Pyrazolopyrimidine Nucleosides. Part III.[1] Synthesis of 1- and 2-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidines from Pyrazole Nucleoside Derivatives

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The trimethylsilyl derivative (6) of 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide (4) was condensed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (7) to give a mixture of nucleosides that were subsequently established as isomers rather than anomers. Removal of the blocking groups from one of the isomers furnished 5-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (12) which was catalytically hydrogenated to afford the pyrazole analogue, 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (13), of AICA riboside. Ring closure of (13) with formic acid-acetic anhydride followed by treatment with base furnished a mixture of nucleosides which were separated and characterized as 1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (16; allopurinol riboside) and 6-methyl-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (17). The other isomer (8) furnished 3-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (11) which was converted by a similar series of reactions into 2-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (15).

THE isolation and structural elucidation of tubercidin (1), toyocamycin (2), and sangivamycin (3) as pyrrolopyrimidine nucleosides was followed by their total synthesis,[2] which stimulated considerable research in this area.[3] These pyrrolopyrimidine nucleosides have been subsequently reported [4] to possess significant biological and chemotherapeutic activity, which has prompted investigations involving the synthesis of closely related nucleosides, *e.g.*, pyrazolo[3,4-*d*]pyrimidine nucleosides which can be viewed as '6-aza' derivatives of the pyrrolo[2,3-*d*]pyrimidine nucleosides.

(1) R = H
(2) R = CN
(3) R = $CONH_2$

4-Aminopyrazolo[3,4-*d*]pyrimidine ribosides (N-1 and N-2) have been synthesized by the chloromercuric procedure [5] and the acid-catalysed fusion procedure.[6] The silylation procedure using 4-chloropyrazolo[3,4-*d*]-pyrimidine as the initial starting material has recently furnished 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidine [7] with the anomeric configuration being unequivocally established for the first time.

All these investigations used preformed pyrazolo[3,4-*d*]pyrimidines in the condensation. We envisaged a new and versatile route for the preparation of pyrazolo-[3,4-*d*]pyrimidine nucleosides *via* ring closure of certain pyrazole nucleosides. In fact, the synthesis of AICA riboside from 5-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)imidazole-4-carboxamide [8] prompted us to investigate this route for the synthesis of the corresponding pyrazole nucleosides for use as precursors in the synthesis of pyrazolo[3,4-*d*]pyrimidine nucleosides.

Treatment of 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide [9] (4) with hexamethyldisilazane and a catalytic amount of ammonium sulphate resulted in the formation of a crystalline bistrimethylsilyl derivative (6). This silylated heterocycle was condensed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (7) in dry acetonitrile to give a mixture (two major components) of nucleosides in a 47% overall yield (ratio *ca.* 13 : 1). Although it was possible to separate these acetylated nucleosides by column chromatography, it was found to be more convenient to remove the blocking groups from the mixture of nucleosides with sodium methoxide in anhydrous methanol from which the predominant isomer was isolated by fractional crystallization. The structure of this isomer was subsequently established (see later) as 3-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (11) (44%).

The mother liquors were reacetylated and column chromatography provided a clean separation of residual (11) [as the acetylated derivative (8)] from the other nucleoside. The acetylated derivative of the other nucleoside was subsequently established (see later) to be 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide (9) (3·4%). A comparison of the u.v. spectra (Table 1) obtained for (8) and (9) established that the mixture of nucleosides was definitely ($\Delta\lambda$ 13—15 nm) isomeric rather than anomeric. These nucleosides are of considerable interest since it has been reported that 3-(3,3-dimethyl-1-triazeno)-pyrazole-4-carboxamide (4) has exhibited activity [9] against leukemia L-1210 and these are the first *N*-substituted derivatives of (4). The synthesis of ring-

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[3] R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocyclic Chem.*, 1971, **8**, 703 and references therein.
[4] K. H. Schram, B. C. Hinshaw, O. Leonoudakis, and L. B. Townsend, 162nd A.C.S. Meeting, Washington, D.C., Sept. 1971, MEDI 15; L. B. Townsend, B. C. Hinshaw, R. L. Tolman, R. K. Robins, and J. F. Gerster, 156th A.C.S. Meeting, Atlantic City, New Jersey, Sept. 1968, MEDI 29; R. J. Suhadolnik in 'Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970, pp. 298—353.
[5] J. Davoll and J. A. Kerridge, *J. Chem. Soc.*, 1961, 2589.
[6] J. A. Montgomery, S. J. Clayton, and W. E. Fitzgibbon, jun., *J. Heterocyclic Chem.*, 1964, **1**, 215.
[7] G. R. Revankar and L. B. Townsend, *J. Chem. Soc.* (*C*), 1971, 2440.
[8] R. P. Panzica and L. B. Townsend, *J. Org. Chem.*, 1971, **36**, 1594.
[9] (*a*) C. W. Noell and C. C. Cheng, *J. Medicin. Chem.*, 1969, **12**, 545; (*b*) C. C. Cheng, *J. Heterocyclic Chem.*, 1968, **5**, 195.

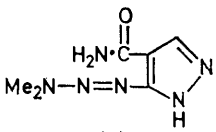
N-substituted derivatives (5) of (4) has not been reported owing to a ready ring closure [9b] of the intermediate diazo-derivative which affords a bicyclic heterocycle and this has also been observed [10] with the corresponding imidazoles.

TABLE 1

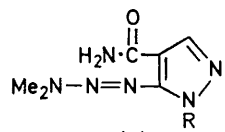
U.v. spectral data [λ/nm (10^{-3} ε)] for certain pyrazole and pyrazolo[3,4-*d*]pyrimidine nucleosides [a]

Compd.	$\lambda^{pH\,1}_{max.}$	$\lambda^{pH\,1}_{min.}$	$\lambda^{MeOH}_{max.}$	$\lambda^{MeOH}_{min.}$	$\lambda^{pH\,11}_{max.}$	$\lambda^{pH\,11}_{min.}$
(9)	320·3 (10·8)	255·5 (6·76)	323·0 (9·85)	251·2 (4·27)	319·5 (9·85)	258·0 (6·54)
(12)	229·4 (17·8) 318·2) (13·0)	255·5 (7·34)	228·5 (14·9) 323·0 (13·0)	252·5 (5·26)	318·2 (12·3)	255·2 (7·34)
(11)	308 (14·3)	252 (8·18)	308 (13·0)	251·8 (7·30)	308 (14·1) 235·5 (12·6)	253·0 (8·38)
(13)	253 (8·26) 230 (8·55)	241 (7·50)	253 (8·00) 236 (7·88)	241 (7·50)	252·8 (9·05) 236·2 (9·31)	
(10)	260 (4·00)	244·5 (3·31)	266·0 (6·46)	240 (3·36)	259 (6·46)	237 (4·29)
(16)	250·5	233	251	232·5	271 255·5	233
(15)	261 (10·2)	235·5 (5·36)	261 (10·0)	237 (5·10)	283·5 (10·7)	237·5 (5·64)

[a] Spectra determined on Beckman DK-2 spectrophotometer.



(4)



(5)

The structure of the major product was established as (11) on the basis of the following data. Catalytic hydrogenation of the dimethyltriazeno-group with Raney nickel provided a nucleoside which was tentatively assigned the structure 3-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (10). It was of considerable interest that the dimethyltriazeno-group of (8) was not reduced under the same conditions which would indicate that there is considerable crowding about this triazeno-group as compared to the triazeno-group of (11).

Treatment of (10) with an excess of diethoxymethyl acetate was followed by hydrolysis with hot water. Prior to treatment with water, the reaction mixture consisted of five components (t.l.c.). After hydrolysis of the reaction mixture there was observed the formation of one new compound which was subsequently isolated as a white crystalline solid, m.p. 186—188° (decomp.). This material was identified as 2-(β-D-ribofuranosyl)-pyrazolo[3,4-*d*]pyrimidin-4-one (15) on the basis of the following data. There were only two sites available for *N*-ribosylation in the initial condensation reaction of (6) and (7) and, precluding glycosyl migration, it was obvious that (15) must be either the 1- or 2-ribosyl derivative of allopurinol (pyrazolo[3,4-*d*]pyrimidin-4-one). It was established that (15) was the 2-isomer rather than the 1-isomer by comparison of the u.v. spectral data for (15) ($\lambda^{pH\,1}_{max.}$ 261, $\lambda^{MeOH}_{max.}$ 261, $\lambda^{pH\,11}_{max.}$ 283·5 nm) with the u.v. spectral data reported [10] ($\lambda^{pH\,3}_{max.}$ 251, and $\lambda^{pH\,12}_{max.}$ 271 nm) for the 1-isomer (1-ribosylallopurinol *).

The assignment of the β-configuration to (15) was tentatively made on the basis of polarimetric and ^{1}H n.m.r. spectroscopic evidence. The specific rotations observed for (15) {$[\alpha]_D$ −83·6° (H_2O); −111·9°, (DMF)} were similar to those reported [6,7] for the 1-β-D- and 2-β-D-ribofuranosides of 4-aminopyrazolo[4,3-*d*]pyrimidine {$[\alpha]_D$ −81·7 and −98·3° (DMF), respectively}. The ^{1}H n.m.r. spectrum of (15) in [$^2H_6$]DMSO displayed a narrow doublet (2·5 Hz) at δ 5·98 which was assigned to the anomeric proton. The small value of this coupling constant strongly supported the tentative assignment of the β-configuration for (15); however, it has been established [12] that the assignment of a *trans* relationship between vicinal hydrogens in a five-membered ring can not be unequivocal unless the coupling constant is 1 Hz or less. Treatment of (15) with dry acetone containing 2,2-dimethoxypropane and a catalytic amount of perchloric acid provided 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (14). A ^{1}H n.m.r. spectrum of (14) in [$^2H_6$]DMSO revealed a coupling constant for H-1′ of 1 Hz which established the β-configuration for (14). Therefore, this established unequivocally the site of ribosylation and the anomeric configuration (β) for (14), (8), (10), (11), and (15).

The minor product isolated from the initial condensation was assumed to be the other *N*-riboside (9) on the basis of the difference in u.v. spectral data between the minor product and the major product of established structure (8) (see later). The anomeric configuration of the minor product was established as β on the basis of a ^{1}H n.m.r. spectrum in $CDCl_3$ (Table 2) which revealed a broad singlet for the peak assigned to the anomeric proton. Therefore, this established the structure of the minor product as 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide (9). Treatment of (9) with sodium methoxide removed the acetyl groups and the resulting product was catalytically hydrogenated with Raney nickel to provide the pyrazole analogue, 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide [13] (13), of AICA riboside.[14] The structural

* The 1-ribosyl derivative of allupurinol has been isolated [11] from the urine of patients using allopurinol for relief from gout.

[10] Treatment of AICA riboside with acetic anhydride has furnished 2-methylinosine *via* an *N*-acetylated intermediate; R. P. Panzica and L. B. Townsend, *J. Heterocyclic Chem.*, 1972, **9**, 623.

[11] T. A. Krenitsky, G. B. Elion, R. A. Strelitz, and G. H. Hitchings, *J. Biol. Chem.*, 1967, **212**, 2675.

[12] R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, 1963, **32**, 155.

[13] This represents a new route for the synthesis of (13) since treatment of (16) with base at elevated temperatures has been previously reported to furnish (13); K. Nakayama and H. Tanaka, Ger.P. 1,939,030/1970.

[14] The 5′-phosphate derivative (AICAR) of AICA riboside has been shown to be an intermediate in the *de novo* pathway of purine biosynthesis; L. B. Townsend in, ' Imidazole Nucleosides and Nucleotides,' *Chem. Rev.*, 1967, **67**, 548 and references therein.

assignment of (13), (12), and (9) was corroborated by the successful conversion of (13) into 1-(β-D-ribofuranosyl)-pyrazolo[3,4-*d*]pyrimidin-4-one (16) (allopurinol riboside) of established structure.[11] This was accomplished by treatment of (13) with formic acid–acetic anhydride, followed by ethanolic sodium hydroxide, to furnish a nucleoside that was chromatographically indistinguishable from an authentic sample [11] of (16). A mass spectrum of (16) showed peaks at *m/e* 268 and 269 which corresponds to the M^+ and $(M + 1)^+$ peaks which would be expected for a riboside of allopurinol (*M*, 268·14). The peak of highest intensity was located at *m/e* 136 which corresponds to the $(B + 1)^+$ fragment $(C_5H_4N_4O)^+$. This was expected to be the major fragment due to a ready cleavage of the glycosidic bond.

Another nucleoside was obtained from the ring closure reaction and assigned the structure 6-methyl-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (17) on the basis of the following data. A u.v. spectrum (see Experimental section) of (17) was nearly identical to that of (16). However, a mass spectrum of (17) was considerably different from that observed for (16). The M^+ and $(M + 1)^+$ peaks (282 and 283, respectively) revealed a difference of 14 mass units between (16) and (17) which suggested the addition of a methyl group. The origin of an additional methyl group could be expected if *N*-acetylation [10] instead of *N*-formylation of the amino-group of (13) had occurred during the ring closure reaction. Ring closure of this intermediate on treatment with base would furnish (17) (*M* 282·16). Indeed, the peak of highest intensity in the mass spectrum of (17) was at 150 ($C_6H_6N_4O^+$; 6-methylallo-

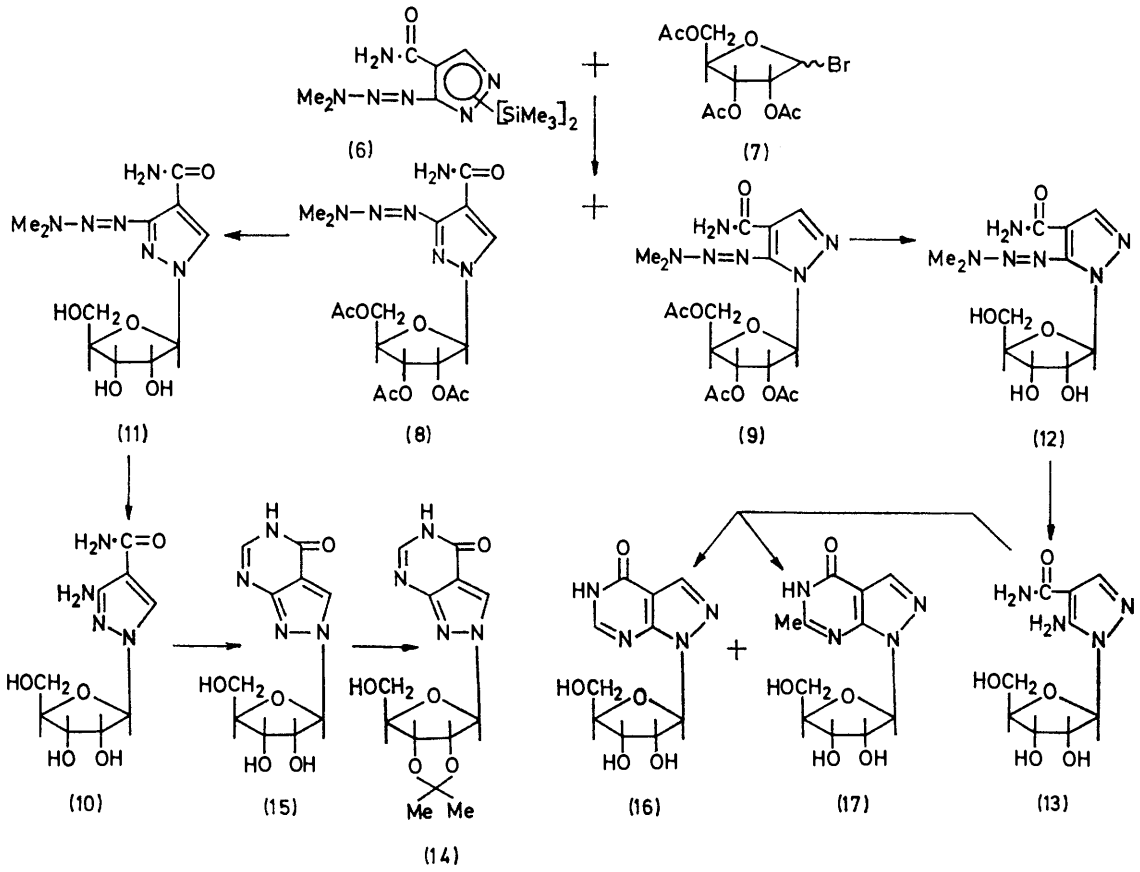


TABLE 2

Physical constants for specific pairs of isomeric pyrazole nucleosides

Compound	M.p. (°C)	$[\alpha]_D^{26}$ (°)	^{1}H N.m.r. parameters [δ(*J*/Hz)] H-1′ ($J_{1,2}$)	H-3	NMe_2	
(9)	166—167	7·8 (*c* 1·0, EtOH)	6·30 (1) [a]	7·91	3·22	3·53
(8)	Syrup		5·83 (3·0) [a]	8·13	3·19	3·58
(12)	220—221	−124 (*c* 0·97, H_2O)	6·05 (3·0) [b]	7·89	3·29	3·60
(11)	217—219 (decomp.)	−33·8 (*c* 1·0, H_2O)	5·68 (4·0) [b]	8·42	3·27	3·60
(13)	226—235 (decomp.)	11·6 (*c* 0·52, H_2O)	5·96 (6) [b]	7·79		
(10)	150—152	−59·9 (*c* 1·0, H_2O)	5·47 (4) [b]	8·20		

[a] $CDCl_3$. [b] [$^2H_6$]DMSO.

purinol fragment) which was assigned as the $(B + 1)^+$ peak obtained by scission of the glycosidic bond of (17).

We have observed what appears to be a general and ready method for assigning the actual site of ribosylation to the pairs of isomers prepared in this investigation by means of ^1H n.m.r. spectroscopy. For each pair of isomers (8) and (9); (11) and (12); (10) and (13) the signal in the n.m.r. spectrum for the pyrazole ring hydrogen of the isomer with the ribofuranosyl group residing on the adjacent ring nitrogen atom appeared downfield (*ca.* 0·48 units) from the signal observed for the pyrazole ring hydrogen of the other isomer. This appears to be general for the glycosides of five-membered nitrogen heterocycles. This same trend has been noted [15] for the glycosides of *v*-triazoles where the isomer with the sugar group attached to the nitrogen atom directly adjacent to the heterocyclic ring hydrogen atom exhibited the furthest downfield signal for the ring hydrogen.

EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover capillary apparatus. ^1H N.m.r. spectra were obtained on Varian A-60 and XL-100-12 spectrometers using $[^2H_6]$dimethyl sulphoxide as solvent and sodium 4,4-dimethyl-4-silapentane-1-sulphonate as an internal standard unless otherwise noted. I.r. spectra were determined in pressed KBr discs with a Beckman IR-8 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer model 141 automatic digital readout polarimeter. Silica gel suitable for chromatographic use was purchased from J. T. Baker Co., and elemental analyses were performed by Heterocyclic Chemical Corp. Unless otherwise noted concentrations were carried out *in vacuo* at 40°.

3-(3,3-*Dimethyl*-1-*triazeno*)-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (11).—A mixture of hexamethyldisilazane (HMDS) (12 ml), dry 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide [9a] (4) (6·22 g, 34·2 mmol), and dry $(NH_4)_2SO_4$ (50 mg) was heated at 140° for 18 h. A clear solution was obtained after *ca.* 20 min and this was followed almost immediately by the separation of a colourless solid. The excess of HMDS was removed by distillation and the crystalline residue was dried *in vacuo* (0·5 mmHg) for 1 h to furnish a bistrimethylsilyl derivative (6) (^1H n.m.r.) of (4). A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (7) [prepared [16] from 11·4 g (36 mmol) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose] in dry CH_3CN (50 ml) was added in one portion to the bistrimethylsilyl derivative (6) and the solution (achieved in *ca.* 10 min) was stirred at room temperature for 20 h under anhydrous conditions and with protection from light. The starting material (6) was no longer detected after 20 h by t.l.c. (SilicAR 7 GF; $CHCl_3$–MeOH, 18 : 1, v/v) but there were observed two new u.v.-absorbing compounds with R_F values of *ca.* 0·6 and 0·5 in a ratio of *ca.* 10 : 1. The reaction mixture was added dropwise (15 min) to a stirred mixture of $NaHCO_3$ (5 g), H_2O (10 ml), and MeOH (15 ml). The resulting mixture was stirred an additional 15 min and then concentrated *in vacuo* to *ca.* 10 ml. Water (30 ml) was then added, the mixture was extracted with CH_2Cl_2 (4 × 50 ml), and the extracts were combined and washed in succession with a saturated $NaHCO_3$ solution (2 × 50 ml), H_2O (4 × 50 ml), and then a saturated NaCl solution (2 × 30 ml). The solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to a light yellow syrup (15·8 g). The syrup was dissolved in dry MeOH (250 ml), sodium methoxide (300 mg) was added, and after 1·5 h the solution was neutralized by the addition of Dowex 50-X-12 (H^+ form, prewashed with dry MeOH). The resin was removed by filtration and the filtrate was concentrated to 150 ml. The solution was left at room temperature for 18 h and the solid that had separated was collected by filtration to yield 4·15 g (35·4%) of 3-(3,3-*dimethyl*-1-*triazeno*)-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (11), m.p. 215—218° (decomp.). Concentration of the mother liquors to 40 ml yielded a second crop of (11) (996 mg, 8·55%), m.p. 214—217° (decomp. with prior softening at 112°). The mother liquors were saved and used in the following experiment. A pure sample had m.p. 217—219° (decomp.) (from MeOH) (Found: C, 42·2; H, 5·8; N, 26·8. $C_{11}H_{18}N_6O_5$ requires C, 42·1; H, 5·8; N, 26·75%).

5-(3,3-*Dimethyl*-1-*triazeno*)-1-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (9) *and* 3-(3,3-*Dimethyl*-1-*triazeno*)-1-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (8).—The filtrate from the preceding experiment was concentrated *in vacuo* to a syrup, dissolved in dry pyridine (40 ml), and again concentrated to a syrup. Pyridine (50 ml), acetic anhydride (25 ml), and anhydrous NaOAc (500 mg) were added to the syrup and the mixture was heated on a steam-bath for 18 h (without the addition of NaOAc the acetylation was incomplete in this time). The solution was then concentrated *in vacuo* to a syrup. The syrup was dissolved in dry MeOH (50 ml) to decompose traces of acetic anhydride. After 1 h, the MeOH solution was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (100 ml) followed by washing in succession with dilute (1%) HCl solution (2 × 25 ml), saturated $NaHCO_3$ solution (20 ml), and then H_2O (2 × 20 ml). The solution was dried (Na_2SO_4), concentrated to a syrup, and then dissolved in $CHCl_3$ (4 ml). The $CHCl_3$ solution was applied to the top of a dry packed column [17] (2 × 70 cm) of silica gel and eluted with $CHCl_3$ (400 ml) and then a 49 : 1 (v/v) mixture of $CHCl_3$–MeOH (10 ml fractions). Fractions 31—42 contained the faster moving isomer (major product in mixture) and fractions 44—65 contained the slower moving isomer. Fractions 31—42 were combined and concentrated to a syrup (1·43 g) with a u.v. spectrum identical with that of the deblocked nucleoside (11). A ^1H n.m.r. spectrum of this material indicated that it was 3-(3,3-dimethyl-1-triazeno)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxamide (8), δ ($CDCl_3$) 5·83 (1H, d, $J_{1,2}$ 3-Hz, H-1′), 8·13 (1H, s, H-5), 3·58br (3H, s, NMe), and 3·19br (3H, s, NMe). Fractions 44—65 were combined and concentrated to give 1·35 g of a syrup. The syrup was dissolved in EtOH (4 ml) and left at 5° for 24 h to yield 530 mg of 5-(3,3-*dimethyl*-1-*triazeno*)-1-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (9) as colourless, needle-like crystals, m.p. 162·5—166·5°. An analytical sample had m.p. 166—167° (from EtOH) (Found: C, 46·6; H, 5·4; N, 19·1. $C_{17}H_{24}N_6O_8$ requires C, 46·35; H, 5·5; N, 19·1%).

3-*Amino*-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (10).—Raney nickel (2 g wet weight) was added to a solution of

[15] G. Alonso, M. T. Garcia-Lopez, G. Garcia-Muñoz, and M. Rico, *J. Heterocyclic Chem.*, 1970, **7**, 1269.

[16] H. Zimmer, A. Koine, and H. Nimz, *Chem. Ber.*, 1960, **93**, 2705.

[17] B. Loev and M. M. Goodman, *Chem. and Ind.*, 1967, 2026.

3-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (11) (5 g, 15·4 mmol) in H_2O (150 ml) to which had been added 2 ml of NH_4OH solution (*d* 0·88). The mixture was hydrogenated at 40 lb in^{-2} for 18 h using a Parr hydrogenator (shaker). The mixture was then flushed with nitrogen and filtered through a layer (1·5 cm) of dry packed Celite. The filter cake was washed with hot H_2O (3 × 15 ml) and the filtrate concentrated *in vacuo*. The residue was dissolved in hot MeOH (20 ml) and a solid separated from the solution (3·13 g, 78·3%), m.p. 148—150°. The addition of EtOH (40 ml) to the mother liquors followed by concentration of the solution to 10 ml on the steam-bath resulted in the deposition of an additional amount (0·69 g) of (10) m.p. 142—147°. An analytical sample had m.p. 148·5—150° (from MeOH) (Found: C, 42·2; H, 5·65; N, 21·85. $C_9H_{14}N_4O_5$ requires C, 41·85; H, 5·46; N, 21·7%).

2-(β-D-*Ribofuranosyl*)*pyrazolo*[3,4-d]*pyrimidine*-4-*one* (15). —Dry 3-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (10) (2 g, 7·75 mmol) was added to diethoxymethyl acetate (15 ml) and the mixture was heated at reflux for 18 h. The clear solution then showed five major spots on t.l.c. (SilicAR 7 GF; C_6H_6–MeOH, 9 : 1, v/v). Water (15 ml) was then added and the mixture was warmed gently on the steam-bath (*ca.* 55°) for 48 h (one major spot, R_F 0·5; SilicAR 7 GF; $CHCl_3$–MeOH, 7 : 3, v/v). The solution was concentrated *in vacuo* and the residue dissolved in H_2O (10 ml) which was followed by another evaporation *in vacuo* to give a syrup. The syrup was dissolved in hot H_2O (4 ml) and EtOH (15 ml) was added. A solid (1·45 g; m.p. 177—185°) precipitated from solution after 12 h at 5°. A second crop of (15) (350 mg; m.p. 185—187°) was obtained after concentration of the mother liquors to *ca.* 8 ml. The crystals were combined and recrystallized from EtOH–H_2O (4 : 1) to yield 1·3 g of (15) as a white solid, m.p. 185—187°, δ 8·96 (1H, s, H-3), 8·11 (1H, s, H-6), and 5·98 (1H, d, $J_{1,2}$ 3-Hz, H-1′) (Found: C, 44·25; H, 4·7; N, 21·05. $C_{10}H_{12}N_4O_5$ requires C. 44·75; H, 4·45; N, 20·9%).

2-(2,3-O-*Isopropylidene*-β-D-*ribofuranosyl*)*pyrazolo*[3,4-d]-*pyrimidin*-4-*one* (14).—A solution of (15) (440 mg) in dry acetone (100 ml), containing 5 ml of 2,2-dimethoxypropane and 8 drops of 70% perchloric acid, was kept at room temperature for 45 min and then 20 ml of methanolic ammonia solution (saturated at −5°) was added in one portion. The solution was concentrated to a syrup which was dissolved in $CHCl_3$ (50 ml) and then washed in succession with H_2O (2 × 15 ml), saturated $NaHCO_3$ solution (15 ml), and H_2O (15 ml). After drying over anhydrous Na_2SO_4 the solution was concentrated *in vacuo* to yield a syrup. Trituration with EtOH (5 ml) gave a powder (250 mg) that was recrystallized from Pr^iOH, m.p. 180—182°, δ 8·8 (1H, s, H-3), 8·04 (1H, s, H-6), 6·25 (1H, s, H-1′), 1·50 (3H, s, Me) and 1·33 (3H, s, Me) (Found: N, 18·7. $C_{13}H_{16}N_4O_5$ requires 18·15%).

5-(3,3-*Dimethyl*-1-*triazeno*)-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (12).—Sodium methoxide (50 mg) was added to dry MeOH (40 ml) containing (1·17 g, 2·76 mmol) of (9) and the solution was left at room temperature. After 1 h, the product started to crystallize out as fine, white crystals. The mixture was kept at 5° for an additional 18 h and the solid was collected by filtration and washed with cold MeOH (10 ml). The solid was air-dried to afford 720 mg (80·5%) of (12); m.p. 224—226° (decomp.) with preliminary softening at 216°. A second crop of crystals (100 mg) was obtained by evaporating the mother liquors to dryness, dissolving the residue in hot EtOH (3 ml), and leaving the solution at room temperature for 18 h. The crystals were combined and dissolved in hot H_2O (5 ml), Pr^i OH (30 ml) was added, and the solution was stirred and cooled to 0° which resulted in the formation of small, white crystals. The solid was collected by filtration and then dried at 120° for 16 h to yield 699 mg of (12), m.p. 220—221° (decomp.) with preliminary shrinking at 215° (Found: C, 42·2; H, 5·65; N, 27·0. $C_{11}H_{18}N_6O_5$ requires C, 42·1; H, 5·8; N, 26·75%).

5-*Amino*-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (13). —A solution of (12) (510 mg) in H_2O (30 ml), containing 8 drops of conc. NH_4OH was hydrogenated over Raney nickel (0·5 g wet weight) at 40 lb in^{-2} for 10 h. The isolation procedure was the same as that used in the preparation of (10). The product was recrystallised from H_2O (3 ml) to give 130 mg (32%) of crystals, m.p. 226—235° (slow decomp.) (Found: C, 41·95; H, 5·45; N, 21·95. $C_9H_{14}N_4O_5$ requires C, 41·85; H, 5·46; N, 21·7%).

Ring Closure of 5-*Amino*-1-(β-D-*ribofuranosyl*)*pyrazole*-4-*carboxamide* (13).—A solution of (13) (14·9 mg, 0·058 mmol) in 99% formic acid (1 ml) and acetic anhydride (5 ml) was heated at reflux for 5 h. Volatile components were removed *in vacuo* (60°) and the residue was dissolved in absolute EtOH (1 ml) containing 2N aqueous NaOH solution (0·07 ml). This solution was kept in a stoppered flask for 3 days and the mixture was again taken to dryness *in vacuo*. Glacial acetic acid (0·5 ml) was added and then the excess of acid was removed *in vacuo*. T.l.c. (SilicaR 7 GF; $CHCl_3$–MeOH, 7 : 3, v/v) indicated the presence of a large amount of starting material (R_F 0·25) as well as two new u.v.-absorbing compounds with R_F values of 0·5 and 0·55. The residue from evaporation of AcOH was applied to a preparative t.l.c. plate (0·5 mm thick, 20 × 40 cm) of SilicaR 7 GF and developed (40 cm) with $CHCl_3$–MeOH (7 : 3 v/v). The slower-moving band was removed and extracted with MeOH to yield material with chromatographic and u.v. properties identical with those of (13). The nucleoside material present in the intermediate band was isolated in the same manner and yielded a very small amount of gum. This gum was dissolved in absolute MeOH (1 ml) and the solution was kept at room temperature for 12 h. The white crystals which had formed were collected by filtration and washed with MeOH (1 ml) to afford *ca.* 2 mg of product, m.p. 270·5—271°, $\lambda_{max.}^{pH\ 1}$

TABLE 3

R_{ad} Values of certain pyrazole and pyrazolo[3,4-*d*]-pyrimidine nucleosides [a-c]

Compound	Chromatographic solvent systems [d] A	B	C
(12)	1·19	1·32	0·90
(11)	1·15	1·06	1·17
(13)	0·98	1·00	1·04
(10)	0·91	0·67	0·94
(16)	1·13	1·22	0·92
(15)	0·96	0·72	0·78

All compounds were run on Whatman No. 1 chromatographic paper and the ascending technique was used. [b] Short-wave u.v. light (254 nm) was used to detect the spots. [c] $R_{ad} = R_F$ of compound/R_F of adenosine. [d] Chromatographic solvent systems: A, propan-1-ol–water (7 : 3, v/v); B, propan-1-ol–ethyl acetate–water (4 : 1 : 2, v/v) upper phase; C, propan-1-ol–ammonium hydroxide (*d* 0·88)–water (6 : 3 : 1, v/v)

250·5, $\lambda_{min.}^{pH\ 1}$ 233, $\lambda_{max.}^{MeOH}$ 251, $\lambda_{min.}^{MeOH}$ 232·5, $\lambda_{max.}^{pH\ 11}$ 271 (shoulder at 255), and $\lambda_{min.}^{pH\ 11}$ 233 nm. The R_F values observed for this material were identical (Table 3) with those found for allopurinol-1-riboside prepared by a separate procedure.[11] The mass spectrum of this material showed the expected pattern for a riboside of allopurinol; *m/e* 268 (M^+), 269 $(M + 1)^+$ and a very large peak at *m/e* 136 corresponding to $C_5H_4N_4O^+[(B + 1)^+]$.

The faster-moving band (R_F 0·55) was treated as above and yielded *ca.* 2 mg of gum which was triturated with dry ether to yield an amorphous powder, $\lambda_{max.}^{pH\ 1}$ 249, $\lambda_{min.}^{pH\ 1}$ 232·5, $\lambda_{max.}^{MeOH}$ 249, $\lambda_{min.}^{MeOH}$ 233, $\lambda_{max.}^{pH\ 11}$ 267·5, (shoulder at 256), and $\lambda_{min.}^{pH\ 11}$ 233 nm. The peaks of highest mass in the mass spectrum were at *m/e* 282 and 283 with the peak of highest intensity being observed at *m/e* 150 $[(B + 1)^+]$. These peaks correspond to those expected for the M^+, $(M + 1)^+$, and $C_6H_6N_4O^+[(B + 1)^+]$ fragments of a riboside of 6-methylpyrazolo[3,4-*d*]pyrimidin-4-one.

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