Quinolizidines. XXVI.[1] A Synthesis of (±)-Deplancheine

Tozo FUJII,* Masashi OHBA, and Noriko SASAKI

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan. *Received March 29, 1989*

A formal racemic synthesis of the *Alstonia* and *Aspidosperma* alkaloid deplancheine (12) has been achieved in the form of the synthesis of the tetracyclic methyl ketone 11 through the "3-acetylpyridine route." The route started with an initial quaternization of the ketal 5 with 2-(3-indolyl)ethyl bromide and proceeded through the intermediates 7 and 8.

Keywords quaternization; pyridinium salt catalytic reduction; piperidine mercuric acetate–edetic acid oxidation; oxidative cyclization; deketalization; sodium borohydride reduction; indoloquinolizidine alkaloid synthesis

The tetracycle **4** represents the parent framework common to indolo[2,3-*a*]quinolizidine alkaloids, which are often referred to as indoloquinolizidine alkaloids.[2] This base itself is also a natural product isolated in partially racemized form from the leaves of *Dracontomelum mangiferum* BL. (Anacardiaceae).[3] It has been a model target selected for synthesis by many investigators[4] who are interested in the syntheses of more complex indoloquinolizidine alkaloids. In 1962, Wenkert and Wickberg[5] prepared the tetracycle **4** from 3-(2-piperidinoethyl)indole (**1**) in 63% yield by oxidative cyclization with 10 molar eq of $Hg(OAc)_2$ in hot 5% aqueous AcOH for 1 h, followed by treatment with H_2S and $NaBH_4$ reduction of the over-oxidized product **3** present as a minor component. The procedure and yield of **4** in this oxidative cyclization (**1**→**2**→**4**) were recently improved by us through the use of 3 molar eq of $Hg(OAc)_2$–edetate disodium (EDTA·2Na) in boiling aqueous EtOH for 3 h.[6] In the present study, the applicability of the modified oxidative cyclization procedure to syntheses of more complex indoloquinolizidine alkaloids was tested in a synthesis of (±)-deplancheine (**12**),[7,8] whose (+)-enantiomer was isolated from *Alstonia* and *Aspidosperma* plants[7c,9] belonging to the family Apocynaceae and was recently assigned the (*R*) configuration.[8]

Quaternization of the ketal **5**, a synthetic equivalent for 3-acetylpyridine, with 2-(3-indolyl)ethyl bromide was effected in $HCONMe_2$ at 80—85 °C for 50 h, and the crude quaternary salt **6** that formed was hydrogenated over Adams catalyst in aqueous EtOH at 35 °C and atmospheric pressure to give the piperidine derivative **7** in 78% overall yield (from **5**). Treatment of **7** with 3 molar eq of $Hg(OAc)_2$–EDTA·2Na in boiling aqueous EtOH for 3 h furnished, after reduction of the over-oxidized product (type **3**) with $NaBH_4$, the tetracyclic ketal **8** in 65% yield. In this oxidative cyclization, the isomeric ketal **9** would be another possible product, but we were unable to find it in the reaction mixture. Such high regioselectivity in the $Hg(OAc)_2$–EDTA oxidation of **7** is comparable to that observed for the structurally analogous 1-(3,4-dimethoxyphenethyl)piperidine system.[10] The relative configuration of **8** was assigned from a consideration of the thermo-

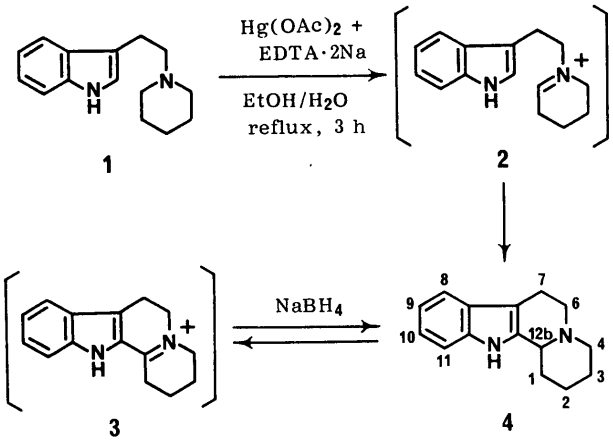

Chart 1

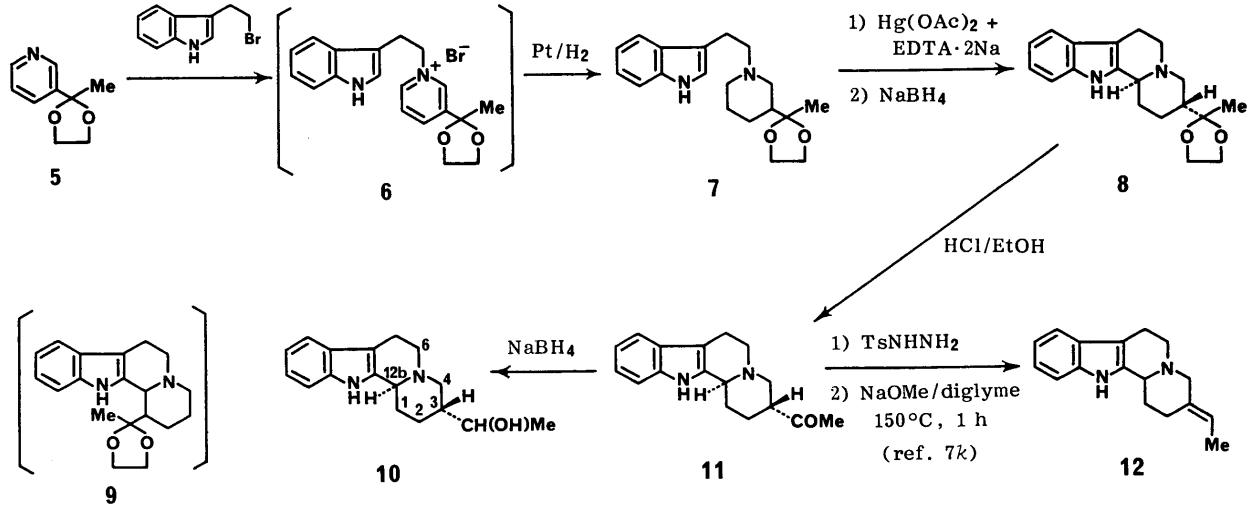

Chart 2

dynamic stabilities of the possible diastereomers, and the whole structure was eventually substantiated by the following self-consistent reaction sequence.

Deketalization of **8** with 1 N aqueous HCl in boiling EtOH for 2 h afforded the methyl ketone **11** in 95% yield. Reduction of **11** with $NaBH_4$ in tetrahydrofuran produced a 1 : 1 mixture of the diastereomeric alcohols **10**[7k,m] (89% yield), from which one isomer (mp 202—204 °C) was separated by recrystallization. The infrared (IR) spectrum of this isomer in $CHCl_3$ at 0.004 M concentration indicated the presence of a *trans*-quinolizidine ring[11] as well as the absence of intramolecular hydrogen bonding between the hydroxy group and N(5), suggesting the hydrogen at C(12b) and the side chain at C(3) to be axial and equatorial, respectively, and hence the same in the methyl ketone **11**. Judging from this IR spectroscopic feature and the melting point, it seemed to be the same diastereomer as the one (mp 199—200 °C) reported by Winterfeldt's group.[12] Finally, the correctness of the whole structure of **11** was confirmed by a direct comparison with an authentic sample.[7k,12a]

Since the methyl ketone **11** has been converted into (±)-deplancheine (**12**) by Pakrashi's group[7k] through the *p*-tosylhydrazone formation followed by thermolysis with sodium methoxide (Chart 2), the above synthesis of **11** from **5** through **6**, **7**, and **8** is tantamount to a new formal racemic synthesis of this alkaloid. It should be emphasized that the present study has confirmed the applicability of the "3-acetylpyridine route",[13] originally designed for the racemic syntheses of all of the benzo[*a*]quinolizidine-type *Alangium* alkaloids, to the syntheses of structurally related indoloquinolizidine alkaloids.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a JASCO A-202 IR spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 nuclear magnetic resonance (NMR) spectrometer, equipped with a ^{13}C Fourier transform NMR system, at 25 °C with Me_4Si as an internal standard. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, s = singlet.

(±)-3-[2-[3-(1,1-Ethylenedioxyethyl)-1-piperidinyl]ethyl]-1*H*-indole (7) A solution of 3-(1,1-ethylenedioxyethyl)pyridine (**5**)[14] (6.61 g, 40 mmol) and 2-(3-indolyl)ethyl bromide[15] (9.41 g, 42 mmol) in $HCONMe_2$ (40 ml) was stirred at 80—85 °C for 50 h. The solvent was removed by evaporation under reduced pressure, and the residual oil was dissolved in H_2O (80 ml). The aqueous solution was washed with benzene and concentrated to dryness *in vacuo* to leave **6** as a brown glass, which was dissolved in H_2O (100 ml). The resulting aqueous solution was hydrogenated over Adams catalyst (300 mg) at 35 °C and atmospheric pressure for 21 h, and EtOH (20 ml) was added to the reaction mixture in order to dissolve the precipitate that deposited during this period. The hydrogenation was then continued for a further 9 h. The catalyst was removed by filtration and washed with H_2O (30 ml). The filtrate and washings were combined, made alkaline with 10% aqueous NaOH, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo*, leaving a pale brown glass. Crystallization of the glass from benzene–hexane (1 : 1, v/v) gave **7** (9.80 g, 78% from **5**) as slightly yellowish prisms. Recrystallization in a similar manner provided an analytical sample as colorless prisms, mp 118—119 °C; MS *m/z*: 314 (M^+); IR $\nu_{max}^{CHCl_3}$ 3500 cm^{-1} (NH); ^1H-NMR ($CDCl_3$) δ: 1.28 (3H, s, Me), 1.6—2.1 (7H, m, two CH_2's, CH, and $ArCH_2$), 2.6—3.3 (6H, m, three NCH_2's), 3.8—4.0 (4H, m, two OCH_2's), 6.95—7.7 (5H, m, aromatic protons), 8.02 (1H, br, NH). *Anal.* Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.47; H, 8.46; N, 8.76.

(±)-3α-(1,1-Ethylenedioxyethyl)-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine (8) A stirred mixture of **7** (3.14 g, 10 mmol) and 0.1 M aqueous $Hg(OAc)_2$–EDTA·2Na·$2H_2O$ [1 : 1 (molar ratio)] (300 ml) in EtOH (150 ml) was heated under reflux for 3 h. After cooling, the mixture was made alkaline (pH 9) with 10% aqueous NH_3 and stirred, after addition of $NaBH_4$ (3.78 g, 100 mmol), at room temperature for 4 h. The reaction mixture was shaken with $CHCl_3$ (80 ml), and an insoluble substance was removed from the mixture by filtration and washed with $CHCl_3$. The aqueous layer of the filtrate was separated from the $CHCl_3$ layer and extracted with $CHCl_3$. The $CHCl_3$ washings and extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a dark brown oil. The oil was passed through an alumina (50 g) column using $CHCl_3$ as the eluent, and the eluate was concentrated *in vacuo* to give a brown glass. Crystallization of the glass from MeOH yielded a first crop (1.50 g) of **8** as slightly yellowish prisms. The mother liquor of this crystallization was concentrated *in vacuo*, and purification of the resulting brown glass by column chromatography [alumina, $CHCl_3$–hexane (2 : 1, v/v)], followed by crystallization from MeOH, gave a second crop (0.52 g) of **8**. The total yield was 2.02 g (65%). Recrystallization of crude **8** from MeOH furnished an analytical sample as colorless prisms, mp 206—207 °C; MS *m/z*: 312 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (NH), 2820, 2770 (*trans*-quinolizidine ring[11]); ^1H-NMR ($CDCl_3$) δ: 1.31 (3H, s, Me), 1.3—3.3 (12H, m, quinolizidine protons), 3.8—4.0 (4H, m, two OCH_2's), 7.0—7.5 (4H, m, aromatic protons), 7.72 (1H, br, NH). *Anal.* Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.04; H, 7.69; N, 8.97.

***cis*-(±)-1-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-3-yl)ethanone (11)** A mixture of **8** (1.87 g, 6 mmol) and 1 N aqueous HCl (20 ml) in EtOH (40 ml) was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of 10% aqueous Na_2CO_3 (30 ml) and $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo* to leave a pale orange glass. Crystallization of the glass from AcOEt gave **11** (1.12 g) as colorless pillars. The mother liquor of this crystallization was concentrated *in vacuo*, and the residue was purified by column chromatography [silica gel, CH_2Cl_2–MeOH (40 : 1, v/v)] to yield a second crop (0.40 g) of **11**. The total yield was 1.52 g (95%). Recrystallization of crude **11** from AcOEt and drying over P_2O_5 at 2 mmHg and 60 °C for 10 h afforded an analytical sample as colorless pillars, mp 155—157 °C[16]; MS *m/z* (relative intensity): 268 (M^+) (98), 267 (90), 239 (22), 225 (59), 223 (17), 197 (37), 184 (61), 170 (100), 169 (77), 168 (22), 156 (25); IR ν_{max}^{KBr} cm^{-1}: 3485 (NH), 2825, 2770 (*trans*-quinolizidine ring[11]), 1693 (CO); ^1H-NMR (Me_2SO-d_6) δ: 1.3—1.55 and 2.0—3.4 (2H and 10H, m each, quinolizidine protons), 2.15 (3H, s, COMe), 6.8—7.1 and 7.2—7.4 (2H each, m, aromatic protons), 10.72 (1H, br, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.08; H, 7.35; N, 10.31. This sample was identical [by comparison of the ^1H-NMR and mass spectra and thin-layer chromatographic mobility [on a silica gel plate with CH_2Cl_2–MeOH (20 : 1, v/v), $CHCl_3$–MeOH (10 : 1, v/v), AcOEt–EtOH (20 : 1, v/v), or Et_2O–EtOH (20 : 1, v/v)]] with that (mp 146 °C)[12a] sent by Prof. Winterfeldt or the one (mp 128 °C)[7k] from Dr. Pakrashi.[17]

[3α(*R),12bα]-(±)- and [3α(*S**),12bα]-(±)-1,2,3,4,6,7,12,12b-Octahydro-α-methylindolo[2,3-*a*]quinolizine-3-methanols (10)** A solution of **11** (537 mg, 2 mmol) in tetrahydrofuran (20 ml) was stirred under ice-cooling, and $NaBH_4$ (76 mg, 2 mmol) was added portionwise in 10 min. After having been stirred at room temperature for 1.5 h, the reaction mixture was poured into H_2O (30 ml), and the aqueous mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a slightly yellowish glass. Purification of the glass by means of column chromatography [silica gel, CH_2Cl_2–MeOH (15 : 1, v/v)] gave **10** (480 mg, 89%) as a colorless solid [mp 180—185 °C (lit. mp 159—160 °C[7k]; mp 192—194 °C[7m])], which was presumed to be a 1 : 1 mixture of two diastereomers on the basis of its ^1H-NMR spectrum in Me_2SO-d_6. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and 70 °C for 8 h yielded a pure sample of one diastereomer as colorless minute needles, mp 202—204 °C (lit.[12b] mp 199—200 °C); MS *m/z* (relative intensity): 271 (M^+ + 1) (15), 270 (M^+) (83), 269 (100), 225 (33), 197 (9), 184 (14), 171 (10), 170 (33), 169 (29), 156 (13), 144 (11); IR ν_{max}^{KBr} cm^{-1}: 3540 (NH), 3420—3280 (OH), 2815, 2770 (*trans*-quinolizidine ring[11]); $\nu_{max}^{CHCl_3}$ (at 0.004 M concentration) cm^{-1}: 3620 (OH), 3490 (NH), 2810, 2760 (*trans*-quinolizidine ring[11]); ^1H-NMR (Me_2SO-d_6) δ: 1.06 [3H, d, J = 6.3 Hz, CH(OH)Me], 1.1—3.1 (12H, m, quinolizidine protons), 3.3—3.6 [1H, m, CH(OH)Me], 4.38 (1H, d, J = 4.9 Hz, OH], 6.8—7.1 and 7.15—7.4 (2H each, m, aromatic protons), 10.67 (1H, s, NH); ^{13}C-NMR (Me_2SO-d_6)

δ: 20.7 [CH(OH)Me], 21.5 [C(7)], 26.0 [C(2)], 29.1 [C(1)], 43.1 [C(3)], 53.1 [C(6)], 57.7 [C(4)], 60.0 [C(12b)], 68.0 [CH(OH)Me], 106.0 [C(7a)], 110.8 [C(11)], 117.2 [C(8)], 118.1 [C(9)],[18] 120.1 [C(10)],[18] 126.5 [C(7b)], 135.7 [C(11a) or C(12a)], 135.9 [C(12a) or C(11a)]. *Anal.* Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.46; H, 8.34; N, 10.29.

Acknowledgment This work was supported by a Grant-in-Aid for Scientific Research (No. 58570869) from the Ministry of Education, Science and Culture, Japan. We are also grateful to Professor E. Winterfeldt (Hannover, West Germany) and Dr. S. C. Pakrashi (Calcutta, India) for generous gifts of the tetracyclic methyl ketone **11**.

References and Notes

1) Paper XXV in this series, T. Fujii, S. Yoshifuji, and H. Ito, *Chem. Pharm. Bull.*, **36**, 3348 (1988).
2) *a*) G. A. Cordell and J. E. Saxton, "The Alkaloids," Vol. 20, ed. by R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, Chapter 1; *b*) Atta-ur-Rahman and A. Basha, "Biosynthesis of Indole Alkaloids," Clarendon Press, Oxford, 1983; *c*) C. Szántay, G. Blaskó, K. Honty, and G. Dörnyei, "The Alkaloids," Vol. 27, ed. by A. Brossi, Academic Press, New York, 1986, Chapter 2.
3) *a*) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, **1966**, 421; *b*) *Idem*, *Aust. J. Chem.*, **19**, 1951 (1966).
4) More than 30 synthetic routes to **4** have been reported. For pertinent information, see *a*) ref. 1 and references cited therein; *b*) S. B. Mandal, V. S. Giri, and S. C. Pakrashi, *Synthesis*, **1987**, 1128.
5) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).
6) T. Fujii, M. Ohba, and N. Sasaki, *Heterocycles*, **22**, 1805 (1984).
7) For previous syntheses of (±)-**12**, see *a*) D. Thielke, J. Wegener, and E. Winterfeldt, *Angew. Chem.*, **86**, 646 (1974); *b*) *Idem*, *Chem. Ber.*, **108**, 1791 (1975); *c*) R. Besselièvre, J.-P. Cosson, B. C. Das, and H.-P. Husson, *Tetrahedron Lett.*, **21**, 63 (1980); *d*) W. R. Ashcroft and J. A. Joule, *ibid.*, **21**, 2341 (1980); *e*) M. Hämeilä and M. Lounasmaa, *Acta Chem. Scand. Ser. B*, **35**, 217 (1981); *f*) L. Calabi, B. Danieli, G. Lesma, and G. Palmisano, *Tetrahedron Lett.*, **23**, 2139 (1982); *g*) G. Lesma, G. Palmisano, and S. Tollari, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1593; *h*) L. E. Overman and T. C. Malone, *J. Org. Chem.*, **47**, 5297 (1982); *i*) T. Imanishi, M. Kushiya, M. Inoue, N. Yagi, and M. Hanaoka, Abstracts of Papers, the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982, p. 419 [T. Imanishi, *Yakugaku Zasshi*, **104**, 549 (1984)]; *j*) P. Rosenmund and M. Casutt, *Tetrahedron Lett.*, **24**, 1771 (1983); *k*) S. B. Mandal and S. C. Pakrashi, *Heterocycles*, **26**, 1557 (1987); *l*) R. Jokela, A. Juntunen, and M. Lounasmaa, *Planta Med.*, **53**, 386 (1987); *m*) S. B. Mandal, V. S. Giri, M. S. Sabeena, and S. C. Pakrashi, *J. Org. Chem.*, **53**, 4236 (1988); *n*) For a review on the elaboration of an ethylidene group in the synthesis of indole alkaloids, see J. Bosch and M. L. Bennasar, *Heterocycles*, **20**, 2471 (1983).
8) For the synthesis of (*S*)-(−)-**12**, see A. I. Meyers, T. Sohda, and M. F. Loewe, *J. Org. Chem.*, **51**, 3108 (1986).
9) *a*) G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, C. Jollès, A. Jousselin, and H. Jacquemin, *J. Nat. Prod.*, **46**, 694 (1983); *b*) D. Guillaume, A. M. Morfaux, B. Richard, G. Massiot, L. Le Men-Olivier, J. Pusset, and T. Sévenet, *Phytochemistry*, **23**, 2407 (1984).
10) *a*) T. Fujii, M. Ohba, and S. Yoshifuji, *Chem. Pharm. Bull.*, **25**, 3042 (1977); *b*) T. Fujii, *Yakugaku Zasshi*, **103**, 257 (1983).
11) *a*) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956); *b*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
12) *a*) E. Winterfeldt, H. Radunz, and T. Korth, *Chem. Ber.*, **101**, 3172 (1968); *b*) V. U. Ahmad, K.-H. Feuerherd, and E. Winterfeldt, *ibid.*, **110**, 3624 (1977).
13) *a*) T. Fujii, M. Ohba, and S. Akiyama, *Chem. Pharm. Bull.*, **33**, 5316 (1985); *b*) T. Fujii, M. Ohba, and J. Sakaguchi, *ibid.*, **35**, 3628 (1987).
14) S. Sugasawa and M. Kirisawa, *Pharm. Bull.*, **3**, 190 (1955).
15) T. Hoshino and K. Shimodaira, *Justus Liebigs Ann. Chem.*, **520**, 19 (1935).
16) When crystallized out of a considerably dilute solution, **11** sometimes gave colorless minute needles of almost the same melting point (mp 156—157 °C) but with an IR spectrum not completely identical in the solid state, suggesting the existence of another crystal form.
17) The difference of these three samples in melting point is most likely due to polymorphism of **11**. According to a private communication from Prof. E. Winterfeldt (Hannover, West Germany), his group of workers have also observed a higher melting point (mp 151 °C) for their later preparations. The IR spectrum (in KBr) of our sample described in footnote 16 was superimposable on those of the two authentic specimens.
18) For the basis of this assignment, see G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975).