10-Hydroxy-4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine Derivatives (Homobenzomorphans) as Analgesics

Shunsaku Shiotani,* Tadashi Kometani,

Department of Chemistry, Toyama Technical College, Hongo 13, Toyama, Japan

Kemmotsu Mitsuhashi,

Faculty of Pharmaceutical Sciences, Josai University, Tawame 1076, Sadako-machi, Saitama, Japan

Tsutomu Nozawa, Akira Kurobe, and Osamu Futsukaichi

Research Laboratory, Nihon Iyakuhin Kogyo Co., Ltd., Hariwara-nakamachi 350-1, Toyama, Japan.
Received December 8, 1975

Six 10-hydroxy-4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine derivatives **17a–f** have been synthesized as potential analgesics. The synthesis of these compounds involved conversion of 4-(2-dimethylaminoethyl)-6-methoxy-α-tetralone derivatives **12a–f** to their *N*-methyl analogues and the subsequent intramolecular Mannich reaction with formaldehyde to give the 7-keto C-ring homobenzomorphans **14a–f** from which **17a–f**, respectively, were obtained. Compounds **17a–f** are as potent as morphine as analgesics (mice).

In continuation of our investigations on the structure–activity relationship of analgesics, we recently reported the synthesis of 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (**1**)[1] and homomorphinans,[2] which were found to possess considerable analgesic activity. It has been reported[3] that 2-methyl-6,7-benzomorphan (the parent framework of 6,7-benzomorphan-type analgesics) possesses considerable analgesic activity, and a phenolic hydroxyl group at the 2' position, a quaternary carbon atom adjacent to the benzene ring, and alkyl groups on the bridge methylene in 6,7-benzomorphan enhance the activity. Therefore, it appeared interesting to introduce these functions into the parent framework **1** and to evaluate the effects of these modifications on the analgesic activity. This paper deals with the synthesis and analgesic activities of 4-methyl- (**17a**), 4,12α-dimethyl- (**17b**),[4] 4,12β-dimethyl- (**17c**),[4] 1,4-dimethyl- (**17d**), 1,4,12α-trimethyl- (**17e**), and 1,4,12β-trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (**17f**) as well as the parent framework **1**.

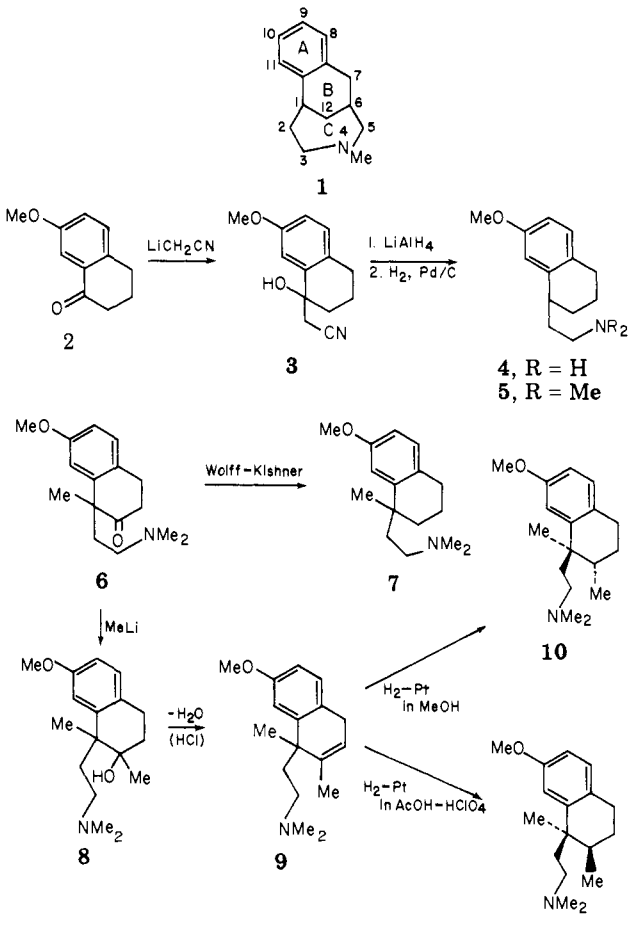
Chemistry. The final compounds **17a–f** were synthesized from 4-(2-dimethylaminoethyl)-6-methoxy-α-tetralone derivatives (**12a–f**) by six-step sequences. These key intermediates **12a–f** were prepared by the following routes.

Reaction of 7-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**2**)[5] with $LiCH_2CN$ gave 1-cyanomethyl compound **3**, which was reduced with $LiAlH_4$, followed by catalytic hydrogenation over Pt in methanol–HCl to give 1-(2-aminoethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**4**). N-Methylation of **4** with HCO_2H–HCHO gave the *N*,*N*-dimethyl derivative **5**, which was oxidized with $Na_2Cr_2O_7$ in aqueous H_2SO_4 to afford 4-(2-dimethylaminoethyl)-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**12a**) (Scheme I).

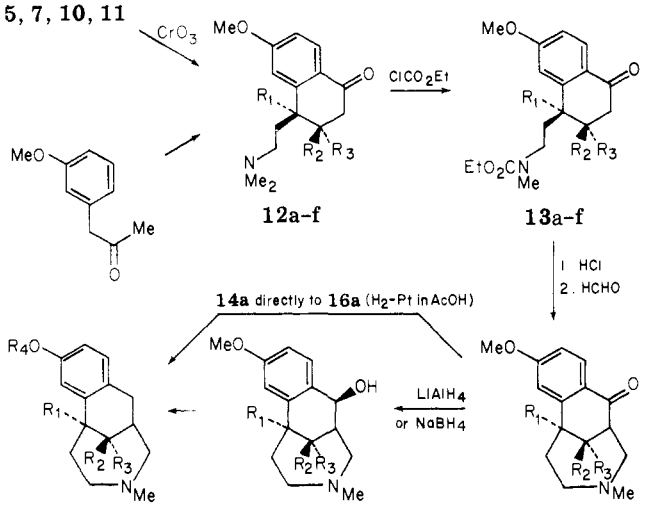
1-Methyl-1-(2-dimethylaminoethyl)-7-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (**6**) prepared from 7-methoxy-β-tetralone by the method of May et al.[6] was reduced by a modified Wolff–Kishner reduction to yield **7**, followed by oxidation with CrO_3 in aqueous H_2SO_4 to give 4-methyl-4-(2-dimethylaminoethyl)-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**12d**).

On the other hand, compound **6** was methylated with MeLi to give 1,2-dimethyl-1-(2-dimethylaminoethyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthol (**8**). Dehydration of **8** gave the 1,4-dihydronaphthalene **9**, the structure of which was confirmed from its NMR spectrum [an olefinic proton at δ 5.67 (poorly split multiplet) and a *C*-methyl signal at δ 1.82 (doublet, J = 0.5 Hz)]. Catalytic hydrogenation of **9** in methanol over Pt gave 1,2-*cis*-dimethyl-1-(2-dimethylaminoethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**10**),[7] while hydrogenation in AcOH–$HClO_4$ yielded the trans isomer **11**. The configurations of **10** and **11** were established by comparison of the chemical shifts of C-2 methyl protons of **10** (δ 0.96) and **11** (δ 1.02) and those of the methyl on the bridge methylene (C-12) of the cyclized compounds **14e** (δ 0.97) and **14f** (δ 1.34), **16e** (δ 0.92) and **16f** (δ 1.36).[8] The stereospecificity

Scheme I



Scheme II



a, $R_1 = R_2 = R_3 = H$ d, R_1 = Me; $R_2 = R_3 = H$
b, $R_1 = R_2 = H$; R_3 = Me e, $R_2 = H$; $R_1 = R_3$ = Me
c, $R_1 = R_3 = H$; R_2 = Me f, $R_3 = H$; $R_1 = R_2$ = Me

of the hydrogenation of **9** may be caused by an anchoring effect of the amino group in the former case, giving the cis isomer, and the steric hindrance of the solvated ammonium cation in the latter case, giving the trans isomer.[2] Compounds **10** and **11** were converted to their respective α-tetralones **12e** and **12f** by oxidation with CrO_3 in aqueous H_2SO_4 (Scheme II).

3-Methyl-4-(2-dimethylaminoethyl)-6-methoxy-3,4-*trans*-dihydro-1(2*H*)-naphthalenone (**12b**) and the 3,4-*cis*-dihydro isomer **12c** were prepared from *m*-methoxyphenylacetone by the method reported by May et al.[3b]

Thus, the 4-(2-dimethylaminoethyl)-α-tetralones **12a–f** were treated with $ClCO_2Et$ in refluxing benzene to give the corresponding carbamates **13a–f**. Subsequent hydrolysis and Mannich reaction with formaldehyde gave the desired 7-oxohomobenzomorphans **14a–f**. Reduction of the ketones **14b–f** with $LiAlH_4$ or $NaBH_4$ afforded the corresponding alcohols **15b–f**, designated as the 7β-OH epimers from the coupling constants of C-7 H with C-6 H ($J_{6,7}$ = 6.0 Hz for **15b**, **15e**, and **15f**, 7.0 Hz for **15c**, 5.0 Hz for **15d**).

Hydrogenolysis of the alcohols **15b–f** over Pd/C gave **16b–f**, respectively. Compound **16a** was obtained by catalytic hydrogenation of the ketone **14a** over Pt in AcOH. Hydrolysis of methoxy compounds **16a–f** by refluxing with hydrobromic acid afforded the final compounds **17a–f**.

Pharmacology. In Table I are given analgesic activities (method of pressure stimuli on mouse tail[9]) and acute toxicities of compounds **1** and **17a–f**. Comparative data for morphine and codeine are also presented. Groups of ten albino male mice, dd strain, were tested at five dose levels. ED_{50} and LD_{50} values were calculated by the Lichfield–Wilcoxon method.[10] In general, the compounds exhibit good analgesic potencies ranging from morphine-like to codeine-like, although they are rather toxic.

A phenolic hydroxyl at the 10 position distinctly increases analgesic activity. The 12β-methyl isomers **17c** and **17f** are more potent than their 12α-methyl counterparts **17b** and **17e**. The quaternary carbon at the 1 position seems to increase analgesic activity.

Thus, it is of interest to note that the effects upon analgesic activity of the phenolic hydroxyl, the quaternary carbon adjacent to the benzene ring, and a methyl group on the bridge methylene (C-12) in 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine are similar to those in the 6,7-benzomorphans.[3]

Table I. Analgesic Activities and Acute Toxicities of 2,3,4,5,6,7-Hexahydro-1,6-methano-1*H*-4-benzazonine Derivatives

Compound	ED_{50}, μmol/kg sc	LD_{50}, μmol/kg iv
1[a]	53.1 (47.7-58.6)[e]	106 (89-126)[e]
17a[b]	10.7 (8.6-13.3)	121 (105-141)
17b[a]	9.9 (8.1-12.6)	184 (167-202)
17c[a]	8.0 (7.0-9.2)	153 (135-173)
17d[a]	7.0 (5.9-8.2)	67 (53-81)
17e[a]	5.2 (4.0-6.6)	126 (111-142)
17f[b]	4.1 (3.6-4.8)	113 (99-128)
Morphine[c]	4.4 (3.6-5.3)	
Codeine[d]	30.7 (27.0-34.7)	

[a] Administered as lactate in saline. [b] Administered as hydrobromide in saline. [c] Administered as hydrochloride in saline. [d] Administered as phosphate in saline. [e] Confidence interval (95%).

Experimental Section

All melting points were determined with a micromelting point apparatus (Yanagimoto) and are uncorrected. Microanalyses were performed by Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical values. Ir spectra were taken on a Hitachi 215 grating infrared spectrometer. NMR spectra were recorded, at 100 MHz, on a JROL PS-100 spectrometer or, at 60 MHz, on a JEOL PMX-60 spectrometer with Me_4Si as an internal standard. Ir and NMR spectra were run on all intermediates and the final compounds. Mass spectra were recorded on a JEOL JMS-01SG mass spectrometer and run on compounds **14b–f** and **16a–c**. All structures are consistent with ir, NMR, and mass spectral data.

1-(2-Dimethylaminoethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (5). To a stirred suspension of $LiCH_2CN$ prepared from BuLi in hexane (15%, 42 ml) and CH_3CN (4.0 g) in THF (50 ml), 7-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**2**)[5] (10.0 g) in THF (25 ml) was added under N_2 and with dry ice–acetone cooling during 30 min; stirring was continued for 2 h at this temperature. After addition of H_2O (5 ml), the cold bath was removed. The mixture (at room temperature) was poured into H_2O (100 ml) and the organic layer separated. The aqueous layer was extracted with Et_2O. The organic layer and the extract were combined, dried ($MgSO_4$), and evaporated to give 13 g of a yellow syrup. Distillation of the crude product afforded 7.6 g of pure **3**: bp 140–160° (0.2 mmHg).

A solution of nitrile **3** (7.6 g) in dry Et_2O (50 ml) was added to a stirred suspension of $LiAlH_4$ (5.0 g) in dry Et_2O (100 ml) over 1.5 h under N_2 and with ice cooling; stirring was continued for 3 h. The mixture was treated with aqueous Rochelle salt solution. The dried (K_2CO_3) organic layer gave 5 g of a basic compound, which was catalytically reduced over Pd/C (10%, 2 g) in MeOH (100 ml)–HCl (12 M, 50 ml) for 3 h at room temperature and under atmospheric pressure to give 4.4 g of crude **4**. Distillation of the crude product gave 4.2 g of pure sample: bp 145–150° (2.5 mmHg).

Primary amine **4** (4.2 g), HCO_2H (10 ml), and formalin (10 ml) were heated on a water bath for 1.5 h. After evaporation to dryness, the residue was dissolved in H_2O, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the solvent gave 4.4 g of crude **5**, which was distilled in vacuo to give 3.6 g of pure **5**: bp 145–157° (4 mmHg). The picrate had mp 139–141.5° (from MeOH). Anal. ($C_{21}H_{26}N_4O_8$) C, H, N.

1-(2-Dimethylaminoethyl)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (7). A mixture of Na (20 g) in diethylene glycol (500 ml), $NH_2NH_2 \cdot H_2O$ (25 g), and **6**[6] (50 g) was heated at 170° for 3 h, cooled, diluted with H_2O, and extracted with Et_2O. The ethereal extract was washed with H_2O, dried (K_2CO_3), and evaporated to give 37.3 g of **7** as a colorless oil: bp 130–160° (1.0 mmHg). The hydrobromide had mp 181–184° (from EtOH). Anal. ($C_{16}H_{25}NO \cdot HBr$) C, H, N.

1-(2-Dimethylaminoethyl)-1,2-dimethyl-7-methoxy-1,4-dihydronaphthalene (9). To a stirred solution of MeLi in dry Et_2O, prepared from Li (24.9 g) and MeI (204 g) in 500 ml of Et_2O, **6** (50 g) was added during 2 h under N_2 and with ice cooling. After stirring for 14 h at room temperature, the reaction mixture was poured into aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined ethereal solutions were dried (K_2CO_3) and evaporated to give crude **8** as a yellow syrup, which was distilled in vacuo to give 41.8 g of pure **8** as a colorless oil: bp 150–160° (1.0 mmHg).

Tertiary alcohol **8** (41.6 g), 10% HCl (300 ml), and EtOH (200 ml) were refluxed for 8 h. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with Et_2O, and dried (K_2CO_3). The residual oil of the ethereal solution was distilled in vacuo to give 25.4 g of **9** as a colorless oil: bp 130–138° (2.5 mmHg). The hydrochloride had mp 200–205° (from EtOH–Et_2O). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

1,2-*cis*-Dimethyl- (10) and 1,2-*trans*-Dimethyl-1-(2-dimethylaminoethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (11). (a) Hydrogenation of **9** (15.1 g) over PtO_2 (2.3 g) in MeOH (100 ml) under atmospheric pressure for 7 days gave crude **10** as a colorless oil, which was purified by recrystallization of its hydrobromide from EtOH–Et_2O to give 12.4 g of pure **10**·HBr: mp 186–190° [lit.[7] mp 195–193° (from Me_2CO)].

(b) Hydrogenation of **9** (10.0 g) over PtO_2 (0.5 g) in AcOH (150 ml) and $HClO_4$ (70%, 5 ml) under atmospheric pressure for 8 h gave, after removal of the catalyst and solvent in vacuo, a residual oil, which was dissolved in H_2O, basified with 20% NaOH, extracted with Et_2O, and dried (K_2CO_3). The residual oil of the ethereal solution was treated with HBr to give crude **11**·HBr, which was recrystallized from EtOH–Et_2O to give 8.6 g of pure **11**·HBr: mp 164–165°. Anal. ($C_{17}H_{27}NO$·HBr) C, H, N.

(c) Hydrogenation of **9** over PtO_2 in EtOH–15% HCl (3:2) under atmospheric pressure afforded a mixture of **10** and **11** (ratio 3:7).

4-(2-Dimethylaminoethyl)-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (12a). To a stirred mixture of **5** (3.5 g) and $Na_2Cr_2O_7$ (6.0 g) in 1 N H_2SO_4 (150 ml) was added 10 N H_2SO_4 (400 ml) at room temperature during 2 h. After stirring for 16.5 h, the mixture was cooled (ice bath), basified with 12 M NH_4OH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the solvent gave 2.5 g of crude **12a**, which was distilled in vacuo to give 2.3 g of pure **12a**: bp 152–158° (0.2 mmHg). The **hydrochloride** had mp 194–197° (from EtOH). Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

4-Methyl- (12d), 3,4-*cis*-Dimethyl- (12e), and 3,4-*trans*-Dimethyl-4-(2-dimethylaminoethyl)-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (12f). To a stirred mixture of **7** (40 g) and CrO_3 (22 g) in 1 N H_2SO_4 (2500 ml) was added 10 N H_2SO_4 (400 ml) at room temperature during 3 h. After stirring overnight, the mixture was cooled (ice bath), basified with 12 M NH_4OH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the solvent gave a brown oil, which was distilled in vacuo to give 28 g of **12d** as a pale yellow oil: bp 120–145° (1.0 mmHg). The hydrochloride had mp 201–205° (from EtOH). Anal. ($C_{16}H_{23}NO_2$·HCl) C, H, N.

Similarly, α-tetralones **12e** and **12f** were obtained from **10** and **11** in 62 and 63% yield, respectively, as the HBr salts. **12e·HBr**: mp 194–196° (from Me_2CO). Anal. ($C_{17}H_{25}NO_2$·HBr) C, H, N. **12f**·HBr: mp 210–214° (from Me_2CO). Anal. ($C_{17}H_{25}NO_2$·HBr) C, H, N.

4-Methyl- (14a), 4,12α-Dimethyl-(14b), 4,12β-Dimethyl-(14c), 1,4-Dimethyl- (14d), 1,4,12α-Trimethyl- (14e), and 1,4,12β-Trimethyl-10-methoxy-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one (14f). To a refluxing solution of **12a** (2.3 g) in benzene (50 ml) was added $ClCO_2Et$ (1.6 g) in benzene (10 ml) during 30 min. After refluxing for 1.5 h, the mixture was cooled, washed with 10% HCl, and dried ($MgSO_4$). Evaporation of the benzene gave 2.7 g of **13a**.

Carbamate **13a** (2.7 g) and 12 M HCl (80 ml) were refluxed for 20 h. The mixture was evaporated to dryness, dissolved in MeOH (50 ml) and formalin (10 ml), and kept at 40° for 2 days. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with Et_2O, and dried (K_2CO_3). The residue (2.0 g) of the ethereal solution was chromatographed on a silica gel (70 g) column. Elution with $CHCl_3$–MeOH (99:1) gave 1.1 g of **14a** as an almost colorless oil. The picrate had mp 194–196° (from MeOH). Anal. ($C_{21}H_{22}N_4O_9$) C, H, N.

Similarly, **14b–f** were obtained from **12b**,[3b] **12c**,[3b] **12d**, **12e**, and **12f** in 29, 32, 26.5, 49.5, and 54.8% yield, respectively. **14b**·HCl: mp 192–195° (from *i*-PrOH). Anal. ($C_{16}H_{21}NO_2$·HCl) C, H, N. **14c**·HCl: mp 195–200° (from *i*-PrOH). Anal. ($C_{16}H_{21}NO_2$·HCl) C, H, N. **14d**·picrate: mp 207–209° (from MeOH). Anal. ($C_{22}H_{24}N_4O_9$) C, H, N. **14e**·HBr: mp 200–203° (from EtOH). Anal. ($C_{17}H_{23}NO_2$·HBr) C, H, N. **14f**·HCl: mp 212–214° (from EtOH). Anal. ($C_{17}H_{23}NO_2$·HCl) C, H, N.

4,12α-Dimethyl- (15b), 4,12β-Dimethyl- (15c), 1,4-Dimethyl-(15d), 1,4,12α-Trimethyl- (15e), and 1,4,12β-Trimethyl-10-methoxy-7β-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (15f). (a) A mixture of **14b** (2.0 g) and $LiAlH_4$ (1.0 g) in dioxane (50 ml) was refluxed for 5 h, cooled (ice bath), treated with aqueous Rochelle salt solution, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the solvents gave 1.5 g of **15b** as a colorless syrup. The picrate had mp 155–156° (from EtOH). Anal. ($C_{22}H_{26}N_4O_9$) C, H, N.

Similarly, **15e** was obtained from **14e** in 83% yield as colorless crystals: mp 109–115° (from cyclohexane). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

(b) To a stirred solution of **14c** (2.8 g) in MeOH (50 ml) was added $NaBH_4$ (2.0 g) during 30 min with ice cooling. After stirring for 2 h at room temperature, the solvent was evaporated. The residual oil was treated with H_2O and $CHCl_3$. The dried ($MgSO_4$) chloroform solution was evaporated to give 2.75 g of **15c** as a colorless oil. The picrate had mp 195° (from MeOH). Anal. ($C_{22}H_{26}N_4O_9$) C, H, N.

Compounds **15d** and **15f** were prepared by similar reduction of **14d** and **14f** in 85.5 and 89.5% yield, respectively. **15d**: mp 145–146° (from benzene). Anal. ($C_{16}H_{23}NO_2$) C, H, N. The hydrochloride had mp 210–215° (from EtOH). **15f·HCl**: mp 208–211° (from EtOH). Anal. ($C_{17}H_{25}NO_2$·HCl) C, H, N.

4-Methyl- (16a), 4,12α-Dimethyl- (16b), 4,12β-Dimethyl-(16c), 1,4-Dimethyl- (16d), 1,4,12α-Trimethyl- (16e), and 1,4,12β-Trimethyl-10-methoxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (16f). (a) Hydrogenation of **14a** (0.5 g) in AcOH (20 ml) over PtO_2 (0.2 g) under atmospheric pressure for 6 h gave, after removal of the catalyst and solvent, a residue which was dissolved in H_2O, made alkaline with 20% NaOH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the solvent gave 0.45 g of **16a** as a colorless oil, distilled at 140–150° (bath temperature, 1.5 mmHg).

(b) A mixture of **15b** (1.5 g), Pd/C (20%, 2.5 g), and $HClO_4$ (70%, 1.0 ml) in AcOH (30 ml) was shaken in H_2 at room temperature and atmospheric pressure for 2 h. After removal of the catalyst and solvent, the residual oil was dissolved in H_2O, basified with 20% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the chloroform gave 1.4 g of **16b** as a colorless oil: bp 130–140° (1.5 mmHg). The picrate had mp 135–137° (from MeOH). Anal. ($C_{22}H_{26}N_4O_8$) C, H, N.

Similarly, **16c–f** were prepared from **15c–f** by catalytic hydrogenation over Pd/C in 69, 62, 64 and 64% yield, respectively. **16c**: bp 130–145° (1.5 mmHg). The picrate had mp 187–189° (from MeOH). Anal. ($C_{22}H_{26}N_4O_8$) C, H, N. **16d**: bp 180–200° (bath temperature, 4.0 mmHg). The hydrobromide had mp 189–191° (from Me_2CO–Et_2O). Anal. ($C_{16}H_{23}NO$·HBr) C, H, N. **16e**: bp 120–140° (bath temperature, 0.4 mmHg). The hydrobromide had mp 196–199° (from EtOH–Et_2O). Anal. ($C_{17}H_{25}NO$·HBr) C, H, N. **16f**: bp 130–145° (bath temperature, 0.5 mmHg). The hydrochloride had mp 184–185° (from EtOH). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

4-Methyl- (17a), 4,12α-Dimethyl- (17b), 4,12β-Dimethyl-(17c), 1,4-Dimethyl- (17d), 1,4,12α-Trimethyl- (17e), and 1,4,12β-Trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (17f). (a) A mixture of **16a** (0.4 g) and 48% HBr (10 ml) was refluxed for 45 min. Evaporation and recrystallization from MeOH gave 0.35 g of **17a**·HBr as colorless crystals: mp 247.5–250.5°. Anal. ($C_{14}H_{19}NO$·HBr) C, H, N.

Compound **17f**·HBr was obtained in 69.3% yield by similar hydrolysis of **16f** with hydrobromic acid: mp 256–259° (from MeOH–Me_2CO). Anal. ($C_{16}H_{23}NO$·HBr) C, H, N.

(b) **16b** (1.4 g) and 48% HBr (15 ml) were gently refluxed for 1 h. After evaporation to dryness, the residue was dissolved in

H_2O and basified with 12 M NH_4OH to precipitate pale violet crystals of **17b**. Recrystallization of the crude crystals from EtOH yielded 0.7 g of pure **17b** as colorless crystals: mp 204°. Anal. ($C_{15}H_{21}NO$) C, H, N.

Similarly, compounds **17c–e** were obtained from **16c–e** in 40, 41, and 79% yield, respectively. **17c**: mp 165° (from EtOH). Anal. ($C_{15}H_{21}NO$) C, H, N. **17d**: mp 245–252° (from EtOH). Anal. ($C_{15}H_{21}NO$) C, H, N. **17e**: mp 208–210° (from MeOH). Anal. ($C_{16}H_{23}NO$) C, H, N.

References and Notes

(1) S. Shiotani and T. Kometani, *Chem. Pharm. Bull.*, **21**, 1053 (1973).
(2) S. Shiotani, *J. Org. Chem.*, **40**, 2033 (1975).
(3) (a) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 404 (1969); (b) H. Inoue, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **18**, 787 (1975).
(4) The α and β designations are with reference to the hydroaromatic ring.
(5) H. O. House and R. J. McCaully, *J. Org. Chem.*, **24**, 725 (1959).
(6) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).
(7) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).
(8) The differences in the *C*-methyl chemical shift between the α-methyl and β-methyl isomers would be the result of a change in environment of the *C*-methyl from a position above the aromatic ring to one away from the aromatic ring.
(9) (a) A. F. Green, P. A. Young, and E. I. Godfrey, *Br. J. Pharmacol.*, **6**, 572 (1951); (b) K. Takagi, T. Kameyama, and K. Yano, *Yakugaku Zasshi*, **78**, 553 (1958); (c) A. Kasahara, H. Kojima, Y. Osada, W. Tsukada, and Y. Oshima, *Yakugaku Zasshi*, **88**, 606 (1968).
(10) J. T. Lichfield and F. Wilcoxon, *J. Pharmacol.*, **96**, 99 (1949).

Synthesis of Aziridinylallylaminophosphine Oxides and Sulfides as Potential Adjuvant Cancer Chemotherapeutic Agents

K. C. Tsou,* D. Bender, N. Santora, L. David, S. Damle,

University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19174

and A. B. Borkovec

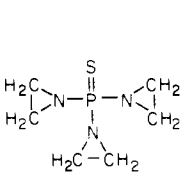
Insect Chemosterilant Laboratory, Agricultural Environmental Quality Institute, United States Department of Agriculture, Agricultural Research Service, Beltsville, Maryland 20705.

Received July 15, 1975

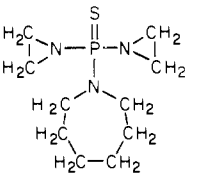
Bis(1-aziridinyl)(hexahydro-1*H*-azepin-1-yl)phosphine sulfide, an active anticancer agent with low hematopoietic toxicity in animals and man, was recommended several years ago for breast cancer adjuvant chemotherapy as an alternate drug to thiotepa. This hope had led to the syntheses of aziridinylallylaminophosphine oxides or sulfides (compounds I–XVII) in our laboratories. The resurgent interest in this area of cancer chemotherapy encouraged us to report our synthetic work as well as their evaluation as both anticancer agents and insect chemosterilants. Based on observed antitumor activity in animals, low chemosterilant activity in female species (insects and rats), and histochemical observation of tissue toxicity in rat testes but not in ovaries, these new agents are of potential interest to the breast cancer adjuvant chemotherapy program.

Bis(1-aziridinyl)(hexahydro-1*H*-azepin-1-yl)phosphine sulfide,[1] an active anticancer agent with low hematopoietic toxicity in animals and man, was recommended several years ago for breast cancer adjuvant chemotherapy as an improvement over thiotepa.[2] This work had provided impetus for us to search for other related drugs that could be useful for similar applications. Allylamino derivatives of some aziridinylphosphine oxides and sulfides were found to have activity in several animal tumor models.[3] Furthermore, the introduction of the diallylamino group does not lead to carcinogenicity. β-(1-Aziridinyl)diallylaminopropionamide was found to cause 100% lymphoma regression in rats without inducing subsequent mammary tumor development in the same rats.[4] These results suggested to us that it might be worthwhile to synthesize additional candidate agents in this area of cancer chemotherapy. The resurgent interest in breast cancer adjuvant chemotherapy with a nitrogen mustard analogue L-phenylalanine (L-PAM)[5] encouraged us to report the syntheses of these new phosphoramides, together with their biological evaluations.

Syntheses. The syntheses of these aziridinyl allylaminophosphine oxides and sulfides were carried out similar to our previous work on the azepinyl analogues and are shown in Scheme I. Essentially, diallylamine was allowed to react with either phosphorus oxychloride or thiophosphoryl chloride to yield the corresponding phosphochloridate or thiophosphochloridate. These intermediates were then used to couple with aziridine or methylaziridine under anhydrous conditions and in the presence of a base such as triethylamine. Further purification was often necessary and high-vacuum distillation over sodium hydroxide pellets was used to obtain polymer-free, analytically pure samples. The preparation

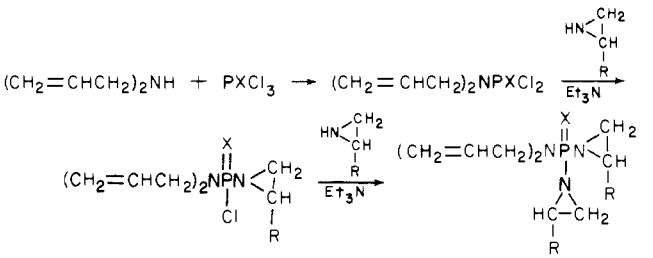


tris(1-aziridinyl)phosphine sulfide ("**thiotepa**")



bis(1-aziridinyl)(hexahydro-1*H*-azepin-1-yl)-phosphine sulfide ("**thiohexadepa**")

Scheme I



* Address correspondence to this author at the Hospital of the University of Pennsylvania, 1515 Ravdin Institute, Philadelphia, Pa. 19104.