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5,6-UNSATURATED HEXOFURANOSYL GLYCOSIDES AND 5′,6′-UNSATURATED HEXOFURANOSYL NUCLEOSIDES

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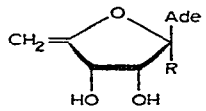
ABSTRACT

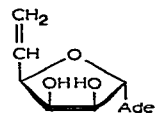
Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside, prepared from methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-D-mannofuranoside with sodium iodide in 2-butanone, was acetolyzed and the product coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of the *N*-benzoyl group with picric acid afforded 9-(2,3-di-*O*-acetyl-5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine. In a similar manner, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranoside was prepared from L-mannose and converted into 9-(2,3-di-*O*-acetyl-5,6-dideoxy-β-L-*xylo*-hex-5-enofuranosyl)adenine, further de-esterified to give the free nucleoside. 2,3:5,6-Di-*O*-isopropylidene-α-L-mannofuranosyl chloride, prepared from L-mannose, gave 9-(2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine, hydrolyzed into 9-α-L-mannofuranosyladenine. Treatment with methanesulfonyl chloride gave the 5′,6′-dimethanesulfonate, which gave with sodium iodide in acetone the 5′,6′-unsaturated nucleoside, further hydrolyzed into 9-(5,6-dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine.

INTRODUCTION

Unsaturated pentofuranosyl nucleosides have been prepared from purine and pyrimidine nucleosides having the double-bond located between the 1′,2′ (Ref. 1), 2′,3′ (Ref. 2), and 3′,4′ (Ref. 3) positions. All of these aldofuranosyl nucleosides have the site of unsaturation within the carbohydrate ring. Nucleosides having an exocyclic 4′,5′ double-bond have been prepared[4,5] and have also been isolated as elimination products during attempts[6,7] at nucleophilic substitution at C-5′. One of these nucleosides, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**1**), exhibited an antibacterial activity[4] similar to that of the ketohexofuranosyl nucleoside antibiotic decoyinine (Angustmycin A, **2**), a compound also reported to have antitumor activity[8]. It was of interest, therefore, to explore further the significance of exocyclic double-bonds of nucleosides in relation to the biological, especially antitumor and antibacterial activity.



1 R = H
2 R = CH_2OH



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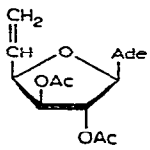

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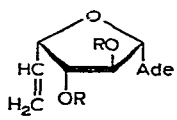


5 R = Ac
6 R = H

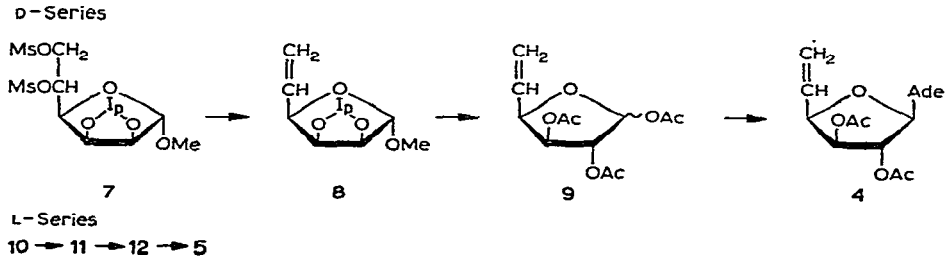
Ade = Adenine

In past work from this laboratory[9,10], hexofuranosyl nucleosides were synthesized that are unsaturated between C-5′ and -6′ and, therefore, the site of the double bond was located outside the furanose ring. One of these compounds, 9-(5,6-dideoxy-α-D-*lyxo*-hex-5-enofuranosyl)adenine (**3**) had antibacterial activity and another related nucleoside derivative, 9-(2,3-di-*O*-acetyl-5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine (**4**) was active against leukemia L1210 cells *in vitro*[11]. It was desirable to improve the synthesis of **4** and to synthesize other related hexofuranosyl nucleosides. The previous[10] two syntheses of **4**, both starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose were time-consuming and tedious. Furthermore, the method of olefin formation from the preformed nucleoside, although smoothly performed in the preparation[9] of **3**, was not achieved with a good yield in the case of **4**, because of competing anhydronucleoside formation during the sodium iodide–acetone reaction at elevated temperatures. Indeed, the synthesis of **4** was best achieved from a preformed, unsaturated carbohydrate derivative[10]. This report describes the preparation of 5,6-unsaturated glycosides and, from them, the desired unsaturated nucleosides.

RESULTS AND DISCUSSION

The preparation of the enantiomeric 9-(2,3-di-*O*-acetyl-5,6-dideoxy-β-*xylo*-hex-5-enofuranosyl)adenines (**4** and **5**) started from D- and L-mannose, rather than from D- and L-glucose. Recently, a remarkably simple and rapid preparation of methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-D-mannofuranoside (**7**) from D-mannose was reported[12], and this preparation has been scaled up many times and utilized in the synthesis of 6-deoxyhexoses[13]. In a manner similar to that used with D-mannose, L-mannose was converted[12,13] into methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-L-mannofuranoside (**10**). Treatment of **7** and **10** with sodium iodide in boiling 2-butanone gave the 5,6-unsaturated glycosides, methyl 5,6-dideoxy-2,3-*O*-

isopropylidene-α-D(and L)-*lyxo*-hex-5-enofuranoside (**8** and **11**), respectively. This reaction required nearly 24 h for completion, and the products **8** and **11** were obtained in very high yields after purification by distillation. Although **8** does not appear to have been described in the literature, **11** has previously been prepared from methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-L-rhamnofuranoside as a minor product during attempts at nucleophilic substitution[14].

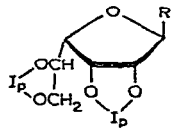


For the conversion of the glycosides **8** and **11** into the enantiomeric 1,2,3-tri-*O*-acetyl-5,6-dideoxy-*xylo*-hex-5-enofuranoses (**9** and **12**), the conditions, first described by Jerkeman[15], have recently been developed into a workable synthetic procedure[13,16]. The limitations of this epimerization have been studied[17–19] and at least two mechanisms[15,17] have been proposed to explain it. The triacetates **9** and **12** were utilized as crude syrups in the synthesis of the nucleoside **4** and its L form **5**.

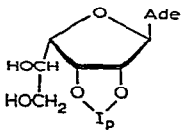
The number of coupling procedures which can be utilized for the preparation of nucleosides are obviously limited by the presence of the unsaturated group and for this reason the titanium tetrachloride procedure[20] was used, although presumably the fusion method [21] may be an alternative choice. Coupling of syrupy **9** and **12** with 6-benzamidochloromercuripurine in the presence of titanium tetrachloride in 1,2-dichloroethane gave crude products, isolated as picrates[22], which were converted[23] into the crystalline nucleosides **4** and **5**. Removal of the acetyl groups of **5** in methanolic sodium methoxide gave 9-(5,6-dideoxy-β-L-*xylo*-hex-5-enofuranosyl) adenine (**6**) which, like its enantiomer[10], was obtained only as an amorphous powder.

An attempt to prepare nucleoside **3** from **8** failed primarily because conditions could not be found that would selectively remove the isopropylidene group and afford the methyl glycoside. The original intention was to block OH-2 and -3 as the benzoic esters and proceed to form the nucleoside in a manner similar to that recently used to prepare 9-α-D-rhamnofuranosyladenine[24]. Application of this route to form 9-(5,6-dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine (**19**) was attempted in order to reduce the number of derivatives of L-mannose that had to be prepared. However, since it was not successful, the synthesis of **19** was performed as previously described[9,25] for **3**. L-Mannose was converted in two steps into 2,3:5,6-di-*O*-isopropylidene-α-L-mannofuranosyl chloride (**14**), which was purified by distillation. The coupling reaction was performed by the method of Davoll and Lowy[26] and, after

selective removal of the *N*-benzoyl and 5′,6′-isopropylidene groups, 9-(2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (**15**) was obtained in crystalline form. Mesylation of **15** gave syrupy **17** which was treated with sodium iodide in acetone to afford 9-(5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranosyl)adenine (**18**). Acid hydrolysis of **18** gave **19**, which had been previously isolated as a minor elimination product from 9-(2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-L-rhamnofuranosyl)-adenine[7]. In addition, acid hydrolysis of **15** gave 9-α-L-mannofuranosyladenine (**16**). Weak antitumor activity[11,27] and inhibition of adenine phosphoribosyl transferase of Ehrlich ascites tumor cells[28] has been observed with the D enantiomer. An alternative and less expensive route to **18** may proceed from D-gulose *via* the known 9-(2,3-*O*-isopropylidene-β-D-gulofuranosyl)adenine[29], if future biological studies should warrant large-scale synthesis.



13 R = OH
14 R = Cl



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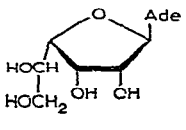

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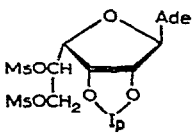

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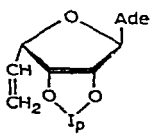

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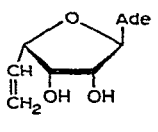

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EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage, and optical rotations with a Rudolph polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer and n.m.r. spectra with a Varian T-60A spectrometer. Moist organic solutions were dried with anhydrous magnesium sulfate, and evaporations were performed *in vacuo* in a rotary evaporator at a bath temperature of 40–45° unless otherwise stated. Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

L-*Mannose.* — Most of the L-mannose utilized in this study was obtained by reduction of L-mannono-1,4-lactone (Pfanstiehl Labs. Inc., Waukegan, Ill. 60085) with sodium borohydride under acidic conditions following the general methodology[30] and slowly crystallized from 2-propanol–methanol mixtures. In some cases, as in the preparation of **10**, the syrupy form was satisfactory for use. Small amounts of L-mannose were also obtained from Pfanstiehl Labs.

*Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-*D*-lyxo-hex-5-enofuranoside* (**8**). — Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-D-mannofuranoside[12] (**7**,

25 g) was treated with sodium iodide (70 g) in 2-butanone (550 ml) for 24 h at reflux. The solvent was evaporated (35°) and the residue was partitioned between chloroform (200 ml) and a sodium thiosulfate solution (250 ml, 10%) .The chloroform layer was washed once more with a sodium thiosulfate solution (250 ml) and then with water (250 ml), dried, and evaporated. The residual oil was distilled to yield 12.4 g (96%), b.p. 87–95° (3 mm Hg), $[\alpha]_D^{22}$ +27.8° (*c* 2.76, chloroform); the i.r. and n.m.r. spectra were identical to those of the L form **11**.

Anal. Calc. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.13; H, 8.13.

*9-(2,3-Di-O-acetyl-5,6-dideoxy-β-*D*-xylo-hex-5-enofuranosyl)adenine* (**4**). — Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (**8**, 1.0 g) was dissolved in a mixture of glacial acetic acid (30 ml) and acetic anhydride (3 ml), chilled in an ice-bath, and sulfuric acid (1.65 ml) was added dropwise. The mixture was kept at room temperature for 65 h and then poured into ice–water (125 ml) and stirred. When the ice had melted, the product was extracted with chloroform (3 × 25 ml) and the chloroform solution was washed with water (100 ml), saturated sodium hydrogencarbonate (100 ml), and again with water. The chloroform solution was dried and evaporated. Several additions and evaporations of benzene gave the triacetate **9** as a clear, colorless oil (1.03 g, 76%); the n.m.r. spectrum showed that the methoxyl and isopropylidene groups had been removed and replaced by acetyl groups (methyl peaks centered at δ 2.08).

The oil (**9**) was dissolved in 1,2-dichloroethane (100 ml) and added to a mixture containing 6-benzamidochloromercuripurine (2.23 g) and Celite-545 (2.2 g), and 20 ml of the solvent was removed by distillation. Titanium tetrachloride (0.35 ml), dissolved in 1,2-dichloroethane (20 ml), was added and the mixture was heated at reflux for 22 h. The reaction mixture was cooled to room temperature and treated with saturated sodium hydrogencarbonate (100 ml). After 1 h of stirring, the mixture was filtered and the filter cake was washed with hot 1,2-dichloroethane (70 ml). The organic layer was separated, evaporated to dryness, and the residue was dissolved in chloroform (70 ml). This was washed with 30% aqueous potassium iodide (2 × 50 ml) and water (100 ml), dried, and evaporated to a syrup, which was dissolved in ethanol (10 ml), treated with 10% ethanolic picric acid (20 ml), and heated at reflux[22]. After 5 min, yellow crystals began to form, and boiling was continued for another 5 min. The flask was kept at room temperature for several h. The picrate was filterd off, dissolved in 80% aqueous acetone (150 ml), and treated with Bio-Rad AG1-X8 (CO_3^{2-}) ion-exchange resin to remove the picrate ion[23]. The mixture was also treated with Darco G-60 charcoal, filtered, and the solution evaporated to afford a white foam which was treated by several additions and evaporation of ethanol until crystallization occurred. Product **4** was crystallized from ethanol in two crops to give 254 mg (20%), m.p. 200–201° with prior softening beginning at ~196°; the i.r. spectrum was identical to that of the previous preparation[10], m.p. 201–203°

*Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-*L*-mannofuranoside* (**10**). — The preparation of **10** was virtually the same as that described[12,13] for the D form (**7**). From syrupy L-mannose (26.6 g) was obtained 22.5 g (39%) of large, white

needles, crystallized from methanol, m.p. 147–148.5°, $[\alpha]_D^{25}$ −32.6° (*c* 1.80, chloroform). When **7** was crystallized from methanol, it had m.p. 147–148°, $[\alpha]_D^{25}$ +33.5° (*c* 1.39, chloroform)[13]. In addition, the i.r. and n.m.r. spectra of **10** and **7** were identical.

Anal. Calc. for $C_{12}H_{22}O_{10}S_2$: C, 36.91; H, 5.68; S, 16.43. Found: C, 36.93; H, 5.69; S, 16.38.

*Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-*L*-lyxo-hex-5-enofuranoside* (**11**). — Treatment of **10** with sodium iodide in 2-butanone, as described for **8**, yielded 9.41 g (82%) of an oil after distillation, b.p. 53–54° (0.8 mm Hg), $[\alpha]_D^{25}$ −27.6° (*c* 2.69, chloroform); lit.[14] :b.p. 76° (bath, 3.2 mm Hg), $[\alpha]_D^{20}$ −23.5° (*c* 1.4, chloroform) and b.p. 40–42° (bath, 12 mm Hg), $[\alpha]_D$ −28 ±2° (*c* 0.7, chloroform); the n.m.r. and i.r. spectra also had the peaks previously reported.

Anal. Calc. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.95; H, 8.16.

*9-(2,3-Di-*O*-acetyl-5,6-dideoxy-β-*L*-xylo-hex-5-enofuranosyl)adenine* (**5**). — Compound **11** (4 g) was acetolyzed as described for the D form **8**. A clear, colorless syrup **12** (3.82 g, 70%) was obtained. It was coupled in a mixture containing 6-benzamidochloromercuripurine (8.3 g), Celite-545 (8.3 g), titanium tetrachloride (1.3 ml), and 1,2-dichloroethane (400 ml), as described for the preparation of **4**. Product **5** was isolated *via* the picrate to afford 748 mg (15%). An analytical sample was recrystallized from methanol, m.p. 199–201° with softening starting at about 194°, $[\alpha]_D^{23}$ −21.9° (*c* 1.30, chloroform); the i.r. and n.m.r. spectra were identical to those of **4**, which was previously reported[10] to have $[\alpha]_D^{23}$ +22.5° (*c* 1.12, chloroform).

Anal. Calc. for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.99; H, 4.93; N, 20.17.

*9-(5,6-Dideoxy-β-*L*-xylo-hex-5-enofuranosyl)adenine* (**6**). — The blocked nucleoside **5** (146 mg) was treated with 0.1M methanolic sodium methoxide (25 ml) for 3 h at room temperature. Neutralization was effected with CG-120 (H^+) ion-exchange resin, which was removed by filtration, and the methanol evaporated. The syrupy residue was dissolved in acetone (20 ml), filtered, and evaporated. The residue was repeatedly dissolved in acetone and evaporated until a hard, white foam (74 mg) was obtained, which was pulverized and dried under high vacuum; the i.r. spectrum was identical to that of the D enantiomer[10].

Anal. Calc. for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 48.95; H, 4.96; N, 26.07.

A picrate was prepared in water, m.p. 204–207° (dec.). The D form[10], prepared in methanol and recrystallized, had m.p. 209–211° (dec.).

*2,3:5,6-Di-*O*-isopropylidene-*L*-mannofuranose* (**13**). — To a solution of dry acetone (150 ml) and sulfuric acid (3.5 ml) was added L-mannose (5 g). The reaction mixture was stirred at room temperature and a clear solution was obtained within about 1 h. After a total reaction time of 3.5 h, the slightly yellow solution was chilled in an ice-bath and treated with conc. ammonium hydroxide (13.5 ml). The precipitate was removed by filtration on a pad of Celite and the filtrate was evaporated to dryness. A solid residue formed which was dissolved in chloroform, dried, and evaporated to a

small volume. Petroleum ether (b.p. 60–110°) was added to incipient turbidity and crystallization occurred, affording 5.67 g, A second crop gave 0.53 g for a total yield of 86%; m.p. 121.5–122.5°, $[\alpha]_D^{24}$ −15.7° (*c* 2.5, ethanol); the i.r. spectrum was identical to that of the D form[25], m.p. 122°, $[\alpha]_D^{19}$ +16.6° (*c* 2.5, ethanol). The L isomer **13** was originally synthesized by Iwadare[31], m.p. 122–122.5°, $[\alpha]_D$ −27° (acetone).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 54.58; H, 7.45.

2,3:5,6-Di-O-isopropylidene-L-mannofuranosyl chloride (**14**). — This compound was prepared from **13** (19 g), as described for the D enantiomer[25], with thionyl chloride in pyridine[32]. The oil was distilled to give 11.6 g (57%), b.p. 135–137° (2.4 mm Hg).

Anal. Calc. for $C_{12}H_{19}ClO_5$: C, 51.70; H, 6.09; Cl, 12.72. Found: C, 51.76; H, 6.30; Cl, 12.65.

9-(2,3-O-Isopropylidene-α-L-mannofuranosyl)adenine (**15**). — The chloride **14** (11.5 g) was treated with 6-benzamidochloromercuripurine (19.8 g) in xylene as described for the D enantiomer[25]. After selective removal of the *N*-benzoyl and 5,6-*O*-isopropylidene groups, product **15** (6.41 g) was crystallized from water. An additional crop (0.72 g) was obtained from the mother liquor *via* the picrate for a total yield of 52%; m.p. 247–250° with softening at 240°, $[\alpha]_D^{24}$ −34° (*c* 1.16, 0.1M hydrochloric acid); lit. (D form)[25]: m.p. 249–250°, $[\alpha]_D^{21}$ +32.5° (*c* 1.26, 0.1M hydrochloric acid); the i.r. spectrum of **15** was identical to that of its enantiomer.

Anal. Calc. for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76. Found: C, 49.69; H, 5.73; N, 20.62.

9-α-L-Mannofuranosyladenine (**16**). — The free nucleoside was obtained by hydrolysis of **15** (1.5 g) in hot, 25% aqueous acetic acid to yield 843 mg (64%), m.p 239–241°, $[\alpha]_D^{24}$ −74.2° (*c* 1.32, M hydrochloric acid); the D form[25] had m.p. 237–237.5°, $[\alpha]_D^{21}$ +74.8° (*c* 3.05, M hydrochloric acid); the i.r. spectrum of **16** was identical to that of the D form.

Anal. Calc. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.36;. H, 5.12; N, 23.33.

9-(5,6-Dideoxy-2,3-O-isopropylidene-α-L-lyxo-hex-5-enofuranosyl)adenine (**18**). — Treatment of **15** (2.28 g) with methanesulfonyl chloride in pyridine, as described for the D enantiomer[9], gave **17** as a tan foam. Elimination was effected with sodium iodide in acetone at 100° to give 562 mg (42% from **15**) of white needles from 1:1 ethyl acetate–petroleum ether (b.p. 30–60°). A sample was recrystallized from methanol–water as feathery needles, m.p. 181.5–183°; the D form[9] had m.p 180.5–181° and the i.r. spectra were identical.

Anal. Calc. for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.43; H, 5.86; N, 22.92.

9-(5,6-Dideoxy-α-L-lyxo-hex-5-enofuranosyl)adenine (**19**). — Compound **18** (500 mg) was treated with 0.05M sulfuric acid at room temperature for 5 days as described for the D form[9]. The product was separated from unreacted starting-material by chromatography[33] on a column (1.8 × 17 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) ion-exchange resin. The column was eluted with 30% aqueous

methanol and 16-ml fractions were collected. Fractions 3 and 4 yielded 14 mg of **18**, m.p. 182°. Fractions 23–63 yielded product **19**, which was crystallized from water (270 mg), m.p. 247–249° (dec.), $[\alpha]_D^{24}$ −52° (*c* 1.12, M hydrochloric acid); lit.[7]: m.p. 246–247°, $[\alpha]_D^{27}$ −52.1° (*c* 0.305, M hydrochloric acid); the m.m.p. and i.r. spectra confirmed the identity of **19**.

Anal. Calc. for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 49.91; H, 4.93; N, 26.38.

ACKNOWLEDGMENT

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