# A Biogenetically Patterned Synthesis of (±)-Cherylline

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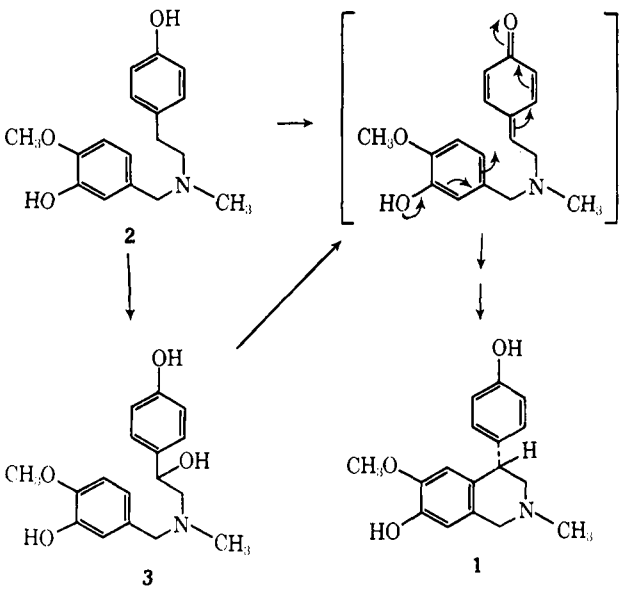
A facile total synthesis of the *Amaryllidaceae* alkaloid cherylline has been achieved *via* base-catalyzed cyclization of *p*-hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)methylamino]methyl}benzyl alcohol (**3**), an intermediate of possible biogenetic significance.

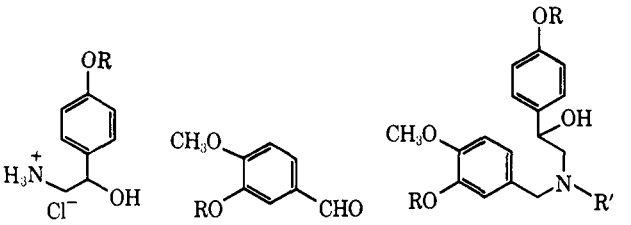
Cherylline, a phenolic 4-phenyltetrahydroisoquinoline alkaloid, has recently been isolated from several *Crinum* species and assigned structure **1**.[2] Although cherylline is unique in structure for an *Amaryllidaceae* alkaloid,[3] its biogenesis likely follows a pathway similar to that operative in the formation of the other alkaloids of this class,[3] *i.e.*, oxidation and cyclization of a suitable derivative of norbelladine. Such a pathway can be envisioned as shown in Scheme I. Direct two-electron

SCHEME I



oxidation of *O*,*N*-dimethylnorbelladine (**2**) could yield an intermediate quinone methide which subsequently cyclizes to cherylline (**1**); alternatively, hydroxylation of **2** could give the heretofore unknown hydroxy-*O*,*N*-dimethylnorbelladine **3**, which would yield the same intermediate upon dehydration.[4] Since we had occasion to prepare compounds similar to **3** during the course of other synthetic work, we decided to investigate the feasibility of this scheme as a synthetic route to (±)-cherylline.[5]

(±)-*O*-Benzyloctopamine hydrochloride (**4**) was prepared in 50% yield by lithium aluminum hydride reduction[6] of *p*-benzyloxybenzaldehyde cyanohydrin. Condensation of **4** with *O*-benzylisovanillin[7] (**5**) in alkaline methanol, followed by addition of sodium borohydride and refluxing, gave the secondary amine **6** in 53% yield. N-Methylation of **6** was accomplished in 73% yield by an N-formylation–lithium aluminum hydride reduction sequence. The resulting tertiary amine **7** was subjected to catalytic hydrogenation to give the desired (±)-hydroxy-*O*,*N*-dimethylnorbelladine **3** in 94% yield.



**4**, R = benzyl; **8**, R = H

**5**, R = benzyl; **9**, R = H

**6**, R = benzyl; R′ = H; **7**, R = benzyl; R′ = $CH_3$; **10**, R, R′ = H

With the hypothetical cherylline precursor in hand, cyclization according to Scheme I was then investigated. Treatment of **3** with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature or at reflux surprisingly led to no reaction; unchanged starting material was recovered in good yield. However, when **3** was refluxed in aqueous ammonium hydroxide solution, the reaction proceeded very smoothly to give (±)-cherylline (**1**) in 79% yield.[8] The synthetic material was indistinguishable from authentic (−)-cherylline[9] in its uv, nmr, and mass spectra as well as in its thin layer chromatographic behavior.[10]

The ease with which **3** could be converted to cherylline proved to be inconvenient at times. When an attempt was made to prepare the hydrochloride of **3** for purposes of elemental analysis, there was obtained after recrystallization (±)-cherylline hydrochloride instead.

(1) This work was supported by Public Health Service Grant CA 10136 from the National Cancer Institute. The high-resolution nuclear magnetic resonance and mass spectrometers used in this investigation were purchased with funds from the National Science Foundation.

(2) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, *J. Org. Chem.*, **35**, 1100 (1970).

(3) For a review of the structure, synthesis, and biosynthesis of Amaryllidaceae alkaloids, see W. C. Wildman in "The Alkaloids," Vol. XI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, pp 308–405.

(4) A third possibility for the biogenesis of cherylline is one involving rearrangement of an 11-hydroxy-5,10b-ethanophenanthridine[3] derivative to a montanine[2]-type skeleton, followed by N-methylation and elimination. Similar laboratory transformations have already been accomplished: Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

(5) For another synthesis of both racemic and natural cherylline, see A. Brossi and S. Teitel, *Tetrahedron Lett.*, 417 (1970); *J. Org. Chem.*, **35**, 3559 (1970).

(6) N. Adityachaudhury and A. Chatterjee, *J. Indian Chem. Soc.*, **36**, 585 (1959).

(7) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931).

(8) For a review of related dihydroxydiarylmethane syntheses, see H. Schnell and H. Krimm, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).

(9) We thank Dr. A. Brossi for providing us with a very generous sample of natural (−)-cherylline.

(10) Subsequent to this work we learned that various 4-phenyl-substituted tetrahydroisoquinolines have been prepared by Dr. A. Rheiner of F. Hoffmann-La Roche & Co., Basle, Switzerland, by way of acid-catalyzed cyclization of similar precursors (personal communication from Dr. A. Brossi, Hoffmann-La Roche, Inc., Nutley, N. J.).

In order to improve the overall efficiency of the cherylline synthesis, a simpler route to precursor **3** was sought. Consequently, (±)-octopamine hydrochloride (**8**) was reductively condensed with isovanillin (**9**) to afford[11] a 66% yield of the hydroxy-*O*-methylnorbelladine **10**. The phenolic amine **10** was refluxed with ethyl formate in the presence of potassium carbonate and the resulting crude *N*-formyl compound was reduced with lithium aluminum hydride in 1,2-dimethoxyethane. Instead of giving the expected hydroxy-*O*,*N*-dimethylnorbelladine **3**, however, this reaction sequence afforded slightly impure (±)-cherylline (**1**) directly. The racemic alkaloid, obtained in 66% yield from **10**, was probably formed by base-catalyzed cyclization of **3** (or a related salt) during hydrolysis of the hydride-reduction reaction mixture. An nmr spectrum of the crude *N*-formyl intermediate indicated that it had not yet undergone cyclization but rather still retained the norbelladine skeleton. In any event, this three-step sequence of reactions provides an extremely simple and efficient total synthesis of racemic cherylline.[12]

The possible involvement of phenolic amine **3** in the biosynthesis of cherylline will have to be determined by feeding experiments. It is interesting to note in this respect that the related amine **10** could likewise be involved in the biosynthesis of members of the 11-hydroxy-5,10b-ethanophenanthridine[3] class of *Amaryllidaceae* alkaloids. We are currently investigating laboratory syntheses based on this latter hypothesis.

## Experimental Section[13]

**(±)-α-(Aminomethyl)-*p*-benzyloxybenzyl Alcohol (*O*-Benzyloctopamine) Hydrochloride (4).**—A solution of 200 g (1.93 mol) of sodium bisulfite in 300 ml of water was added slowly with stirring to a solution of 84.0 g (0.396 mol) of *p*-benzyloxybenzaldehyde (mp 72–74°) in 300 ml of ethanol–20% tetrahydrofuran. The mixture was stirred at room temperature for 2 hr; the resulting white bisulfite adduct was filtered, rinsed with an ether–20% ethanol mixture, and resuspended in 200 ml of water. To this stirred suspension was slowly added a solution of 60.0 g (1.22 mol) of sodium cyanide in 200 ml of water and the resulting mixture was stirred at room temperature for 12 hr. Extraction with ethyl acetate afforded 90 g (95%) of *p*-benzyloxybenzaldehyde cyanohydrin: ir ($CHCl_3$) 2.80, 2.98 (OH), 4.54 (C≡N), 6.22, 6.64, 8.04, 9.80 μ.

A solution of the crude cyanohydrin (90 g) in 500 ml of tetrahydrofuran was added dropwise to a stirred suspension of 55.0 g (1.45 mol) of lithium aluminum hydride in 2 l. of the same solvent. The reaction mixture was stirred for 12 hr at room temperature and for 1 hr at reflux. The excess hydride was destroyed with saturated aqueous potassium sodium tartrate, *ca.* 10 g of anhydrous sodium sulfate was added, and the mixture was refluxed for 1 hr. The salts were removed by filtration and washed thoroughly with tetrahydrofuran, and the combined filtrates were evaporated to give 78 g of crude solid amine. A solution of the crude amine in an ether–chloroform–ethanol (7:2:1) mixture was cooled to 10° and saturated with dry hydrogen chloride gas with vigorous stirring. The resulting white crystalline salt was isolated by filtration, washed with anhydrous ether, and dried under vacuum to give 53 g (48%) of *O*-benzyloctopamine hydrochloride (**4**), mp 190–195°. Recrystallization from wet acetone–ether afforded pure material, mp 194–196°.

*Anal.* Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.48; Cl, 12.67; N, 5.01. Found: C, 64.53; H, 6.46; Cl, 12.89; N, 4.80.

Basification of a portion of *O*-benzyloctopamine hydrochloride gave the free amine, mp 101–103°, after recrystallization from aqueous ethanol.

***p*-Benzyloxy-α-{[(3-benzyloxy-4-methoxybenzyl)amino]methyl}benzyl Alcohol (6).**—To a solution of 43.5 g (0.179 mol) of *O*-benzylisovanillin[7] (**5**) and 50.0 g (0.179 mol) of *O*-benzyloctopamine hydrochloride (**4**) in 2.5 l. of absolute ethanol was added 55 g of sodium bicarbonate and the mixture was refluxed with stirring under nitrogen for 2 hr. The solution was cooled with stirring in an ice bath while 10 g (0.26 mol) of sodium borohydride was added in small portions over a period of 30 min and then was refluxed for 2 hr, during which time an additional 10 g of sodium borohydride was added. After evaporation of the ethanol under reduced pressure, the residue was dissolved in dilute hydrochloric acid, neutralized by addition of solid sodium bicarbonate, and extracted thoroughly with ethyl acetate. The resulting crude product was recrystallized from hexane–ethyl acetate to give 45.0 g (53%) of **6**, mp 105–109°. One additional recrystallization afforded pure material: mp 109–111°; ir ($CHCl_3$) 2.76, 2.90, 6.20, 6.62, 8.00 (broad), 8.80, and 9.75 μ; nmr ($CDCl_3$, 90 MHz) δ 2.69 (m, 2, $NCH_2$), 3.67 (s, 2, $ArCH_2N$), 3.79 (s, 3, $OCH_3$), 4.68 (dd, 1, $J$ = 5 and 8 Hz, ArCHO), 4.97 (s, 2, benzyl), 5.09 (s, 2, benzyl), 6.67–7.59 (m, 17, aromatic); molecular ion at $m/e$ 469.2258 (calcd for $C_{30}H_{31}NO_4$, 469.2253).

The amine gave a crystalline hydrochloride, mp 166–169° (from wet acetone–ether).

***p*-Benzyloxy-α-{[(3-benzyloxy-4-methoxybenzyl)methylamino]methyl}benzyl Alcohol (7).**—A mixture of 2.00 g (4.26 mmol) of amine **6**, 1.0 g of anhydrous potassium carbonate, and 1.0 g of 3-Å molecular sieves in 50 ml of ethyl formate was refluxed under nitrogen for 12 hr. The reaction mixture was filtered, the residue was washed with absolute ethanol, and the combined filtrates were evaporated under reduced pressure. The resulting white powder was dissolved in tetrahydrofuran, excess lithium aluminum hydride was added, and the mixture was stirred for 4 hr at room temperature and 4 hr at reflux. After decomposition of the excess hydride with saturated aqueous potassium sodium tartrate, removal of the salts by filtration, and evaporation of the solvent, the residue was crystallized from acetone to give 1.50 g (73%) of the tertiary amine **7**: mp 86–88°; ir ($CHCl_3$) 2.76, 2.90 (OH), 6.20, 6.62, 8.10 (broad), and 9.75 μ; nmr ($CDCl_3$, 60 MHz) δ 2.18 (s, 3, $NCH_3$), 2.44 (m, 2, $NCH_2$), 3.28, 3.57 (AB pattern, 2, $J$ = 12.5 Hz, $ArCH_2N$), 3.80 (s, 3, $OCH_3$), 4.58 (dd, 1, $J$ = 4.5 and 9 Hz, ArCHO), 4.96 (s, 2, benzyl), 5.06 (s, 2, benzyl), 6.7–7.4 (m, 17, aromatic); molecular ion at $m/e$ 483.2418 (calcd 483.2409).

*Anal.* Calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90. Found: C, 77.25; H, 7.08; N, 2.64.

***p*-Hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)methylamino]methyl}benzyl Alcohol (3).**—Hydrogen was introduced into a stirred solution of 200 mg (0.414 mmol) of the bisbenzyl ether **7** in 50 ml of absolute ethanol containing 50 mg of 10% palladium on charcoal *via* a gas dispersion tube. After 55 min the catalyst was removed by filtration through Celite 545 and the solvent was evaporated under reduced pressure. The resulting colorless glass was crystallized from ether–hexane to give 118 mg (94%) of the hydroxy-*O*,*N*-dimethylnorbelladine **3**: mp 65–74°, homogeneous to thin layer chromatography (ethyl acetate–chloroform–ethanol, 85:11:4); ir ($CHCl_3$) 2.80, 3.0 (OH), 6.18, 6.27, 8.29, and 9.70 μ; nmr (acetone-$d_6$, 60 MHz) δ 2.24 (s, 3, $NCH_3$), 2.48 (m, 2, $NCH_2$), 3.32, 3.58 (AB pattern, 2, $J$ = 13 Hz, $ArCH_2N$), 3.75 (s, 3, $OCH_3$), 4.63 (dd, 1, $J$ = 5.5 and 8 Hz, ArCHO), 6.50–7.20 (m, 7, aromatic); mass spectrum (elec-

(11) M. A. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, **92**, 1090 (1970).

(12) A reviewer has suggested that both of these routes to cherylline might actually be the result of acid-catalyzed rather than base-catalyzed cyclization; in the first case general acid catalysis by ammonium ion could take place, and in the second case cyclization could occur during acidification of the reaction mixture with hydrochloric acid. We find, however, that cherylline is also produced, although not as cleanly, when **3** is refluxed with 3 mol equiv of sodium hydroxide in water. In addition, the conversion of **10** to cherylline is still successful when the acidification step is replaced by treatment of the reaction mixture with a pH 7 buffer. We therefore feel that the key cyclization step is occurring by base catalysis in this work.

(13) Melting points were measured on a Kofler microscope hot stage and are uncorrected. Infrared and ultraviolet spectra were determined with Perkin-Elmer Model 137 and 202 spectrophotometers, respectively. Nuclear magnetic resonance spectra were measured at 60 MHz with a Varian Associates Model A-60 or at 90 MHz with a Bruker HFX-10 spectrometer. High-resolution mass spectra were obtained using an Associated Electronics Industries MS 902 instrument. Thin layer chromatographies were carried out using silica gel GF. Tetrahydrofuran and dimethoxyethane were purified by distillation from lithium aluminum hydride immediately prior to use. Extracts of reaction products in organic solvents were washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure using a rotary evaporator. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

tron impact) $m/e$ 285 ($M^+ - H_2O$); mass spectrum (chemical ionization, methane) $m/e$ 304 ($M + H^+$). The compound was too unstable for elemental analysis.

A sample of amine **3** was converted to a hydrochloride, mp 194–230°, by treatment of a solution of it in ethanol–ether with gaseous hydrogen chloride at 0°. Repeated recrystallization of the salt from ethanol–ether gave white crystals, mp 241–243°; the mixture melting point with (±)-cherylline hydrochloride (see below) was undepressed. The amine regenerated upon basicification of this salt was identical with cherylline in thin layer chromatographic behavior.

**(±)-Cherylline (1). Method A.**—A solution of 120 mg (0.396 mmol) of amine **3** in 50 ml of 4% aqueous ammonia was refluxed for 7 hr. The resulting pale yellow solution was acidified with concentrated hydrochloric acid, neutralized with sodium bicarbonate, and extracted thoroughly with ethyl acetate. The residue obtained upon evaporation of the solvent was crystallized from ether–hexane to give 93 mg (82%) of crude (±)-cherylline, mp 125–200°, identical in thin layer chromatographic behavior with authentic material[9] except for a trace of a polar impurity (ethyl acetate–chloroform–ethanol, 85:11:4). Several recrystallizations from benzene–methanol gave pure (±)-cherylline: mp 209–212° (reported[5] mp 215–216°); identical with (−)-cherylline[9] in tlc, nmr, uv, and mass spectrum; ir (KBr) 2.99, 6.21, 6.29, 6.64, 7.86, 7.98, and 8.91 μ; nmr (acetone-$d_6$, 60 MHz) δ 2.28 (s, 3), 2.38, 2.82 (ABX pattern, 2, $J_{AB}$ = 11.0 Hz, $J_{AX}$ = 7.5 Hz, $J_{BX}$ = 5.5 Hz), 3.42 (s, 2), 3.52 (s, 3), 3.98 (dd, 1, $J$ = 5.5 and 7.5 Hz), 6.27 (s, 1), 6.45 (s, 1), 6.62, 6.93 (AA'BB' pattern, 4, $J$ = 8.5 Hz); uv max (ethanol) 226 nm (sh, ε 14,000), 280 (3900), 285 (4000), and 295 (sh, 2500); mass spectrum $m/e$ 285, 242, 241, 227, 225, 211, 210, 181.

*Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.40; H, 6.71; N, 4.69.

A sample of (±)-cherylline was converted to its hydrochloride and recrystallized from ethanol–ether to give 1 HCl, mp 240–243° (the salt first melted at 185°, resolidified at *ca.* 190°, then melted again at the specified temperature).

***p*-Hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)amino]methyl}-benzyl Alcohol (10).**—A mixture of 836 mg (5.50 mmol) of isovanillin[14] (**9**), 1.04 g (5.50 mmol) of (±)-octapamine hydrochloride[14] (**8**), and 500 mg of sodium bicarbonate in 50 ml of methanol was stirred at 50° for 30 min. The reaction mixture was cooled in an ice bath, 1.00 g (26.3 mmol) of sodium borohydride was slowly added, and the resulting solution was stirred at room temperature for 30 min. Most of the solvent was evaporated under reduced pressure; the residue was dissolved in dilute hydrochloric acid, neutralized with sodium bicarbonate, and extracted with ethyl acetate to give 1.05 g (66%) of crude crystalline amine **10**, mp 115–135°. Two recrystallizations from ethyl acetate–methanol afforded the pure compound: mp 150–152°; ir (KBr) 3.0, 6.21, 6.29, 6.64, 7.97, 8.21, and 9.74 μ; nmr (DMSO-$d_6$, 90 MHz) δ 2.62 (d, 2, $J$ = 6 Hz, $NCH_2$), 3.67 (s, 2, $ArCH_2N$), 3.74 (s, 3, $OCH_3$), 4.62 (t, 1, $J$ = 6 Hz, ArCHO), 6.56–7.23 (m, 7, aromatic).

A sample of **10** was treated with excess acetic anhydride in pyridine at −10° to afford the tetraacetyl derivative as a colorless glass.

*Anal.* Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 62.76; H, 6.23; N, 2.79.

**(±)-Cherylline (1). Method B.**—To a solution of 100 mg (0.330 mmol) of phenolic amine **10** in 30 ml of ethyl formate–ethanol 3:1 was added 200 mg of potassium carbonate and 1 g of 3-Å molecular sieves. The mixture was refluxed under nitrogen for 8 hr. The solids were filtered and washed with ethanol, and the combined filtrates were evaporated under reduced pressure.

A suspension of the resulting white solid in 1,2-dimethoxyethane was treated with excess lithium aluminum hydride and the mixture was refluxed under nitrogen for 50 hr. The excess hydride was decomposed with saturated aqueous potassium sodium tartrate solution and the resulting suspension was refluxed for 3 hr. The solvent was decanted and the residue was dissolved in dilute hydrochloric acid, neutralized with sodium bicarbonate, and extracted with ethyl acetate. Crystallization of the crude product from ether–hexane afforded 62 mg (66%) of (±)-cherylline (**1**), identical in all respects with the material prepared by method A above.

(14) Aldrich Chemical Co., Milwaukee, Wis.

**Registry No.**—**1**, 26996-80-5; **1** HCl, 29002-62-8; **3**, 29002-63-9; **4**, 29002-64-0; **6**, 29002-65-1; **6** HCl, 29002-66-2; **7**, 29038-87-7; **10**, 29002-67-3.

# Notes

## A New Synthesis of 1,3-Dimethylcytosines

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The discovery of 3-methylcytidine[1] and 1-methyladenosine[2] as minor basic components of nucleic acid stimulated our interest in the chemistry of the iminopyrimidines, which have customarily been made by alkylation of the parent aminopyrimidines. In this note we will describe a new synthesis of 1,3-dimethylcytosine derivatives as a part of the exploitation of our preparative methods of pyrimidine derivatives of the imino type.

Heating of 6-amino-1,3-dimethyluracil (I) with phosphorous oxychloride at 240–250° for 10 hr afforded 6-chloro-1,3-dimethylcytosine (Ia) in 92% yield. The structure of Ia was assigned on the basis of the following evidence. Compound Ia shows a secondary amino stretching absorption band at 3250 $cm^{-1}$ (Nujol). The nuclear magnetic resonance spectrum ($CF_3COOH$) of Ia shows singlets at 3.73 ($CH_3$), 3.86 ($CH_3$), and 6.67 ppm ($C_5$ H in pyrimidine), and two broad bands at 7.72 and 8.18 ppm ($=N^+H_2$). The mass spectrometry reveals a parent ion ($m/e$ 173) and M + 2 ion, which suggests that one chlorine atom is contained in the molecule. The structure of Ia was finally established by catalytic dechlorination over palladium/carbon to the known 1,3-dimethylcytosine[3–6] (Ib) and by its conversion into the starting material I by treatment with aqueous sodium

(1) (a) R. H. Hall, *Biochem. Biophys. Res. Commun.*, **12**, 36b (1963); (b) R. H. Hall, *Biochemistry*, **4**, 661 (1965).

(2) (a) A. Hampton and D. I. Magrath, *J. Amer. Chem. Soc.*, **79**, 3250 (1957); (b) A. Hampton and M. H. Maguire, *ibid.*, **83**, 150 (1961).

(3) G. H. Hilbert, *ibid.*, **56**, 190 (1934).

(4) The infrared spectroscopic data of Ib were reported by Angell: C. L. Angell, *J. Chem. Soc.*, 504 (1961).

(5) G. W. Kenner, C. B. Reese, and A. R Todd, *ibid.*, 855 (1955).

(6) P. Brookes and P. D. Lawley, *ibid.*, 1348 (1962).