as leaves, mp 124—126°. *Anal.* Calcd. for C_{12}H_{17}NO_{3} (4): C, 61.71; H, 8.09; N, 4.50. Found: C, 62.12; H, 8.16; N, 4.43. IR ν_{max} 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_{3}), 2.96 (3H, s, NCH_{3}), 3.04 (3H, s, NCH_{3}), 5.25 (1H, broad, OH).

1-Acetoxynonamino-4,4,4-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_{12}H_{17}NO_{3} (5): C, 61.71; H, 8.09; N, 4.50. Found: C, 61.65; H, 8.27; N, 4.62. IR ν_{max} 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 × CH_{2}), 2.16 (3H, s, OAc), 2.88 (3H, s, NCH_{3}), 2.97 (3H, s, NCH_{3}), 3.28 (2H, s, CH_{2}CON<).

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Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents.

III. 5,6,7,8-Tetrahydrodibenz[c,e]azocine and Its 6-Substituted Derivatives

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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 that the 6-β-bromoethylated derivative (1) 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, 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


2) This forms Part XVIII of "Studies on the Syntheses of Benzo/heterocyclic Compounds" by S. Kobayashi, *ibid.*

3) Location: 1-78, Sho-machi, Tokushima, 770, Japan.


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

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 and 17. The apogalanthamine skeleton of compound 17 was formed by two different procedures: (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 procedure (i). Later, Kotera, et al. synthesized compound 12 in low yield from dibromide 21 by procedure (i). Recently, Jeffs, et al. 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.

![Chemical structures](image)

**Chart 1**

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Compound 11 was prepared as follows: the dibromide (21) was obtained from 23 by the method of Ahmed and Hall. 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 reported that 24 was prepared by heating diphenide (25) with potassium cyanide. However, on re-examination of the reaction reported by Chatterjee we obtained 10-cyano-9-hydroxyphenanthrene (26) instead of 24. Compound 26 seemed to be formed from 24, as described in the previous paper. This reaction seems to be a new method for preparation of cyano-hydroxyphenanthrene derivatives.

Therefore, reduction of the cyano-ester (27), prepared from the bromo-ester (28), 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...

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esters. Therefore, we attempted to cleave and brominate the lactone ring in 25 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_{34}BrO, mp 185–188°. This product was concluded to be 4-bromomethyl-fluorenone (31) from its infrared (IR) ν_{max} cm⁻¹: 1700(C=O), nuclear magnetic resonance (NMR) [(CDC) 6: δ: 4.86(2H, s, ArCHBr) 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 tribromide has been employed for cleaving and brominating a lactone.

6-Substituted Derivatives of Dibenzoazocine 10

The oily 6-methylated product (11) obtained by treatment of 10 with formalin and sodium borohydride was crystallized as its neutral stypnate, mp 183–185°, which was converted to the acidic stypnate, mp 193–195° (dec.), by addition of stypnic acid in acetone. The acidic stypnate was identical with a sample of the stypnate 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 stypnate.

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 amorphous 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-8E 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[e,e]azocine (11)—By Procedure (i): According to Ahmed and Hall, 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 methanoline 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 stypnate, mp 194–195° (from benzene). Anal. Calcd. for C_{16}H_{17}N•C_{6}H_{5}N=O: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.28; H, 4.20; N, 12.13. IR ν_{max} cm⁻¹: 1635 (characteristic absorption of an acidic stypnate).

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 NaBH₄ (40 mg) was added to the mixture with stirring for 30 min. The resulting solution was mixed with AcOH (0.2 ml) and H₂O (10 ml). Working up in the usual way gave 11 (19 mg, 90.5%) as a colorless oil. NMR (CDCl₃) δ: 7.48–7.24 (8H, m, aromatic H), 5.59 and 3.12 (each 1H, d, J=14 Hz, AB-type of C-5 H₂), 3.36–2.08 (4H, m, ArCH₂CH₂N), 2.47 (3H, s, NCH₃). The oil was crystallized as yellow cubes of the neutral stypnate of 11, mp 183–185° (from acetonitrile).

NMR (CDCl₃) δ: 8.99 (1H, d, aromatic H of stypnic acid), 4.16 and 3.68 (each 1H, d, J=14 Hz, AB-type of C-5 H₂), 2.79 (3H, s, NCH₃). IR ν_{max} cm⁻¹: 1655, 1520 (characteristic absorption of a neutral stypnate). The stypnate as converted to its acidic stypnate, mp 193–195° (dec.) (from acetone) by addition of stypnic acid in acetone. This acidic stypnate was identical with a sample of the stypnate prepared from 21 by procedure (i) by direct comparison of their physical and spectral data.

5,6,7,8-Tetrahydrodibenz[e,e]azocine (10)—To a suspension of LiAlH₄ (114 mg), AlCl₃ (280 mg), and dry ether (12 ml) was added the cyano-ester (27) (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), PBr₃ (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 Na₂CO₃ and the alkaline solution was extracted with ether. The

extract was washed with H₂O, dried, and evaporated to give white plates (113 mg, 48.3% yield from 27) of 10, mp 115—117° (from ether) (lit.16 mp 119—120°). Anal. Calcd. for C₂₃H₂₂N: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.89; H, 6.88; N, 6.76. 1R: 8424 cm⁻¹; 3340 (NH). MS m/e: 209 (M⁺). NMR (CDCl₃) 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 H₄), 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 Diphenile (25) with Boron Tribromide—A solution of BB₃ (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. H₂SO₄ (8 ml) and refluxed for 2 hr. The solvent was evaporated off and the resulting residue was mixed with H₂O (100 ml) and extracted with ether. The extract was washed with H₂O, 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 SiO₂ (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.15 mp 51.5—52.5°). This material was identical with an authentic sample of 28 by direct comparison of their physical and spectral data. On further elution of the SiO₂ 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 BB₃ (280 mg) in dry dichloromethane (7.5 ml) was stirred at room temperature for 9 hr. To the reaction mixture was added H₂O (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 SiO₂—CH₂Cl₂—CCl₄ (2:1). Anal. Calcd. for C₃₁H₂₆BrO: C, 61.56; H, 3.32. Found: C, 61.92; H, 3.54. UV λmax nm (log ε): 258—265 (4.71).

6-Acetyl-5,6,7,8-tetrahydrodibenzo[e,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 C₁₈H₁₄NO: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.96; H, 6.81; N, 5.55. 1R: 1640 (C=O). NMR (CDCl₃) δ: 7.89 (1H, m, C-4-H), 5.32 and 3.22 (each 1H, d, J = 7 Hz, AB-type of C-5 H₄), 4.07 and 3.23 (each 1H, m, C-7 H), 2.96 and 2.43 (each 1H, m, C-8 H₄), 2.09 (3H, s, CH₃CO).

6-Ethyl-5,6,7,8-tetrahydrodibenzo[e,e]azocine (12)—Compound 13 (60 mg), LiAlH₄ (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 (CDCl₃) δ: 3.67 and 2.91 (each 1H, d, J = 13 Hz, AB-type of C-5 H₄), 1.21 (3H, t, J = 7 Hz, NCH₂CH₃). Styrphic acid (26 mg) in H₂O (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 styrphate, mp 174.5—175.5°. Anal. Calcd. for C₁₉H₁₈N·C₂H₄N₂O₂: C, 57.26; H, 6.40; N, 11.61. Found: C, 57.46; H, 4.69; N, 11.49. 1R: 3130 cm⁻¹; 1635 (characteristic absorption of an acidic styrphate). NMR (CDCl₃) δ: 8.96 (1H, s, aromatic H of styphic acid), 1.48 (3H, t, J = 7 Hz, NCH₂CH₃).

6-(β-Chloroethyl)-5,6,7,8-tetrahydrodibenzo[e,e]azocine (14)—A mixture of 10 (85 mg), ethylene chlorohydrin (264 mg), and Et₃N (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 Al₂O₃—benzene—acetone (4:1) to give the 6-β-hydroxyethyl product 15 as a colorless oil (75 mg, 72.9%). NMR (CDCl₃) δ: 3.55 and 3.09 (each 1H, d, J = 14 Hz, AB-type of C-5 H₄).

The oil (15) (45 mg) was dissolved in conc. HCl (3 drops) and concentrated to dryness. The residue (55 mg), SOCl₂ (0.3 ml) and CHCl₃ (3 ml) were refluxed for 3 hr. Evaporation of the solvent gave hydrochloride of 14 as amorphous material (35 mg, 63.6% from 15). Anal. Calcd. for C₁₉H₁₄Cl·HCl·1/4H₂O: C, 55.28; H, 6.28; N, 4.48. Found: C, 55.04; H, 6.08; N, 4.39.

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