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Purines. II.[1] An Alternative Synthesis of 1-Alkoxy-9-alkyladenine Salts[2]

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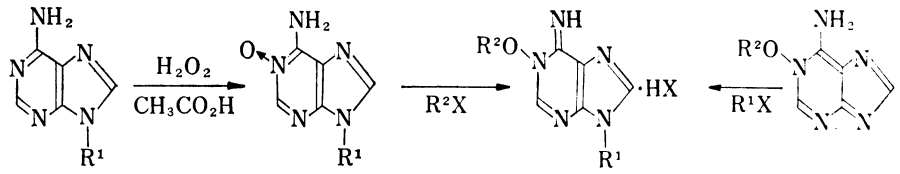
Treatment of 9-alkyladenines (Ia,b,c) with 30% aqueous hydrogen peroxide in acetic acid at 30° produced the corresponding 9-alkyladenine 1-oxides (IIa,b,c) in 51—71% yield. The 1-N-oxides were found to undergo alkylation almost exclusively at the oxygen atoms of the N-oxide groups when treated separately with methyl iodide, ethyl iodide, and benzyl bromide in N,N-dimethylacetamide at room temperature, and the corresponding salts (III) of all the nine possible 1-alkoxy-9-alkyladenines were obtained in excellent yields. 1-Ethoxyadenosine hydriodide and 1-benzyloxyadenosine perchlorate were also prepared from adenosine 1-oxide (IId) in a similar way. The ultraviolet and nuclear magnetic resonance spectral data on the 1-alkoxyadenine derivatives obtained in the previous and present studies are collected in Tables II and III.

In connection with our recently published study[1,5] of the alkylation of 1-alkoxyadenines (IV) leading to 1-alkoxy-9-alkyladenine salts (III), we were interested in investigating the site of alkylation of 9-alkyladenine 1-oxides (II) as well as adenosine 1-oxide (IId). This paper reports the details of our initial research in this area, which has been concerned with an alternative synthesis of III from 9-alkyladenines (I) through II. A number of the results described here have been recorded in a preliminary form.[6]



Ia, b, c, d IIa, b, c, d IIIe – o IV

a : $R^1=CH_3$
b : $R^1=C_2H_5$
c : $R^1=C_6H_5CH_2$
d : $R^1=\beta$-D-ribofuranosyl

Chart 1

Treatment of 9-methyladenine (Ia)[1,5] with 30% aqueous hydrogen peroxide in acetic acid at 30° gave 9-methyladenine 1-oxide (IIa) in a mediocre yield. Similarly, 9-ethyladenine 1-oxide (IIb) and 9-benzyladenine 1-oxide (IIc) were separately obtained from the corresponding 9-alkyladenines (Ib,c)[1,5] in 69—71% yield. The 1-N-oxide structure was assignable by

1) For Part I in this series, see T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).
2) A preliminary communication[6] on this subject has been published earlier.
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5) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1017 (1965).
6) T. Fujii, C. C. Wu, T. Itaya, and S. Yamada, *Chem. Ind.* (London), **1966**, 1598.

TABLE I. Alkylation of 9-Substituted Adenine 1-Oxides (II)

Product	Alkylating reagent	Reaction time (hr)	Yield (%)	Appearance and recrystn. solvent[a]	mp[b] (°C)	Formula	Analysis (%) C	H	N
1-Methoxy-9-methyladenine hydriodide (IIIe)[1,5]	MeI	36	98	colorless pillars (A)	214—215	$C_7H_{10}ON_5I$	— —	— —	— —	— —
1-Methoxy-9-ethyladenine hydriodide (IIIf)	MeI	12	98	colorless prisms (D)	184	$C_8H_{12}ON_5I$	Calcd. 29.92 Found 30.00	3.77 3.58	21.81 21.61
1-Methoxy-9-ethyladenine picrate	—	—	—	yellow pillars (E)	208—209	$C_{14}H_{14}O_8N_8$	Calcd. 39.81 Found 40.07	3.34 3.44	26.54 26.60
1-Methoxy-9-benzyladenine hydriodide (IIIg)	MeI	70	97	colorless prisms (A)	213—215	$C_{13}H_{14}ON_5I$	Calcd. 40.74 Found 40.86	3.68 3.78	18.28 18.23
1-Methoxy-9-benzyladenine picrate	—	—	—	yellow pillars (E)	212—213	$C_{19}H_{16}O_8N_8$	Calcd. 47.11 Found 47.26	3.33 3.39	23.14 22.86
1-Ethoxy-9-methyladenine hydriodide (IIIh)	EtI	36	94	colorless prisms (A)	203—204	$C_8H_{12}ON_5I$	Calcd. 29.92 Found 29.87	3.77 3.97	21.81 22.01
1-Ethoxy-9-methyladenine picrate	—	—	—	yellow needles (B)	220—221	$C_{14}H_{14}O_8N_8$	Calcd. 39.81 Found 39.89	3.34 3.56	26.54 26.75
1-Ethoxy-9-ethyladenine hydriodide (IIIi)[1,5]	EtI	50	97	colorless prisms (D)	186	$C_9H_{14}ON_5I$	— —	— —	— —	— —
1-Ethoxy-9-benzyladenine hydriodide (IIIj)	EtI	75	92	colorless needles (A)	167—168	$C_{14}H_{16}ON_5I$	Calcd. 42.33 Found 42.38	4.06 3.71	17.63 17.49
1-Ethoxy-9-benzyladenine picrate	—	—	—	yellow needles (E)	212	$C_{20}H_{18}O_8N_8$	Calcd. 48.20 Found 48.46	3.64 3.57	22.48 22.47
1-Benzyloxy-9-methyladenine hydrobromide (IIIk)[c]	$C_6H_5CH_2Br$	20	99	colorless needles (E)	207	$C_{13}H_{14}ON_5Br\cdot\frac{1}{2}H_2O$	Calcd. 45.23 Found 45.46	4.38 4.51	20.29 20.28
1-Benzyloxy-9-methyladenine picrate	—	—	—	yellow needles (C)	209—210	$C_{19}H_{16}O_8N_8$	Calcd. 47.11 Found 46.98	3.33 3.74	23.14 23.31
1-Benzyloxy-9-ethyladenine hydrobromide (IIIl)	$C_6H_5CH_2Br$	13	99	colorless prisms (A)	203—204	$C_{14}H_{16}ON_5Br$	Calcd. 48.01 Found 47.90	4.61 4.49	20.00 20.05
1-Benzyloxy-9-ethyladenine picrate	—	—	—	yellow pillars (E)	200—201	$C_{20}H_{18}O_8N_8$	Calcd. 48.20 Found 48.64	3.64 3.70	22.48 22.54
1-Benzyloxy-9-benzyladenine hydrobromide (IIIm)[1,5,d]	$C_6H_5CH_2Br$	46	94	colorless pillars (E)	218	$C_{19}H_{18}ON_5Br\cdot H_2O$	— —	— —	— —	— —
1-Ethoxyadenosine hydriodide (IIIn)[c]	EtI	24	—	colorless minute crystals (E)	132—134	$C_{12}H_{18}O_5N_5I\cdot\frac{1}{2}H_2O$	Calcd. 32.15 Found 32.13	4.27 4.36	15.63 15.65
1-Benzyloxyadenosine perchlorate (IIIo)[d]	$C_6H_5CH_2Br$	1	93	colorless pillars (A)	149—151	$C_{17}H_{20}O_9N_5Cl\cdot H_2O$	Calcd. 41.51 Found 41.76	4.51 4.65	14.24 14.21

a) The letter in parentheses refers to the recrystallization solvent with A, water; B, 30% aq. ethanol; C, 50% aq. ethanol; D, 70% aq. ethanol; E. abs. ethanol.
b) with decomposition *c*) as a hemihydrate *d*) as a monohydrate

analogy with the 1-N-oxidation by Brown and co-workers[7] of adenosine (Id) and 2′,3′-O-isopropylideneadenosine (type I) and by similarity of the ultraviolet (UV) spectra of the products (IIa,b,c), as shown in Table II, with those of adenosine 1-oxide (IId), which was

7) *a*) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958); *b*) M.A. Stevens and G.B. Brown, *ibid.*, **80**, 2759 (1958).

prepared[8] according to the reported[7a] procedure. In addition, identity of IIc with the sample obtained previously[1,6] by debenzylation of 1-benzyloxy-9-benzyladenine also gave strong support to the assigned structure.

The 1-N-oxides (IIa,b,c) described above underwent alkylation almost exclusively at the oxygen atoms of the N-oxide groups when treated separately with methyl iodide, ethyl iodide, and benzyl bromide in N,N-dimethylacetamide at room temperature, resulting in formation of the corresponding salts (III) of all the nine possible 1-alkoxy-9-alkyladenines in good yields. The results are summarized in Table I.

The location of the second alkyl group (R^2) was established for three 1-alkoxy-9-alkyladenine salts [IIIe ($R^1=R^2=CH_3$;X=I), IIIi ($R^1=R^2=C_2H_5$; X=I), and IIIm ($R^1=R^2=C_6H_5CH_2$; X=Br)], in which the two alkyl groups were same, by direct comparison with the authentic samples synthesized previously[1,5] by alkylation of 1-alkoxyadenines (IV: $R^2=CH_3$, C_2H_5, $C_6H_5CH_2$). As exemplified in Table II, all the alkylated products (III) have

Table II. Ultraviolet Spectra of Adenine Derivatives Attached to Oxygen Functions at the 1-Position

Compound[a]	UV Spectra							
	Solvent E[b]		Solvent A[c]		Solvent N[d]		Solvent B[e]	
	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$
IIa	234	37.2	258	10.2	232	37.0	232	25.2
	263	6.5	—	—	261	6.8	268	7.2
	298	1.9	—	—	292	1.7	302	3.0
IIb	234	41.2	259	11.1	232	42.5	231	27.7
	263	7.4	—	—	261	7.3	268	7.4
	299	2.0	—	—	291	2.1	302	3.3
IIc	234	43.7	259	12.6	232	44.6	231	27.5
	263	7.9	—	—	262	8.1	268	8.6
	300	2.0	—	—	291	2.0	305	4.0
IId[7,8]	234	38.8	257	11.3	232	39.8	231	22.9
	262	7.1	—	—	261	7.7	268	7.9
	300	2.1	—	—	295	2.1	307	4.2
IIIe	258	11.9	260	12.2	258	12.2	257	12.4
IIIf	259	12.0	260	12.2	259	12.3	258	12.6
IIIg	259	13.0	260	13.2	259	13.2	257	13.0
IIIh	259	12.4	260	11.9	259	12.0	257	12.2
IIIi	259	12.9	260	12.0	259	12.1	257	12.4
IIIj	260	12.7	260	12.5	260	12.1	258	12.9
IIIl	259	11.9	261	12.2	261	12.1	258	12.2
IIIm	259	12.7	260	12.5	260	12.2	258	12.6
IIIn	257	12.2	258	12.6	258	13.8	256	12.0
IIIo	259	12.7	258	12.4	258	12.4	256	12.6

a) For full names of the compounds (III), see Table I.
b) 95% aqueous ethanol
c) 0.1N hydrochloric acid (pH 1)
d) 0.005M phosphate buffer (pH 7)
e) 0.1N aqueous sodium hydroxide (pH 13)

8) Although our anhydrous sample of IId, mp 219—221° (decomp.), $[\alpha]_D^{30}-50.1°$ ($c=0.674$, water), had the melting point considerably higher than the reported[7a] one [mp 155° (decomp. point 160°)], it was characterized by correct analysis (Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.32; H, 4.89; N, 24.89.) and identified by direct comparison with the sample of IId which Drs. G.B. Brown and J.C. Parham of Sloan-Kettering Institute for Cancer Research kindly sent to us. They have also observed this higher melting point in recent years. When recrystallized from water and dried over P_2O_5 at 60° and 3 mmHg for 14 hr, IId gave a monohydrate as colorless prisms, mp 224—225° (decomp.); $[\alpha]_D^{30}-47.7°$ ($c=0.769$, water). *Anal.* Calcd. for $C_{10}H_{13}O_5N_5\cdot H_2O$: C, 39.87; H, 5.02; N, 23.25. Found: C, 39.79; H, 5.04; N, 23.40.

Table III. NMR Spectra of 1-Alkoxyadenine Derivatives

Compound[a]	Chemical shift (τ)[b]											
	Methyl protons				Methylene protons				Phenyl protons		NH protons	Purine protons
	OMe	OEt	$N_{(9)}Me$	$N_{(9)}Et$	OEt	$OCH_2C_6H_5$	$N_{(9)}Et$	$N_{(9)}CH_2C_6H_5$	$OCH_2C_6H_5$	$N_{(9)}CH_2C_6H_5$		
1-Methoxyadenine hydriodide[1,5]	5.80 (s)	—	—	—	—	—	—	—	—	—	(o)	0.87 (s), 1.45 (s)
1-Ethoxyadenine hydriodide[1,5]	—	8.56 (t)	—	—	5.56 (q)	—	—	—	—	—	(o)	0.89 (s), 1.45 (s)
1-Benzyloxyadenine hydrobromide[1,5)c]	—	—	—	—	—	4.53 (s)	—	—	2.50 (m)	—	(o)	1.12 (s), 1.45 (s)
IIIe	5.78 (s)	—	6.11 (s)	—	—	—	—	—	—	—	0.0 (b)	0.81 (s), 1.45 (s)
IIIf	5.78 (s)	—	—	8.53 (t)	—	—	5.66 (q)	—	—	—	0.0 (b)	0.83 (s), 1.37 (s)
IIIg	5.80 (s)	—	—	—	—	—	—	4.47 (s)	—	2.65 (s)	0.0 (b)	0.83 (s), 1.25 (s)
IIIh	—	8.55 (t)	6.11 (s)	—	5.53 (q)	—	—	—	—	—	0.3 (b), −0.2 (b)	0.83 (s), 1.45 (s)
IIIi	—	8.55 (t)	—	8.55 (t)	5.56 (q)	—	5.68 (q)	—	—	—	0.4 (b), −0.2 (b)	0.83 (s), 1.35 (s)
IIIj	—	8.55 (t)	—	—	5.54 (q)	—	—	4.44 (s)	—	2.63 (s)	0.1 (b)	0.82 (s), 1.20 (s)
IIIk	—	—	6.15 (s)	—	—	4.54 (s)	—	—	2.50 (m)	—	0.1 (b)	1.05 (s), 1.45 (s)
IIIl	—	—	—	8.54 (t)	—	4.53 (s)	5.67 (q)	—	2.50 (m)	—	0.0 (b)	1.03 (s), 1.35 (s)
IIIm	—	—	—	—	—	4.56 (s)	—	4.47 (s)	2.50 (m)	2.64 (s)	0.0 (b)	1.01 (s), 1.20 (s)
IIIn	—	8.55 (t)	—	—	(o)	—	—	—	—	—	0.3 (b), −0.3 (b)	0.73 (s), 1.12 (s)
IIIo	—	—	—	—	—	4.58 (s)	—	—	2.51 (m)	—	0.2 (b), −0.3 (b)	1.12 (s), 1.22 (s)

a) For full names of the compounds (III), see Table I.
b) Measured on 10% (w/v) DMSO or DMSO-d_6 solutions. The letter in parentheses designates the multiplicity or shape of the signal: b=broad, m=multiplet, o=obscure, q=quartet with J=7 cps, s=singlet, t=triplet with J=7 cps.
c) as a monohydrate.

similar UV spectra indicative of identical positional disubstitution. The nuclear magnetic resonance (NMR) spectra of III measured on dimethyl sulfoxide (DMSO) solutions also suggest the substitution at the oxygen atom. As shown in Table III, compound IIIe ($R^1=R^2=CH_3$; X=I) exhibits two methyl signals at 6.11 and 5.78 τ. The former signal seems to be the one due to the $N_{(9)}$-methyl group since each of the other 9-methyl derivatives (IIIh,k), which do not possess the methoxyl group, displays a three-proton singlet in the region of 6.11—6.15 τ, whereas the salts (IIIf,g,i,j,l,m), which carry at the 9-position alkyl groups other than the methyl, do not show any signals in the same region or in its vicinity. Consequently, the methyl signal at 5.78 τ is ascribed to the $CH_3O\text{-}N_{(1)}$ group. The previously reported[1,5] 1-methoxyadenine hydriodide also reveals its methyl signal in this region. This assignment would be also reasonable in view of the large deshielding effect of the ONH_2 group[9] in DMSO solution. Similarity in chemical shifts for the second methyl groups of all the methylated products (IIIe,f,g) indicates the identical positional substitution. An analogous interpretation is also permissible for the ethylated products (IIIh,i,j). In the cases of the benzylated products (IIIk,l,m), however, it is found that the $N_{(9)}$-benzylic methylene protons are somewhat more deshielded than the O-benzylic methylene protons.

The O-alkylation described above was then extended to include a nucleoside derivative. Thus, ethylation of adenosine 1-oxide (IId) with ethyl iodide in the same way afforded 1-ethoxyadenosine hydriodide (IIIn), and benzylation of IId with benzyl bromide, followed by treatment with ammonium perchlorate, gave 1-benzyloxyadenosine perchlorate (IIIo)[10] in a good yield (see Table I).

It should be pointed out that the present synthetic method (I→II→III) is capable of preparing 1-alkoxy-9-alkyladenine salts (III) possessing any combinations of two kinds of alkyl groups in the molecule in excellent yields. On the other hand, cross alkylation of 1-alkoxyadenines (IV) leading to the 9-alkylated salts (III) in which R^1 and R^2 are different gives a complicated pattern of products[11] in certain cases depending on the nature of the alkyl groups. It will be fully reported elsewhere in the near future.

Experimental[12]

9-Methyladenine 1-Oxide (IIa)——To a solution of 3.65 g (24.5 mmoles) of 9-methyladenine (Ia)[1,5] in 125 ml of acetic acid was added 12.5 ml of 30% aq. hydrogen peroxide. The mixture was kept standing at 30° for a week and then stirred with 2 g of 5% palladium-on-charcoal until a test with potassium iodide–starch paper became negative. The mixture was filtered, and the filtrate was evaporated *in vacuo* to dryness, leaving a brownish solid. The solid was dissolved in boiling water and treated with charcoal. The charcoal was filtered while hot, and the filtrate was concentrated to a small volume to afford colorless prisms, mp 292—294° (decomp.), shown to be homogeneous by paper chromatography using solvent systems A, B, C, and D. Yield, 2.08 g (51%). Recrystallization from water furnished an analytical sample of the same melting point, pK_a 2.65±0.11. *Anal.* Calcd. for $C_6H_7ON_5$: C, 43.63; H, 4.27; N, 42.21. Found: C, 43.70; H, 4.46; N, 42.06. The UV spectral data are given in Table II.

9) T. Fujii, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 345 (1967).
10) Preparation of 1-benzyloxyadenosine, mp 157°, in a similar way has been briefly reported by J.A. Montgomery and H.J. Thomas, *Chem. Commun.*, **1969**, 458.
11) T. Fujii, T. Itaya, and S.Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1452 (1966).
12) All melting points are corrected. Paper chromatographies were developed on Toyo Roshi No. 51 filter paper by the ascending method with 1-butanol: water: acetic acid (75:20:5, v/v) (solvent A), 1-butanol: conc. aq. ammonium hydroxide: water (4:1:1, v/v) (solvent B), 2-propanol: 1% aq. ammonium sulfate (2:1, v/v) (solvent C), or isopentyl alcohol: 0.05 M phosphate buffer (pH 7) (10:1, v/v) (solvent D). Spots were detected by means of UV absorbance and/or the Dragendorff spray. Spectra reported herein were measured on a Cary Model 11 UV and visible-range spectrophotometer, a JASCO-DS-301 or-402G IR spectrophotometer, or a JEOL 3H-60 NMR spectrometer using tetramethylsilane as an internal standard. Optical rotations were determined on a Yanagimoto OR-20 polarimeter or a JASCO DIP-SL polarimeter. Acid dissociation constants were determined as described previously.[1]

9-Ethyladenine 1-Oxide (IIb)——A mixture of 4.90 g (0.03 mole) of 9-ethyladenine (Ib),[1,5] 20 ml of acetic acid, and 15 ml of 30% aq. hydrogen peroxide was kept at 30° for 5 days. The mixture was treated in the same way as described for IIa. The residual solid obtained by evaporation of the acetic acid was washed with ether and recrystallized from ethanol to give 3.84 g (71%) of colorless minute prisms, mp 280—283° (decomp.); pK_a 2.66±0.12; UV (see Table II). *Anal.* Calcd. for $C_7H_9ON_5$: C, 46.92; H, 5.06; N, 39.09. Found: C, 47.07; H, 5.24; N, 39.23.

9-Benzyladenine 1-Oxide (IIc)——This was prepared from 9-benzyladenine (Ic)[1,5] in the same manner as above and recrystallized from 90% aq. ethanol to produce colorless needles, mp 280—281° (decomp.). Yield, 69%. *Anal.* Calcd. for $C_{12}H_{11}ON_5$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.53; H, 4.57; N, 29.26. Identity of this sample with the one[1,6] obtained by debenzylation of 1-benzyloxy-9-benzyladenine was verified by mixed melting-point test, paper chromatography, and by comparison of UV (see Table II) and IR spectra.

Alkylation of 9-Alkyladenine 1-Oxides (II)——The procedures employed for methylation of IIc and ethylation and benzylation of IId will be described below in detail. The other alkylations were accomplished similarly.

1-Methoxy-9-benzyladenine Hydriodide (IIIg)——A suspension of 7.24 g (0.03 mole) of IIc in a mixture of 17.04 g (0.12 mole) of methyl iodide and 20 ml of N,N-dimethylacetamide was stirred at room temp. for 70 hr. The resulting precipitates were filtered, washed with a small amount of ethanol to give 6.43 g of IIIg. The filtrate and washings were combined, and to this solution was added 200 ml of ether. The precipitates that formed were filtered and dried to give additional 4.74 g of IIIg. Total yield, 11.17 g (97%). For analysis the product was recrystallized from water (see Tables I, II, and III).

1-Methoxy-9-benzyladenine Picrate——This salt was prepared from a small portion (0.3 g) of the hydriodide (IIIg) by dissolving it in 2 ml of water and adding *ca.* 1 ml of a saturated solution of picric acid in water. Recrystallization from ethanol yielded an analytical sample (see Table I).

1-Ethoxyadenosine Hydriodide(IIIn)——A mixture of 850 mg (3 mmoles) of IId, 3.10 g (20 mmoles) of ethyl iodide, and 4 ml of N,N-dimethylacetamide was stirred at room temp. for 24 hr. The reaction mixture was evaporated *in vacuo* to leave a light brown oil, which turned hygroscopic powder when triturated with a small amount of 2-propanol. A portion of the powder was recrystallized from ethanol and dried over phosphorus pentoxide at room temp. *in vacuo* for 72 hr to give an analytical sample of a hemihydrate of IIIn (see Tables I, II, and III), $[\alpha]_D^{30}$ −28° (c=1.12, l=0.5, water).

1-Benzyloxyadenosine Perchlorate (IIIo)——A mixture of 9.04 g (0.03 mole) of the monohydrate[8] of IId, 25.7 g(0.15 mole) of benzyl bromide, and 150 ml of N,N-dimethylacetamide was stirred at room temp. for 1 hr. To the resulting clear solution was added 600 ml of ether, and the precipitates that formed were separated from the supernatant fluid by decantation. The precipitates were dissolved in 150 ml of warm water and a warm (*ca.* 50°) solution of 18 g of ammonium perchlorate in 75 ml of water was added. The mixture was cooled, and the colorless pillars that formed were filtered, washed with a small volume of cold water, and dried to give 13.7 g (93%) of a monohydrate of IIIo, mp 149—151° (decomp.). Recrystallization from water and drying over phosphorus pentoxide at room temp. and 2 mmHg for 24 hr gave an analytical sample of the monohydrate (see Tables I, II, and III), $[\alpha]_D^{28}$ −20.6° (c=0.631, l=1, water).

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