A literature survey (20, 21) revealed that glaucine and *O*-methylatheroline had not been found previously in *G. oxylobum* and predicentrine had not been detected in the genus *Glaucium*.

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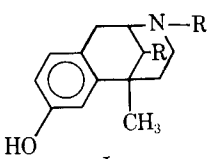
Synthesis of 5,6-Benzo-2-azabicyclo[2.2.2]octane Derivatives as Potential Benzomorphan-Type Analgesic Agents

RONALD F. BORNE [x], SAY-JONG LAW, PHILIP W. WIRTH, and JAMES C. MURPHY

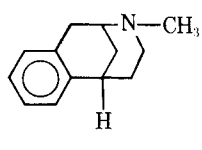
Abstract □ The synthesis of two *N*-substituted 5,6-benzo-2-azabicyclo[2.2.2]octane analogs of benzomorphan-type analgesics *via* benzyne addition to appropriate *N*-substituted *N*-alkyl-2-pyridones is described. Neither derivative possessed observable analgesic activity at the doses tested.

Keyphrases □ 5,6-Benzo-2-azabicyclo[2.2.2]octanes, *N*-substituted—synthesized, analgesic activity evaluated, mice □ Structure–activity relationships—*N*-substituted 5,6-benzo-2-azabicyclo[2.2.2]octanes synthesized, analgesic activity evaluated, mice □ Analgesic activity—*N*-substituted 5,6-benzo-2-azabicyclo[2.2.2]octanes evaluated, mice

The structural features of narcotic analgesics related to morphine have been well documented (1, 2). Studies of structure–analgesic activity requirements within the benzomorphan-type analgesics have also received considerable attention. While the structural features of benzomorphans are generally incorporated in structures such as I, many analogous structures have been demonstrated to possess significant analgesic activity. For example, 2-methyl-6,7-benzomorphan (II) (3), 7-methoxy-2-methyl-B-norbenzomorphan (III) (4), and 5-methano-3-methyl-6-phenyl-1,2,3,4,5,6-hexahydro-3-benzazocine (IV) (5)



I



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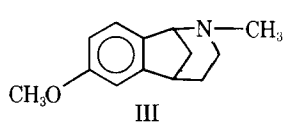
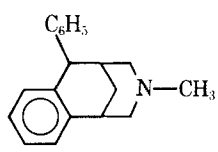


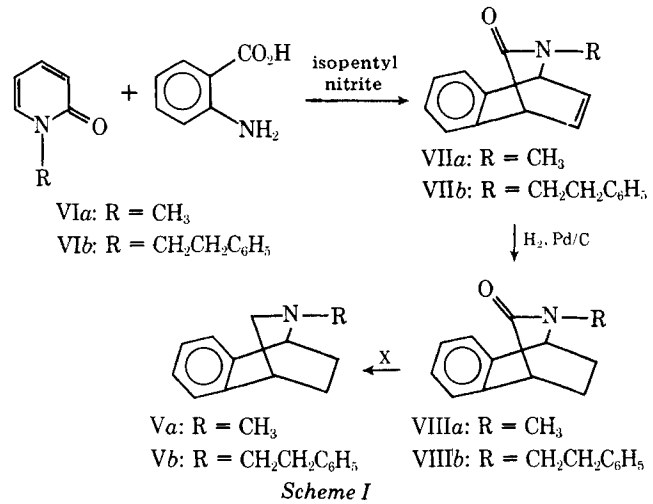
III



IV

possessed analgesic potencies comparable to that of codeine.

Compounds II–IV all lack "quaternary central carbon atoms," a structural feature once thought to be essential for activity (1, 2). Additionally, II and IV lack phenolic functions, and IV contains only a one-carbon separation from the basic nitrogen and the central carbon atom. While the active benzomorphans are characterized by the presence of a basic nitrogen atom 4.1 Å from the center of an



Scheme I

aromatic ring and 1.5 Å above the plane of that ring, derivatives possessing these characteristics alone proved to be inactive as analgesics (6). This discussion illustrates the flexibility of structural features for analgesic activity within the benzomorphan series.

These factors, along with interest in 2-azabicyclo[2.2.2]-octane analogs of analgesics (7), prompted the preparation and evaluation of V*a* and V*b* for analgesic and central nervous system (CNS) activity. These analogs lack a quaternary carbon atom, a phenolic function, and a two-carbon separation between the basic nitrogen and the central carbon atom but do orient the basic nitrogen 3.6 Å from the center of the aromatic ring and 1.3 Å above the plane of this ring. Additionally, these analogs may be considered as semirigid analogs of phenethylamine derivatives.

DISCUSSION

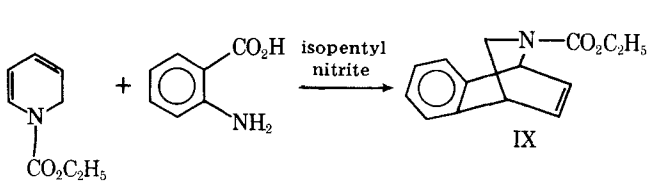
Chemistry—The synthetic approach to V*a* was essentially that previously reported (8) with some modifications (Scheme I). Benzyne was generated by the action of isopentyl nitrite on anthranilic acid in the presence of *N*-methyl-2-pyridone (VI*a*). The adduct, VII*a*, was obtained in only 10% yield. Subsequent catalytic hydrogenation gave VIII*a*, which was further reduced with sodium bis(2-methoxyethoxy)aluminum hydride (X) to give V*a*.

The synthesis of V*b* was somewhat more difficult. The synthesis of IX (Scheme II) was attempted with the anticipation that reduction, carbamate hydrolysis, and subsequent reductive alkylation with phenylacetaldehyde would give V*b*. However, condensation of benzyne with *N*-carbethoxy-1,2-dihydropyridine yielded no isolatable adduct. Thus, VI*b* was prepared by the oxidation of the quaternary salt obtained from pyridine and 2-bromoethylbenzene with potassium hydroxide and potassium ferricyanide. Condensation of this pyridone and benzyne gave only a 7% yield of VII*b*. Isolation of the diazonium salt prior to benzyne generation did not improve the yield of the adduct. Catalytic hydrogenation of VII*b* gave VIII*b* in a 92% yield. Subsequent lactam reduction gave V*b* in an overall 6% yield from VI*b*.

Pharmacology—Compounds V*a* and V*b* were evaluated for analgesic activity in mice using the D'Amour–Smith (9) tail-flick method. The toxicity of both compounds limited the maximum doses at which they could be evaluated. Both compounds failed to display analgesic activity, V*a* at 25 mg/kg and V*b* at 50 mg/kg, but produced some CNS effects.

Compound V*a* was tested at 50, 25, and 10 mg/kg. The 50-mg/kg dose was lethal to all subjects within 12 min of injection. Death was preceded by profuse salivation, Straub tail, and tremors. The 25-mg/kg dose produced tremors which lasted for about 20 min following injection. Consistent failure in tests involving muscular coordination was seen at 25 mg/kg, but spontaneous activity and reactivity were not affected. The 10-mg/kg dose produced no effects within the scope of this screen.

Compound V*b* was tested at 100, 50, and 25 mg/kg. All mice injected with 100 mg/kg died within 10 min of injection following clonic convulsions. The mice injected with 50 mg/kg showed a loss of spontaneous activity as evidenced by observer ratings and failures on the dish, pedestal, and chimney tests. Both the finger touch and tail pull tests showed a loss of reactivity. No ptosis or loss of skeletal muscle tone was observed. The pinna reflex was abolished, indicating that the effect of V*b* at 50 mg/kg may not be purely depressant. One death occurred within 24 hr at 50 mg/kg, while only marginal effects and no lethality were observed at 25 mg/kg.



Scheme II

EXPERIMENTAL[1]

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]oct-7-en-3-one (VII*a*)—A solution of anthranilic acid (20.0 g, 0.145 mole) in 125 ml of acetone was added dropwise over 1.0 hr to a refluxing solution of 15.0 g (0.137 mole) of VI*a* and 20.0 g (0.17 mole) of isopentyl nitrite in 400 ml of dichloromethane. The reaction mixture was refluxed an additional 1.0 hr and the resulting solution was washed with 2 × 200 ml of 10% hydrochloric acid and 2 × 200 ml of water. The organic phase was dried over sodium sulfate and evaporated to give a dark oil.

The oil was taken up in benzene, placed on a basic alumina column[2] (80–200 mesh, 520 g), and eluted with ether–benzene (1:1). Isopentyl alcohol eluted first, followed by the adduct, VII*a* (2.5 g, 10%); NMR: δ 3.0 (s, 3H, NCH_3), 4.8 (doublet of doublets, 1H, J = 2.5 Hz), 5.2 (doublet of doublets, 1H, J = 2.5 Hz), and 7.1–7.7 (m, 6H, olefinic and aromatic); IR (liquid film): 1680 cm^{-1} (NC=O).

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]octan-3-one (VIII*a*)—To a solution of VII*a* (4.8 g, 0.026 mole) in 100 ml of ethanol was added 10% palladium-on-charcoal (0.48 g), and the resulting mixture was hydrogenated at 3.1 kg/cm^2. The mixture was filtered through diatomaceous earth[3], and the filtrate was evaporated to give a clear oil (3.9 g, 81%); NMR: δ 2.95 (s, 3H, NCH_3), 4.0 (s, 1H, NCH), and 7.25 (s, 4H, aromatic); IR (liquid film): 1680 cm^{-1} (NC=O).

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]octane (V*a*)—A solution of VIII*a* (2.3 g, 0.012 mole) in benzene (40 ml) was added dropwise to X (14 ml of a 70% benzene solution, 0.048 mole), and the resulting solution was refluxed for 3 hr. Ethanol was added to the cooled, stirring solution until bubbling ceased. Water was added until precipitation ceased. The precipitate was removed by filtration, and the filtrate was separated into organic and aqueous phases. The aqueous phase was extracted with chloroform (2 × 30 ml); the organic extracts were combined, dried over sodium sulfate, and evaporated to give a residue.

Distillation of the residue gave an oil (1.0 g, 47%), bp 70°/0.45 mm; NMR: δ 1.27–2.5 (m, 5H, H at C-7, C-8, and C-3), 2.03 (NCH_3), 2.97 (broad, 1H, H at C-4), 3.2–3.4 (doublet of doublets, 1H, H at C-3), 3.6 (broad, 1H, H at C-1), and 7.2–7.4 (broad, 4H, aromatic); *m/e* 173 (M+) and 144 (base). The hydrochloride salt was prepared in the normal manner, mp 236.5–238.5°.

Anal.—Calc. for $C_{12}H_{16}ClN$: C, 68.72; H, 7.69; N, 6.68. Found: C, 68.63; H, 7.73; N, 6.53.

1-(2-Phenylethyl)-2-pyridone (VI*b*)—To a solution of 13.0 g (0.049 mole) of 1-(2-phenylethyl)pyridinium bromide (prepared from pyridine and 2-bromoethylbenzene, mp 123–125°) in 60 ml of water was added a solution of 65.0 g (0.2 mole) of potassium ferricyanide in 400 ml of water. After addition was complete, a yellow suspension was obtained. Benzene (125 ml) was added, and the reaction mixture was warmed to 40°. A so-

[1] All melting points were taken on a Mel-Temp apparatus and are corrected. IR spectra were obtained with a Beckman IR-33 spectrophotometer. NMR spectra were taken in deuterochloroform on a Jeolco C-60-HL spectrometer, and values are reported in parts per million (δ) from tetramethylsilane as the internal standard. Mass spectral data were obtained on a Dupont model 21-492 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Sodium bis(2-methoxyethoxy)aluminum hydride (Red Al) was purchased from Aldrich Chemical Co.

[2] Fisher.

[3] Celite.

lution of potassium hydroxide (27.0 g, 0.5 mole) in 75 ml of water was added dropwise, and the resulting mixture was stirred for 2 hr.

The organic layer was separated, and the aqueous layer was extracted with benzene (2 × 75 ml). The organic phases were combined, dried over sodium sulfate, and evaporated to give a tan solid (6.5 g, 66%). Recrystallization from benzene–petroleum ether yielded colorless crystals, mp 104–106°; IR (mineral oil): 1660 cm^{-1} (C=O).

2-(2-Phenylethyl)-5,6-benzo-2-azabicyclo[2.2.2]oct-7-en-3-one (VII*b*)—A solution of anthranilic acid (61.6 g, 0.45 mole) in 500 ml of ethanol was cooled to 5°. Concentrated hydrochloric acid (35 ml) was added followed by isopentyl nitrite (85 ml). The temperature was maintained below 10° throughout addition. Ether (500 ml) was added; the resulting diazonium salt was collected by filtration, washed with anhydrous ether, and suspended in 650 ml of dichloromethane. To the suspension were added 18.3 g (0.092 mole) of VI*b* and 35.0 g (0.6 mole) of propylene oxide in 50 ml of dichloroethane. The mixture was stirred at room temperature for 1.5 hr, and the solvents were evaporated.

The residual oil was taken up in benzene, placed on a silica gel column[4] (0.05–0.20 mm, 800 g), and eluted with ether–hexane (1:1) to give 1.75 g (7%) of VII*b*, mp 124–125°; NMR: δ 2.73 (t, 2H, $CH_2C_6H_5$), 3.4–3.7 (m, 2H, NCH_2), 4.5–4.7 (doublet of doublets, 1H, H at C-4), 4.8–4.9 (doublet of doublets, 1H, H at C-1), and 6.5–7.3 (broad, 11H, olefinic and aromatic); IR (mineral oil): 1675 cm^{-1} (C=O); *m/e* 275 (M+) and 128 (base).

Anal.—Calc. for $C_{19}H_{17}NO$: C, 82.85; H, 6.23; N, 5.09. Found: C, 82.81; H, 6.26; N, 5.38.

2-(2-Phenylethyl)-5,6-benzo-2-azabicyclo[2.2.2]octan-3-one (VIII*b*)—A solution of 3.56 g (0.0129 mole) of VI*b* in 175 ml of ethanol was hydrogenated in the presence of 0.4 g of palladium-on-charcoal at 3.1 kg/cm^2 until hydrogen uptake ceased. The catalyst was removed by filtration, and the filtrate was evaporated to give a solid. The solid was recrystallized from benzene–petroleum ether to yield 3.3 g (92%) of VIII*b*, mp 127–129°; IR (KBr): 1665 cm^{-1} (C=O); *m/e* 277 (M+) and 130 (base).

Anal.—Calc. for $C_{19}H_{19}NO$: C, 82.27; H, 6.90; N, 5.05. Found: C, 82.33; H, 7.00; N, 5.01.

2-(2-Phenylethyl)-5,6-benzo-2-azabicyclo[2.2.2]octane (V*b*)—A solution of 2.18 g of VIII*b* (0.0079 mole) in 40 ml of benzene was added dropwise to X (8 ml, 0.0277 mole), and the resulting mixture was refluxed for 4 hr. The mixture was cooled, ethanol and water were added to destroy excess hydride, and the mixture was filtered. The organic phase of the filtrate was separated, and the aqueous layer was extracted with chloroform (2 × 30 ml).

The organic phases were combined, dried over sodium sulfate, and evaporated to give a residue which was chromatographed on a silica gel column[4] (0.05–0.20 mm, 45 g). Elution with ether–hexane (1:1) gave 1.85 g (89%) of V*b*; NMR: δ 1.27–2.9 (m, 9H, $NCH_2CH_2C_6H_5$ and H at C-7, C-8, and C-3), 2.9–3.1 (broad, 1H, H at C-4), 3.32–3.5 (doublet of doublets, 1H, H at C-3), 3.7–3.9 (broad, 1H, H at C-1), and 7.0–7.4 (broad, 9H, aromatic); *m/e* 263 (M+) and 172 (base). The hydrochloride salt was prepared in the normal manner, mp 142–144°.

Anal.—Calc. for $C_{19}H_{22}ClN$: C, 76.11; H, 7.40; Cl, 11.83; N, 4.67. Found: C, 76.30; H, 7.42; Cl, 11.76; N, 4.77.

Pharmacological Methods—Both V*a* and V*b* were tested for biological activity with blind screening techniques standard to this laboratory. All tests were conducted in groups of four to six male Swiss mice, 18–23 g, and were conducted according to published protocols (10, 11). This mouse assay consists of: (*a*) rating of spontaneous activity, (*b*) rating of skeletal muscle tone, (*c*) the tail pull and finger touch tests of reactivity, (*d*) the righting time test, (*e*) measurement of pinna reflex, (*f*) the test for catalepsy, (*g*) the dish test, (*h*) the pedestal test, (*i*) the traction test, (*j*) the chimney test, and (*k*) a modification of the D'Amour–Smith tail flick test for analgesia (9).

The tail-flick test was performed 30 min after intraperitoneal injection. All other tests were performed at 15 and 60 min postinjection. Sixteen standard observations of autonomic activity and abnormal behavior were made in addition to the tests listed. Appropriate vehicle and positive controls were included in the test protocols.

[4] Woelm.

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