desired product was isolated as white crystals (0.19 g, 30.5%): mp 177-178 °C; ^{1}H NMR (90 MHz, CCl_4) δ 0.83 (s, 9 H, *t*-Bu), 0.90-2.05 (m, 9 H, C(2,6)H), 2.1 (m, 1 H, C(1)H), 7.46 (m, 6 H, C(meta,para)H), 7.77 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, *m/e* 340 (M^+).

Anal. Found: C, 78.12; H, 8.61.

Acknowledgment. We are grateful to J. Espiñeira and G. Uribe for recording the C-13 NMR spectra and to Mr. H. Pastrana for some preliminary experiments. Partial financial support from CONACYT (No. 140105G 203-035) and NSF INT-8312711 is gratefully acknowledged.

Registry No. **2**, 13689-20-8; **3**, 100702-02-1; **4**, 100702-03-2; **5**, 100702-04-3; **6**, 100702-05-4; cyclohexyl chloride, 542-18-7; chlorodiphenylphosphine, 1079-66-9; *trans*-4-methycyclohexyl *p*-toluenesulfonate, 34866-36-9; *trans*-4-phenylcyclohexyl *p*-toluenesulfonate, 100702-06-5; *trans*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate, 7453-04-5; *cis*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate, 7453-05-6.

(24) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383-3384.

Reaction of 16-Bromo-17-oxo Steroids with Potassium Cyanide

Mitsuteru Numazawa,* Mutsumi Satoh, Satoshi Satoh, and Masao Nagaoka

Tohoku College of Pharmacy, 4-1 Komatsushima-4-chome, Sendai 983, Japan

Yoshio Osawa*

Medical Foundation of Buffalo, Inc., Buffalo, New York 14203

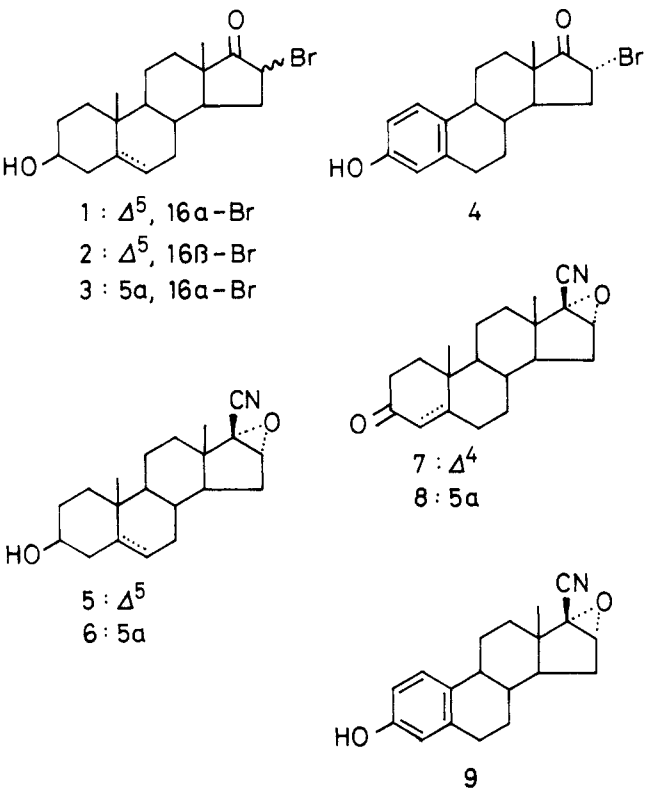
Received September 25, 1985

Recent studies on the reaction of 16-bromo-17-oxo steroids with nucleophiles indicated that equilibration between 16α- and 16β-bromo ketones precedes displacement of bromine with hydroxide ion and morpholine, with the ture intermediate being the 16β isomer, that 16α-substituted 17-oxo compounds are formed by S_N2 displacement of the 16β-bromo ketone (Scheme I, path a),[1] and that direct S_N2 displacement of bromine by sulfur nucleophiles is possible in the case of the α-bromo ketone without prior epimerization of the bromo ketones (path b).[2]

On the other hand, reaction of the 16-bromo ketone with methoxide ion[3] and hydrazine[4] produces the 16α-hydroxy derivatives probably by attack of the nucleophiles at the 17-carbonyl function via three-membered ring (epoxide) intermediates (path c). However, the presumed epoxide intermediates have not yet been isolated.

In conjunction with our investigation of the reaction of 16-bromo-17-oxo steroids with the nucleophiles, we explored the reaction of 16α- and 16β-bromo ketones 1 and 2 with potassium cyanide. The reaction produced 17β-cyano-16α,17α-epoxy derivative **5** by a mechanism that is stereochemically equivalent to an S_N2 displacement.

Chart I



Results and Discussion

Reaction of 16α- and 16β-bromo-3β-hydroxy-5-androsten-17-ones (**1**, **2**) with 2 equiv of potassium cyanide was carried out under controlled conditions (aqueous pyridine,[1a,b] room temperature, 24 h). Both **1** and **2** gave in high yield[5] the same product, 17β-cyano-16α,17α-epoxide derivative **5**, whose total structure was unambiguously determined by X-ray crystallography.[6] When **1** and **2** were separately treated with the nucleophile in a similar way for a shorter time (3 h), they were recovered in ca. 70% as an equilibrated mixture of **1** and **2** in the ratio of 1:1.2, which is consistent with the previously reported results,[1a,b] along with product **5** in ca. 30% yield.[7] Similar treatment of **1** and **2** in D_2O-pyridine (2 equiv, 24 h) gave **5**-*16-d* (more than 97 atom %). Moreover, when **1**-*16-d* and **2**-*16-d*, obtained by treatment of **1** with NaOD under controlled conditions, were separately subjected to reaction with cyanide (2 equiv, 24 h), the product **5** isolated did not retain deuterium at all.

The results indicated that equilibration between the 16α- and 16β-bromo ketones precedes the formation of the epoxy nitrile, in which the true intermediate is the 16β-bromo isomer and not the 16α-isomer in analogy with the reaction[1] of the bromo ketones with hydroxide ion and morpholine. Hence, the formation of the epoxy nitrile can be best rationalized as in Scheme II. Cyanide ion is considered to eject the bromide by internal displacement,

(1) (a) Numazawa, M.; Osawa, Y. *J. Am. Chem. Soc.* **1980**, *102*, 5402. (b) Numazawa, M.; Nagaoka, M.; Osawa, Y. *J. Org. Chem.* **1982**, *47*, 4024. (c) Numazawa, M.; Kimura, K.; Nagaoka, M. *Steroids* **1981**, *38*, 557. (d) Numazawa, M.; Nagaoka, M. *Steroids* **1982**, *39*, 345. (e) Numazawa, M.; Nagaoka, M.; Tsuji, M.; Osawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1983**, 121.

(2) Numazawa, M.; Madarame, M.; Ogata, M.; Kimura, K. *J. Org. Chem.* **1984**, *49*, 3231.

(3) Hassner, A.; Catsoulacos, P. *J. Org. Chem.* **1966**, *31*, 3149.

(4) Catsoulacos, P.; Hassner, A. *J. Org. Chem.* **1967**, *32*, 3723.

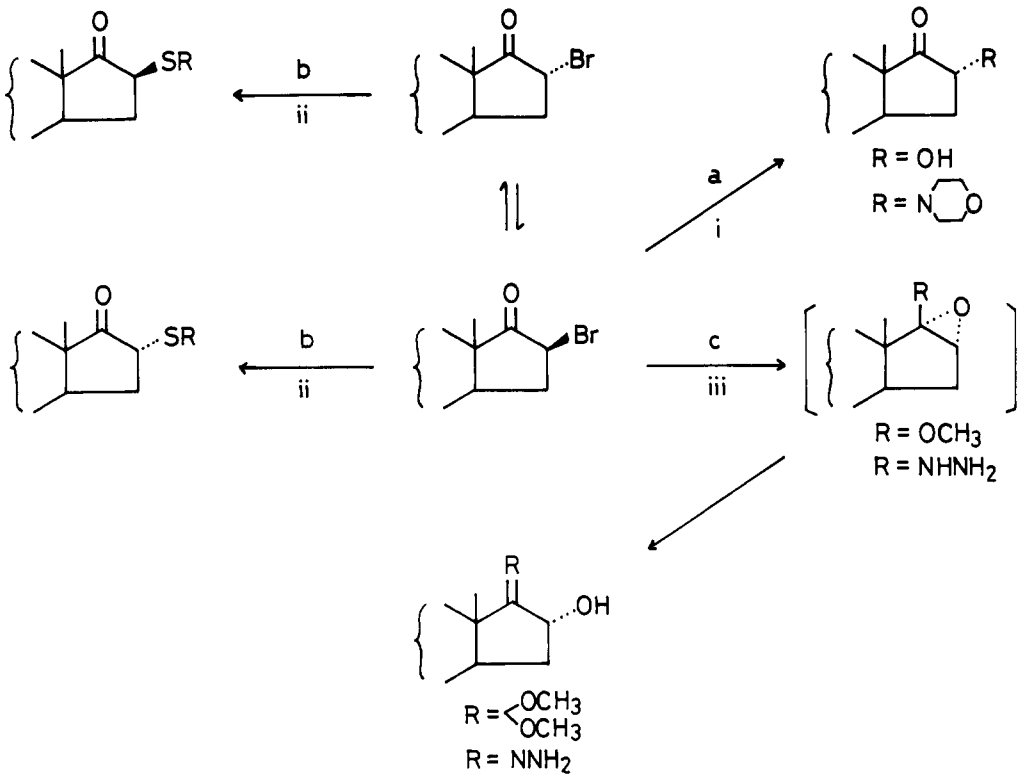
(5) The production of the 16α-hydroxy-17-oxo derivative (ca. 5%) was observed by TLC analysis of the reaction mixture.

(6) Swenson, D. C.; Duax, W. L.; Numazawa, M.; Osawa, Y. *Cryst. Struct. Commun.* **1982**, *11*, 617.

(7) The ^{1}H NMR spectra of **1**, **2**, and **5** proved useful for the quantitative analysis of the mixtures without isolation. The signals at δ 0.90 (s, 3 H) and 4.57 (m, 1 H) for **1**, δ 1.09 (s, 3 H) and 4.37 (t, 1 H) for **2**, and δ 0.98 (s, 3 H) and 3.83 (s, 1 H) for **5** correspond to the H at the C-18 angular methyl and the H at C-16, respectively.

0022-3263/86/1951-1360$01.50/0

Scheme I[a]



[a] Key: i, OH^- or morpholine; ii, RSH; iii, CH_3O^- or H_2NNH_2.

giving the epoxy nitrile, a process stereochemically equivalent to an S_N2 reaction. It has been reported that a similar process converted a 21-bromo-20-oxo steroid into the 20-cyano-20,21-epoxy derivative.[8] However, this is the first report that demonstrates unambiguously that attack of a nucleophile at the 17-carbonyl function of a 16-bromo 17-ketone on the β-face[9] proceeds to give an epoxide. Moreover, the formation of the 16,17-epoxy nitrile supports the putative 16α,17α-epoxide mechanism involved in the reaction of the 16-bromo ketone with methoxide ion[3] and hydrazine[4] (Scheme I, path c).

The present results along with the previous ones[1,2] clearly show that three types of nucleophilic substitution sequence are possible in the reaction of a 16-bromo-17-oxo steroid with nucleophiles, depending on the nucleophile used.

Similarly, 16α-bromo ketones **3** and **4** were coverted into the corresponding epoxy nitriles **6** and **9** in high yields. Oxidation of the epoxy nitrile **6** with a 8 N CrO_3 solution gave the 3-oxo derivative **8**. Moreover, the oxidation of compound **5** having a 5-en-3β-ol followed by the epimerization of the double bond with an alumina produced the 4-en-3-oxo derivative **7**.

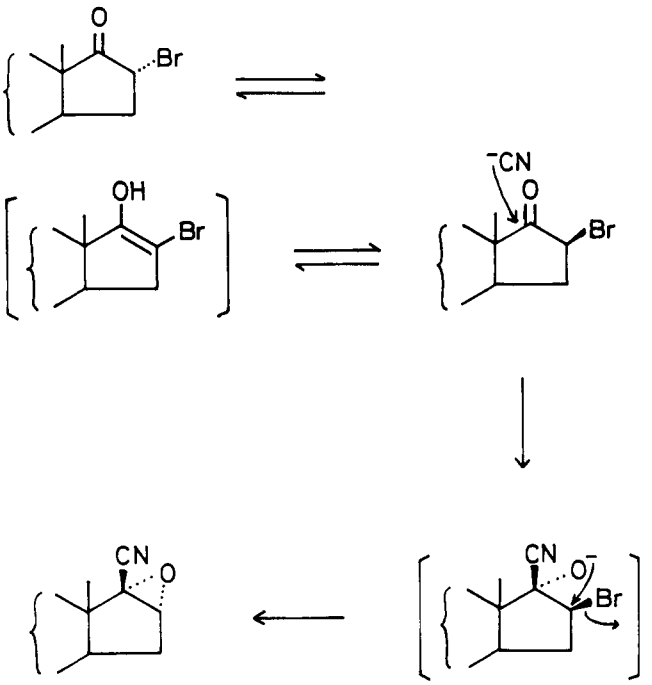
Experimental Section

General Methods. Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on KBr pellets.

[16-^{2}H]-16α- and 16β-bromo-3β-hydroxy-5-androsten-17-ones (*1-16-d*, *2-16-d*) were obtained by treatment of 1[1b] with NaOD according to the previous method.[2] *1-16-d*: 19% d_0, 81% d_1. *2-16-d*: 4% d_0, 96% d_1.

Reaction of 1, *1-16-d*, 2, and *2-16-d* with KCN. A solution of KCN (38 mg, 0.54 mmol) in 1.5 mL of H_2O was added to a solution of **1**, *1-16-d*, **2**, or *2-16-d* (100 mg, 0.27 mmol) in 4 mL of pyridine. The reaction mixture was stirred at room temperature for 3 or 24 h. After this time, the reaction mixture was poured into 5% HCl solution and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). After evaporation of the solvent, a solid residue (80–90 mg) was obtained.

Scheme II



17β-Cyano-16α,17α-epoxy-5-androsten-3β-ol (5). The residue obtained above from **1** or **2**,[1b] using a 24-h-reaction time, was repeatedly crystallized from MeOH to give **5** (64 mg, 75% from **1**; 61 mg, 72% from **2**) as colorless leaflets: mp 194–196 °C; IR 3400 (OH), 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, s, 18-Me), 1.03 (3 H, s, 19-Me), 3.53 (1 H, br m, 3α-H), 3.83 (1 H, s, 16β-H), 5.40 (1 H, m, 6-H); $[\alpha]_D$ −20.0° (*c* 1.0, $CHCl_3$). Anal.

(8) Deghenghi, R.; Gandry, R. *Can. J. Chem.* **1961**, *39*, 1553.

(9) The preferential β-face attack of hydroxide ion at the 17-carbonyl group of a 16α-hydroxy-17-ketone has previously been suggested by us.[1a,b]

Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.70; H, 8.78; N, 4.23.

[16β-^{2}H]-5, was obtained by the similar treatment of **1** or **2** with KCN in D_2O (99 atom %)-pyridine as above. **5-*16-d***: mp 194–196 °C; MS, 2% d_0 and 98% d_1 (from **1**), 3% d_0 and 97% d_1 (from **2**).

17β-Cyano-16α,17α-epoxy-5α-androstan-3β-ol (6) was obtained in 75% yield from 16α-bromo-3β-hydroxy-5α-androstan-17-one (**3**)[1b] in a similar manner: mp 189–190 °C (colorless needles, from MeOH); IR 3400 (OH), 2250 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s, 19-Me), 0.97 (3 H, s, 18-Me), 3.50 (1 H, br m, 3α-H), 3.80 (1 H, s, 16β-H); $[\alpha]_D$ +47.8° (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.96; H, 9.48; N, 4.14.

17β-Cyano-16α,17α-epoxy-4-androsten-3-one (7). Compound **5** (100 mg, 0.32 mmol) was dissolved in 16 mL of acetone. To this solution was added dropwise slight excess of a 8 N CrO_3 solution with stirring below 5 °C, and then the solution was allowed to stand for 10 min. After this time, the mixture was poured into ice water (250 mL). The precipitate (95 mg) was collected by filtration, dried under vacuum, and then dissolved in 2 mL of hexane–AcOEt (9/1). The solution was passed through a column of Al_2O_3 (5 g, activity II–III) and set aside at room temperature overnight. After this time, the adsorbed streoid was eluted with the solvent and then repeatedly recrystallized from acetone to give **8** (50 mg, 50%) as colorless plates: mp 242–243 °C; IR 2250 (CN), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-Me), 1.13 (3 H, s, 19-Me), 3.80 (1 H, s, 16β-H), 5.70 (1 H, s, 4-H); $[\alpha]_D$ +167.2° (*c* 0.40, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}O_2N$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.96; H, 8.25; N, 4.23.

17β-Cyano-16α,17α-epoxy-5α-androstan-3-one (8). Oxidation of compound **6** with a 8 N $CrCO_3$ solution similarly as above gave **8** (65%): mp 180–181 °C (colorless needles, from MeOH); IR 2200 (CN), 1690 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, s, 18-Me), 1.03 (3 H, s, 19-Me), 3.80 (1 H, s, 16β-H); $[\alpha]_D$ +73.3° (*c* 0.43, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.37; H, 8.94; N, 4.12.

17β-Cyano-16α,17α-epoxy-1,3,5(10)-estratrien-3-ol (9). In a similar manner as described in the synthesis of compound **5**, 16α-bromo-3-hydroxy-1,3,5(10)-estratrien-17-one (**5**)[1c] gave **10** (61%): mp 212–216 °C (colorless needles, from ether); IR 3400 (OH), 2245 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-Me), 3.97 (1 H, s, 16β-H), 6.67–7.23 (3 H, m, aromatic proton); $[\alpha]_D$ +24.4° (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.21; H, 7.22; N, 4.70.

Acknowledgment. We thank Professor Toshio Nambara and Dr. Kadzutake Shimada of Tohoku University for mass and elemental analysis and Mieko Ogata and Carol Yarborough for their able technical assistance. This research was supported in part by USPHS Grants HD-04945 and PR-05716.

Registry No. **1**, 1093-91-0; **1-*16-d***, 100702-72-5; **2**, 74644-60-3; **2-*16-d***, 100702-73-6; **3**, 28507-02-0; **4**, 71765-95-2; **5**, 100702-67-8; [16β-^{2}H]-**5**, 100702-74-7; **6**, 100702-68-9; **7**, 100702-69-0; **8**, 100702-70-3; **9**, 100702-71-4.

Efficient Conversion of (1*R*,5*R*)-(+)-α-Pinene to (1*S*,5*R*)-(−)-Nopinone

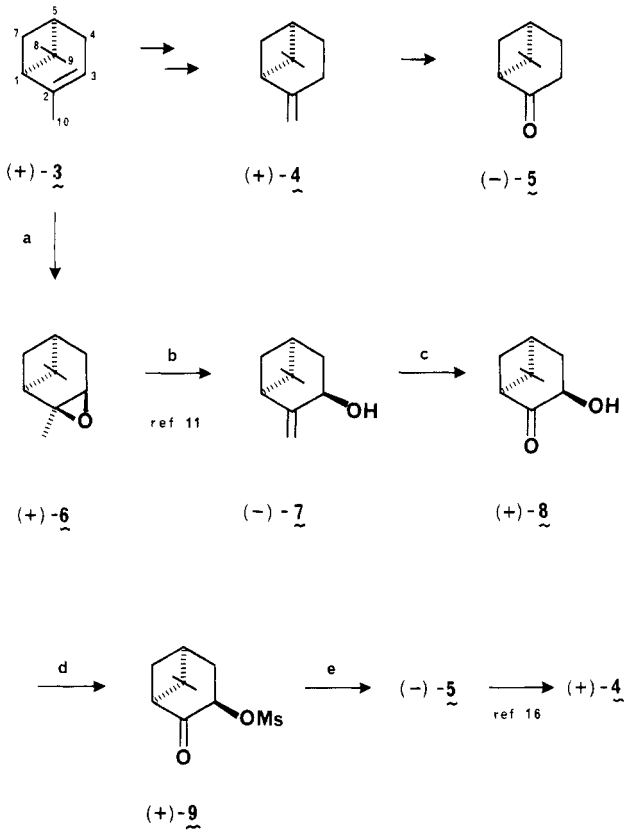
Pierre Lavallée*[1] and Gilles Bouthillier

Department of Chemistry, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1

Received October 3, 1985

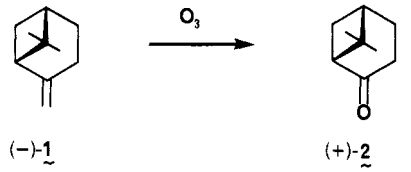
In connection with synthetic investigations in this laboratory, (1*R*,5*S*)-(+)- and (1*S*,5*R*)-(−)-nopinone were required as chiral starting materials. Since (1*S*,5*S*)-(−)-β-pinene (**1**) of high optical purity is available commercially,

Scheme I[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 93%. (b) Et_2NLi, Et_2O, reflux, 6–10 h, 95%. (c) 1°, O_3, MeOH, −78 °C; 2°, Me_2S, 100%. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 91% crude. (e) $CrCl_2$, aqueous HCl–acetone, 1 h, 25 °C, CO_2 atm, 89%.

(1*R*,5*S*)-(+)-nopinone (**2**) is readily accessible by simple ozonolysis according to several procedures.[2]



Unfortunately, the enantiomer (1*R*,5*R*)-(+)-β-pinene (**4**) is scarcely produced by nature[3] and the acid, base, or neutral interconversion between α and β forms is in favor of the thermodynamically more stable α-pinene.[4,5] However, stepwise interconversions of (1*R*,5*R*)-(+)-α-pinene (**3**) to (+)-β-pinene (**4**) (Scheme I) have been reported with low to modest efficiency. A four-step sequence[6a] provided

(1) Fellow of the Ministère de la Science et de la Technologie du Québec, 1982–1987.

(2) (a) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50–52 and references cited therein. (b) Lewis, K. G.; Williams, G. J. *Aust. J. Chem.* **1968**, *21*, 2467–2472 and references cited therein. (c) Meinwald, J.; Gassman, P. G. *J. Am. Chem. Soc.* **1960**, *82*, 5445–5450. (d) For a recent and very efficient optical purification of (+)- and (−)-nopinone via the corresponding (−)- and (+)-*cis*-nopinol, see: Boger, D. L., Mullican, M. D.; Hellberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904–1911.

(3) (a) Baslas, K. K. *Perfum. Essent. Oil Rec.* **1959**, *50*, 823–827. (b) Zir'yalov, N. P. *Zh. Prikl. Khim. (Leningrad)* **1947**, *20*, 1304–1307; *Chem. Abstr.* **1948**, *42*, 9085*i*. (c) Nelson, E. K. *J. Am. Chem. Soc.* **1933**, *55*, 3400–3402. (d) Rutovskii, B. N.; Vinogradova, I. V. *J. Prakt. Chem.* **1928**, *120*, 41–48; *Chem. Abstr.* **1929**, *23*, 1896.

(4) (a) Brown, C. A. *Synthesis* **1978**, 754–755 and references cited therein. (b) Rudakov, G. A.; Ivanova, L. S.; Borovskaya, A. G. *Zh. Org. Khim.* **1975**, *11*, 2275–2279; *Chem. Abstr.* **1976**, *84*, 165037*q*.

(5) Banthorpe, D. V.; Whittaker, D. *Chem. Rev.* **1966**, *66*, 643–656.

0022-3263/86/1951-1362$01.50/0