Tetrahydropyrrolidoacenaphthene and Benzazapropellane Derivatives as Potential Analgetics and Narcotic Antagonists[1]

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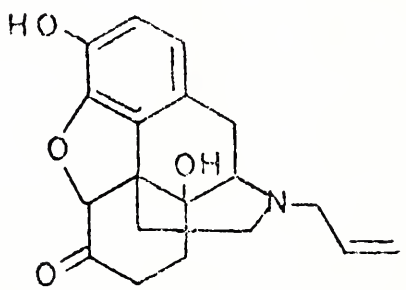
Introduction

The activity of a 3a, 4,5,6-tetrahydroposuccinimido (3,4-b) acenaphthen-10-one as a psychotic stimulant and hallucinogen (1) suggested the desirability of testing some related structures, containing a fused pyrrolidine ring and one or more quaternary carbon atoms, with the nitrogen of the pyrrolidine substituted by methyl or allyl, as possible analgetics or narcotic antagonists. Principal activity of either type is usually associated with polycyclic systems having one or more quaternary bridgehead carbons and a cyclic tertiary amine.

In general, a benzene ring is held perpendicular to the plane of the cyclic amine by cyclic bridging as in the morphinans, or benzomorphans, e.g., naloxone (1), or cyclazocine (2), (2).



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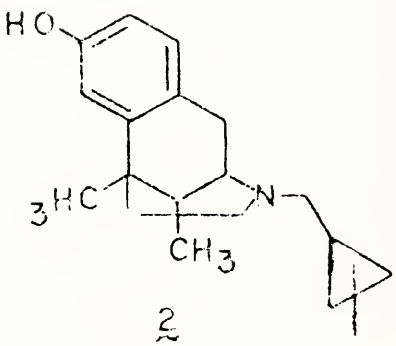

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Campaigne, Roelofs and Weddleton (4) had developed synthetic procedures for the preparation of the anti-convulsant 3a,4,5,6-tetrahydrosuccinimido[3,4-b]-acenaphthen-10-one, (3) and Campaigne and Mehra the azapropellanes 4 and 5 (Scheme I) (5). The N-alkylation and subsequent reduction of these compounds would produce structures seeming to fit all structural criteria for narcotic agonist and more especially antagonist activity.

Weddleton (8) had investigated the N-alkylation of 3 rather extensively and had attempted the reduction of the N-methyl derivative, **6a.** Campaigne and Mehra (5) prepared a variety of N-substituted derivatives of 4, including **7a** and **7b,** and studied the reduction of **7a** to form **10a.** With this background, we prepared compounds **9, 10** and

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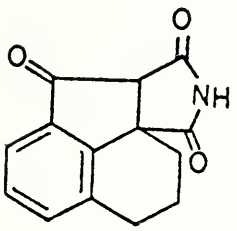
11 (Scheme I) where R = methyl or allyl, in sufficient quantities to permit their biological screening.

Chemistry. Alkylation of **4** and **5** was accomplished using methyl iodide or allyl bromide in the presence of two equivalents of potassium carbonate. In the case of **3b**, sodium hydride oil dispersion was employed as the base. All of the reductions were run in tetrahydrofuran solution with tenfold molar excess lithium aluminum hydride. The resulting amino alcohols were obtained free of intermediate reduction products;

Scheme 1



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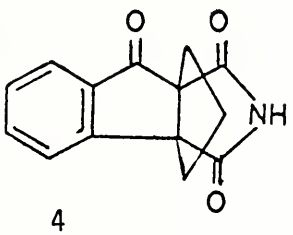

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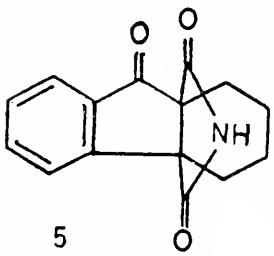

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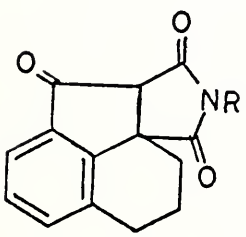

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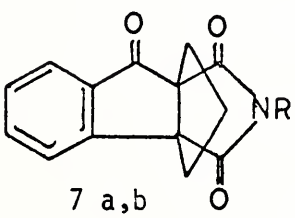
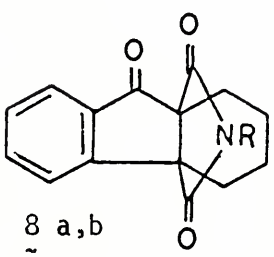
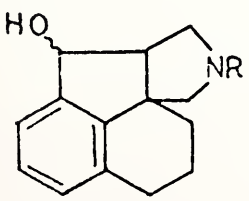


7 a,b

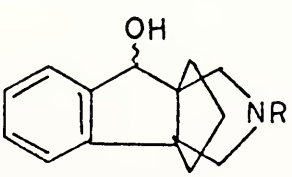


8 a,b

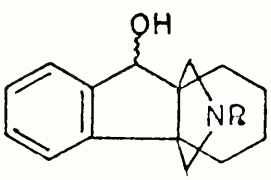
a, R=CH_3
b, R=$CH_2CH=CH_2$



9 a,b



10 a,b



11 a,b

this being demonstrated by the lack of any observable carbonyl absorption in the infrared spectra of the crude reaction products.

Since the amino alcohols **9, 10,** and **11** gave hygroscopic hydrochlorides, and the use of other salts such as oxalates would complicate the biological analysis, the purification of the viscous oily free bases was accomplished by distillation of these materials under high vacuum from small scale bulb to bulb Hickman flasks, where the distilling bulb was packed with glass wool which served both as a bubble source and an absorbent for the small amount of colored impurities which were present.

Pharmacological Results. Samples of **9a, 9b, 10a, 10b, 11a,** and **11b** were submitted to the Division of Narcotic Addiction and Drug Abuse, National Institutes of Mental Health, Rockville, Maryland for pharmacological evaluation.

In preliminary pharmacological evaluation,[2] **11a** showed weak analgetic activity in rats at high doses of 40 mg/kg in the tail pinch and phenylquinone writhing tests. Compound **11b** showed no such activity at doses ranging from 7.5 to 30 mg/kg. Neither compound exhibited antagonism against morphine.

Samples of **9a, 9b, 10a** and **10b** were screened for analgetic (pain killing) activity by Dr. Everette L. May of U.S. Public Health Service Section of Medicinal Chemistry, to whom we are indebted for providing the preliminary screening data. Compounds **9a** and **10a** showed mild analgetic activity at doses of 20-40 mg/kg in mice using the Nilsen electric shock test (7). Compound **9b** also exhibited very weak analgetic activity at 20-40 mg/kg. A typical ED_{50} for morphine in such tests is 0.8 mg kg. These compounds were inactive as morphine antagonists in morphine-dependent monkeys.

In summary, all of the N-methyl compounds prepared in this investigation exhibited weak analgetic activity at high dose levels. The N-allyl compounds are generally inactive as analgetics.

Experimental

Melting points were determined in open capillary tubes in a Mel-Temp heated block apparatus and are corrected. A Perkin-Elmer Model 137 Infrared Spectrophotometer was used to record all infrared spectra in the range 2.5 to 15 μ. All solids were measured in potassium bromide mulls, and all liquids were measured as liquid films. Mass spectra were obtained on a Varian Associated CH-7 mass spectrometer. Exact masses were determined on an AE1 MS-9 double focusing mass spectrometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

N-Methyl-3a,4,5,6,tetrahydrosuccinimido-[3,4-b]acenaphthen 10-one. *(6a)*

Following a modification of the procedure of Calberson and Wilder (3), a mixture of 5 g (0.02 mole) of 3 (4), 5.7 g (0.04 mole) of potas-

[2] We are indebted to Jo Ann Nuite, National Institutes of Mental Health, Bethesda, Maryland, for these preliminary results.

sium carbonate, and 2.84 g. (0.02 mole) of methyl iodide in 25 ml of DMF was stirred at room temp. for 20 hours and poured over 250 g. of ice. The resulting precipitate was recrystallized from 95% ethanol to yield 4.84 g. (95%) of white crystals melting at 152-153.5°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.31; N, 5.49. Found: C, 70.94; H, 5.45; N, 5.31.

N-Allyl-3a,4,5,6-tetrahydrosuccinimido-[3,4]acenaphthen-10-one. **(6b)**

A 250 ml round bottom flask was charged with 24.1 g (0.1 mole) of **3**, 75 ml dry DMF, and 4.2 g (0.1 mole of 56% sodium hydride oil dispersion. The mixture was stirred at room temp. and when evolution of gas ceased, 12.1 g (8.65 ml, 0.1 mole) of allyl bromide was added. The mixture was allowed to stir 20 hours at room temp., then poured into 300 ml of water, to form an oily precipitate. The water was decanted and the remaining mass triturated with hexane. The resulting grayish solid **6** was recrystallized from isopropanol yielding 23.3 g (83%) of white crystals, mp 106-108°. After two recrystallizations, the analytical sample melted at 110-111° (8).

Anal. Calcd. for $C_{17}H_{16}NO_3$: C, 72.34; H, 5.67; N, 4.96. Found: C, 72.49; H, 5.51; N, 4.95.

8-Methyl-7,9-dioxo-11,12-benzo-8-aza[4.3.3]propellan-10-one. **(8a)**.

To a solution of 1 g (3.93 mmole) of **5** (5) in 20 ml dry DMF was added 1.1 g (8.0 mmole) of potassium carbonate and 0.25 ml (0.57 g, 4.0 mmole) of methyl iodide. The reaction mixture was stirred 24 hours at room temp. then poured into 100 g crushed ice. The resulting precipitate and aqueous solution was extracted with ether (2 x 75 ml) and the ether extracts dried over magnesium sulfate. Evaporation of the ether yielded 1.32 g (91%) of a slightly yellow oil which solidified under vacuum to white microcrystals, mp 125-129°. Recrystallization from cyclohexane yielded **8a** as microprisms, mp 125-126.5°; i.f. (μ) 3.5 (C-H), 5.8-6.1 (CO), 13.3 (ArH).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.30; H, 5.57; N, 5.21; MW, 269. Found: C, 71.68; H, 5.44; N, 5.25; M+269.

8-Allyl-7,9-dioxo-11,12-benzo-8-aza[4.3.3]propellan-10-one. **(8b)**.

In a similar manner, 1.0 g of **5** was allowed to react with 0.35 ml (0.48 g, 4.0 mmole) of a allyl bromide, to produce 1.0 g (95%) of a yellow-green oil which was crystallized from dilute ethanol to give white crystals of **8b**, mp 74-75°; i.r. (μ) 3.30, 3.45, 3.52 (C-H), 5.65, 5.85, 6.03 (CO), 13.25 (ArH).

Anal. Calcd. for $C_{18}H_{18}NO_3$: C, 72.97; H, 6.08; N, 4.73; MW, 295. Found: C, 73.10; H, 5.98; N, 4.63; M+295.

N-Methyl-3a,4,5,6,-tetrahydropyrrolido[3,4-b]acenaphthen-10-ol. **(9a)**.

The procedure of Weddleton (8) was used as follows: to a suspension of 6 g (0.1 mole) of LAH in dry THF was added a solution of 2.55 g (0.01 mole) of **6a** dissolved in 75 ml dry THF. The mixture was brought to gentle reflux. After 20 hours the reaction was quenched with water and 6N sodium hydroxide as described by Fieser (6), and the THF solution dried over magnesium sulfate. Evaporation of the

solvent yielded 2.21 g (97%) of **9a** as a light brown oil. Bulb to bulb distillation of 200°/1.00 mm gave 2.15 g of **9a** as a clear yellow glass; i.r. (μ) 2.85 (OH), 13.0 (ArH); Calcd. for $C_{15}H_{19}NO$: exact mass, 229.1467. Found: 229.1468.

The hydrochloride of **9a** was obtained from ether and dry HCl as a white hygroscopic solid, melting at 256-258° (dec) after recrystallization from isopropanol (8).

Anal. Calcd. for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 67.70; H, 7.68; N, 5.11; Cl, 13.31.

N-Allyl-3a,4,5,6-tetrahydropyrrolido[3,4-b]acenaphthen-10-ol. (9b).

A solution of 2.81 g (0.01 mole) of **6b** dissolved in 45 ml of dry THF was added dropwise to a slurry of 6 g (0.1 mole) of LAH in 50 ml of the same solvent. The system was then allowed to gently reflux for 48 hours, and worked up as before to yield 2.4 g (94%) of a tan oil. Bulb to bulb distillation at 200°/1.0 mm yielded **9b** as a clear yellow glass: i.r. (μ) 2.96 (OH), 6.0 (C=C), 13.1 (ArH); exact mass, calcd. for $C_{17}H_{21}NO$: 255.1623; found: 255.1601.

3-Methyl-7,8-benzo-3-aza[3.3.3]propellan-6-ol. (10a).

Following a procedure previously reported (5), 2.1 g (9.15 mmole) of **7a** was dissolved in 50 ml dry THF and added dropwise to a slurry of 6.0 g (0.10 mole) of LAH in the same solvent. After 24 hours of gentle reflux, the reaction was quenched and worked up as previously described yielding 1.3 g of **10a** (56.7%) as a tan oil. Bulb to bulb distillation yielded analytical **10a** at 120°/0.15 mm; as a colorless viscous oil; i.r. (μ) 2.9 (OH), 13.3, 14.1 (ArH); calcd. for $C_{15}H_{19}NO$: exact mass, 229.1472; found: 229.1467. The hydrochloride (ether, dry HCl) melted at 222-224° (dec.) as previously reported (5).

3-Allyl-7,8-benzo-3-aza[3.3.3]propellan-6-ol. (**10b**).

A slurry of 1.4 g (5.8 mmole) of **7b** (5) and 2.0 g (50 mmole) of LAH in 200 ml dry THF was gently refluxed for 6½ days. After working up, the filtrate was dried and the solvent removed under vacuum, yielding 1.2 g (90%) of **10b** as a slightly tan viscous oil. Bulb to bulb distillation from a 135-140° oil bath at 0.17 mm produced a clear colorless glass; i.r. (μ) 2.9 (OH), 10.9 (allyl), 13.2 (ArH); exact mass. calcd. for $C_{17}H_{21}NO$: 255.1623; found: 255.1629.

8-Methyl-11,12-benzo-8-aza[4.3.3]propellan-10-ol. (**11a**).

A solution of 1.34 g (5 mmole) of **8a** dissolved in 50 ml of dry THF was dropped into a slurry of 2.0 g (50 mmole) of LAH in 75 ml of the same solvent. The mixture was refluxed 36 hours, then worked up as before, yielding 1.3 g of **11a** as a slightly cloudy colorless oil. Bulb to bulb distillation (95°/0.15 mm) produced 1.20 g (97%) of **11a** as a colorless oil: i.r. (μ) 2.9 (OH), 3.45-3.6 (CH), 6.1 (C=C), 13.2 (ArH); exact mass. calcd. for $C_{16}H_{21}NO$: 243.1618; found: 243.1623.

8-Allyl-11,12-benzo-8-aza[4.3.3]propellan-10-ol. (**11b**).

To a slurry of 2.0 g (0.05 mole) of LAH in 75 ml of dry THF was added dropwise a solution of 1.0 g (3.39 mmole) of **8b**. The reaction mixture was refluxed 24 hours and worked up as before yielding 0.97 g

of a clear yellow oil. Hickman distillation (90°/0.12 mm) yielded 0.91 g (99%) of **11b** as a colorless viscous liquid; i.r. (μ) 2.9 (OH), 6.1 (C=C), 10.85 (allyl C-H), 13.2 (ArH); exact mass calcd. for $C_{18}H_{23}NO$: 269.1816; found: 269.1780.

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