183° (with sintering above 178°) (Found: C, 37·5; H, 4·1; N, 22·7. $C_{10}H_{13}O_5N_5S$ requires C, 38·1; H, 4·2; N, 22·2%).

5-*Amino*-7-*hydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Azaguanosine* ").—The above methylthio-compound (0·5 g.) was aminated as described under the preparation of

guanosine. Isolated through the lead salt and crystallised from water (1 c.c.), the 5-amino-7-hydroxy-compound (40 mg., 8%) formed needles, m. p. 250—252° (decomp.) (Found: N, 29·8. Calc. for $C_9H_{12}O_5N_6$: N, 29·6%). After hydrolysis of the compound with boiling N-hydrochloric acid for 2 hr. the ultraviolet spectrum was essentially that of 5-amino-7-hydroxy-*v*-triazolo-[*d*]pyrimidine (max. at 250 mμ in 0·1N-HCl), but the shoulder at 266mμ was obscured. When more concentrated acid was used for the hydrolysis the absorption shifted to longer wavelengths; with 6N-hydrochloric acid for 30 min.[9] the absorption in 0·1N-hydrochloric acid showed a maximum at 270 mμ, with a shoulder at 255 mμ. A similar curve was obtained when 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine and ribose were heated together under the same acid conditions, but not when either component was omitted.

(?)*7-Hydroxy-5-methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*.—A solution of the 7-amino-compound (0·5 g.) and sodium nitrite (1·2 g.) in hot water (12 c.c.) was cooled rapidly and treated with glacial acetic acid (1·2 c.c.). After 24 hr. the *7-hydroxy-compound* (0·28 g., 56%) was isolated through the lead salt; it formed needles (from water), m. p. 214—215° (Found: C, 38·0; H, 4·2; N, 21·9. $C_{10}H_{13}O_5N_5S$ requires C, 38·1; H, 4·2; N, 22·2%).

Diacetyl Derivative of 5-Amino-7-hydroxy-v-*triazolo*[d]*pyrimidine*.—The triazolopyrimidine (15·5 g.) and acetic anhydride (155 c.c.) were boiled together under reflux for 2 hr. Collected after cooling and washed with ethanol, the *diacetyl derivative* (23·2 g.; 96%) formed needles, m. p. 219° (decomp.) (Found: C, 40·6; H, 4·2; N, 35·4. $C_8H_8O_3N_6$ requires C, 40·7; H, 3·4; N, 35·6%).

5-Acetamido-x-*chloromercuri-7-hydroxy*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride*.—Condensation of the chloromercuri-compound (31 g.) with tri-*O*-benzoyl-D-ribofuranosyl chloride (1·15 mol.; from 42 g. of the 1-acetate) gave a pale yellow gum (41·5 g., 90%), which was boiled under reflux for 1 hr. with a solution of sodium methoxide prepared from sodium (2·5 g.) and methanol (400 c.c.). The mixture was evaporated to dryness and a solution of the residue in water (500 c.c.) was made just acidic with acetic acid, heated to boiling, and treated with charcoal. A first crop (7·33 g.) was collected after 18 hr. at room temperature; the filtrate was then evaporated to 200 c.c., then cleared by heat, and a second crop (4·62 g.) collected after 5 hr. A third crop (4·13 g.) was obtained by evaporating the mother-liquors to 50 c.c.

The first crop on recrystallisation gave (?)*5-amino-7-hydroxy*-2-β-D-*ribofuranosyl*-v-*triazolo*-[d]*pyrimidine* (6·28 g.) as needles (from water), sintering at 230—235°, $[\alpha]_D^{20}$ −79° (*c* 0·77 in 0·1N-NaOH) (Found: C, 37·8; H, 4·8; N, 29·1. $C_9H_{12}O_5N_6$ requires C, 38·0; H, 4·3; N, 29·6%).

Recrystallisation of the second crop gave 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo-[*d*]pyrimidine (3·9 g.), m. p. 251—253° (decomp.), undepressed by admixture with the material obtained by the other route, $[\alpha]_D^{21}$ −97° (*c* 1·0 in 0·1N-NaOH) (Found: C, 38·3; H, 4·3; N, 28·9. Calc. for $C_9H_{12}O_5N_6$: C, 38·0; H, 4·3; N, 29·6%).

The third crop contained about 85% of the 3-ribofuranosyl derivative, but further purification of this material by recrystallisation was difficult. On deamination (see below), however, it yielded pure 5 : 7-dihydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (m. p. and mixed m. p.).

5 : 7-*Dihydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" *8-Azaxanthosine* ").—A solution of 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (0·3 g.) and barium nitrite monohydrate (1 g.) in hot water (4 c.c.) was cooled rapidly and treated with glacial acetic acid (1 c.c.). After 5 hr. barium was removed by addition of one equivalent (8·06 c.c.) of N-sulphuric acid. Evaporation of the filtrate below 15° and crystallisation of the residue from 5 : 2 ethanol–water (4 c.c.) gave the *dihydroxy-compound* (0·14 g., 47%) as needles, m. p. 198—199° (decomp.) after recrystallisation, $[\alpha]_D^{24}$ −103° (*c* 1·02 in 0·1N-NaOH) (Found: C, 37·4; H, 3·9; N, 24·5. $C_9H_{11}O_6N_5$ requires C, 37·9; H, 3·9; N, 24·6%).

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