Syn-1,2-Di(hydroxyimino)-1-pyridyl-2-phenylethane Methiodides (Xa,b,c)—In this series the general effectiveness of the various isomers should be pointed out; in the case of DFP inhibition the picolinic and isonicotinic derivatives have an activity comparable with that of 2-PAM and 4-PAM respectively. The activity diminishes in the case of TEPP inhibition; in this case the X*b* isomer is inactive.

In conclusion it is possible to affirm that, as it had already been found in the series reported in the preceding note (6), quaternary pyridine derivatives containing a hydroxyimino group in the β position of the side chain generally retain a reactivating activity, in whatever position the attachment to the ring may be; in some case this activity is higher than that of the isomer containing the same group in the α-position.

Since a phenyl group can shield the hydroxyimino group in relation to the active site of enzyme, a series of β-hydroxyimino derivatives containing hydrogen instead of the phenyl group was synthesized; the activity of these products will be reported in a following note.

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The Synthesis of Pyrrolidine-Substituted Nicotine Analogs

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Abstract □ As part of a program to synthesize nicotine homologs and analogs, the potentially versatile condensation of 3-pyridyl lithium with a 1-pyrroline-1-oxide (cyclic nitrone) has been studied. The product, an *N*-hydroxynornicotine derivative, was obtained in moderate yield and could be converted by way of the corresponding myosmine and nornicotine compounds to the desired gem-dimethylnicotine homolog. Spectral characteristics of these and certain side products are reported.

Keyphrases □ Nicotine analog, pyrrolidine substituted—synthesis □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

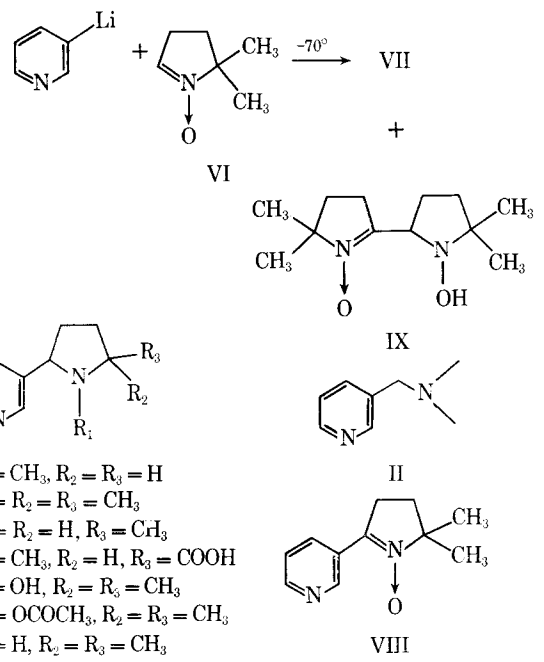
Nicotine (I), the principal alkaloid found in most varieties of tobacco, has served as a valuable chemical probe in the investigation of peripheral cholinergic transmission (1). More recently, increasing attention has been directed to nicotine's central activity (2, 3) and has included psychopharmacological studies relating to animal behavior (4, 5). These interests have led to many attempts to define the structural parameters responsible for this compound's cholinomimetic activity (6–8). Studies directly concerned with structural features of nicotine itself suggest that, for nonquaternary compounds capable of exerting effects within the CNS, the 3-pyridylaminomethyl system, II, is essential for high nicotinic activity (9–11). In order to explore the effects on central and peripheral activity of compounds closely related to nicotine, a program has been initiated to synthesize nicotine-like compounds in which the pyrrolidine ring is substituted. In this paper the authors report their studies on the synthesis of the gem-dimethylnicotine homolog, III, by a reaction sequence that should be applicable to a large number of such derivatives. The methylnornicotine, IV, (12) and the carboxynicotine, V (13), both presumably as diastereoisomeric mixtures, were the only such nicotine analogs found in the literature.

THEORETICAL

Nicotine has been prepared by several routes (14, 15); however, on review, none of these appeared to offer the required versatility demanded by the present problem. The fact that 1-pyrroline-1-

oxides (cyclic nitrones) undergo condensation with Grignard reagents to yield the corresponding hydroxylamines (16) and the availability of many such nitrones (16–18) suggested that these compounds might serve as useful intermediates for the substituted pyrrolidine moiety of our nicotine derivatives. Because of the instability of pyridyl Grignard reagents (19), 3-pyridyl lithium, readily prepared from 3-bromopyridine and *n*-butyl lithium in moderate yields (20, 21) was employed in the condensation reaction with the nitrone, 5,5-dimethyl-1-pyrroline-1-oxide (VI). A crystalline product was isolated from the reaction which, on the basis of elemental analysis and spectral data, could be assigned the structure of the desired hydroxynornicotine, VII. The IR spectrum showed bands characteristic for free and bonded hydroxyl stretching (3,580 and 3,125 cm^{-1}). The NMR spectrum (Table I) was also in complete agreement with the proposed structure. The coupling pattern for the pyridine protons (not included in Table I) was nearly identical with that reported for nicotine (22) and other 3-substituted pyridines (23) thus eliminating the possibility of any unexpected rearrangements. Further support for Structure VII was obtained by oxidation of the hydroxylamine to the nitrone, VIII. As anticipated, the UV spectrum of VIII showed a chromophore ($\lambda_{max.}$ 300 mμ) characteristic of a conjugated nitrone (24) and the 4.0 p.p.m. multiplet assigned to the C_5 methine proton of VII was no longer present (Table I).

In addition to the hydroxylamine, VII, a second minor crystalline product was obtained which, according to its physical and spectral properties, could be identified as the known dimer, IX. The m.p. and principal IR bands corresponded to reported values (25) and the NMR spectrum (see *Experimental*) was in complete agreement with the proposed structure. Dimerization of cyclic nitrones under base catalysis is a well-documented reaction (25) and it would appear that in the present case butyl lithium and/or pyridyl lithium catalyzed the reaction.

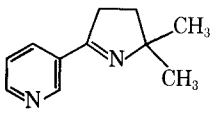


I, $R_1 = CH_3$, $R_2 = R_3 = H$
III, $R_1 = R_2 = R_3 = CH_3$
IV, $R_1 = R_2 = H$, $R_3 = CH_3$
V, $R_1 = CH_3$, $R_2 = H$, $R_3 = COOH$
VII, $R_1 = OH$, $R_2 = R_3 = CH_3$
XV, $R_1 = OCOCH_3$, $R_2 = R_3 = CH_3$
XVI, $R_1 = H$, $R_2 = R_3 = CH_3$

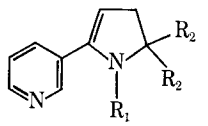
Subsequent conversion of the hydroxylamine to eventually yield the nicotine analog, III, was first examined by attempted dehydration of VII to the pyrroline, X, with acetic anhydride. Although the pyrroline was obtained in low yield, the principal product from this reaction proved to be a hygroscopic oil for which satisfactory data could not be obtained. In addition to the expected pyridine signals, the NMR spectrum (Table I) showed a one-proton triplet coupled (J = 3 c.p.s.) to a two-proton doublet and a single band integrating for nine methyl protons. Based on the above data, this product has been assigned the *N*-acetyl-2-pyrroline structure, XI, which presumably arose by acetylation of the intermediate 1-pyrroline, X. Analogous acylations of both cyclic (26, 27) and open-chain (28) imines were found in the literature. Further structure proof was obtained by partial hydrolysis of Compound XI which yielded the ketoamide, XII, similar to the reported (26) hydrolysis product, Compound XIII, of *N*-benzoylmyosmine (XIV).

In order to avoid the complications arising from acetylation of the pyrroline, the *N*-acetoxy compound, XV, was prepared with acetyl chloride. Thermal deacetylation then gave the desired pyrroline in 76% yield. As has been reported with related systems, the 1-pyrroline could be readily reduced to provide the nornicotine analog, XVI (12).

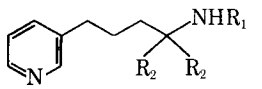
A second, more direct route to XVI employing a zinc dust reduction was also explored. With zinc and HCl, a mixture of products was obtained from which no pure substance could be characterized. The NMR spectrum of the crude isolate suggested that the pyridine ring had suffered reduction as well as the hydroxylamine. Under more mild conditions using acetic acid, Compound XVI could be obtained in 87% yield. Finally, methylation of the secondary amine with formic acid–formaldehyde gave the desired gem-dimethylnicotine derivative, III, in 92% yield. Together with the moderate yield of the initial condensation product, the two subsequent high-yield steps establish a convenient route to pyrrolidine-substituted nicotine derivatives. The preparation of additional members of this series is currently under investigation.



X



XI, $R_1 = COCH_3$, $R_2 = CH_3$
XIV, $R_1 = COC_6H_5$, $R_2 = H$



XII, $R_1 = COCH_3$, $R_2 = CH_3$
XIII, $R_1 = COC_6H_5$, $R_2 = H$

EXPERIMENTAL

Unless otherwise specified, all reactions were performed under a nitrogen atmosphere and solvents were concentrated *in vacuo* by means of a rotary evaporator. Melting points were determined (Hoover-Thomas apparatus) and are uncorrected. UV spectra were recorded in 95% ethanol ($\lambda_{max.}$) and 0.01 *N* ethanolic HCl ($\lambda^{H^+}_{max.}$) on a spectrophotometer (Cary model 11), IR spectra ($\nu_{max.}$) in 5–10% chloroform solution on a spectrophotometer (Perkin-Elmer model 337), and NMR spectra (δ) also on a spectrometer (model A-60 A, Varian Associates). Microanalyses were performed by the Microanalytical Laboratories, University of California, Berkeley, and Istituto Superiore di Sanità, Rome, Italy.

1-Hydroxy-2,2-dimethyl-5-3′-pyridylpyrrolidine (VII)—To a solution of butyl lithium (57.2 g. of a 22.6% solution in hexane, 200 m*M*) in 200 ml. anhydrous ether maintained at −70° was added 3-bromopyridine (31.6 g., 200 m*M*) in 100 ml. anhydrous ether over a 30-min. period with rapid stirring. The nitrone, VI (16) (17.0 g., 150 m*M*) in 125 ml. anhydrous ether was then added over a period of 45 min. At the end of the addition plus 30 min. the cooling bath was removed and stirring continued for an additional 30 min. The reaction mixture was treated with ammonium chloride (25 g.) in 175 ml. water, the ether layer separated and the aqueous layer extracted with ether (5 × 200 ml.), and saved (see below). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed. Crystallization of the residue from benzene followed by sublimation at 80° (0.01 mm.) gave the pure hydroxylamine, VII (10.0 g., 35%): m.p. 127–128°; $\lambda_{max.}$ 268 mμ (ϵ 1,950), 262 (2,660), 257 shoulder (2,400); $\lambda^{H^+}_{max.}$ 260 mμ (ϵ 4,640); $\nu_{max.}$ 3,580 $cm.^{-1}$ (free OH), 3,125 (bonded OH).

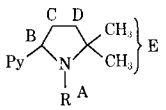
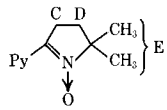
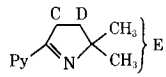
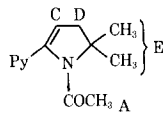
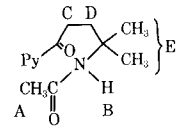
Anal.—Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.65; H, 8.65; N, 14.74.

The dipicrate (from ethanol) melted at 149–151°.

Anal.—Calcd. for $C_{23}H_{22}N_8O_{15}$: C, 42.44; H, 3.41; N, 17.25. Found: C, 42.17; H, 3.53; N, 17.03.

The above aqueous layer was further extracted with chloroform. After drying ($MgSO_4$) and concentrating, a crystalline solid was obtained which on recrystallization from chloroform–petroleum ether yielded pure 2-(1′-hydroxy-5′,5′-dimethylpyrrolidine-2′-yl)-5,5-dimethyl-1-pyrroline-1-oxide (IX): m.p. 177–178° [lit. (25) 177°]; $\nu_{max.}$ 3,190 and 1,610 $cm.^{-1}$ [lit. (25) 3,190 and 1,611 $cm.^{-1}$]; δ $CDCl_3$ 1.08,

Table I—Proton Magnetic Resonance Spectra (60Mc.p.s.) of Nicotine Analogs and Related Compounds[a]

Compound[b]	No.	Chemical Shift A	B	C	D	E	Coupling Constant c.p.s.
				C and D			
R = CH_3	III	2.03 (s)[c]	3.57 (q)	~2.0 (m)		0.98 (s), 1.22 (s)	J_{BC} ~5
R = OH	VII	7.05 (b)[d]	4.05 (q)	~1.9 (m)		1.17 (s), 1.25 (s)	J_{BC} ~6
R = $OCOCH_3$	XV	1.85 (s)	4.30 (q)	~2.0 (m)		1.22 (s), 1.28 (s)	J_{BC} ~8
R = H	XVI	1.65 (s)[d]	4.35 (t)	~1.9 (m)		1.23 (s)	J_{BC} ~7
	VIII	—	—	3.05 (t)	2.14 (t)	1.47 (s)	J_{CD} ~7
	X	—	—	2.96 (t)	1.80 (t)	1.27 (s)	J_{CD} ~8
	XI	1.62 (s)	—	5.25 (t)	2.55 (d)	1.62 (s)	J_{CD} ~3
	XII	1.92 (s)	5.7 (b)[d]	3.02 (t)	2.16 (t)	1.37 (s)	J_{CD} ~8

[a] Spectra were taken in deuteriochloroform as solvent and are reported in p.p.m. relative to tetramethylsilane as internal standard (TMS = 0.0 p.p.m.). [b] Py = 3-Pyridyl. [c] Letters in parentheses indicate multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, and b = broad. [d] Exchangeable proton.

1.20, 1.38, and 1.42 p.p.m. (s) CC*H*$_3$, 2.75 (m) C*H*$_2$CN, 4.30 (m) C*H*N, 6.00 (b) O*H*.

2-3′-Pyridyl-5,5-dimethyl-1-pyrroline-1-oxide (VIII)—Filtered air was bubbled through a suspension of the hydroxylamine, VII (500 mg., 2.6 m*M*) in 50 ml. water containing 25 mg. of cupric sulfate pentahydrate and 5 ml. of concentrated ammonium hydroxide for 4 hr. The resulting homogeneous solution was then exhaustively extracted with chloroform, the combined extracts dried ($MgSO_4$), and concentrated to dryness to give 490 mg. (98%) of a milky oil which solidified on standing overnight. Sublimation at 80° (0.5 mm.) gave the pure nitrone, VIII: m.p. 65–66°; $\lambda_{max.}$ 300 mμ (ϵ 11,240), 236 (4,950); $\lambda_{max.}^{H+}$ 306 mμ (ϵ 9,050), 248 (7,850); $\nu_{max.}$ 3,660[1] and 3,340[1] cm.$^{-1}$, 1,565 (C=N→O).

Anal.—Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.48; H, 7.39; N, 14.84.

The monopicrate was obtained from ethanol, m.p. 177–179°.

Anal.—Calcd. for $C_{17}H_{17}N_5O_8$: C, 48.69; H, 4.09; N, 16.69. Found: C, 48.83; H, 4.09; N, 16.66.

Reaction of 1-Hydroxy-2,2-dimethyl-5-3′-pyridylpyrrolidine (VII) with Acetic Anhydride—The hydroxylamine, Compound VII (10.5 g., 54.6 m*M*) was heated at reflux for 3 hr. in 100 ml. acetic anhydride. The reaction mixture was concentrated and the residue dissolved in chloroform. After several aqueous bicarbonate washes, which were back-extracted with chloroform, the combined, dried ($MgSO_4$) chloroform layers were concentrated and the residual dark-brown oil vacuum-distilled to give two fractions: Fraction A, 1.0 g., b.p. 55–60° (0.1 mm.) and Fraction B, 6.4 g., b.p. 60–100° (0.1 mm.). Fraction A (1.0 g., approximately 5 m*M*) in 10 ml. hot 95% ethanol was added to a hot ethanolic solution of picric acid (2.6 g., 12 m*M*). After standing overnight at 5°, 2.0 g. (3.1 m*M*) of 2-3′-pyridyl-5,5-dimethyl-1-pyrroline dipicrate was obtained. Recrystallization from ethanol provided an analytical sample, m.p. 187–188°.

Anal.—Calcd. for $C_{23}H_{20}N_8O_{14}$: C, 43.65; H, 3.18; N, 17.72 Found: C, 43.43; H, 3.24; N, 17.49.

The free base, X, was obtained in 96% yield by chromatographing the dipicrate (700 mg.) on alumina (100 g.) in 2% methanolic chloroform. Short-path distillation at 90–100° (0.05 mm.) gave an analytical sample: $\lambda_{max.}$ 265 mμ shoulder (ϵ 3,825), 235 (11,190); $\lambda_{max.}^{H+}$ 275 mμ shoulder (ϵ 6,820), 250 (12,090); $\nu_{max.}$ 1,625 cm.$^{-1}$ (pyrroline C=N).

Anal.—Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.90; H, 8.29; N, 15.95.

Fraction B in ethanol was treated with picric acid to form a small amount of the above pyrroline dipicrate (m.p. 186–187°). The remaining ethanol solution was added to chloroform and extracted with dilute phosphoric acid. After extracting with chloroform to remove any remaining picric acid, the combined aqueous extracts were made strongly basic and extracted several times with chloroform. Short-path distillation at 85–100° (0.01 mm.) of the residue obtained after drying ($MgSO_4$) and concentrating the combined chloroform extract yielded 3.9 g. product analyzing as a partial hydrate of 1-acetyl-2-3′-pyridyl-5,5-dimethyl-2-pyrroline (XI): $\nu_{max.}$ 1,622 cm.$^{-1}$ (C=O).

Anal.—Calcd. for $C_{13}H_{16}N_2O \cdot 1/3H_2O$: C, 70.3; H, 7.5; N, 12.6. Found: C, 70.3; H, 7.4; N, 12.7.

3-Pyridyl-3-methyl-3-acetamidobutyl Ketone (XII)—The *N*-acetylpyrroline, X (2.16 g., 10 m*M*) was heated at reflux for 2 hr. in 50 ml. 6 *N* HCl. After concentrating to 10 ml., the concentrate was made strongly basic and exhaustively extracted with ether. The dried ($MgSO_4$) ether was removed and the oily residue crystallized from benzene to give the pyridyl ketone, XII (0.9 g., 53%). After sublimation the compound melted sharply at 135°: $\lambda_{max.}$ 273 mμ shoulder (ϵ 2,990), 266 (3,690), 264 shoulder (3,530), 229 (9,830); $\lambda_{max.}^{H+}$ 270 mμ shoulder (ϵ 3,950), 265 (4,700), 262 shoulder (4,490), 225 (4,725); $\nu_{max.}^{nujol}$ 3,280 cm.$^{-1}$ (NH), 1,700 (ketone C=O), 1,650 (NC(=O)CH_3).

Anal.—Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.87; H, 7.90; N, 11.89.

1-Acetoxy-2,2-dimethyl-5-3′-pyridylpyrrolidine (XV)—The hydroxylamine, VII (1.92 g., 10 m*M*) in 40 ml. anhydrous benzene was

[1] These bands, characteristic for free and bonded OH stretching, have been reported for other nitrones (16, 29) and can be best explained by assuming the nitrone exists in part in the enol form.

treated with freshly distilled acetyl chloride (0.80 g., 10 m*M*) while stirring vigorously. The gummy mass which separated dissolved within 5 min. Stirring was continued at room temperature for 12 hr. during which time a fluffy white solid precipitated. This solid (2.1 g.) was dissolved in aqueous bicarbonate and the resulting solution extracted with chloroform. Work-up of the chloroform extract gave, after sublimation at 80° (0.05 mm.), the *N*-acetoxy compound, XV (1.6 g., 69%): m.p. 61–62°; $\lambda_{max.}$ 299 mμ (ϵ 1,100) 268 (2,540), 262 (3,090), 256 (2,760); $\lambda^{H^+}_{max.}$ 259 mμ (ϵ 5,300); $\nu_{max.}$ 1,780 cm.$^{-1}$, 1,760 (C=O).

Anal.—Calcd. for $C_{13}H_{18}N_2O_3$: C, 49.25; H, 4.57; N, 15.11. Found: C, 49.25; H, 4.41; N, 14.96.

The above acetoxy compound (5.1 g., 21.8 m*M*) was heated at 100° neat for 60 hr, and then added to aqueous bicarbonate. Extraction into chloroform followed by drying ($MgSO_4$), removal of the solvent and distillation at 74–76° (0.2 mm.) gave the 1-pyrroline, X, with IR and NMR spectra identical to the 1-pyrroline obtained from the treatment of the hydroxylamine, VII, with acetic anhydride.

2,2-Dimethyl-5-3′-pyridylpyrrolidine (XVI)—(*a*) The pyrroline, X (175 mg., 1.0 m*M*) was treated at room temperature with sodium borohydride (1.9 g., 50 m*M*) in 25 ml. water–methanol (3:1) for 4 days. Five chloroform extracts, individually backwashed with water, were combined and dried ($MgSO_4$). The residue obtained after solvent removal was purified by short path distillation at 65–70° (0.05 mm.) to yield the pyrrolidine, XVI (140 mg., 80%): $\lambda_{max.}$ 268 mμ shoulder (ϵ 2,250), 260 (3,180), 258 shoulder (ϵ 2,625); $\lambda^{H^+}_{max.}$ 266 mμ shoulder (4.050), 258 (4,850); $\nu^{neat}_{max.}$ 3,280 cm.$^{-1}$ (NH).

Anal.—Calcd. for $C_{11}H_{16}N_2$: C, 74.95; H, 9.25; N, 15.90. Found: C, 74.81; H, 9.25; N, 15.83.

The dipicrate (from ethanol) melted at 185–186°. The m.p. with the dipicrate of the hydroxylamine, VII (m.p. 187–188°) was depressed—174–185°.

Anal.—Calcd. for $C_{23}H_{22}N_8O_{14}$: C, 43.53; H, 3.50; N, 17.67. Found: C, 43.31; H, 3.61; N, 17.83.

(*b*) To a vigorously stirred solution of the hydroxylamine, VII (12.0 g., 63 m*M*) in 150 ml. 50% aqueous acetic acid maintained at 60° was added all at once purified zinc dust (8.0 g., 0.123 g. Atm.). The temperature rose to 80° and stirring was continued for 1 hr. The cooled reaction mixture was filtered, the filtrate made strongly alkaline with NaOH, and exhaustively extracted with chloroform. After drying ($MgSO_4$) and removing the solvent, the residual oil was distilled to yield 9.5 g. (87%) of pure pyrrolidine, XVI, b.p. 89–90° (0.5 mm.), having identical spectral characteristics with the above pyrroline reduction product.

1,2,2-Trimethyl-5,3′-pyridylpyrrolidine (III).—To the ice-cold nornicotine derivative, XVI (8.8 g., 50 m*M*) was added 90% formic acid (13 ml., 224 m*M*) and 36% formaldehyde (10.6 g., 126 m*M*). The resulting solution was heated at reflux under a slow nitrogen sweep for 9 hr. when CO_2 evolution ceased (no $BaCO_3$ precipitate). The cooled solution was treated with concentrated HCl (40 ml.) and then concentrated to near dryness. The residue in 50 ml. water was made strongly alkaline with NaOH and extracted several times with chloroform. The solvent was dried ($MgSO_4$), concentrated, and the residue distilled to yield 8.7 g. (92%) of the gem-dimethylnicotine derivative, III: b.p. 75–76° (0.2 mm.); $\lambda_{max.}$ 267 mμ shoulder (ϵ 2,200), 262 (2,870), 257 (2,700); $\lambda^{H^+}_{max.}$ 260 (4,910); $\nu_{max.}$ 2,795 cm.$^{-1}$ (C—H of N—CH_3).

Anal.—Calcd. for $C_{12}H_{18}N_2$: C, 75.75; H, 9.53; N, 14.72. Found: C, 75.79; H, 9.66; N, 14.82.

The dipicrate (from ethanol) melted at 225–226°.

Anal.—Calcd. for $C_{24}H_{24}N_8O_{14}$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.27; H, 3.99; N, 17.08.

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