as leaves, mp 124—126°. *Anal.* Calcd. for $C_{16}H_{25}NO_5$ (**4**): C, 61.71; H, 8.09; N, 4.50. Found: C, 62.12; H, 8.16; N, 4.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 1735, 1700, 1628. NMR ($CDCl_3$) ppm; 0.94 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.84—2.53 (2H, ABq, $J=11.5$ Hz, CH_2), 1.96—2.32 (2H, ABq, $J=10$ Hz, CH_2), 2.03 (3H, s, OAc), 2.14—2.85 (3H, m), 2.64 (2H, s, CH_2), 2.96 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 5.25 (1H, broad, OH).

1-Acetoxy-N,N,4,4-tetramethylcyclooctane-2,6-dione-1-acetamide (**5**)——A mixture of compound **3** (133 mg, 0.5 mmol), 40% dimethylamine (100 mg, 1 mmol) and chloroform (2 ml) was stirred at room temperature for 2 hr. The mixture was diluted with chloroform (10 ml). The chloroform layer was washed with water, dried over magnesium sulfate, and condensed. The resulting residue was kept in a refrigerator overnight giving a crystalline solid. Recrystallization from *n*-hexane gave compound **5** as prisms (110 mg, (71%), mp 103—104°. *Anal.* Calcd. for $C_{16}H_{25}NO_2$ (**5**): C, 61.71; H, 8.09; N, 4.50. Found: C, 61.65; H, 8.27; N, 4.62. IR ν_{max}^{KBr} cm^{-1}: 1730 (ester), 1710 (ketone), 1690 (ketone), 1635 (amide). NMR ($CDCl_3$) ppm: 1.09 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.88—3.10 (8H, m, $4\times CH_2$), 2.16 (3H, s, OAc), 2.88 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 3.28 (2H, s, $CH_2CON<$).

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UDC 547.895.04 : 547.473.04

Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents. III.[1] 5,6,7,8-Tetrahydrodibenz[*c*,*e*]azocine and Its 6-Substituted Derivatives[2]

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The apogalanthamine analogs, 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**10**) and its N-substituted derivatives (**11**—**15**) were synthesized. Boron tribromide was found to be effective for cleavage and bromination of the lactone ring in diphenide (**25**). This is the first time it has been employed as a cleaving and brominating agent for a lactone.

Keywords——apogalanthamine analog; α-adrenergic blocking agent; tetrahydrodibenz[*c*,*e*]azocine; intramolecular cyclization; diphenide; boron tribromide; cyanohydroxyphenanthrene

Recently Ishida, *et al.* reported[4] that the 6-β-bromoethylated derivative (**1**)[5] of 10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**2**) has an irreversible α-adrenergic blocking action and blocks the response of rat aortic strips to adrenaline rather than their response to 5-hydroxytryptamine (5-HT). On the other hand, tests on the apogalanthamine analogs,[1] compound **2** and its 6-alkylated derivatives (**3** and **4**), 10,11-dimethoxy- and 11,12-dimethoxydibenz[*c*,*e*]azocine (**5** and **6**, respectively) and their 6-alkylated derivatives (**7**, **8**, and **9**), and 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**10**) and its 6-substituted derivatives (**11**—**13**) showed

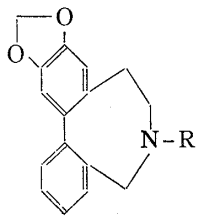
1) *a*) Part I: S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, and H. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 3312 (1977) *b*) Part II: M. Kihara and S. Kobayashi, *ibid.*, **26**, 155 (1978).
2) This forms Part XVIII of "Studies on the Syntheses of Benzoheterocyclic Compounds" by S. Kobayashi, Part XVII: ref. Ib.
3) Location: *1-78, Sho-machi, Tokushima, 770, Japan.*
4) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Jpn. J. Pharmacol.*, **26**, 607 (1976).
5) S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **23**, 3036 (1975).

that compound **11** had the strongest reversible α-adrenolytic activity, which was stronger than that of 5-HT.[6]

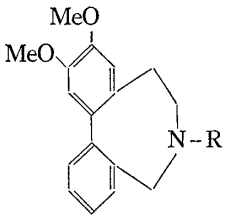
This paper reports the syntheses of compound **10** and its 6-substituted derivatives (**11**—**15**).

Previously we reported the syntheses of the apogalanthamine derivatives **16**[7] and **17**.[8] The apogalanthamine skeleton of compound **17** was formed by two different procedure: (i) intermolecular cyclization of the dibromide (**18**) with an amine and (ii) intramolecular cyclization of the bromo-amine (**19**) in the presence of a base. The yield of the cyclic amine (**20**) from **19** by procedure (ii) was better than that of **17** from **18** by prodecure (i). Later, Kotera, *et al.*[9] synthesized compound **12** in low yield from dibromide **21** by procedure (i). Recently, Jeffs, *et al.*[10] also obtained the 6-benzyl compound **22** in low yield from **21** by procedure (i).

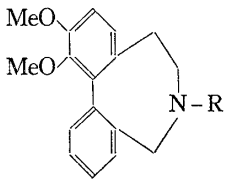
We synthesized compound **10** and **11** in good yields from monomethyl diphenate (**23**) using procedure (i) or (ii) as the last step.



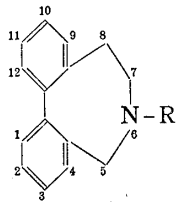
1: R=CH_2CH_2Br
2: R=H
3: R=Me
4: R=Et



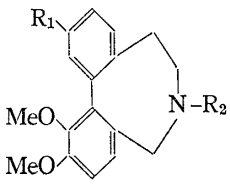
5: R=H
7: R=Me



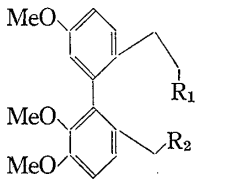
6: R=H
8: R=Me
9: R=Et



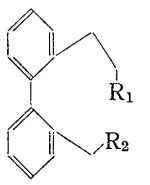
10: R=H
11: R=Me
12: R=Et
13: R=Ac
14: R=CH_2CH_2Cl
15: R=CH_2CH_2OH
22: R=$CH_2C_6H_5$



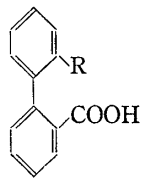
16: R_1=H, R_2=Me
17: R_1=OMe, R_2=Me
20: R_1=OMe, R_2=H



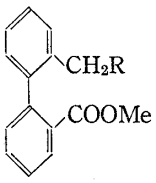
18: R_1=R_2=Br
19: R_1=NH_2, R_2=Br



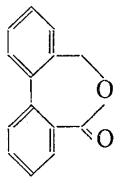
21: R_1=R_2=Br
29: R_1=NH_2, R_2=OH
30: R_1=NH_2, R_2=Br



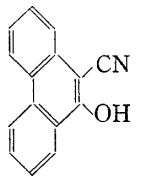
23: R=COOMe
24: R=CH_2CN



27: R=CN
28: R=Br



25



26

Chart 1

6) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Chem. Pharm. Bull.* (Tokyo), **25**, 1851 (1977).
7) S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, **1957**, 638.
8) J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), **12**, 696 (1964).
9) K. Kotera, M. Motomura, S. Miyazaki, T. Okada, Y. Hamada, R. Kido, K. Hirose, M. Eigyo, H. Jyoyama, and H. Sato, *Shionogi Kenkyusho Nenpo*, **17**, 88 (1967).
10) P.W. Jeffs, J.F. Hansen, and G.A. Brine, *J. Org. Chem.*, **40**, 2883 (1975).

Compound **11** was prepared as follows: the dibromide (**21**) was obtained from **23** by the method of Ahmed and Hall.[11] The dibromide (**21**) was cyclized to **11** by procedure (i) 13.3% overall yield from **23**.

Next, we attempted to synthesize compound **10** *via* the cyano-acid (**24**), since Chatterjee[12] reported that **24** was prepared by heating diphenide (**25**) with potassium cyanide. However, on re-examination[13] of the reaction reported by Chatterjee[12] we obtained 10-cyano-9-hydroxyphenanthrene (**26**) instead of **24**. Compound **26** seemed to be formed from **24**, as described in the previous paper.[13] This reaction seems to be a new method[14] for preparation of cyano-hydroxyphenanthrene derivatives.

Therefore, reduction of the cyano-ester (**27**),[13] prepared from the bromo-ester (**28**),[13] with lithium aluminum hydride (LAH) in the presence of aluminum chloride was carried out. The resulting amine (**29**) was brominated with phosphorus tribromide to the bromo-amine (**30**). Intramolecular cyclization [procedure (ii)] to compound **10** was accomplished by heating **30** with ethanolic potassium hydroxide. Compound **10** was obtained in 15.3% overall yield from **23**. This compound (**10**) was identified by its physical and spectral data.

The bromo-ester (**28**) was also prepared from diphenide (**25**) using boron tribromide. Boron tribromide, known to demethylate phenolic methyl ethers, was found to hydrolyze

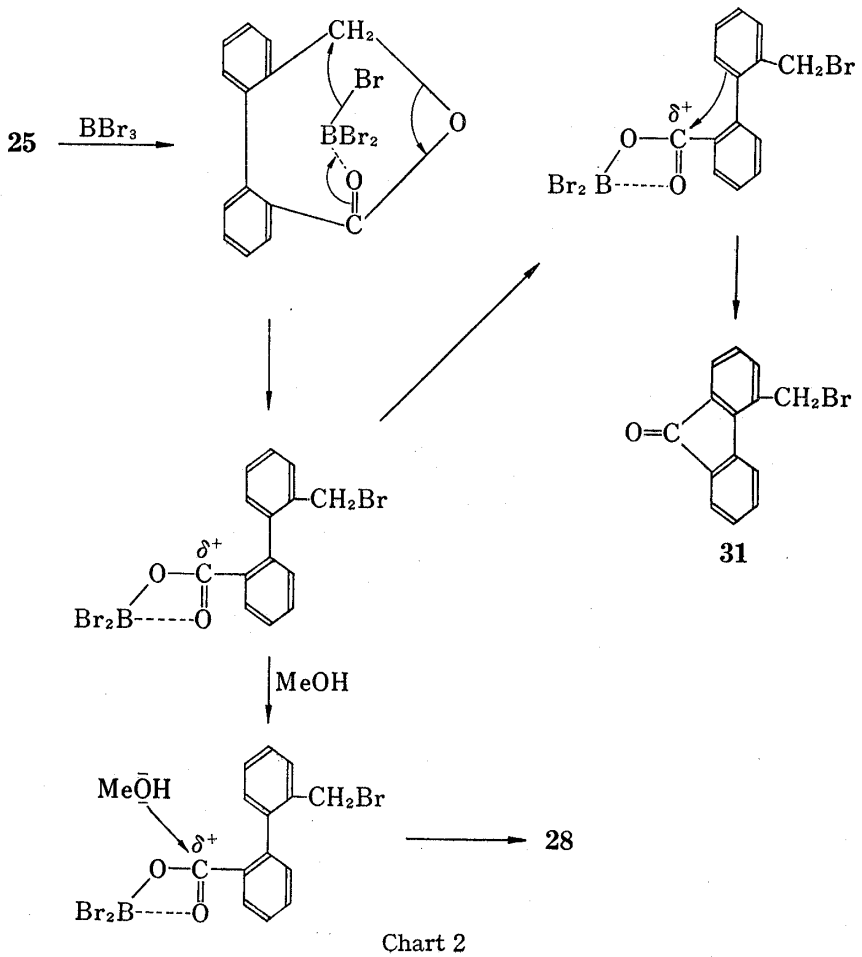


Chart 2

11) S.R. Ahmed and D.M. Hall, *J. Chem. Soc.*, **1959**, 3383.
12) N. Chatterjee, *J. Ind. Chem. Soc.*, **12**, 418 (1935).
13) S. Kobayashi, K. Kitamura, A. Miura, M. Fukuda, and M. Kihara, *Chem. Pharm. Bull.* (Tokyo), **20**, 694 (1972).
14) S. Kobayashi, M. Kihara, and T. Shingu, *Yakugaku Zasshi*, **96**, 1448 (1976).

esters.[13] Therefore, we attempted to cleave and brominate the lactone ring in **25**[15] with this reagent. The reaction of **25** with boron tribromide at room temperature for 30 min, followed by esterification of the product with dry methanol gave the bromo-ester (**28**) in 53.2% yield from **25**. However, the reaction of **25** with boron tribromide for 9 hr gave an unexpected product (17.6%), $C_{14}H_9BrO$, mp 185—188°. This product was concluded to be 4-bromomethylfluorenone (**31**) from its infrared (IR) [ν_{max}^{KBr} cm^{-1}: 1700(C=O)], nuclear magnetic resonance (NMR) [($CDCl_3$) δ: 4.86(2H, s, $ArCH_2Br$) and 7.33—7.83(7H, m, aromatic H)], and Mass [*m/e*: 272(M^+)] spectral data. On the basis of these facts, the formation of the ester (**28**) and the fluorenone (**31**) seems to be explained by the reactions shown in Chart 2. This is the first time boron tribormide has been employed for cleaving and brominating a lactone.

6-Substituted Derivatives of Dibenzazocine 10

The oily 6-methylated product (**11**) obtained by treatment of **10** with formalin and sodium borohydride was crystallized as its neutral styphnate, mp 183—185°, which was converted to the acidic styphnate, mp 193—195° (dec.), by addition of styphnic acid in acetone. The acidic styphnate was identical with a sample of the styphnate prepared from **21** by procedure (i), as shown by direct comparison of their spectral and physical data.

Compound **10** was acetylated with acetyl chloride to the 6-acetyl derivative **13**. Reduction of **13** with LAH gave the 6-ethylated product **12** as an oil, and this was converted to its acidic styphnate.

Treatment of **10** with ethylene chlorohydrin in the presence of triethylamine gave the amino-alcohol **15** and this was chlorinated with thionyl chloride to the hydrochloride of the 6-β-chloroethylated product **14** as amorphic material.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi EPI-G2 model for IR spectra, a Hitachi RMU-6E model for mass spectra, and a JEOL JNM-PS 100 or a Hitachi R-22 model for NMR spectra using TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

6-Methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (11)——By Procedure (i): According to Ahmed and Hall,[11] the dibromide (**21**) was prepared from **23** in 32.7% yield.

The dibromide (**21**) (265 mg) and dry MeOH (20 ml), which was saturated with methylamine at −20°, were heated in a sealed tube at 130° for 3 hr. Working up in the usual way gave an oil (**11**) (206 mg), which was crystallized as yellow needles (143 mg, 40.7% from **21**, 13.3% overall yield based on **23**) of its acidic styphnate, mp 194—195° (from benzene). *Anal.* Calcd. for $C_{16}H_{17}N \cdot C_6H_3N_3O_8$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.28; H, 4.20; N, 12.13. IR ν_{max}^{KBr} cm^{-1}: 1635 (characteristic absorption of an acidic styphnate).[1a]

From **10**: Compound **10** (20 mg) was added to a solution of boric acid (20 mg) and formalin (0.2 ml) in MeOH (2 ml), and stirred at room temperature for 5 min. Then $NaBH_4$ (40 mg) was added to the mixture with stirring for 30 min. The resulting solution was mixed with AcOH (0.2 ml) and H_2O (10 ml). Working up in the usual way gave **11** (19 mg, 90.5%) as a colorless oil. NMR ($CDCl_3$) δ: 7.48—7.24 (8H, m, aromatic H), 3.59 and 3.12 (each 1H, d, J=14 Hz, AB-type of C-5 H_2), 3.36—2.08 (4H, m, $ArCH_2CH_2N$), 2.47 (3H, s, NCH_3). The oil was crystallized as yellow cubes of the neutral styphnate of **11**, mp 183—185° (from acetone–ether). NMR ($CDCl_3$) δ: 8.99 (1/2H, s, aromatic H of styphnic acid), 4.16 and 3.68 (each 1H, d, J=14 Hz, AB-type of C-5 H_2), 2.79 (3H, s, NCH_3). IR ν_{max}^{KBr} cm^{-1}: 1585, 1520 (characteristic absorption of a neutral styphnate).[1a] The styphnatew as converted to its acidic styphnate, mp 193—195° (dec.) (from acetone) by addition of styphnic acid in acetone. This acidic styphnate was identical with a sample of the styphnate prepared from **21** by procedure (i) by direct comparison of their physical and spectral data.

5,6,7,8-Tetrahydrodibenz[*c,e*]azocine (10)——To a suspension of $LiAlH_4$ (114 mg), $AlCl_3$ (380 mg), and dry ether (12 ml) was added the cyano-ester (**27**)[13] (330 mg) in dry ether (15 ml) at room temperature and the mixture was stirred for 1 hr. Working up in the usual way gave **29** as an oil (169 mg). A mixture of the oil (**29**) (169 mg), PBr_3 (2 ml), and dry benzene (4 ml) was allowed to stand at room temperature overnight and then the mixture was refluxed with EtOH (80 ml) and 25% KOH (60 ml) for 2 hr. Evaporation of the solvent gave a residue, which was extracted with ether. The ethereal solution was extracted with 4% HCl. The acidic solution was made alkaline with Na_2CO_3 and the alkaline solution was extracted with ether. The

15) S. Kobayashi, F. Senoo, M. Kihara, (née Azekawa), K. Sakata, and A. Miura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1262 (1971).

extract was washed with H_2O, dried, and evaporated to give white plates (113 mg, 48.3% yield from **27**) of **10**, mp 115—117° (from ether) (lit.[10] mp 119—120°). *Anal.* Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.89; H, 6.88; N, 6.76. IR ν_{max}^{KBr} cm^{-1}: 3340 (NH). MS *m/e*: 209 (M^+). NMR ($CDCl_3$) δ: 7.44—7.20 (8H, m, aromatic H), 3.90 and 3.14 (each 1H, d, $J=14$ Hz, AB-type of C-5 H_2), 3.48—3.28 [1H, m, C-7-H (lower)], 2.92—2.70 [2H, m, C-7-H (higher) and C-8-H (lower)], 2.40—2.14 [1H, m, C-8-H (higher)], 1.76 (1H, s, NH).

The Reaction of Diphenide (25) with Boron Tribromide——A solution of BBr_3 (10 g) in dry dichloromethane (20 ml) was added to a solution of **25** (2 g) in dry dichloromethane (16 ml) at room temperature over a period of 4 min. The solution was stirred for 30 min and then mixed with dry MeOH (870 ml) and conc. H_2SO_4 (8 ml) and refluxed for 2 hr. The solvent was evaporated off and the resulting residue was mixed with H_2O (100 ml) and extracted with ether. The extract was washed with H_2O, dried, and evaporated to a residue, which was treated with hot petr. ether. The starting material (**25**) (391 mg, mp 130—133°) insoluble in hot petr. ether was obtained. The petr. ether solution which was separated from **25** was chromatographed in petr. ether on SiO_2 (40 g). The petr. ether eluate (4.1 l) gave an oil, which was triturated with petr. ether to give white prisms (1.544 g, 53.2%) of **28**, mp 51.5—52.5° (from petr. ether) (lit.[13] mp 51.5—52.5°). This material was identical with an authentic sample[13] of **28** by direct comparison of their physical and spectral data. On further elution of the SiO_2 with benzene and evaporation of the solvent, an additional crop (79 mg, total 470 mg, mp 130—133°) of **25** was obtained.

A solution of **25** (83 mg) and BBr_3 (280 mg) in dry dichloromethane (7.5 ml) was stirred at room temperature for 9 hr. To the reaction mixture was added H_2O (1 ml). Working up in the usual way gave a yellow oil (67 mg), which afforded **31** (19 mg, 17.6%, mp 185—188°) as yellow prisms and **25** (40 mg, 48.2%), mp 130—132°) by preparative thin-layer chromatography (TLC) with SiO_2–[CH_2Cl_2–CCl_4 (2: 1)]. *Anal.* Calcd. for $C_{14}H_9BrO$: C, 61.56; H, 3.32. Found: C, 61.92; H, 3.54. UV λ_{max}^{EtOH} nm (log ε): 258—265 (4.71).

6-Acetyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (13)——Solutions of acetyl chloride (529 mg) in benzene (2 ml) and 10% NaOH (4 ml) were added alternately to **10** (95 mg) in benzene (2 ml) and the mixture was stirred at room temperature for 1.5 hr and then at 45° for 50 min. Working up in the usual manner gave white prisms (53 mg, 46.5%) of **13**, mp 105—106° (from ether). *Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.96; H, 6.81; N, 5.55. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). NMR[16] ($CDCl_3$) δ: 7.89 (1H, m, C-4-H), 5.32 and 3.22 (each 1H, d, $J=14$ Hz, AB-type of C-5 H_2), 4.07 and 3.23 (each 1H, m, C-7 H_2), 2.96 and 2.43 (each 1H, m, C-8 H_2), 2.09 (3H, s, CH_3CO).

6-Ethyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (12)——Compound **13** (60 mg), $LiAlH_4$ (400 mg), and dry ether (60 ml) were refluxed for 5 hr. Working up in the usual way gave an oil (44 mg, 77.6%) of **12**. NMR ($CDCl_3$) δ: 3.67 and 2.91 (each 1H, d, $J=13$ Hz, AB-type of C-5 H_2), 1.21 (3H, t, $J=7$ Hz, $NCH_2C\underline{H}_3$). Styphnic acid (26 mg) in H_2O (2.1 ml) was added to a solution of the oil (**12**) (25 mg) in 0.5% HCl (0.84 ml). The resulting precipitate was recrystallized from benzene to give yellow prisms (23 mg, 45.3%) of the acidic styphnate, mp 174.5—175.5°. *Anal.* Calcd. for $C_{17}H_{19}N \cdot C_6H_3N_3O_8$: C, 57.26; H, 4.60; N, 11.61. Found: C, 57.46; H, 4.59; N, 11.49. IR ν_{max}^{KBr} cm^{-1}: 1635 (characteristic absorption of an acidic styphnate).[16a] NMR ($CDCl_3$) δ: 8.96 (1H, s, aromatic H of styphnic acid), 1.48 (3H, t, $J=7$ Hz, $NCH_2C\underline{H}_3$).

6-(β-Chloroethyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (14)——A mixture of **10** (85 mg), ethylene chlorohydrin (264 mg), and Et_3N (413 mg) was refluxed for 16.5 hr. Working up in the usual manner gave an oil (99 mg), which was purified by preparative TLC using Al_2O_3–[benzene–acetone (4: 1)] to give the 6-β-hydroxyethyl product **15** as a colorless oil (75 mg, 72.9%). NMR ($CDCl_3$) δ: 3.55 and 3.09 (each 1H, d, $J=14$ Hz, AB-type of C-5 H_2).

The oil (**15**) (45 mg) was dissolved in conc. HCl (3 drops) and concentrated to dryness. The residue (55 mg), $SOCl_2$ (0.3 ml) and $CHCl_3$ (3 ml) were refluxed for 3 hr. Evaporation of the solvent gave the hydrochloride of **14** as amorphous material (35 mg, 63.6% from **15**). *Anal.* Calcd. for $C_{17}H_{18}ClN \cdot HCl \cdot 1/4H_2O$: C, 65.28; H, 6.28; N, 4.48. Found: C, 65.04; H, 6.08; N, 4.39.

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16) The assignment was verified by both double resonance and homonuclear INDOR decoupling experiments.