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Purines. XIX.[1] The Direct N^6-Alkylation of 1-Alkoxy-9-alkyladenines: An Alternative Synthesis of N^6,9-Dialkyladenines[2]

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1-Alkoxy-9-alkyladenines (VIIIa, b, c) have been found to undergo alkylation mainly at the N^6-position when treated with alkyl halide in N,N-dimethylacetamide. The structure of the resulting N^6-alkylated derivatives (IXa, b, c) has been established by comparison with authentic IXa (X=I, ClO_4) and by catalytic hydrogenolysis of IXb, c (X=ClO_4) to N^6, 9-dialkyladenines (XIb, c). In the case of the benzyl analog (IXc: X=ClO_4), removal of the benzyloxy group at the 1-position has also been effected stepwise through the 1-oxide (Xc).

The occurrence of all the five possible N-substituted adenines in nature and the great interest in their biological activities have multiplied the number of known general methods for the selective synthesis of each positional isomer of N-alkyladenines from adenine (I).[4] These methods involve the direct alkylation of adenine, with[5] or without[5b,c,6] the aid of an easily removable blocking and/or directing group, under various reaction conditions alone or in combination with the subsequent Dimroth rearrangement.[5a,h,l] For the synthesis of certain N^6-aralkyl- or N^6-aryladenines, the exchange amination reaction of Whitehead and Traverso[6a,7] has also been used.

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6) *a*) N.J. Leonard and J.A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962); *b*) J.W. Jones and R.K. Robins, *ibid.*, **84**, 1914 (1962); *c*) N.J. Leonard and R. Laursen, *Biochemistry*, **4**, 354 (1965); *d*) C.J. Abshire and L. Berlinguet, *Can. J. Chem.*, **42**, 1599 (1964); *e*) H.J. Schaeffer and R. Vince, *J. Med. Chem.*, **8**, 710 (1965); *f*) J.A. Montgomery and H.J. Thomas, *J. Heterocyclic Chem.*, **1**, 115 (1964); *g*) T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 1334 (1972); *h*) T.C. Myers and L. Zeleznick, *J. Org. Chem.*, **28**, 2087 (1963); *i*) K. Yamauchi, M. Hayashi, and M. Kinoshita, *ibid.*, **40**, 385 (1975).
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The blocking and/or directing groups employed in the alkylation of I are the benzyl group at the 1-,[5a] 3-,[5b,6f] or 9-position,[5a] alkoxyl group at the 1-position,[5d,e] acetyl,[5f] benzoyl,[5d,f,n,6f] or dimethylaminomethylene group[5g] at the N^6-position, β-D-ribofuranosyl,[5a,h,l] propenyl,[5i] or β-cyanoethyl group[5m] at the 9-position, and pivaloyloxymethyl group at the 7-[5j,k] or 9-position.[5j] In the case of the alkoxyl group, its placement at the 1-position of I orients alkylation to the 9-position to give the corresponding 1-alkoxy-9-alkyladenine salt (type VII).[5d,e] We have also found that the methoxyl group at the N^6-position of 9-substituted adenines orients methylation mainly to the 7-position and partly to the N^6-position.[8] In the present work, the study on such a directing effect of the alkoxyl group has been extended to include a further alkylation of 1-alkoxy-9-alkyladenines (type VIII), which are readily prepared from adenine 1-oxide (IV) *via* 1-alkoxyadenines (VI)[5d,e,9] or from 9-alkyladenine 1-oxides (III).[10]

Treatment of 1-methoxy-9-methyladenine (VIIIa), prepared freshly from the corresponding hydriodide salt (VIIa: X=I) as described previously,[5e] with methyl iodide in N,N-dimethylacetamide (DMAC) at 50° for 25 hr produced 1-methoxy-N^6,9-dimethyladenine hydriodide (IXa: X=I) in 51% yield. The structure of the product was confirmed by direct comparison with an authentic sample of the hydriodide (IXa: X=I), which was previously synthesized[11] from XIa through Xa (Chart 1). When the ethyl homolog (VIIIb) was treated with ethyl iodide in a similar manner, the N^6-ethylated product could be isolated, after conversion into the perchlorate salt (IXb: X=ClO_4), in 41% overall yield. It may be seen from Table I that the perchlorate (IXb: X=ClO_4) and IXa (X=I) had similar ultraviolet (UV)

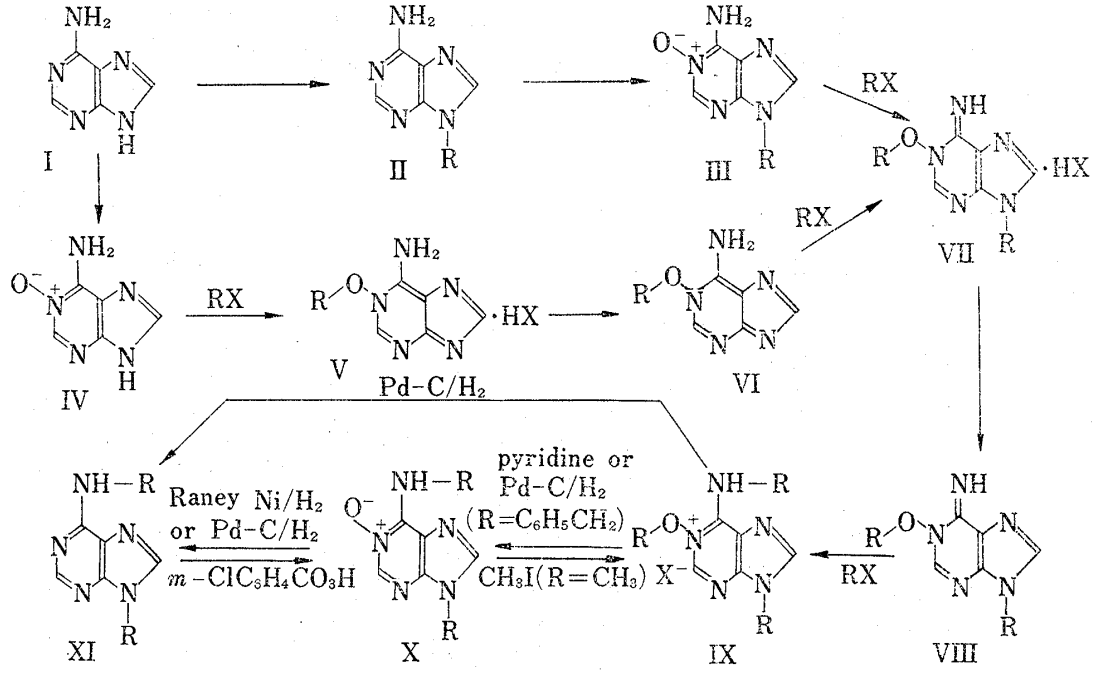

Chart 1

8) T. Fujii, F. Tanaka, K. Mohri, T. Itaya, and T. Saito, *Tetrahedron Letters*, **1973**, 4873.
9) T. Fujii, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **22**, 2466 (1974).
10) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).
11) T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **22**, 2211 (1974).

spectra indicative of identical positional trisubstitution. Final identification as IXb (X=ClO_4) rested on its hydrogenolysis (Pd-C/H_2) to N^6,9-diethyladenine (XIb), identical with a sample prepared from 9-ethyladenine (IIb) by ethylation with ethyl iodide and the Dimroth rearrangement of the resulting 1,9-diethyladenine hydriodide.

Table I. Ultraviolet Spectra of Adenine Derivatives

Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max} (nm)	$\varepsilon\times10^{-3}$	λ_{max} (nm)	$\varepsilon\times10^{-3}$	λ_{max} (nm)	$\varepsilon\times10^{-3}$	λ_{max} (nm)	$\varepsilon\times10^{-3}$
IXa (X=I)	264	12.9	263	13.1	263	13.1	261[e]	12.8
IXa (X=ClO_4)[11]	264	13.3	264[f]	13.3	—	—	261[e,g]	13.6
IXb (X=ClO_4)	266	13.4	265	13.7	265	13.7	263[e]	13.1
IXc (X=ClO_4)	268	16.3	268[f]	16.3	—	—	266[e,g]	17.8
Xa (dihydrate)[11]	238	40.7	264[f]	13.4	—	—	238[g]	35.1
	272	8.4					274[g]	8.2
Xc	241	46.3	266[f]	16.9	—	—	240[g]	35.8
	275	11.2					277[g]	10.8
XIb	269	16.4	265	18.0	269	17.3	269	17.4
1,9-Diethyladenine hydriodide	261	12.6	261	12.7	261	12.6	260	13.6

a) 95% (v/v) aq. ethanol
b) 0.1 N aq. HCl (pH 1)
c) 0.005 M phosphate buffer (pH 7)
d) 0.1 N aq. NaOH (pH 13)
e) Unstable.
f) Determined in 0.1 N HCl in 95% aq. ethanol.[12]
g) Determined in 0.1 N NaOH in 95% aq. ethanol.[12]

The benzyl analog (VIIIc) was also found to undergo benzylation mainly at the N^6-position when allowed to react with benzyl bromide in DMAC at 30° for 70 hr. The product was isolated in the form of the perchlorate (IXc: X=ClO_4) in 84% overall yield. Proof of the correctness of structure IXc (X=ClO_4) was provided by the UV spectra (Table I) of the salt similar to those of the methyl (IXa: X=ClO_4) or ethyl analog (IXb: X=ClO_4) and by the chemical behavior as described below. Hydrogenolysis of IXc (X=ClO_4) using hydrogen and palladium-on-charcoal furnished N^6,9-dibenzyladenine (XIc)[6g,12] in 89% yield. Alternatively, this conversion could be carried out stepwise through Xc. When the hydrogenolysis was interrupted at the moment of completing absorption of one molar equivalent of hydrogen, it gave the 1-oxide (Xc) (86% yield) and XIc (11% yield) with no detectable amount of the starting material (IXc: X=ClO_4). This fact suggests that the cleavage of the N-benzyloxy group at the C—O bond is much faster than that at the N—O bond, being in agreement with the previous observation[5e] with VIIIc. The debenzylation of IXc (X=ClO_4) was alternatively accomplished by treating the salt with hot pyridine to afford Xc in 95% yield, paralleling our experience in reactions of VIIa, b, c (X=I, Br, ClO_4)[13] and IXa (X=I)[11] with nucleophiles. As shown in Table I, the similarity of UV spectrum between Xc and authentic Xa[11] permitted the assignment of the 1-oxide structure to the former. Catalytic hydrogenolysis of Xc using Raney Ni or palladium-on-charcoal as catalyst provided XIc in a good yield.

Probably the most salient feature of the above alkylation study is the finding that the alkylation of 1-alkoxy-9-alkyladenines (type VIII) occurs mainly at the N^6-position. Although no other direct evidence than this finding is available at present, we prefer to consider the ionic structure (XII) (Chart 2) to be of major significance among the resonance structures

12) N.J. Leonard, K.L. Carraway, and J.P. Helgeson, *J. Heterocyclic Chem.*, **2**, 291 (1965).
13) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 958 (1972).

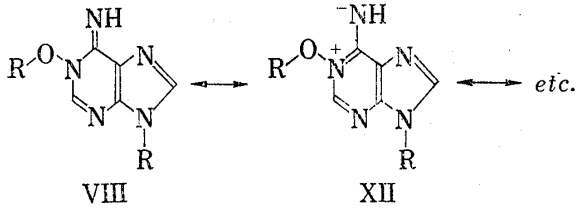

Chart 2

for the free base of 1-alkoxy-9-alkyladenine. Our recent work[14] on the reaction of 1,9-dialkyladenine with methyl iodide has revealed that this type of free base also undergoes methylation predominantly at the N^6-position. This result and that of more recent work of Singer *et al.*[15] on alkylation of 1-methyladenosine also appear to be in favor of the view on the important contributing structure described above.

Furthermore, the direct or two-step removal of the 1-alkoxyl group of the alkylated product (IX) as shown in Chart 1 has completed a new alternative synthetic route to N^6,9-dialkyladenines (XI) from I through VII and IX. In this connection it should be of great interest to note that all the four possible N^x,N^9-dialkyladenines can now be synthesized from 1-alkoxy-9-alkyladenine (type VIII) by use of the alkoxyl group as an easily removable blocking and/or directing or activating group: 1,9-dialkyladenine by N^6-alkylation (as described above) followed by the Dimroth rearrangement and hydrogenolysis (the structural transformation reverse to what is accomplished by the usual Dimroth rearrangement);[11] 3-methyl-9-alkyladenine by ring-opening in the pyrimidine moiety followed by $LiAlH_4$ reduction, recyclization, and hydrogenolysis;[16] 7,9-dialkyladenine by N^7-alkylation of the Dimroth rearrangement product (N^6-alkoxy-9-alkyladenine) followed by hydrogenolysis;[8] N^6,9-dialkyladenine by the present method.

Experimental[17]

1-Methoxy-N^6,9-dimethyladenine Hydriodide (IXa: X=I)——A dried, crude sample of 1-methoxy-9-methyladenine (VIIIa) was freshly prepared from the corresponding hydriodide salt (VIIa: X=I) (614 mg, 2 mmoles) as described previously.[5e] The total amount of the free base (VIIIa) and methyl iodide (1.42 g, 10 mmoles) were stirred in N,N-dimethylacetamide (DMAC) (50 ml) at 50° for 25 hr. The mixture was concentrated to dryness *in vacuo* to leave a dark oil, which was triturated with ether. The resulting insoluble precipitates were collected by filtration, washed with a little ethanol, and dried, giving a slightly brownish solid (330 mg, 51%), mp 142.5—144° (decomp.). Recrystallization of the solid from ethanol produced IXa (X=I) as colorless prisms, mp 154.5—155° (decomp.); UV (Table I). *Anal.* Calcd. for $C_8H_{12}ON_5I$: C, 29.92; H, 3.77; N, 21.81. Found: C, 30.20; H, 3.91; N, 21.70. Identity of this sample with authentic IXa (X=I)[11] was established by paper chromatography, mixed melting-point test, and IR spectrum.

1-Ethoxy-N^6,9-diethyladenine Perchlorate (IXb: X=ClO_4)——1-Ethoxy-9-ethyladenine hydriodide (VIIb: X=I)[5e] (670 mg, 2 mmoles) was converted into the free base (VIIIb) as described previously.[5e] A mixture of the total amount of VIIIb and ethyl iodide (1.56 g, 10 mmoles) in DMAC (50 ml) was stirred at 75—80° for 8 hr. The mixture was evaporated to dryness *in vacuo*, leaving a dark oil. After addition of triethylamine (300 mg), the oil was chromatographed on a 25-g alumina column using ethyl acetate–ethanol (10: 1, v/v) as eluent. Evaporation of the solvents from fractions containing the N^6-ethylated product left a slightly yellowish oil, which was dissolved in a little ethanol. To the ethanolic solution was added a small amount of 70% aq. $HClO_4$ and ether (in that order). The precipitates that resulted were filtered off, washed with ether, and recrystallized from ethanol to give IXb (X=ClO_4) (274 mg, 41%) as colorless prisms, mp 170—172°

14) *a*) Y. Taguchi, Bach. Pharm. Sci. Thesis, Kanazawa University, March, 1974; *b*) K. Sakamoto, M. Pharm. Sci. Thesis, Kanazawa University, March, 1975.
15) B. Singer, L. Sun, and H. Fraenkel-Conrat, *Biochemistry*, **13**, 1913 (1974).
16) T. Fujii, T. Itaya, K. Mohri, and T. Saito, *J. Chem. Soc., Chem. Comm.*, **1973**, 917.
17) All melting points are corrected. Spectra reported herein were determined with a Hitachi Model 323 UV spectrophotometer, a JASCO-IRA-2 IR spectrophotometer, or a JEOL-JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard. Paper chromatographies were developed as described previously.[10] The following abbreviations are used: b=broad, DMSO=dimethyl sulfoxide, m=multiplet, s=singlet.

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(decomp.). Repeated recrystallizations from ethanol provided an analytical sample, mp 172.5—173° (decomp.); UV (Table I). *Anal.* Calcd. for $C_{11}H_{13}O_5N_5Cl$: C, 39.35; H, 5.40; N, 20.86. Found: C, 39.18; H, 5.24; N, 20.64.

1-Benzyloxy-N^6,9-dibenzyladenine Perchlorate (IXc: X=ClO$_4$)——The monohydrate[5e] (3.01 g, 7 mmoles) of 1-benzyloxy-9-benzyladenine hydrobromide (VIIc: X=Br) was quickly dissolved in hot H_2O (200 ml). The aqueous solution was immediately cooled and adjusted to pH 8 with a saturated solution of $NaHCO_3$ in H_2O. The oil that separated out was extracted with chloroform. The chloroform solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving a yellowish solid (VIIIc). A solution of the solid and benzyl bromide (6 g, 35 mmoles) in DMAC (7 ml) was then stirred at 30° for 70 hr. The resulting mixture was triturated with ether (100 ml) and an insoluble solid was separated by decantation. After having been washed with ether repeatedly, the solid was quickly dissolved in hot H_2O (*ca.* 750 ml) and a saturated solution of $NaClO_4$ in H_2O was added until there was no further increase in precipitate. The resulting mixture was chilled to deposit IXc (X=ClO$_4$) (3.08 g, 84%), which was collected by filtration and recrystallized from ethanol to yield an analytical sample as colorless prisms, mp 201.5—202.5°; UV (Table I); NMR (DMSO-d_6) τ: 4.38—4.85 (6H, m, three $C_6H_5C\underline{H}_2$' s), 2.32—3.00 (15H, m, three C_6H_5' s), 1.32 and 1.00 (1H each, s, purine protons), −0.35 (1H, b, NH). *Anal.* Calcd. for $C_{26}H_{24}O_5N_5Cl$: C, 59.83; H, 4.63; N, 13.42. Found: C, 60.00; H, 4.68; N, 13.31.

N^6,9-Dibenzyladenine 1-Oxide (Xc)——i) By Hydrogenolysis of IXc (X=ClO$_4$): A solution of IXc (X=ClO$_4$) (522 mg, 1 mmole) in ethanol (200 ml) was hydrogenated over 10% Pd-C (264 mg) at room temperature and atmospheric pressure. After about 20 sec, one equivalent mole of H_2 was taken up and the reaction was interrupted at that moment. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness *in vacuo*, leaving a colorless oil, in which the absence of the starting material was shown by thin-layer chromatography (TLC). The oil was dissolved in 80% aq. ethanol (10 ml) and the solution was made basic (pH 8) with conc. aq. NH_4OH. The ethanolic solution was then evaporated to dryness *in vacuo* and the residual oil was washed with a little H_2O. After having been dried, the oil was chromatographed on preparative TLC plates (silica gel) using ethyl acetate–ethanol (7: 1, v/v) as eluent, affording the following two products: N^6,9-dibenzyladenine (XIc) (33 mg, 11%), crystallized from 90% aq. ethanol in colorless needles of mp 172.5—173.5° (lit.[12] mp 174.5—175.5°) and identified with authentic XIc[12] by comparison of IR spectrum; the 1-oxide (Xc) (286 mg, 86%). The 1-oxide was recrystallized from ethanol to give an analytical sample as almost colorless prisms, mp 144—145.5° (with previous sintering at 139°); UV (Table I); NMR (DMSO-d_6) τ: 4.72 and 4.53 (2H each, s, two $C_6H_5C\underline{H}_2$' s), 2.62 (10H, s, two C_6H_5' s), 1.53 and 1.32 (1H each, s, purine protons), 1.02 (1H, b, NH). *Anal.* Calcd. for $C_{19}H_{17}ON_5$: C, 68.86; H, 5.17; N, 21.14. Found: C, 68.91; H, 5.26; N, 20.95.

ii) By Debenzylation of IXc (X=ClO$_4$) with Pyridine: A mixture of IXc (X=ClO$_4$) (261 mg, 0.5 mmole) and pyridine (5.4 ml) was stirred at 90° for 3 hr. After cooling, the mixture was filtered and the residual colorless precipitates were washed with a little H_2O and dried to give Xc (106 mg, 64%). The filtrate and washings were combined and evaporated to dryness *in vacuo*. The resulting solid was washed with a little H_2O and dried to yield a second crop (51 mg, 31%); total yield 157 mg (95%). Recrystallization of the crude sample from ethanol gave Xc as colorless prisms, mp 145—145.5° (with previous sintering at 139°), shown to be identical with the sample prepared by method-(i).

N^6,9-Diethyladenine (XIb)——i) By the Dimroth Rearrangement of 1,9-Diethyladenine: A solution of 1,9-diethyladenine hydriodide (636 mg, 1.99 mmoles), prepared as described below, in 0.2 N aq. NaOH (20 ml) was stirred at 95° for 10 min. The mixture was evaporated *in vacuo* to leave a colorless solid, which was dried and extracted with hot benzene (200 ml). Evaporation of the solvent from the benzene extracts left a colorless solid (358 mg, 94%), mp 105—106°. Recrystallization from hexane produced XIb as colorless prisms, mp 106—107°; UV (Table I). *Anal.* Calcd. for $C_9H_{13}N_5$: C, 56.52; H, 6.85; N, 36.63. Found: C, 56.67; H, 6.93; N, 36.70.

ii) By Hydrogenolysis of IXb (X=ClO$_4$): A solution of IXb (X=ClO$_4$) (168 mg, 0.5 mmole) in ethanol (55 ml) was hydrogenated over 10% Pd-C (400 mg) at 45—50° and atmospheric pressure for 36 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*, leaving a colorless solid. The solid was dissolved in H_2O (10 ml) and the aqueous solution was passed through a column of Amberlite IRA-410 (HCO_3^-) (3 ml). The column was then eluted with H_2O (130 ml) and the eluate (140 ml) was evaporated to dryness *in vacuo*. Since the resulting solid, mp 94—106°, was shown not to be homogeneous by TLC, it was purified on preparative thin-layer silica gel plates using ethyl acetate–ethanol (5: 1, v/v) as eluent, furnishing XIb (65.8 mg, 69%), mp 106—107°, identical with the sample obtained by method-(i).

1,9-Diethyladenine Hydriodide——A mixture of 9-ethyladenine[6g] (326 mg, 2 mmoles) and ethyl iodide (1.56 g, 10 mmoles) in DMAC (50 ml) was stirred at 80° for 7 hr. To the solution was added ether (20 ml) and the yellowish precipitates that resulted were collected by filtration, washed successively with ether and a little ethanol, and recrystallized from H_2O to provide colorless needles (344 mg, 54%), mp 277—278° (decomp.). Repeated recrystallizations from H_2O gave an analytical sample of the 1-ethylated product as colorless needles, mp 282—282.5° (decomp.); UV (Table I). *Anal.* Calcd. for $C_9H_{14}N_5I$: C, 33.87; H, 4.42; N, 21.95. Found: C, 33.74; H, 4.53; N, 21.88.

N^6,9-Dibenzyladenine (XIc)——i) From IXc (X=ClO$_4$): A solution of IXc (X=ClO$_4$) (524 mg, 1 mmole)

in ethanol (180 ml) was hydrogenated over 10% Pd-C (530 mg) at room temperature and atmospheric pressure for 6.5 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting oil was triturated with boiling H_2O (40 ml) and an insoluble solid that separated out was filtered off, washed with H_2O, and dried to give the free base of XIc (270 mg, 86%), mp 172—172.5°, shown to be identical (by mixed melting-point test and IR spectroscopy) with authentic XIc.[12] The filtrate and washings were combined and adjusted to pH 8 with conc. aq. NH_4OH to produce a second crop (10 mg, 3%); total yield 280 mg (89%).

ii) By Hydrogenolysis of Xc over Pd-C: The 1-oxide (Xc) (100 mg, 0.302 mmole) was hydrogenated in ethanol (50 ml) containing 1 equivalent mole of $HClO_4$ using 10% Pd-C (100 mg) as catalyst at room temperature and atmospheric pressure for 7 hr. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness *in vacuo*, leaving a colorless oil, which was dissolved in ethanol (8 ml). The solution was made basic (pH 8) with conc. aq. NH_4OH and evaporated to dryness *in vacuo*. The resulting solid was washed with H_2O and dried to yield XIc (80 mg, 84%), mp 169—172°, identical with an authentic sample.[12]

iii) By Hydrogenolysis of Xc over Raney Ni: A solution of Xc (100 mg, 0.302 mmole) in ethanol (50 ml) was hydrogenated over Raney Ni W-2 catalyst (0.3 ml) at room temperature and atmospheric pressure for 1.5 hr. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to leave a colorless solid (92 mg, 97%), mp 170—172°. On recrystallization from ethanol, it gave colorless needles, mp 172.5—173°, identical with authentic XIc.[12]

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