Table 2. Preparation of β-keto and enamine phosphonates.

Run	R'X	Method[b]	Reaction Products	Yield (%)[a]
14	$CH_2=CHCH_2Br$	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_2CH=CH_2$	62
15	CH_3I	A	$(EtO)_2P(O)CH(C(=O)Ph)CH_3$	86
16	CH_3I	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_3$	82
17	$PhCH_2Br$	A	$(EtO)_2P(O)CH(C(=O)Ph)CH_2Ph$	62
18	$PhCH_2Br$	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_2Ph$	67

[a]Isolated yield. [b]Method A: hydrolysis, Method B: H_2O work up.

red solution of diethyl alkanephosphonate (1 mmol) in dry THF (5 m*l*) was added n-butyllithium (1.1 mmol, 1.6 M in hexane) at -78 °C under nitrogen atmoshere. After being stirred for 1 hr at -78 °C, nitrile (1.1 mmol) was added and the reaction mixture was warmed to rt and stirred for an additional 2 hr. Hydrolysis was accomplished by addition of 5 N sulfuric acid (1 m*l*) for 2 hr at rt. Normal work up gave the β-keto phosphonate, which was purified by short-path column chromatography on silica gel (8/2: ethylacetate/ether).

Tandem addition-alkylation is as follows: After the similar treatment of nitrile (1.1 mmol) at -78 °C, the mixture was warmed slowly to -20 °C for 3 hr. Alkyl halide (1.1 mmol) was added dropwise, the mixture was warmed up to rt. usual H_2O work up gave the crude enamine phosphonate and hydrolysis described above gave the β-keto phosphonate.

All the products were characterized by their infrared, ^{1}H-nmr, ^{31}p-nmr spectra as well as GC-Mass.[6] The infrared spectra of β-keto phosphonates indicate that the products probably exist to some extent in the enol form. In summary, we have discovered a convenient procedure for the preparation of β-keto phosphonate and enamine phosphonates. This method is complementary to the existing procedures (especially fully substituted β-keto phosphonates) and sometimes could be the method of choice because of its simplicity and high yield.

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6. Spectral data for compound (Run 1): ^{1}H nmr ($CDCl_3$) 8.18(m, 2H), 7.60(m, 3H), 4.21(m, 4H), 3.65(d, J = 22Hz, 2H), 1.40(t, 6H); ^{31}P nmr($CDCl_3$) +22.8; IR(neat) 1690(C = O), 1270, and 1030 cm^{-1}; Mass (70 eV), *m/z* (%) 256(M^+, 2), 77(40), 105(100), spectral data for compound (Run 18): ^{1}H nmr($CDCl_3$) 7.18-7.20(m, 10H), 5.80(s, 2H, NH_2), 4.00(m, 4H), 3.40(d, =J18Hz, 2H), 1.22(t, 6H); IR(neat) 3200-3500(NH_2), 1620, 1400, 1210 and 1030 cm^{-1}; Mass (70 eV), *m/z* (%) 345(M^+, 1), 77(85), 91(67), 208(100).

Synthesis of some novel 3-substituted pyridazin-6-ones and Pyridazine Nucleosides

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The synthetic method and reactivity of pyridazine were investigated during few decades.[1-3] However, pyridazine derivatives have not been studied extensively compared with other diazines because they do not occur as natural products. Recently, some pyridazines were found to possess biological activity.[1] Townsend and his coworkers[4] have designed and synthesized some polysubstituted pyridazine nucieosides by the exchange or interchange of carbon and nitrogen atoms on the heterocyclic base portion of the nucleosides such as uridine, 6-azauridine and 3-deazauridine.

In the course of our studies on some biologically active pyridazine nucleosides, we have attempted the synthesis of

some novel pyridazin-6-ones and pyridazine nucleosides. In the present paper, we report the reaction of 3,6-dichloropyridazine (2) with hydrazine and malononitrile and also the synthesis of some novel pyridazin-6-ones (4, 8) and pyridazine nucleosides.

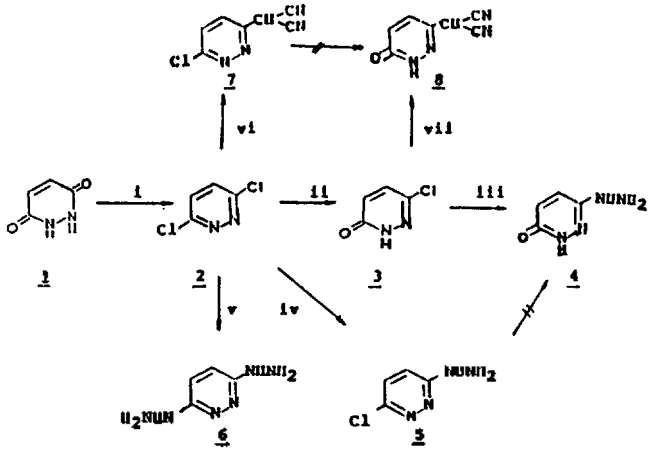
Compound 2 was prepared by known method[5] from 3,6-pyridazindione (1).

Compound 2 was treated with the mixture of acetic acid and water according to Kuraishi method[6] to afford 3-chloropyridazin-6-one (3) in 40% yield, whereas reaction of compound 2 with aqueous sodium hydroxide solution (4%) at reflux gave compound 3 in 84% yield.

The reaction of compound 2 with one and two equivalent of hydrazine hydrate in ethanol gave respectively compound 5 in 41% yield and compound 6 in 70% yield. Few synthetic methods of compound 5 have been reported.[7]

In order to synthesize compound 4 from compound 5, treatment of compound 5 with aqueous sodium hydroxide solution (4%) or methanolic hydrochloric acid solution (10%) at reflux did not produce compound 4. Therefore, we slected other route to synthesize compound 4 from compound 3. Reaction of 3 with hydrazine (99%) at reflux gave compound 4 in 60% yield.

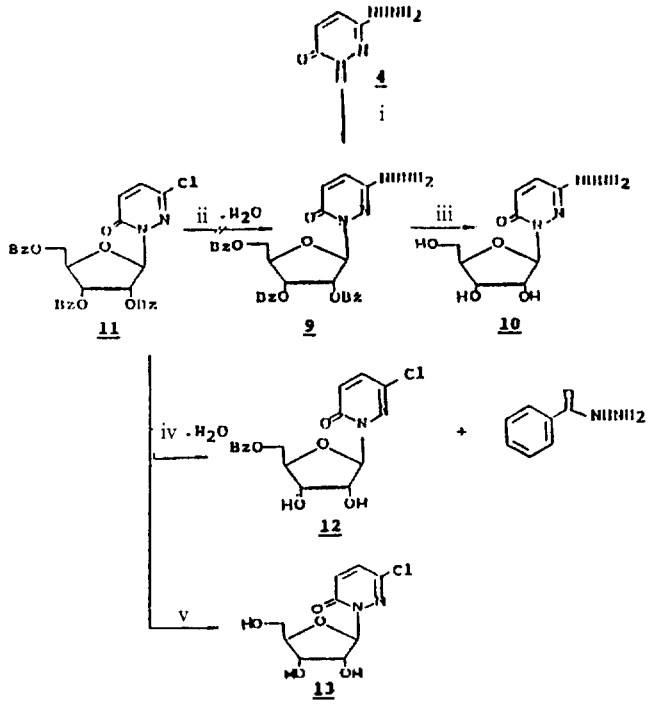
On the other hand, we attempted to synthesize compound 8 *via* 7 from compound 2. Treatment of compound 2 with malononitrile and sodium hydride in tetrahydrofuran afforded compound 7 in 82% yield. Reaction of compound 7 with aqueous sodium hydroxide solution (4%) or methanolic hyrochloride acid solution (10%) did not yield compound 8. Therefore, we have synthesized compound 8 by treatment of compound 3 with malononitrile and sodium hydride in THF in 60% yield.



(i) $POCl_3$. (ii) 4% NaOH solution. (iii) hydrazine. (iv) 1eq. hydrazine hydrate, ethanol. (v) 2eq. hydrazine hydrate, ethanol. (vi) $CH_2(CN)_2$, NaH, THF. (vii) $CH_2(CN)_2$, NaH, THF.

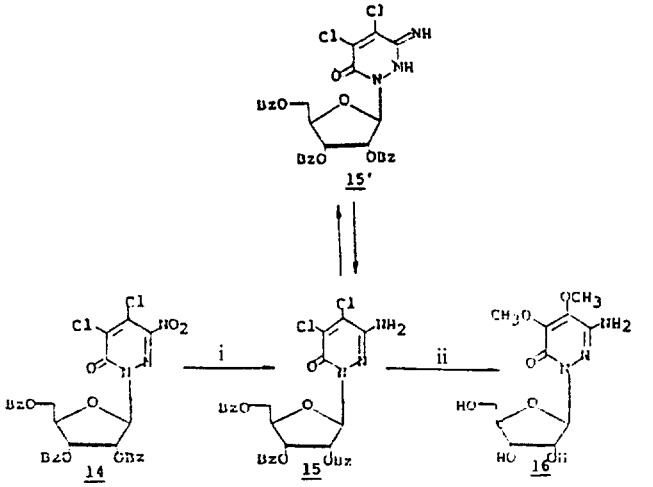
Scheme 1

We also attempted to synthesize some novel pyridazine nucleosides such as compound 10 and 16. Silylation of 4 was accomplished using hexamethyldisilazane, with a catalytic amount of ammonium sulfate, to yield 3-hydrazino-6-[(trimethylsilyl)oxy]pyridazine, which was used in the subsequent reaction without purification. The silyl derivative was condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (TBAR) by a stannic chloride catalyzed silyl procedure[8] to furnish nucleoside 9 in 91% yield, whereas reaction of compound 11[4b] with hydrazine hydrate gave compound 12 and 13 instead of compound 9[9]. Treatment of compound 9 with sodium methoxide in methanol afforded compound 10 in 83% yield.



(i) HMDS, TBAR. (ii) $NH_2NH_2 \cdot H_2O$. (iii) NaOMe, MeOH, Amberlite IRC-50 (H^+). (iv) $NH_2NH_2 \cdot H_2O$ at room temp. (v) $NH_2NH_2 \cdot H_2O$, reflux.

Scheme 2



(i) $NaBH_4$, $SnCl_2 \cdot H_2$, $CHCl_3$. (ii) NaOMe, MeOH, Anberlite IRC-50 (H^+).

Scheme 3

On the other hand, reduction of nucleoside 14[4a] with sodium borohydride-stannous chloride dihydrate (1:1 equiv.) in chloroform gave nucleoside 15 in 72% yield. This assignment was based on ^{1}H-NMR and IR spectrum obtained for the debenzoylated product 16 by treatment with sodium methoxide in methanol.

Proof of the structure of each compound is based on analytical and spectroscopic data reported in detail in the experimental section.

Additional chemical transformations of these novel compounds are currently under investigation in our laboratory.

Experimental

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270–50 spectrophotometer. ^{1}H-NMR spectra were measured in DMSO-d_6 solution at 80 MHz on a Bruker AW instrument. Chemical-shift values reported in δ unit (ppm) relative to an internal standard (tetramethylsilane). Elemental analyses were performed by LECO micro-C.H.N. determinator (CHN-600) instrument. Nucleosides were detected by treatment with sulfuric acid followed by charring. Open bed column chromatography was carried out on Silica-Gel 60 (Merck) using gravity flow.

3-Chloropyridazin-6-one (3). Compound 2[5] (20g, 134 mmol) was added to 4% aqueous sodium hydroxide solution (400 m*l*) and refluxed for 4 hours. The reaction mixture was cooled to room temperature, and adjusted to pH 4–5 by adding 10% acetic acid (20 m*l*). The resulting yellow solid was filtered, washed with cold water (30 m*l*) and dried in air. The crude product was recrystallized from MeOH/water (1:1 v/v) to give compound **3** as a white needle in 84% (14.46g) yield. mp 138–139 °C (lit.[6,10] 138–139 °C); IR (KBr) 3480, 3090, 2810, 1670, 1600, 1500, 1480, 1460 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.04 (bs, NH, D_2O exch.), 7.4 (d, H_4, J = 8 Hz), 6.9 (d, H_5, J = 8 Hz).

3-Hydrazinopyridazin-6-one (4). A mixture of **3**(2.5g, 19.2 mmol) and hydrazine (15 m*l*) was refluxed for 10 hours. Excess hydrazine was evaporated under reduced pressure, and then the residue was poured into water with stirring. The resulting precipitate was filtered, washed with water (10 m*l* × 3) and dried in air. The crude product was recrystallized from ethanol/water (2:1 v/v) to give compound **4** in 60% (1.43g) yield. mp 197–199 °C; IR(KBr) 3400, 3340, 3210, 1710, 1620 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.2 (d, H_4, J = 8 Hz), 6.8 (d, H_5, J = 8Hz), 5.9(s, NH, D_2O exch.); Anal. Calcd. for $C_4H_6N_4O$; C, 38.7; H, 4.05; N, 45.16. Found; C, 38.3; H, 4.02; N, 44.42.

6-Chloro-3-hydrazinopyridazine (5). To a solution of **3** (4g, 27 mmol) in ethanol (60 m*l*) was added hydrazine hydrate (1.4 m*l*, 28.7 mmol) and the mixture was refluxed for 24 hours. The reaction mixture was cooled to 5 °C. The product as a white needle was filtered, washed with ethanol (5 m*l* × 3) and dried in air to give compound **5** in 41% (1.6g) yield. mp 137–138 (lit.[7] 138–139 °C). IR(KBr) 3200, 3130, 3050, 1620, 1520, 1410, 1400 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.08 (d, H_4, J = 8 Hz), 7.51 (d, H_5, J = 8 Hz), 3.5 (bs, NH, D_2O exch.), 2.0 (bs, NH_2, D_2O exch.); Anal. calcd. for $C_4H_5N_4Cl$: C, 33.2; H, 3.50; N, 38.8: Found, C, 33.0; H, 3.6; N, 38.2.

3,6-Dihydrazinopyridazine (6). To a solution of **3**(2g, 13.5 mmol) in methanol (30 m*l*) was added hydrazine hydrate (1.44 m*l*, 28.7 mmol) and the mixture was refluxed for 48 hours. The reaction mixture was cooled to 5 °C. The resulting white precipitate was filtered and recrystallized from water to give compound **6** in 70% (1.38g) yield; mp 195–196 °C (lit.[11] 195–196 °C). IR(KBr) 3300, 3200, 1650, 1600, 1410 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 7.20 (d, H_4, J = 8 Hz), 6.88 (d, H_5, J = 8 Hz), 5.38 (s, NH, D_2O exch.), 2.0 (s, NH_2, D_2O exch.); Anal. calcd. for $C_4H_8N_6$: C, 34.3; H, 5.62; N, 60.11: Found; C, 34.3; H, 5.7; N, 60.0.

6-Chloro-3-dicyanomethylenepyridazine (7). To a solution of malononitrile (2.65g, 40 mmol) in THF (40 m*l*) was added sodium hydride (1.6g, 40 mmol, 60% in oil) and stirred at 10 °C for 30 min. To the above mixture, **3**(5.9g, 39.8 mmol) was added and stirred at room temperature for 10.5 hours. After 2 m*l* of water was added, the solution was filtered. The filtrate was evaporated under reduced pressure. The crude product was applied to an open-bed silica gel column (3 × 30 cm). The column was eluted with chloroform/methanol (9.5:0.5, v/v), and the eluent containing the product (as determined by TLC) was evaporated under reduced pressure to give compound **7** in 82% (5.678g) yield. mp 263–265 °C (lit.[12,13] 268–270 °C); IR(KBr) 3450, 2170, 2150, 1630 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.85 (bs, NH, D_2 exch.), 7.65 (d, H_4, J = 7 Hz), 6.43 (d, H_5, J = Hz); Anal. calcd. for $C_7H_3N_4Cl$; C, 47.08; H, 1.69; N, 31.31: Found, C, 47.1; H, 1.38; N, 31.61.

3-Dicyanomethylenepyridazin-6-one (8). To a solution of malononitrile (1.66g, 25.19 mmol) in THF (60 m*l*) was added sodium hydride (1.99g, 127.71 mmol, 60% in oil) and stirred at 10 °C for 30 min. The solution of **3**(3g, 22.9 mmol) in THF (20 m*l*) was added to the reaction mixture, and stirred at room temperature for 6.5 hours. After 2 m*l* of water was added, the reaction mixture was stirred for 10 min. The reaction mixture was evaporated under reduced pressure and the resulting residue was dissolved in hot methanol and filtered. The filtrate was coevaporated with silica gel (3g) and applied to an open-bed silica gel column (3 × 30 cm). The column was eluted with chloroform/methanol (9.5:0.5, v/v), and the eluent containing the product (as determined by TLC) was evaporated under reduced pressure to give compound *8* in 60% (2.19g) yield. mp 139–141 °C; IR(KBr) 3500, 3400, 3250, 3100, 2205, 2190, 1640 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.20 (bs, NH, D_2O exch.), 7.81 (d, H_4, J ≈ 7 Hz), 6.62(d, H_5, J = 7 Hz); Anal. calcd. for $C_7H_4N_4O$; C, 52.50; H, 2.51; N, 34.98: Found, C, 51.87; H, 2.21; N, 34.39.

3-Hydrazino-1-(2,3,5-tri-O-benzoyl-β-D-ribofurazosyl)pyridazin-6-one (9). Compound 4(0.6g, 4.84 mmol) was silylated by heating at reflux for 2 hours in hexamethyldisilazane (30 m*l*) with ammonium sulfate (0.2g). The excess hexamethyldisilazane was removed by distillation under reduced pressure and the remaining solid was used without further purification. The silylated heterocycle and 1-O-acetyl-2,3,5-tri-O-benzoyl-1-β-D-ribofuranose (2.4g, 4.75 mmol) were dissolved in dry dichloroethane (30 m*l*) and the solution was cooled to 0 °C. Stannic chloride (1.25 m*l*, 10.8 mmol) was added and the the solution heated at reflux temperature for 0.5 hours. The reaction mixture was cooled to 0 °C, and absolute ethanol (25 m*l*) and sodium bicarbonate (3.5g, 43.7 mmol) were added. The mixture was stirred for an additional 2 hours. The resulting gelatinous mass was evaporated to dryness under reduced pressure. The remaining solid mass was extracted with boiling chloroform (100 m*l* × 2). The chloroform extracts were combined and passed through silica gel column (2.5 × 20 cm). The eluent was evaporated under reduced pressure. The resulting crude product was evaporated under reduced pressure. The resulting

crude product was recrystallized from ethanol to give compound **9** as a white powder in 80% (2.17g) yield. mp 125–128 °C, IR(KBr), 3520, 3400, 3100, 1750, 1640, 1620, 1470 cm^{-1}, ^1H-NMR (DMSO-d_6) δ 9.25 (d, NH, D_2O exch.), 8.18–6.82 (m, Bz-H, $H_4 + H_5$), 6.75 (d, H'_1, J = 2 Hz), 6.28–5.62 (m, $H'_4 + H'_5$), 5.25 (s, NH_2, D_2O exch.); Anal. calcd. for $C_{30}H_{26}N_4O_8$; C, 63.15; H, 4.56; N, 9.82: Found, C, 63.83; H, 4.43; N, 10.10.

3-Hydrazino-1-β-D-ribofuranosylpyridazin-6-one (10). Nucleoside 9(0.7g, 1.2 mmol) was dissolved in a mixture of methanol (15 m*l*) and ethylacetate 920 m*l*. Sodium methoxide (0.1g, 1.85 mmol, 80%) was added, and the reaction mixture was stirred for 18 hours at room temperature. Amberlite IRC-50 resin (H^+-form, 2g) was added, and the mixture was stirred for an additional 14 hours. The mixture was filtered and the resin was washed with methanol (100 m*l*). The combined filtrates were coevaporated with silica gel (3g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 × 45 cm). The column was eluted with 600 m*l* of chloroform/methanol (98:2 v/v). After the first 110 m*l* of eluent was discarded, the eluent was collected in 6 m*l* fractions. The fractions containg nucleoside product (as determined by TLC) were combined and evaporated under reduced pressure to give nucleoside **10** in 83% (390 mg) yield. mp 116–118 °C; IR(KBr) 3450, 3400, 3350, 2950, 1640, 1600 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 9.25 (s, NH, D_2O exch.), 7.20 (d, H_4, J = 7 Hz), 6.90 (d, H_5, J = 8 Hz), 6.34 (d, H'_1, J = 3 Hz), 5.32–4.8 (m, $OH'_2 + OH'_3 + OH'_5 + NH_2$, D_2O exch.), 4.35–3.71 (m, $H'_2 + H'_3 + H'_4 + H'_5$); Anal. calcd. for $C_9H_{14}N_4O_5$; C, 41.86; H, 5.46; N, 21.69: Found, C, 41.97; H, 5.18; N, 22.13.

3-Amino-4,5-dichloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (15). A mixture of nucleoside 14[4d] (4g, 6.12 mmol), sodium borohydride (0.464g, 12.14 mmol), stannous chloride dihydrate (2.756g, 12.14 mmol) and chloroform (400 m*l*) was stirred for 24 hours at room temperature. The reaction mixture was filtered and washed with chloroform (25 m*l* × 2). The combined filtrate was concentrated to 15–20 m*l* under reduced pressure. The residue was applied to an open-bed silica gel column (2.5 × 30 cm). The column was eluted with 800 m*l* of chloroform/methanol (200:1 v/v). After first 40 m*l* of eluent was discarded, the eluent was collected in 6 m*l* fractions. The fractions containing nucleoside product were combined and evaporated under reduced pressure to give nucleoside **15** as an yellow powder in 72% (2.75g) yield. mp 120–121 °C; IR(KBr) 3400, 3390, 3310, 3070, 1730, 1670, 1540 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 9.5 (s, NH, D_2O exch.), 9.0 (s, NH, D_2O exch.), 7.2–8.2 (m, Bz-H), 6.7 (d, H'_1, J = 3 Hz), 6.0–6.4 (m, $H'_2 + H'_3$), 4.5–5.0 (m, $H'_4 + H'_5$); Anal. calcd. for $C_{30}H_{23}N_3O_8Cl_2 \cdot 1\frac{1}{2}H_2O$; C, 55.31; H, 4.02; N, 6.45; Found, C, 55.37; H, 3.88; N, 6.35.

3-Amino-4,5-dimethoxy-β-D-ribofuranosylpyridazin-6-one (16). Nucleoside **15** (1g, 1.613 mmol) was dissolved in a mixture of tetrahydrofuran (1.5 m*l*) and methanol (15 m*l*). Sodium methoxide (0.4g, 7.4 mmol, 80%) was added, and the reaction mixture was stirred for 17 hours at room temperature. Amberlite IRC-50 resin (H^+-form, 2g) was added, and the mixture was stirred for an additional 14 hours. The mixture was filtered and the resin was washed with hot methanol (15 m*l*). The combined filtrates were coevaporated with silica gel (3g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 × 45 cm). The column was eluted with 400 m*l* of chloroform/methanol (9:1 v/v). After the first 100 m*l* of eluent was discarded, the eluent was collected in 6 m*l* of fractions. The fractions containing nucleoside (as determined by TLC) were combined and evaporated under reduced pressure to give nucleoside **16** as a white powder in 80% (0.39g) yield. mp 211–213 °C; IR (KBr) 3420, 3390, 3400, 2980, 1620, 1580, 1560, 1450 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 9.6 (s, NH, D_2O exch.), 6.27 (d, H'_1, J = 3 Hz), 5.37–4.29 (m, $OH'_2 + OH'_3 + OH'_5$, D_2O exch.), 4.37–3.73 (m, $H'_2 + H'_3 + H'_4 + H'_5$). Anal. calcd. for $C_{11}H_{17}N_3O_7$; C, 42.89; H, 5.56; N, 13.64: found, C, 42.67; H, 5.59; N, 14.11.

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