Nucleosides. 117. Synthesis of 4-Oxo-8-(β-D-ribofuranosyl)-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (OPTR) *via* 3-Amino-2*N*-carbamoyl-4-(β-D-ribofuranosyl)pyrazole (ACPR) Derivatives (1)

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Reaction of 2-formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (VII) with semicarbazide hydrochloride followed by sodium ethoxide treatment afforded an α,β-mixture of 3-amino-2*N*-carbamoyl-4-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)pyrazole (IX). Conversion of IX to 4-oxo-8-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (XIII) was achieved by treatment of IX with ethylorthoformate. The β-isomer IXb gave only the β-isomer XIIIb, and the α-isomer IXa was converted exclusively into the α-isomer XIIIa. Upon deprotection with 3% *n*-butanolic hydrogen chloride, both IXa and IXb gave the same mixture of the α- and β-isomers of 3-amino-2*N*-carbamoyl-4-(D-ribosyl)pyrazole, which were separated by chromatography.

The syntheses of the hitherto unknown compounds, 3-amino-2*N*-carbamoylpyrazole (IVa) and its 4-methyl analog (IVb) are also reported. Experimental details of the synthesis of 3-amino-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (XIIb), an important intermediate for "purine-like" *C*-nucleosides, are also described.

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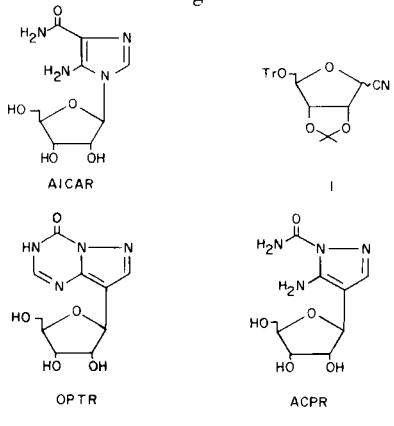
It is well known that 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (AICAR, Figure 1) is a key intermediate not only in the *de novo* synthesis of purine nucleotides (2) but also in the chemical synthesis of various purine nucleosides (3,4). In previous publications (5,6) from our laboratory, we described the synthesis of *C*-nucleoside analogues of some purine and pyrimidine nucleosides starting from 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (I). This report deals with the further utilization of I in the synthesis of the known (7) biologically active *C*-nucleoside, 4-oxo-8-(β-D-ribofuranosyl)-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (OPTR) *via* derivatives of 3-amino-2*N*-carbamoyl-4-(β-D-ribofuranosyl)pyrazole (ACPR, a *C*-nucleoside analogue of AICAR). We also report herein experimental details of the synthesis of 3-amino-4-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)pyrazole (5).

Reported attempts (8) to synthesize 3-amino-2*N*-carbamoylpyrazole (IVa, the aglycon of ACPR, Scheme I) were unsuccessful. Although treatment of aminopyrazole (IIIa) with potassium cyanate in aqueous acetic acid [a method used for the synthesis of *N*-carbamoylpyrazoles (9)] failed to afford IVa, we found that IVa or its 4-methyl analogue IVb could be prepared by cyclization of formylacetonitrile (IIa) or α-formylpropionitrile (IIb) with semicarbazide. The structure of IVa was established by elemental analyses and by its conversion into the known (7) pyrazolotriazine Va by ring closure with ethylorthoformate. The methyl analogue IVb exhibited uv spectral

Figure 1



characteristics similar with those of IVa, and gave analyses consistent with the assigned structure. Compound IVb was also converted to the pyrazolotriazine derivative Vb by treatment with ethylorthoformate.

The ribosylacetonitrile (I, Scheme II) was formylated, as described previously (5,6), and the crude sodium enolate (VI) was neutralized with acetic acid. The aldehydic product VII (10) was purified by chromatography on a silica gel column. One of the epimers could be crystallized from ethanol as the mono-ethanolate. Treatment of VII (the ribosyl analogue of II) with excess semicarbazide hydrochloride in a two-phase system (methylenechloride-water) afforded the corresponding semicarbazone VIII as an α,β-mixture. Base-catalyzed cyclization of VIII with one equivalent of sodium hydroxide in ethanol immedi-

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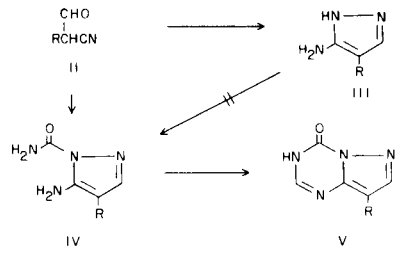
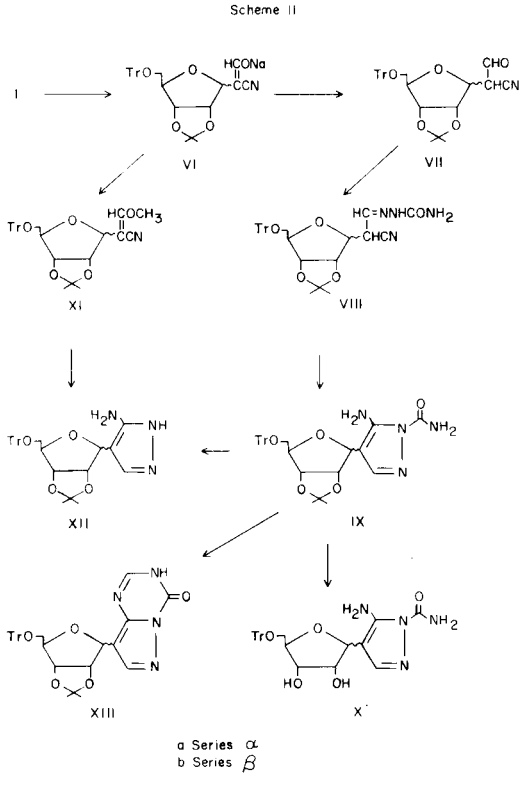
Scheme I



a Series R=H
b Series R=Me

Scheme II



a Series α
b Series β

ately gave two pairs of products. If the reaction mixture was left more than 10 minutes at room temperature, or if an excess of base was employed, the more polar pair became the predominant products. All the products were separated by chromatography. The more polar pairs were found to be identical with the known (5) epimers of aminopyrazole derivatives XII. The less polar products were the α- and β-epimers (IX) of protected ACPR. Obviously, IX is very unstable to base and is readily converted into XII. The α-isomer IXa was obtained in crystalline form, whereas the β-isomer IXb was obtained only as an amorphous powder. [However, it was found later that both epimers (IXa and IXb) gave the same α,β-mixture of ACPR upon deprotection.]

In a large-scale preparation of IX, brief treatment of VIII with ethanolic sodium ethoxide was found to minimize the formation of XII, and the α-isomer IXa could be directly crystallized from the reaction mixture in about 50% yield. The β-isomer IXb was isolated from the mother liquor in about 20% yield as a powder. The uv spectral characteristics of IX are very similar to those of IV. Configurational assignment at C-1′ for these epimeric C-nucleosides IX was made on the basis of ^{1}H nmr data. The chemical shift of H-1′ of the α-epimer IXa (δ 5.07) appeared at lower field than that of the corresponding β-isomer IXb (δ ~4.7). The difference in the chemical shifts of the two isopropylidene methyl signals (11) for IXa (Δδ 20.7 Hz) is smaller than that of the corresponding β-isomer (Δδ 21.7 Hz). These assignments were further confirmed chemically by treatment of IXa and IXb separately with sodium hydroxide. Compound IXa gave only the α-isomer of the aminopyrazole *C*-nucleoside XIIa, whereas the β-nucleoside IXb was converted exclusively into XIIb.

Deprotection of IX by treatment with methanolic hydrogen chloride was studied. It was found that the carbamoyl linkage of IX was slightly more stable than the trityl and isopropylidene groups as the thin layer chromatography (tlc) examination of the reaction showed initial formation of a pair of unprotected products X, which were rapidly converted further into the free aminopyrazole derivatives and then decomposed. We found, however, that 3% *n*-butanolic hydrogen chloride is eminently superior to methanolic hydrogen chloride for deprotection of IX as the products precipitated, preventing further hydrolysis of the carbamoyl function. Both the α and β-isomers of IX gave the same mixture of three products (two major and one minor, as judged by tlc). The two major components (X) were separated by preparative tlc and obtained as hygroscopic solids. The uv spectra of these compounds were consistent with the 3-amino-2*N*-carbamoylpyrazole structure, and these compounds were analyzed as the monohydrate of ACPR. The ^{1}H nmr spectra of these isomers, however, did not offer conclusive evidence for the size of lactol ring of the carbohydrate moiety and the configuration at C-1′, as the H-1′ signal appeared at δ 4.24 as a singlet for one isomer and at δ 4.20 as a doublet ($J_{1',2'}$ = 9.7 Hz) for the other. The coupling between H-1′ and H-2′ of the latter isomer appears to be too large for a furanosyl derivative, and the difference in chemical shifts of H-1′ of these isomers is too close to assign the configuration at C-1′.

Cyclization of the protected ACPR (IX) with ethylorthoformate went smoothly. The β-isomer (IXb) gave the β-isomer of protected OPTR (XIIIb) (7,12) as the major product, and IXa afforded exclusively the α-isomer XIIIa. It was also found that protected OPTR (XIII, as an α,β-mixture) could be obtained directly from the semicarbazone VIII by treatment with ethylorthoformate,

although the yield was low. Treatment of free ACPR isomers X with ethylorthoformate, however, caused extensive decomposition. Both isomers of ACPR (X) (treated separately) gave the same mixture of several products including isomeric OPTR, as indicated by tlc. From a reaction mixture of the isomeric mixture of ACPR with ethylorthoformate, OPTR was isolated in low yield as the only characterizable product.

In an earlier Communication (5), we reported the synthesis of an α,β-mixture of aminopyrazole *C*-nucleoside XII and separation of the isomers XIIa and XIIb. These isomers XII served as intermediates in the synthesis of the corresponding 4-oxo-8-(D-ribofuranosyl)-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazines (5). Compounds XII could not be obtained in our hands by treatment of VII with hydrazine under various conditions. Compounds XII, however, could be prepared by base catalyzed cyclization of the 2-methoxyacrylate derivative XI with hydrazine. Since XII were found to be versatile intermediates in the synthesis of several purine-like *C*-nucleosides (7), an alternate route to XII has been developed (13). All attempts at deprotection of XII led to a mixture from which no pure product could be isolated.

Neither isomers of ACPR showed significant inhibitory activity against P815 mouse leukemic cells (14).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Tlc was performed on Uniplates purchased from Analtech Co., Newark, Del., and column chromatography on silica gel G60 (70-230 mesh, ASTM, Merck). ^{1}H nmr spectra were recorded on a JEOL PFT-100 spectrometer, and TMS was the internal standard for organic solvents, DSS for deuterium oxide; chemical shifts are reported in parts per million (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Values given for coupling constants are first order. Uv spectra were measured on a Unicam SP-800 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

3-Amino-2*N*-carbamoylpyrazole (IVa).

To a stirred solution of sodium hydride (11.6 g., 50% in mineral oil) in ether (50 ml.) and ethanol (1 ml.) was added dropwise a solution of ethylformate (50 ml.) and acetonitrile (10.3 g.) in ether (30 ml.). The mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue dissolved in water (100 ml.) and neutralized with acetic acid to *p*H ~ 7. Semicarbazide hydrochloride (25 g.) was added to the solution, and the mixture was shaken for 5 hours, neutralized with 1*N* sodium hydroxide to *p*H ~ 7 and then extracted with chloroform (100 ml. x 5). The combined extracts were evaporated to dryness, and the residue was triturated with a small amount of chloroform until colorless, fine crystals (2.4 g.) were obtained, m.p. 108-110° (collapsed, then slowly decomposed with effervescence over a wide temperature range); uv: λ max 262.5 nm (*p*H 5-9), 268 (*p*H 1); ^{1}H nmr (DMSO-d_6): δ 5.28 (d, 1H, H-4, $J_{4,5}$ = 1.9 Hz), 6.38 (broad s, 2H, exchangeable), 7.26 (d, 1H, H-5, $J_{4,5}$ = 1.9 Hz), 7.49 (broad s, 2H, exchangeable).

Anal. Calcd. for $C_4H_6N_4O$: C, 38.10; H, 4.76; N, 44.44. Found: C, 37.87; H, 4.84; N, 44.13.

Attempts at crystallization from hot water caused decomposition of this product.

When a solution of IVa (100 mg.) in 0.2 *N* sodium hydroxide (5 ml.) was heated at 50-60° for 5 minutes, the uv characteristics of IVa were completely lost, and the solution showed uv spectra similar to those of 3-aminopyrazole (15).

2-Amino-2*N*-carbamoyl-4-methylpyrazole (IVb).

To a suspension of sodium hydride (11.6 g., 50% in mineral oil) in ether (50 ml.) and ethanol (1 ml.) was added dropwise a solution of ethylformate (40 ml.) and propionitrile (13.7 g.) in ether (30 ml.). After stirring for 3 hours, ether (30 ml.) was added, and the stirring was continued overnight. The solvent was removed *in vacuo* below 30°; the residual gray powder dissolved in cold water (100 ml.) and neutralized with acetic acid to *p*H ~7.

To this solution was added semicarbazide hydrochloride (27 g. dissolved in 100 ml. of water); the mixture was shaken for 4 hours and neutralized with 1*N* sodium hydroxide. The colorless needles which precipitated were collected, washed with cold water and air-dried to yield 2 g. of IVb, m.p. 160-162° (collapsed); uv: λ max 269 nm (*p*H 5-9), 271 (*p*H 1); ^{1}H nmr (DMSO-d_6): δ 1.79 (s, 3H, Me), 6.10 (broad s, 2H, exchangeable), 7.16 (s, 1H, H-5), 7.44 (broad s, 2H, exchangeable).

Anal. Calcd. for $C_5H_8N_4O$: C, 42.86; H, 5.71; N, 40.00. Found: C, 42.92; H, 5.95; N, 39.91.

Compound IVb (100 mg.) was dissolved in 0.2 *N* sodium hydroxide (5 ml.), and the solution was heated at 50-60° for 5 minutes. The uv absorption characteristics of the solution changed: λ max 230 nm (*p*H 7), 243 (*p*H 1) (16).

4-Oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (Va).

A mixture of IVa (3.0 g.) and ethylorthoformate (30 ml.) was heated at 100-110° for 15 hours. The colorless crystals which precipitated were collected by filtration and recrystallized from water to yield 1.7 g. of Va, m.p. 255-257° [lit. (7), m.p. 256-257°]. This product was indistinguishable from an authentic sample (7,12) of Va.

8-Methyl-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (Vb).

A mixture of IVb (3.0 g.) and ethylorthoformate (20 ml.) was heated at 100-110° for 15 hours. The colorless crystals were filtered and recrystallized from water to yield 1.9 g. of Vb, m.p. 315-318°; uv: λ max 268 nm (*p*H 7), 263 (*p*H 2), 272 (*p*H 13); ^{1}H nmr (DMSO-d_6): δ 2.14 (s, 3H, Me), 7.96 (s, 2H, H-2.4), 12.4 (broad s, NH, dissociable).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 47.91; H, 4.12; N, 37.31.

2-Formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (VII).

To a mixture of I (6) (45.5 g.) and sodium hydride (7 g., 50% in mineral oil) in dry ether (100 ml.) was added 2 ml. of absolute ethanol, followed immediately by dropwise addition of a mixture of ethylformate (50 ml.) and ether (100 ml.). The mixture was stirred for 15 hours, and the solvent was evaporated *in vacuo* below 30°. The residue was dissolved in water (300 ml.), neutralized with acetic acid to *p*H ~ 7 and extracted with chloroform (200 ml. x 3). The combined organic extracts which contained two products, as judged by tlc [R*f* 0.6 major component, R*f* 0.45 minor, methylenechloride-methanol (20:1)] were dried (sodium sulfate) and evaporated. The major component was separated by column chromatography [methylenechloride-

methanol (40:1) as the eluent] and crystallized from ethanol to give 34 g. of colorless crystals, m.p. 140-141°; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, 3H, CH_3CH_2, J = 7.0 Hz), 1.33 (s, 3H, isopropylidene Me), 1.52 (s, 3H, isopropylidene Me), 3.08 (q, 1H, H-5′, $J_{5',5''}$ = 10.3; $J_{4',5'}$ = 3.7 Hz), 3.29 (q, 1H, H-5″, $J_{5',5''}$ = 10.3; $J_{4',5''}$ = 5.4 Hz), 3.47 (q, 2H, CH_3CH_2, J = 7 Hz), 4.26 (m, 1H, H-4′), 4.5-5.0 (m, 4H, H-1′, 2′, 3′, CHCN), 7.2-7.4 (m, trityl).

Anal. Calcd. for $C_{30}H_{29}NO_5 \cdot C_2H_5OH$: C, 72.58; H, 6.61; N, 2.64. Found: C, 72.75; H, 6.43; N, 2.62.

Semicarbazone of 2-Formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (VIII).

A mixture of compound VII (30 g.) in methylenechloride (200 ml.) and semicarbazide hydrochloride (15 g.) in water (150 ml.) was shaken for 20 hours. The organic layer was separated, washed with saturated sodium bicarbonate solution and water, dried (sodium sulfate), and then evaporated to dryness to a glass *in vacuo*. Tlc showed the presence of a small amount of VII. An analytical sample was obtained by high-pressure liquid chromatography using a Porasil type B column and methylenechloride-methanol (80:1) as the eluent; uv: no maximum between 250 and 300 nm in methanol. Addition of a drop of 1*N* sodium hydroxide produced a λ max at 265 nm. This peak did not disappear upon neutralization with 1*N* hydrochloric acid; ^{1}H nmr (deuteriochloroform) showed this sample to be a mixture of two isomers: δ 1.32, 1.35, 1.52 (isopropylidene Me with relative intensities of approximately 1:1:2), ~3.2 (m, 2H, H-5′, 5″), 3.93 (m, 1H, H-4′), 4.2-4.9 (m, ~3H, H-1′,2′,3′), 7.1-7.4 (m, 15-18H, aromatic), broad signals for dissociable H's at ~ 10.1 (1H), ~7.1 (1H), ~5.6 (2H).

Anal. Calcd. for $C_{31}H_{32}N_4O_5 \cdot H_2O$: C, 66.66; H, 6.09; N, 10.04. Found: C, 66.33; H, 5.82; N, 9.89.

3-Amino-2*N*-carbamoyl-4-(2,3-*O*-isopropylidene-5-*O*-trityl-α- and β-ribofuranosyl)pyrazole (IXa and IXb).

The semicarbazone (VIII, 35 g.) was dissolved in ethanolic sodium ethoxide (freshly prepared by dissolving 1.58 g. of metallic sodium in 100 ml. of ethanol). After 10 minutes at room temperature, the solution was neutralized to *p*H ~ 7 with acetic acid, and the precipitated sodium acetate was removed by filtration. The filtrate was concentrated to about half of its volume *in vacuo* below 30°. The mixture was cooled in an icebox for 2 hours; the crystalline IXa was collected by filtration, 15 g., m.p. 113-115°; uv λ max 267 nm (methanol). Addition of a drop of 1*N* sodium hydroxide or 1*N* hydrochloric acid shifted the peak to 265 nm; ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 3H, isopropylidene Me), 1.55 (s, 3H, isopropylidene Me), 3.2-3.4 (m, 2H, H-5′,5″), 4.27 (t, 1H, H-4′), 4.6-4.9 (m, 2H, H-2′,3′), 5.07 (d, 1H, H-1′, $J_{1',2'}$ = 2.4 Hz), 7.2-7.5 (m, aromatic).

Anal. Calcd. for $C_{31}H_{32}N_4O_5$: C, 68.88; H, 5.92; N, 10.37. Found: C, 68.49; H, 5.83; N, 10.55.

The filtrate was evaporated *in vacuo* to a syrup which was chromatographed over silica gel column (700 g.) using petroleum ether-ethyl acetate (4:1) as the eluent. Two fractions were separated. One of the fractions gave 6.4 g. of crystalline IXa, and the other fraction afforded 2.5 g. of IXb as a powder; uv for IXb: λ max 265 nm (methanol). Addition of a drop of 1*N* sodium hydroxide or hydrochloric acid shifted the peak to 266 nm; ^{1}H nmr for IXb (deuteriochloroform): δ 1.35 (s, 3H, isopropylidene Me), 1.57 (s, 3H, isopropylidene Me), 3.2-3.6 (m, 2H, H-5′,5″), 4.16 (m, 1H, H-4′), 4.6-4.8 (m, 3H, H-1′,2′,3′), 7.2-7.4 (m, aromatic).

Anal. Found for IXb: C, 68.65; H, 5.89; N, 10.02.

To a solution of IXb (100 mg.) in 5 ml. of methanol was heated at 50-60° for 5 minutes. Tlc examination (methylene chloride-methanol 9:1) showed that the mixture contained only one nucleosidic product corresponding to the β-aminopyrazole derivative XIIb. The uv absorption characteristics were consistent with structure XIIb.

In a similar experiment using IXa instead of IXb, only one nucleosidic product corresponding to the α derivative XIIa was detected by tlc and characterized by uv spectroscopy.

Hydrolysis of IXa.

A mixture of IXa (540 mg.) and 3% hydrogen chloride in *n*-butanol (10 ml.) was stirred at room temperature for 10 minutes, and the colorless precipitate (125 mg.) was collected by filtration.

The precipitate was very hydroscopic. Tlc examination (*i*-propanol-ethylacetate-water 4:4:1) showed that the precipitate contained two major and one minor components. The two major components were separated by preparative tlc using Analtech 1000 μ plates and *i*-propanol-ethylacetate-water (4:14:1) as the solvent. From the upper band, 20 mg. of one isomer of ACPR was obtained as a hygroscopic powder; uv: λ max 266 nm (*p*H 5-9), 263 (*p*H 2); ^{1}H nmr (DMSO-d_6): δ 4.24 (s, 1H, H-1′), 7.38 (s, 1H, H-5).

Anal. Calcd. for $C_9H_{14}N_4O_5 \cdot H_2O$: C, 39.13; H, 5.84; N, 20.28. Found: C, 39.08; H, 5.69; N, 20.29.

From the lower band, 18 mg. of another ACPR isomer was obtained as a colorless powder; uv: λ max 267 nm (*p*H 5-9), 262 (*p*H 2); ^{1}H nmr (DMSO-d_6): δ 4.20 (d, 1H, H-1′), 7.26 (s, 1H, H-5). This compound is very hygroscopic and best analyses were obtained as the monohydrate. Found: C, 39.38; H, 5.65; N, 19.81.

4-Oxo-3*H*-8-(2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (XIIIa).

A mixture of IXa (500 mg.) and ethylorthoformate (4 ml.) was heated at 100-110° for 15 hours. The mixture was concentrated to half its volume *in vacuo*. The crystals were collected by filtration and recrystallized from ethanol to yield 115 mg. of XIIIa, m.p. 154-156° [lit. (7) 155-156°]. The ^{1}H nmr parameters were indistinguishable from those of reported (7,12) for this compound.

Tlc (chloroform-methanol 10:1) of the mother liquor showed the presence of only XIIIa as the nucleosidic product.

4-Oxo-3*H*-8-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (XIIIb).

A mixture of IXb (300 mg.) and ethylorthoformate (5 ml.) was heated to 100-110° for 15 hours. The solvent was removed *in vacuo*, and the residual syrup was chromatographed on a silica gel column using methylene chloride-methanol (20:1) as the eluent. From the major fraction, 130 mg. of XIIIb was obtained as a syrup. The ^{1}H nmr spectrum of this syrup was identical with that of an authentic sample (7,12).

Conversion of XIIIb to OPTR has been reported (7).

3-Amino-4-(2,3-*O*-isopropylidene-5-*O*-trityl-α- and β-D-ribofuranosyl)pyrazole (XIIa and XIIb).

A mixture of compound XI (6) (488 mg.) and anhydrous hydrazine (0.5 g.) in 0.5*M* ethanolic sodium ethoxide (40 ml.) was heated at reflux for 15 hours. After neutralization of the mixture with 1*N* hydrochloric acid, the syrup which separated was extracted with chloroform (50 ml.), dried (sodium sulfate) and evaporated *in vacuo* to dryness. Tlc examination (benzene-methanol 9:2) showed that the residue contained two major products (*Rf* 0.44 and 0.48) which were separated by column

chromatography using benzene-methanol (19:1) as the eluent. The α-nucleoside XIIa (107 mg.) was obtained as crystals, m.p. 102-106°, whereas the β-nucleoside XIIb (76 mg.) was isolated as a glass. The physical properties of these aminopyrazole nucleosides XII have been described in previous reports (5,13).

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