Imidazo[1,2-*a*]-*s*-triazine Nucleosides. Synthesis and Antiviral Activity of the N-Bridgehead Guanine, Guanosine, and Guanosine Monophosphate Analogues of Imidazo[1,2-*a*]-*s*-triazine[1]

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The first chemical synthesis of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**), the corresponding nucleoside and nucleotide, and certain related derivatives of a new class of purine analogues containing a bridgehead nitrogen atom is described. Condensation of 2-amino-4-chloro-6-hydroxy-*s*-triazine (**2**) with aminoacetaldehyde dimethyl acetal followed by the ring annulation gave the guanine analogue **8**. A similar ring annulation of 4-(2,2-dimethoxyethylamino)-*s*-triazine-2,6-dione (**5**) gave imidazo[1,2-*a*]-*s*-triazine-4,6-dione (**9**). Direct glycosylation of the trimethylsilyl derivative of **8** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride, followed by debenzoylation, gave the guanosine analogue 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12b**), which on deamination gave the xanthosine analogue **13**. Phosphorylation of **12b** gave 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one 5′-monophosphate (**11**). The anomeric configuration has been determined unequivocally by using NMR of the 2′,3′-*O*-isopropylidene derivative **10** and the site of ribosylation has been established by using ^{13}C NMR spectroscopy. These compounds were tested against type 1 herpes, type 13 rhino, and type 3 parainfluenza viruses in tissue culture. Moderate rhinovirus activity was observed for several compounds at nontoxic dosage levels.

The naturally occurring purine and pyrimidine nucleosides and nucleotides have attracted considerable attention in recent years, since these natural and several synthetic analogues exhibit a wide variety of specific biological activity. Such activity is largely due to the structural similarities of these nucleosides to the natural enzyme substrates. It is therefore of immense interest to synthesize such structural analogues which have the potential either to emulate or to antagonize the functions of the naturally occurring purine nucleosides and nucleotides in the hope that specific inhibition of viral-induced enzymes may yield useful chemotherapeutic agents against viral infections.

In recent years, many such unnatural nucleosides have been described[2] which resemble at first glance the natural purine nucleosides but actually differ in some minor aspect. However, these unnatural nucleosides have often exhibited little or no biological activity. Such inactivity may be correlated with lack of appropriate binding; thus the function of the various nitrogen atoms of purine nucleosides as binding sites for certain important nucleic acid enzymes has become the subject of considerable interest.[3] The observation that N_3 of the purine type nucleosides is probably involved in stabilizing the syn conformation through intramolecular hydrogen bonding[4] has stimulated considerable activity toward the synthesis and biological evaluation of certain aza or deaza analogues of purine nucleosides.

The significance of guanine nucleotide metabolism in a variety of microbiological and mammalian systems has recently been reviewed.[5] We recently described the first chemical synthesis of 1-deazapurine[2r] and 3-deazapurine[2s] nucleoside analogues containing a bridgehead nitrogen atom. In this paper, we present a preliminary report on the synthesis and in vitro antiviral activity of the guanine, guanosine, and guanosine monophosphate analogues in the imidazo[1,2-*a*]-*s*-triazine series. This ring system, which may be regarded as 5-aza-7-deazapurine, is of particular interest since it retains both N_1 and N_3 of purine with only C_5 and N_7 interchanged.

The complete synthetic route consists of three parts: synthesis of an appropriate imidazo[1,2-*a*]-*s*-triazine; conversion of the starting imidazo[1,2-*a*]-*s*-triazine to the required nucleoside; and, finally, the phosphorylation of the nucleoside to the corresponding 5′-monophosphate. The synthesis of the imidazo[1,2-*a*]-*s*-triazine ring may be approached by starting either with an appropriate 2-aminoimidazole or with a 1,3,5-triazine derivative. During the course of the present work, Moffatt and co-workers[6] used the former procedure to prepare several imidazo-[1,2-*a*]-*s*-triazine nucleosides. We have explored the latter approach[7] to synthesize the requisite imidazo[1,2-*a*]-*s*-triazines since the starting material, cyanuric chloride, is readily available. Although the key intermediate in our synthetic approach, 2-amino-4-chloro-6-hydroxy-*s*-triazine (**2**), is reported in the literature,[8] it has not been fully characterized. We prepared compound **2** in excellent yield by the selective amination of cyanuric chloride, followed by the controlled hydrolysis of one of the halogens of 2-amino-4,6-dichloro-*s*-triazine (**3**)[9] (Scheme I). Since commercial cyanuric chloride is often contaminated with cyanuric acid, it is advisable to distill the cyanuric chloride before use for best results. Condensation of **2** with aminoacetaldehyde dimethyl acetal in aqueous basic media at reflux temperature gave crystalline 2-amino-4-(2,2-dimethoxyethylamino)-*s*-triazin-6-one (**6**) in a 68% yield. The hydrolysis of the acetal groups of **6** was achieved readily by heating **6** in 6 N hydrochloric acid on a steam bath under a stream of nitrogen. The free base, 2-amino-4-(2-hydroxyvinyleneamino)-*s*-triazin-4-one (**7**), was obtained by careful neutralization of the aqueous solution of the hydrochloride salt of **7**. Ring annulation of either **7** or the hydrochloride salt in concentrated sulfuric acid at 95 °C for 1.5 h gave crystalline 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (5-aza-7-deazaguanine, **8**)[10] in a 71% yield. The assignment of this structure was based on the elemental analysis and the fact that the NMR (D_2O–NaOD) spectrum of **8** revealed two doublets centered at δ 7.07 (J = 2.0 Hz, C_7H) and 7.34 (J = 2.0 Hz, C_6H). However, conclusive evidence for structure **8** was obtained

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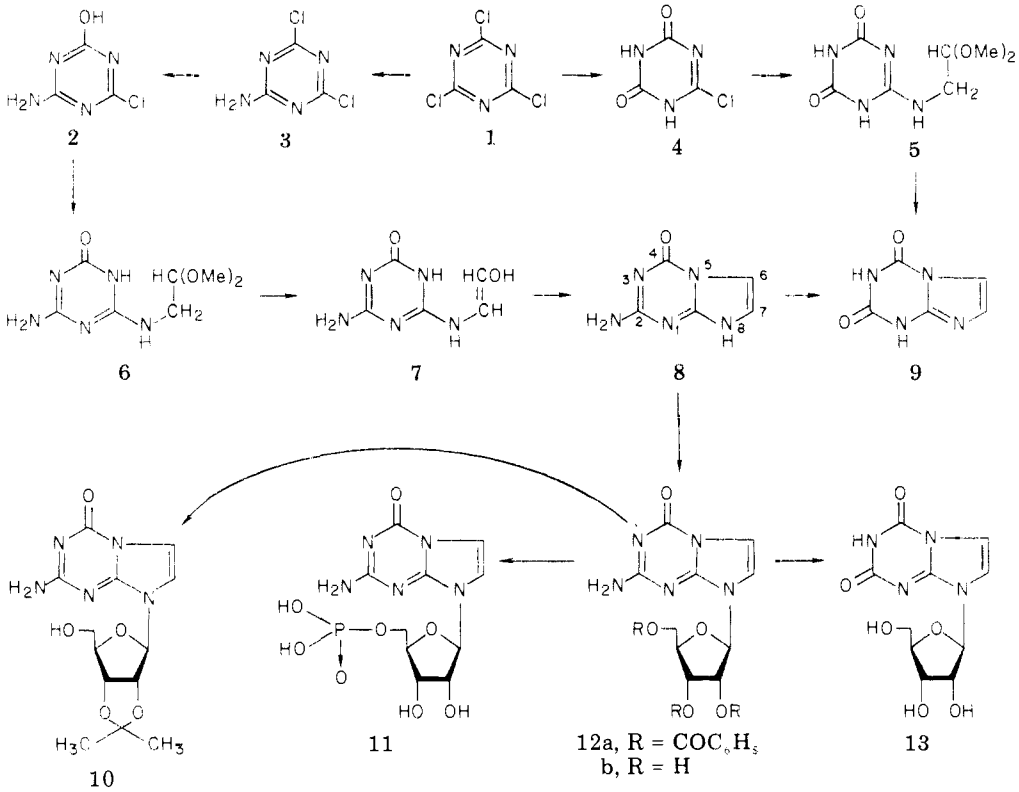
Scheme I



by carbon-13 NMR spectroscopy as discussed later. Deamination of **8** in aqueous acetic acid with barium nitrite at ambient temperature provided crystalline imidazo-[1,2-*a*]-*s*-triazine-2,4-dione (5-aza-7-deazaxanthine, **9**) in good yield. The structure of **9** was confirmed by NMR, chromatographic mobility, and elemental analysis. Alternatively, compound **9** was also obtained starting with 2-chloro-*s*-triazine-4,6-dione (**4**)[11] which in turn was obtained by the controlled hydrolysis of freshly distilled cyanuric chloride. Condensation of **4** with aminoacetaldehyde dimethyl acetal in aqueous media at reflux temperature furnished crystalline 4-(2,2-dimethoxyethylamino)-*s*-triazine-2,6-dione (**5**) in 90% yield. The hydrolysis of the protecting acetal group with 3 N hydrochloric acid, followed by ring annulation by heating with concentrated sulfuric acid at 90 °C for 1 h, afforded **9**. The identity of this compound was confirmed by rigorous comparison of the physicochemical data obtained for **9** prepared from **8**.

The glycosylation of **8** was next considered. Treatment of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one with hexamethyldisilazane in the presence of ammonim sulfate, according to the general procedure described by Wittenburg,[12] gave a gummy bis(trimethylsilyl) derivative which, without further purification, was treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in anhydrous 1,2-dichloroethane containing stannic chloride[13] at room temperature. Under these conditions and after silicic acid column chromatography, a 56.3% yield of 2-amino-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12a**) was obtained as a light yellow, chromatographically homogeneous foam. Nucleoside **12a** was the only nucleoside product which could be detected by TLC or column chromatography procedures. Debenzoylation of **12a** with methanolic sodium methoxide at ambient temperature gave a good yield of 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (5-aza-7-deazaguanosine, **12b**). Deamination of **12b** in aqueous acetic acid with barium nitrite at ambient temperature provided crystalline 5-aza-7-deazaxanthosine (**13**). The purity of these nucleosides was assured by elemental analysis and by NMR spectroscopy.

Although the anomeric configuration of **12b** could tentatively be assigned as β on the basis of several empirical rules,[14] and by a large negative specific rotation ($[\alpha]^{25}_{D}$ −25.9°), this could not be used for the unequivocal assignment of anomeric configuration, since there are no imidazo[1,2-*a*]-*s*-triazine ribonucleosides available for comparison. Therefore, a more rigorous proof for the anomeric configuration was in order for this interesting heterocyclic nucleoside series. The NMR spectra of **12b** in Me_2SO-d_6 revealed a doublet (for C_1·H) centered at δ 5.85 with a $J_{1,2}$ of approximately 5.0 Hz, which suggested the preparation of the 2′,3′-*O*-isopropylidene derivative in order to reduce the magnitude of the coupling constant to within the acceptable limits.[15] Isopropylidenation[16] of **12b** with 70% perchloric acid and 2,2-dimethoxypropane in anhydrous acetone at room temperature furnished 2-amino-8-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (**10**) in good yield. The NMR spectrum of **10** in Me_2SO-d_6 exhibited a coupling constant of 2.5 Hz for the anomeric doublet and also revealed the difference between the chemical shift of the two methyl signals of the isopropylidene group to be 0.19 ppm, a difference characteristic of the β configuration.[17] Based on these data, the β configuration for **10** and, hence, for **11**, **12b**, and **13** was assigned unequivocally. The similarities of IR and UV spectra (see the Experimental Section) of **8** and **12b**, and also the recognized influence[2p] of a bulky substituent (like the electron-donating trimethylsilyloxy group) adjacent to the potential glycosylation site, strongly suggest N_8 as the site of ribosylation.

However, the glycosylation site of **12b** is established by using carbon-13 NMR spectroscopy. Several NMR studies recently have demonstrated the potential use of carbon-13 NMR spectroscopy as a general unequivocal method for the assignment of glycosylation site in fused heteroaromatic compounds.[2q,18] The assignments were based on

Table I. Carbon-13 Chemical Shifts of the 2-Aminoimidazo[1,2-*a*]-*s*-triazin-4-one Anion, **12b**, and **16**

compd	chemical shift, δ, ppm				
	C_2	C_4	C_6	C_7	C_9
anion of **8** (**A**)	153.1	162.9	106.3	126.4	153.7
12b (**B**)	150.3	165.5	108.6	114.5	150.9
Δδ, **A**-**B**	+2.8	−2.6	−2.3	+11.9	+2.8
16[a]	149.3	157.9	102.7	110.7	139.2
	149.4				

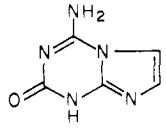
[a] In Me_2SO-d_6 containing 10% H_2O and 10% D_2O.

the reports by Grant and co-workers[19] that nitrogen protonation resulted in an upfield shift for the carbon α to the protonated nitrogen while a downfield shift was observed for the β carbon.

The carbon-13 chemical shifts of the anion of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**) as well as the nucleoside **12b** are summarized in Table I. The anion of the base **8** is formed by neutralization with lithium hydroxide in Me_2SO-d_6. The base itself is insoluble in Me_2SO-d_6. The C_6 and C_7 carbons showed large ^{13}C–^1H splittings caused by the directly attached protons. The C_7 carbon is expected to occur considerably downfield to the C_6 carbon due to the deshielding effect of the adjacent nitrogen.[20] The C_4 and C_2 carbons were assigned by comparison with the carbon-13 chemical shifts reported[21] for cytidine and uridine as well as 7-chloroimidazo[1,2-*c*]pyrimidin-5-one.[2s] The C_9 carbon is distinguished from the C_2 carbon by the appearance of a long-range proton–carbon-13 coupling which is more likely to occur at C_9.

By comparing the chemical shifts of the anion of **8** and those of nucleoside **12b**, a large upfield shift of 11.9 ppm is observed for C_7 and a small downfield β shift of 2.3 ppm is observed for the C_6 carbon, indicating that N_8 is the ribosylation site. Furthermore, the ribosylation site is confirmed by the appearance of multiplet structures for each arm of the C_7 doublet in the nucleoside **12b** in the proton-coupled spectrum. In the base anion, each arm of the C_7 doublet is further split by the H-6 proton with a geminal coupling constant ($^2J_{C_7-H_6}$) of 10 Hz. In the case of nucleoside **12b**, the spin splitting pattern for C_7 was further complicated by the vicinal coupling ($^3J_{C_7-H_1'}$) of ~5 Hz caused by the anomeric proton resulting in the appearance of four peaks for each arm of the C_7 doublet. Since the ^{13}C–^1H splitting pattern for the remaining carbons in the nucleoside and base anion is essentially identical, the observed vicinal coupling indicates that the ribose must be attached to N_8. The magnitude of the vicinal coupling constant is known to depend on the torsion angle[22] so that this long-range interaction may not be observable in cases where the coupling constant is small. However, in favorable cases, this long-range nuclear spin coupling of the anomeric proton can provide direct information on the glycosylation site.

To determine whether the structure of **8** corresponds to the guanine analogue or that of the possible isoguanine analogue, 4-aminoimidazo[1,2-*a*]-*s*-triazin-2-one (**14**), we



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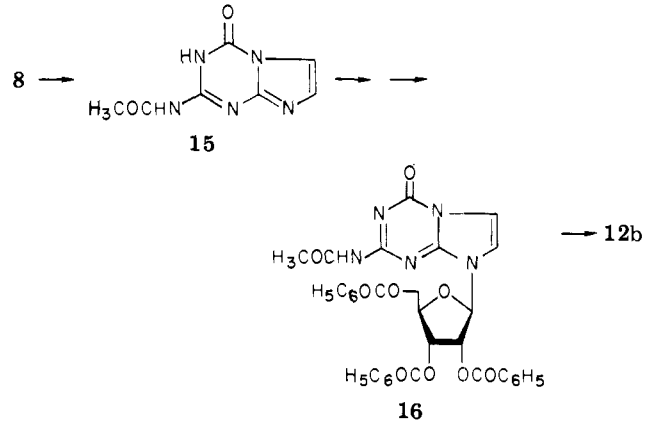
have also synthesized 2-acetamidoimidazo[1,2-*a*]-*s*-triazin-4-one (**15**) and the corresponding blocked nucleoside **16** (Scheme II). Acetylation of **8** with acetic anhydride

Scheme II



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16

a reflux temperature in the presence of phosphoric acid gave a 70.8% yield of **15**. Condensation of the trimethylsilyl derivative of **15** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride was accomplished using exactly the same conditions as described above for **12a**, furnishing an 85% yield of 2-acetamido-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (**16**). Careful investigation of the reaction mixture furnished chromatographic (TLC) evidence of the presence of another nucleoside product in a very small amount. However, no attempt was made to isolate it. Removal of the protecting groups of **16** by the treatment with methanolic sodium methoxide at room temperature provided a good yield of **12b**, establishing the structure (site of glycosylation and anomeric configuration) of **16**. The carbon-13 chemical shifts of **16** in Me_2SO-d_6 containing 10% H_2O and 10% D_2O are summarized in Table I. A doublet was observed for the C_2 carbon in **16**, as a result of deuterium substitution of the exchangeable protons. Recently, Newmark and Hill[23] have observed that the carbons α to the NH in amides show a 0.1-ppm isotope shift of the CNH compared to the CND when 10% H_2O and 10% D_2O were added to the amide solution. The 0.1-ppm deuterium isotope splitting observed for the C_2 carbon is consistent with our assignment of the structure 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one for **8**.

Direct phosphorylation[24] of unprotected **12b** with phosphorus oxychloride using trimethyl phosphate as solvent at 0–5 °C for 5 h, followed by hydrolysis, furnished a rather low yield (27.5%) of the N-bridgehead GMP analogue, 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one 5′-monophosphate (**11**), which was isolated in the free acid form after ion-exchange chromatography. The structure of this GMP analogue was confirmed by the NMR spectrum and elemental analysis. The purity was assured by the homogeneity in several thin-layer systems and on paper electrophoresis (phosphate buffer, pH 7.2, and borate buffer, pH 9.2).

Antiviral Evaluation. Inhibition of the virus-induced cytopathic effect (CPE) was used as the initial indicator of antiviral activity. CPE was observed in human carcinoma of the nasopharynx (KB) cells after infection with type 1 herpes virus, type 3 parainfluenza virus, or type 13 rhino virus. In this system, monolayers (19–24 h) of cells were exposed to 320 $CCID_{50}$ of virus and concentrations of each compound ranging in one-half log dilutions from 1000 to 1 μg/mL were added within 15 min. The degree of CPE inhibition and compound cytotoxicity were observed microscopically after 72 h of incubation at 37 °C and scored numerically in order to calculate a virus rating (VR) as previously described.[25] Significance of antiviral activity in terms of VR's has been assigned as follows: 0.5,

Table II. Comparative in Vitro Antirhinovirus Activity of Ribavirin and Certain Imidazo[1,2-*a*]-*s*-triazines

no.	compd	virus ratings[a] 1A[c]	2[c]	8[c]	13[c]	30[c]
8	2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one	0.6	0.8	0.6	0.6	0.6
9	imidazo[1,2-*a*]-*s*-triazine-2,4-dione	*b*	*b*	*b*	0.1	*b*
12a	2-amino-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one	*b*	*b*	*b*	0.1	*b*
12b	2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one	0.5	0.6	0.4	0.4	0.2
11	2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one 5′-monophosphate	0.3	0.7	0.4	0.3	0.2
13	8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazine-2,4-dione	*b*	*b*	*b*	0.1	*b*
	1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (Ribavirin)	0.7	0.7	0.7	0.6	0.6

[a] The virus rating (VR) was determined by comparing CPE development in drug-treated cells (T) and virus control cells (C). The CPE value (0–4) assigned to T for each drug level was subtracted from that of C, and the differences (C – T) were totaled. If partial toxicity was evident at any drug level, the C – T of that level was divided by 2. The sum of all C – T values was then divided by ten times the number of test cups used per drug level. [b] Not determined. [c] Rhino virus type.

slight or no activity; 0.5–0.9, moderate activity; and ≥1.0, marked activity. Only rhino virus activity was observed for this class of synthetic compounds which led us to the evaluation of their efficacy as antiviral agents against four additional rhino viruses. The results of a single experiment in parallel with 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (Ribavirin)[26] are shown in Table II. Of the compounds tested, 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**) and 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12b**) had approximately equal, moderate antiviral activity against all five rhino viruses, comparable with Ribavirin. Slight antiviral activity was observed with 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one 5′-monophosphate (**11**). Essentially no antiviral activity was seen with 5-aza-7-deazaxanthosine (**13**) and the other compounds.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in Me_2SO-d_6 as well as in D_2O–NaOD using DSS as an internal standard. The presence of water as indicated by elemental analyses was verified by NMR. ^{13}C NMR spectra of 5% Me_2SO-d_6 solutions were obtained at 22.6 MHz with a Bruker HX-90E Fourier transform spectrometer, equipped with a Bruker-Nicolet data system, Model B-NC-12. Chemical shifts were measured from Me_2SO-d_6 and converted to the Me_4Si scale using the relationship δ Me_4Si = δ Me_2SO-d_6 + 39.5 ppm. Ultraviolet spectra (UV, sh = shoulder) were recorded on a Cary Model 15 spectrophotometer and infrared spectra (IR) on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and the results are within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was run on silica gel F-254 (EM Reagents) plates. ICN Woelm silica gel (70–230 mesh) was used for column chromatography. Detection of components on TLC was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30 °C.

2-Amino-4-chloro-6-hydroxy-*s*-triazine (2). 2-Amino-4,6-dichloro-*s*-triazine[9] (**3**, 16.5 g, 0.1 mol) was suspended in 250 mL of water containing sodium hydroxide (4.4 g, 0.11 mol), and the mixture was stirred at room temperature for 15 h. The mixture was filtered to remove 5.0 g of unreacted starting material before the cooled (0–5 °C), clear, colorless filtrate was neutralized (pH 6.8–7.0) with glacial acetic acid. The white solid that separated was collected, washed with cold water (5 × 25 mL), and dried. It was crystallized from hot water to yield 7.5 g (73.4%, based on the recovery of the starting material): mp >320 °C (lit.[8] mp 300 °C); UV λ_{max} (pH 1) 255 nm (ε 7400); UV λ_{max} (pH 7) 250 nm (ε 4600); UV λ_{max} (pH 11) 247 nm (ε 3600). Anal. ($C_3H_3ClN_4O$, 146.54) C, H, N.

2-Amino-4-(2,2-dimethoxyethylamino)-*s*-triazin-6-one (6). A suspension of 2-amino-4-chloro-6-hydroxy-*s*-triazine (**2**, 15.0 g, 0.102 mol) in 250 mL of water was treated with sodium hydroxide (4.095 g, 0.102 mol), and the mixture was stirred to obtain a clear solution which was treated with aminoacetaldehyde dimethyl acetal (12.9 g, 0.12 mol). The mixture was heated under gentle reflux for 2.5 h with stirring and then cooled to room temperature. The crystalline solid that separated was collected and washed with cold water (2 × 25 mL). Recrystallization from a large excess of water gave the title compound as needles: 15.0 g (68.0%); mp 285 °C dec. Anal. ($C_7H_{13}N_5O_3$, 215.21) C, H, N.

2-Amino-4-(2-hydroxyvinyleneamino)-*s*-triazin-4-one (7). A solution of 2-amino-4-(2,2-dimethoxyethylamino)-*s*-triazin-6-one (**6**, 8.0 g, 0.037 mol) in 6 N hydrochloric acid (160 mL) was heated on a steam bath in an evaporating dish under a stream of nitrogen to dryness. The residue was coevaporated with water (2 × 50 mL) followed by ethanol (2 × 50 mL). The dry residue was triturated with cold ethanol and filtered. The residue was washed with cold ethanol (2 × 10 mL) followed by ether and dried to yield the dihydrochloride salt. The salt was dissolved in water (100 mL) and carefully neutralized with solid sodium bicarbonate before it was stored in the refrigerator overnight. The white solid that separated was collected and crystallized from water as needles to yield 4.9 g (78.0%): mp >310 °C (begins to discolor above 200 °C); UV λ_{max} (pH 1) 232 nm (ε 20400); UV λ_{max} (pH 7 and 11) 234 nm (ε 8650). Anal. ($C_5H_7N_5O_2$, 169.15) C, H, N.

2-Aminoimidazo[1,2-*a*]-*s*-triazin-4-one (5-Aza-7-deazaguanine, 8). A solution of 2-amino-4-(2-hydroxylvinyleneamino)-*s*-triazin-4-one (**7**, 6.0 g, 0.035 mol) in concentrated sulfuric acid (16.0 mL) was heated at 95 °C for 1.5 h with stirring and was poured (after cooling to room temperature) into ice–water (50 mL) containing sodium carbonate (20.0 g). The pH of the solution was adjusted to 6.5–7.0 using additional base before it was stored in the refrigerator overnight. The solid that deposited was collected, washed with cold water (3 × 15 mL), and then crystallized from water with the aid of Norit as tiny, off-white needles: 3.8 g (70.9%); mp >330 °C; NMR (D_2O–NaOD) δ 7.07 (d, J = 2.0 Hz, C_7H), 7.34 (d, J = 2.0 Hz, C_6H); UV λ_{max} (pH 1) 242 nm, sh (ε 9400), 261 (13600); UV λ_{max} (pH 7) 252 nm (ε 12000); UV λ_{max} (pH 11) 255 nm (ε 10600). Anal. ($C_5H_5N_5O$, 151.13) C, H, N.

4-(2,2-Dimethoxyethylamino)-*s*-triazine-2,6-dione (5). To a solution of 2-chloro-*s*-triazine-4,6-dione disodium salt[11] (**4**, 1.91 g, 0.01 mol) in water (10 mL) was added aminoacetaldehyde dimethyl acetal (1.15 g, 0.011 mol), and the mixture was heated under gentle reflux for 2 h with efficient stirring. The hot solution was filtered and the filtrate was cooled before it was acidified (pH 6.0) with glacial acetic acid. The white solid that separated was collected, washed with cold water (3 × 10 mL), and crystallized from a large excess of water to yield 2.1 g (89.6%): mp 240 °C, melts, resolidifies, and melts with decomposition at 280 °C. Anal. ($C_7H_{12}N_4O_4 \cdot H_2O$, 234.21) C, H, N.

Imidazo[1,2-*a*]-*s*-triazine-2,4-dione (5-Aza-7-deazaxanthine, 9). Method 1. A solution of 4-(2,2-dimethoxyethylamino)-*s*-triazine-2,6-dione (**5**, 10.0 g, 0.042 mol) in 3 N hydrochloric acid (100 mL) was heated on a steam bath in an evaporating dish under a stream of nitrogen to dryness. The residue was coevaporated with water (2 × 50 mL) followed by ethanol (2 × 50 mL) and was triturated with ethanol and chilled. The white solid was collected, washed with ethanol (50 mL) followed by anhydrous ether, and dried to yield 6.5 g of 4-(2-hydroxyvinyleneamino)-*s*-triazine-2,6-dione hydrochloride. A solution of the hydrochloride salt in concentrated sulfuric acid (15.0 mL) was heated at 90 °C for 1 h with stirring under anhydrous conditions before it was poured (after cooling to room temperature) into ice–water (50 mL) containing sodium carbonate (20.0 g). The pH of the solution was adjusted to 4 using additional base before it was allowed to stand in the refrigerator overnight. The crystalline solid that separated was collected, washed with cold water (2 × 25 mL), and then recrystallized from water as needles to yield 3.9 g (60.0%): mp >320 °C; NMR (Me_2SO-d_6) δ 7.10 (d, J = 2.0 Hz, C_7H), 7.42 (d, J = 2.0 Hz, C_6H), 11.90 (br, 2, NH); UV λ_{max} (pH 1) 231 nm (ε 8900), 248 (8100); UV λ_{max} (pH 7) 234 nm (ε 9600), 251 (9300); UV λ_{max} (pH 11) 246 nm (ε 9600). Anal. ($C_5H_4N_4O_2$, 152.11) C, H, N.

Method 2. 2-Aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**, 0.5 g) and barium nitrite (1.5 g) were dissolved in hot water (10 mL). The solution was cooled to room temperature rapidly and treated with glacial acetic acid (2.0 mL) before the reaction mixture was stirred at room temperature for 20 h in a loosely stoppered reaction flask. The barium ions were precipitated with 1 N sulfuric acid and the barium sulfate was filtered off before the filtrate was evaporated to dryness. The residue was crystallized twice with water to yield 0.28 g (55.6%), mp >320 °C. Mixture melting point and spectral and chromatographic properties are identical with those of the compound prepared by method 1.

2-Amino-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (12a). A mixture of dry 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**, 3.02 g, 0.02 mol), freshly distilled hexamethyldisilazane (15.0 mL), and a few crystals of ammonium sulfate (25 mg) was heated at reflux temperature for 15 h with the exclusion of moisture. The clear, slightly brown solution was fractionated by distillation to remove excess of hexamethyldisilazane and the residual gum was presumed to be the bis(trimethylsilyl) derivative which was used without further purification. To a solution of the above trimethylsilyl derivative in anhydrous 1,2-dichloroethane (100 mL) was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10.09 g, 0.02 mol) followed by stannic chloride (7.0 g, 0.027 mol). The reaction mixture was protected from moisture and stirred for 30 h at ambient temperature. The brown reaction solution was then poured into 200 mL of chloroform, with efficient stirring and keeping the mixture basic at all times. The resulting emulsion was filtered through a Celite pad which was washed with chloroform (3 × 25 mL). The combined organic layer was washed with water (2 × 100 mL) before it was dried over anhydrous sodium sulfate. The solvent was evaporated to a light brown foam which was chromatographed on an open-bed, silica gel column (5 × 75 cm) prepacked in ethyl acetate and eluted with ethyl acetate–water–1-propanol (4:2:1, v/v, upper phase). The band containing the requisite product was collected and the solvent evaporated to leave 6.8 g (56.30%) of a light yellow, chromatographically homogeneous foam: $[\alpha]^{25}_D$ −32.0° (*c* 1.0, Me_2SO); UV λ_{max} (pH 1) 233 nm (ε 45 800), 268 (18 800); UV λ_{max} (pH 7) 235 nm (ε 39 400), 263 sh (24 700); UV λ_{max} (pH 11) 234 nm (ε 42 300), 260 sh (20 600). Anal. ($C_{31}H_{25}N_5O_8 \cdot 0.5H_2O$, 604.57) C, H, N.

2-Amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (12b). Method 1. To a solution of 2-amino-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12a**, 6.04 g, 0.01 mol) in anhydrous methanol (200 mL) was added 1 N sodium methoxide in methanol until the pH of the solution was 8.5–9.0, and the resulting solution was stirred at ambient temperature for 20 h with the exclusion of moisture. The solid that separated was collected by filtration (A) and crystallized from water with the aid of decolorizing carbon as microneedles. The filtrate from above (A) was neutralized with glacial acetic acid before it was evaporated to dryness. The residue was dissolved in water (100 mL) and the aqueous solution was extracted with chloroform (4 × 50 mL) before it was decolorized with carbon. The aqueous filtrate was concentrated to ~15 mL and stored in the refrigerator overnight. The crystalline solid that deposited was collected and the combined crystals were recrystallized from water to yield 2.2 g (77.7%): mp 251–252 °C dec; $[\alpha]^{25}_D$ −25.9° (*c* 1.0, H_2O); NMR (Me_2SO-d_6) δ 5.85 (d, J = 5.0 Hz, C_1·H), 7.0 (br s, NH_2), 7.47 (d, J = 2.0 Hz, C_7H), 7.55 (d, J = 2.0 Hz, C_6H), and other sugar protons; UV λ_{max} (pH 1) 238 nm, sh (ε 8800), 264 (14 700); UV λ_{max} (pH 7) 210 nm (ε 28 800), 256 (13 800); UV λ_{max} (pH 11) 217 nm (ε 4700), 256 (13 800); IR 1620 (C=O of heterocycle), 3360 cm^{-1} (NH_2). Anal. ($C_{10}H_{13}N_5O_5$, 283.24) C, H, N.

Method 2. 2-Acetamido-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**16**, 3.18 g, 0.005 mol) was treated with 1 N sodium methoxide in a similar fashion to that described in method 1 above to give 1.25 g (88.3%) of a product with identical melting point and IR, NMR, UV, TLC, and elemental analyses as that obtained in method 1.

8-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-*s*-triazine-2,4-dione (13). 2-Amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12b**, 2.83 g, 0.01 mol) and barium nitrite (9.0 g) were dissolved in hot water (40 mL), and the solution was cooled to room temperature rapidly before it was treated with glacial acetic acid (9.0 mL). The mixture was stirred at room temperature for 20 h in a loosely stoppered, round-bottom flask. The barium ions were precipitated with 1 N sulfuric acid and the barium sulfate was filtered off. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (4 × 75 cm) prepacked in ethyl acetate and eluted with ethyl acetate–water–1-propanol (4:2:1, v/v, upper phase). The appropriate fractions were pooled and the solvent was evaporated before the residue was triturated with cold anhydrous ethyl ether. The amorphous solid that separated was collected and rechromatographed on preparative TLC (silica gel) using the above solvent system to yield 1.05 g (32.8%) as amorphous solid: mp >220 °C dec; UV λ_{max} (pH 1 and 7) 233 nm (ε 10 800), 256 (10 200); UV λ_{max} (pH 11) 247 nm (ε 11 900). Anal. ($C_{10}H_{12}N_4O_6 \cdot 2H_2O$, 320.26) C, H, N.

2-Amino-8-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (10). 2,2-Dimethoxypropane (2.0 mL) and 70% perchloric acid (2.0 mL) were added to dry acetone (400 mL). The mixture was protected from moisture and stirred at room temperature for 5 min before 2-amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**12b**, 1.42 g, 0.005 mol) was added in one portion. The mixture was stirred for 3 h and pyridine (2.0 mL) was added. The volume was reduced to about 25 mL; 10% aqueous sodium carbonate solution (40 mL) was added before the remaining acetone was removed. Cold water (20 mL) was added to the aqueous solution which was then left at 5 °C overnight. The crystals that deposited were collected and recrystallized from aqueous ethanol as needles to yield 1.1 g (67.8%): mp 222–224 °C; NMR (Me_2SO-d_6) δ 1.34 (s, CH_3), 1.53 (s, CH_3), 5.95 (d, J = 2.5 Hz, C_1·H), 7.03 (br s, NH_2), 7.41 (d, J = 2.0 Hz, C_7H), 7.52 (d, J = 2.0 Hz, C_6H), and other sugar protons; UV λ_{max} (pH 1) 237 nm, sh (ε 7100), 265 (11 600); UV λ_{max} (pH 7) 210 nm (ε 22 300), 256 (10 600); UV λ_{max} (pH 11) 216 nm (ε 2300), 255 (11 000). Anal. ($C_{13}H_{17}N_5O_5$, 323.21) C, H, N.

2-Amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one 5′-Monophosphate (11). Redistilled phosphorus oxychloride (1.0 g) and trimethyl phosphate (10.0 mL) were cooled to 0 °C in an ice bath. Dry 2-amino-8-(β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (**12b**, 1.0 g, 0.0035 mol) was added all at once and the mixture was stirred at 0–5 °C until solution was complete (20 min) before it was allowed to stand in the refrigerator (3–4 °C) for 4.5 h with occasional agitation. The clear, colorless reaction mixture was poured into ice–water (50 mL) containing sodium carbonate (1.5 g) with efficient stirring and external cooling. The mixture was occasionally stirred in the ice bath for 1 h and the pH was monitored at 5–6 by adding sodium carbonate when needed. The pH-stabilized solution was extracted with ether (2 × 50 mL) and the aqueous phase was concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution; the pH was adjusted to 6–7 and then applied to a column containing Dowex 1-X2 (100–200 mesh, formate form, 50 mL). The resin was washed with water (2.5 L) to remove

unreacted **12b** and the inorganic salts. The compound was obtained by gradient elution (0.1 M formic acid to water). The eluent containing the compound was pooled, concentrated to about 50 mL, frozen, and lyophilized to yield 0.42 g of the 5′-monophosphate which was slightly impure on TLC (silica gel, 2-propanol–concentrated ammonium hydroxide–water, 7:1:2, v/v). The impure phosphate was dissolved in water (10 mL) and passed through a column containing fresh formate resin (50 mL). It was eluted as above to yield 0.37 g (27.5%) of analytically pure 11 as an amorphous powder after workup as above: mp 205 °C dec; $[\alpha]^{25}_D$ −19.0° (*c* 1.0, H_2O); NMR (Me_2SO-d_6) δ 5.85 (d, *J* = 5.5 Hz, C_1·H), 7.05 (br s, NH_2), 7.41 (d, *J* = 2.4 Hz, C_7H), 7.58 (d, *J* = 2.5 Hz, C_6H), and other sugar protons; UV λ_{max} (pH 1) 239 nm, sh (ε 7150), 265 (11 650); UV λ_{max} (pH 7) 211 nm (ε 22 150), 257 (10 900); UV λ_{max} (pH 11) 257 nm (ε 10 900). Anal. ($C_{10}H_{14}N_5O_8P·H_2O$, 381.23) C, H, N.

2-Acetamidoimidazo[1,2-*a*]-*s*-triazin-4-one (15). A suspension of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (**8**, 4.53 g, 0.03 mol) in acetic anhydride (100 mL) was heated under reflux with the exclusion of moisture. A drop of phosphoric acid (reagent grade, 85%) was added, and complete dissolution was then attained after refluxing for 2–3 min. Refluxing was continued for 1 h before the acetic anhydride was removed in vacuo. The residual syrup was triturated with cold water (100 mL) for 1 h and then refrigerated overnight. The solid that separated was collected, washed with water (3 × 10 mL), and crystallized twice from water to yield 4.1 g (70.8%): mp 312–313 °C; NMR (Me_2SO-d_6) δ 2.24 (s, 3, acetyl CH_3), 7.42 (d, *J* = 1.5 Hz, C_7H), 7.57 (d, *J* = 1.5 Hz, C_6H), 11.40 (br, NH). Anal. ($C_7H_7N_5O_2$, 193.16) C, H, N.

2-Acetamido-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (16). A mixture of dry 2-acetamidoimidazo[1,2-*a*]-*s*-triazin-4-one (**15**, 1.93 g, 0.01 mol; dried at 80 °C over P_2O_5 under vacuum overnight), freshly distilled hexamethyldisilazane (8 mL), and a few crystals of ammonium sulfate (15 mg) was heated at reflux temperature for 20 h with the exclusion of moisture. The suspension was fractionated by distillation to remove excess of hexamethyldisilazane, and the residual solid [presumed to be the bis(trimethylsilyl) derivative] was dissolved in anhydrous 1,2-dichloroethane (50 mL). To the solution was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (5.05 g, 0.01 mol) followed by stannic chloride (3.5 g, 0.0135 mol), and the mixture was stirred at ambient temperature under anhydrous conditions for 45 h. The slightly brown reaction solution was then poured into a cold, saturated aqueous sodium bicarbonate solution (100 mL) containing chloroform (100 mL), with stirring and keeping the mixture basic at all times. The resulting emulsion was filtered through a Celite pad which was washed with chloroform (3 × 25 mL). The combined organic layer was washed with water (2 × 50 mL) before it was dried over anhydrous sodium sulfate. The solvent was evaporated and the residual cream-colored foam was dissolved in chloroform (2 mL). The solution was applied to an open-bed, silica gel column (2.5 × 60 cm) and the column was eluted with chloroform–acetone (9:1, v/v). The fractions containing the desired product were pooled and the solvent was evaporated to leave a chromatographically homogeneous foam which was triturated with anhydrous ether to yield 5.4 g (84.7%) of an amorphous solid, mp >150 °C (softens). Anal. ($C_{33}H_{27}N_5O_9$, 673.06) C, H, N.

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Antiviral Activity of Some β-Diketones. 4. Benzyl Diketones. In Vitro Activity against Both RNA and DNA Viruses

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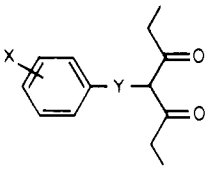
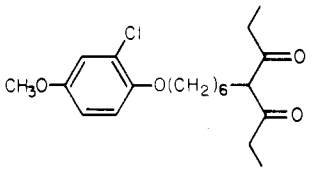
The synthesis and in vitro antiviral evaluation of a series of substituted benzyl β-diketones are described. The introduction of a styryl group onto the phenyl ring enhanced activity against herpesvirus type 2. The 4-methoxystyryl homologue 8 was evaluated extensively in vitro and was found to be effective against both RNA and DNA viruses. Compound 8 was evaluated in the mouse vagina against herpes simplex type 1 and produced a significant increase in survival rate as well as in survival time.

We have recently reported on the broad-spectrum in vitro antiviral activity of some β-diketones of the general structure I.[1,2] Several members in both of these series have



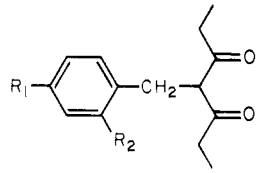
Ia, Y = $(CH_2)_n$
b, Y = $O(CH_2)_n$

exhibited activity against both DNA and RNA viruses, and one compound (II), designated as WIN 38,020, is currently



II

being considered for clinical trials against herpetic infections. This paper deals with the antiviral activity of a related series of compounds III where essentially the alkyl bridge in I has been replaced by a benzyl group.



III

Chemistry. The initial compound prepared in this series (9) was synthesized according to Scheme I. Ketone 1[3] was reduced with diborane in THF to give alcohol 2 in quantitative yield. The compound was not purified but treated directly with *p*-toluenesulfonic acid to give the stilbene 3.[4] The ultraviolet absorption spectra of 3 exhibited peaks characteristic of *trans*-stilbenes (see the Experimental Section). Furthermore, GC analysis indicated the presence of only one component. Consequently, 3 was assigned the trans configuration. The reaction of 3 with cuprous cyanide gave 4 in excellent yield. The melting point of 4 was identical with that of the compound prepared by Dale[5] which was identified as the trans isomer. The nitrile 4 was hydrolyzed with ethanolic hydrogen chloride to give the ester 5 which was reduced with lithium aluminum hydride to alcohol 6. Conversion of alcohol 6 with hydrogen bromide to 7 proceeded smoothly as did the alkylation of the lithium salt of heptanedione to produce 8. Demethylation of 8 with boron tribromide gave 9 in 19% yield.

As our synthetic program progressed, an alternate and more direct synthetic approach was investigated and is shown in Scheme II. The phosphonate ester 10 was coupled with the appropriate aldehyde according to the procedure of Seus and Wilson[6] to give the *trans*-stilbenes 11–14 which were converted with NBS to bromides 15–17.

The 2-chloro-4-methoxyphenyl homologue 23 was prepared by the procedure shown in Scheme III and was subsequently converted to 24.

The reaction of 2-chloro-4-methoxyphenyldiazonium chloride with 4-methylcinnamic acid[7] gave 21 in 23.3% yield as a single component and was assigned the trans configuration on the basis of its UV spectra.

Compound 27 was prepared as described in Scheme IV.

The synthesis of compound 36 required several steps which are outlined in Scheme V. 4-Bromo-4′-methoxybenzophenone 28[8] was converted to the nitrile 29 via treatment with cuprous cyanide in DMF. Hydrolysis of 29 with ethanolic hydrogen chloride provided ester 30 which was hydrogenated with 10% palladium on charcoal to the ester 31. Acid 32, obtained from 31 by hydrolysis with aqueous sodium hydroxide, was reduced with sodium in isoamyl alcohol producing a mixture of 33 and partially reduced material. This mixture was further reduced with 10% palladium on charcoal to give 33 as a cis–trans mixture. The next series of steps consisted of the reduction of 33 with diborane in THF followed by treatment of the resulting alcohol 34 with phosphorous tribromide and, finally, the reaction of bromide 35 with the lithium salt of 3,5-heptanedione to give 36 as a mixture of cis–trans isomers.

Compounds 43 and 44 were prepared according to the procedure outlined in Scheme VI and compounds 45–48

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