was compound **19**, tetraphenylphosphonium bromide.

Whether this new series of compounds, active also against American trypanosomiasis,[16] visceral leishmaniasis,[17] and malaria,[18] will provide the "lead" which will culminate in new drugs effective against the African trypanosomes remains to be seen. Relatively little is known of the biological activity of phosphorus as the phosphonium salt. It is known that phosphorus as phosphates is required by virtually all forms of life, have more known functions than any other mineral element within the human body, and is perhaps the single most important mineral constituent required for cellular activity. On the other hand, phosphorus in the white or yellow elemental form is very toxic, with injury occurring to the gastrointestinal tract, liver, muscles, myocardium, kidney, and central nervous system. Elemental phosphorus in the red, granular, nonabsorbable form is essentially inert to the mammalian system. In the present studies, toxicity was observed at the upper dose levels with all compounds except compound **10** (Table I). It should be noted, however, that curative activity was seen at lower doses without observable toxic side effects. For example, compound **4** was curative at a dose level of 26.5 mg/kg. Toxicity was not seen until the drug level was increased eightfold, i.e., to 212 mg/kg. Further studies seem warranted in an attempt to find new and better chemotherapeutic agents for inclusion in the armamentarium required for the control of African trypanosomiases.

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Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepines

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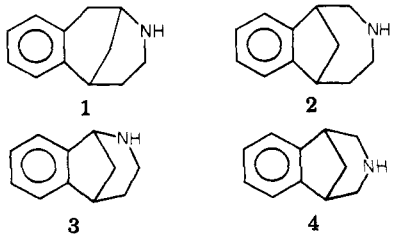
2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepine (**4**) has been synthesized from 2,3-dioxobenzonorbornene. Oxidative cleavage of the diketone to *cis*-1,3-indandicarboxylic acid, followed by closure to the corresponding anhydride, conversion to the imide, and lithium aluminum hydride reduction, gave **4**. Compound **4** and its N-derivatives show no analgesic activity in the mouse hot-plate assay and little antagonist activity in a tail-flick assay.

Recently there has been much interest in the synthesis and properties of potential analgesics having a "simplified" morphine ring system. The morphine-type analgesic activities of the 6,7-benzomorphan **1**[1] (ED_{50} = 10.2 mg/kg),



1 **2** **3** **4**

benzazocine **2**[2] (ED_{50} = 4.9 mg/kg), and *B*-norbenzomorphan **3**[3] (reported as one-third the activity of codeine) and their respective derivatives prompted us to investigate the structurally related compound 2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (**4**) to see if the change in the N position would dramatically affect its pharmacologic activity. We report the synthesis and analgesic testing results of several members of ring system **4**.

Chemistry. The key to the synthesis of **4** was the preparation of the heretofore unknown *cis*-1,3-indandicarboxylic acid (**8**). Our initial approach, which involved oxidative cleavage of benzonorbornadiene to **8**, was unsuccessful. Thus, ozonolysis of benzonorbornadiene[4] using a variety of solvents and workup procedures resulted mainly in the isolation of intractable material. Other traditional oxidizing methods including neutral per-

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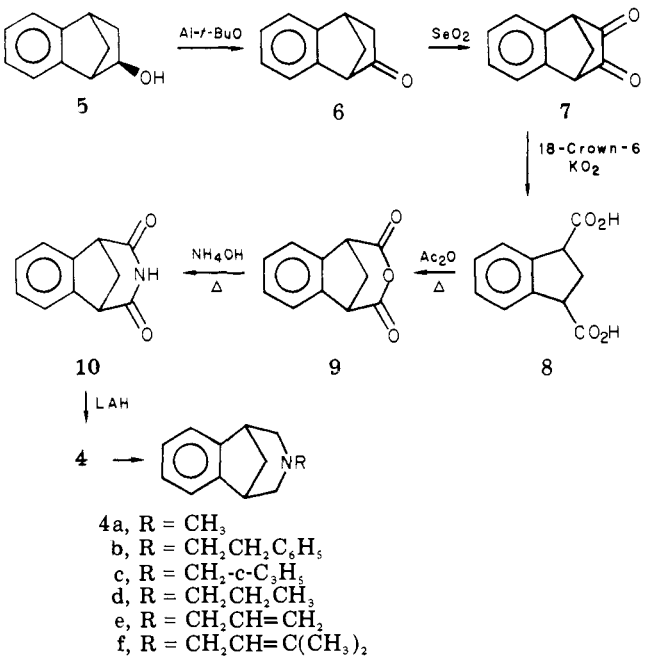
Scheme I



4a, R = CH_3
b, R = $CH_2CH_2C_6H_5$
c, R = CH_2-c-C_3H_5
d, R = $CH_2CH_2CH_3$
e, R = $CH_2CH{=}CH_2$
f, R = $CH_2CH{=}C(CH_3)_2$

manganate[5] and permanganate and 18-crown-6[6] were also unsuccessful, as were attempts to oxidatively cleave *cis*-2,3-dihydroxybenzonorbornane[7] using conventional reagents such as periodate[8] and permanganate.[9] In the usual case, these procedures resulted in overoxidation of the starting material.[10] The stepwise oxidation illustrated in Scheme I finally provided the desired diacid 8 in 90% yield from 7.

The synthesis of 2,3-dioxobenzonorbornene (7) involved a series of known procedures. Benzonorbornadiene, obtained from *o*-fluorobromobenzene,[4] was converted to the acetate by addition of acetic acid.[11] Saponification gave *exo*-benzonorborneol (5),[11] which was oxidized to benzonorborneone (6)[12] with aluminum *tert*-butoxide.[13] Oxidation of 6 with SeO_2 provided diketone 7.[14]

Diacid 8 was prepared cleanly and in high yield by treatment of 7 with potassium superoxide and 18-crown-6.[15] Anhydride 9, obtained by heating 8 in acetic anhydride,[16] was dissolved in NH_4OH and heated[17] to provide imide 10. Reduction of 10 with LAH[18] gave the parent methanobenzazepine 4, which was alkylated with the appropriate halide or methylated by formic acid–formaldehyde.[2]

Pharmacology and Conclusions. Analgesic potencies were determined on aqueous solutions of the oxalate salts by the Eddy hot-plate method[19] on mice. Compound **4e** has slight antinociceptive activity: ED_{50} (sc) = 15.6 mg/kg; LD_{50} (sc) = 47 mg/kg (codeine ED_{50} = 5.8 mg/kg). None of the other compounds showed significant analgesic activity, and all compounds except 4b are very toxic.

Since agonist–antagonists show little activity in the hot-plate assay,[20] three of the derivatives (**4c–e**) were tested using a tail-flick antagonist assay. Compound **4c** acts like an antagonist of morphine introduced at an ED_{80} dose level. It antagonizes the ED_{80} of morphine ca. 58% at 0.3 mg/kg. Compound **4d** antagonizes the ED_{80} of morphine ca. 47% at 1.0 mg/kg and **4e** ca. 56% at 3.0 mg/kg. Dose–response curves in these assays were erratic. These tests showed that **4c–e** had only weak antagonist activity, suggesting that the compounds are not strong agonist–antagonists.

Clearly, the change in the nitrogen position in proceeding from 3 to 4 manifests itself by an almost total loss of antinociceptive activity and a marked increase in toxicity.

Experimental Section

Melting points were taken in capillary tubes and are uncorrected. Elemental analyses (indicated by C, H, and N when within ±0.4% of calculated values) were performed by Dr. Franz Kasler of the University of Maryland. IR (Beckman IR-8 or Perkin-Elmer 281) and NMR (Varian XL-100, EM-360, HR-220, or A-60) spectra are consistent with assigned structures.

***cis*-1,3-Indandicarboxylic Acid (8).** A solution of 3.6 g (21 mmol) of 7, 0.24 g (0.91 mmol) of 18-crown-6, 6.1 g (86 mmol) of finely ground potassium superoxide, and 100 mL of dry benzene (distilled from CaH_2) was protected from moisture and stirred overnight at room temperature. The mixture was poured cautiously into 109 mL of water. The aqueous phase was separated, acidified with 5% HCl, and extracted with four 50-mL portions of ether. Ether extracts were dried and concentrated in vacuo, and the resulting yellow solid recrystallized from xylene to give 3.9 g (90%) of 8: mp 192–192.5 °C; IR (KBr) 3800–2100, 1710, 1480, 1420 cm^{-1}; NMR (acetone-d_6) δ 2.7 (2 H, m, methylene), 4.1 (2 H, m, benzylic), 7.2–7.8 (4 H, m, aromatic). Anal. ($C_{11}H_{10}O_4$) C, H.

1,3-Indandicarboxylic Acid Anhydride (9). A sample of 8 (10.8 g, 52.4 mmol) was treated with 200 mL of acetic anhydride and heated at 100 °C for 1 h. Solvent was removed in vacuo and the resulting oil distilled [210–230 °C bath (0.2 mm)] to give a yellow solid, which was recrystallized from CCl_4 to give 9.5 g (96%) of white needles: mp 102–102.5 °C; IR ($CDCl_3$) 1815, 1770, 1750 cm^{-1}; NMR ($CDCl_3$) δ 2.5–3.0 (2 H, m, methylene), 4.0–4.5 (2 H, m, benzylic), 7.1–7.6 (4 H, m, aromatic). Anal. ($C_{11}H_8O_3$) C, H.

1,3-Indandicarboxylic Acid Imide (10). A sample of **9** (9.5 g, 51 mmol) was dissolved in 140 mL of concentrated NH_4OH. Excess ammonia and water were removed in vacuo, leaving an oily residue. The oil was distilled in a Kugelrohr [210–250 °C (0.5 mm)], and the resulting brown solid was recrystallized from CCl_4–acetone to give 2.9 g (31%) of colorless cubes of **10**: mp 230–231.5 °C; IR ($CDCl_3$) 3380, 1715, 1230, 1105 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (2 H, m, methylene), 4.0 (2 H, m, benzylic), 7.1–7.7 (4 H, m, aromatic). Anal. ($C_{11}H_9NO_2$) C, H, N.

2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepine (4) Oxalate. A solution of 3.6 g (20 mmol) of 10 in 88 mL of dry THF (distilled from CaH_2) was added dropwise to a stirred, refluxing solution of 2.0 g (53 mmol) of LAH in 175 mL of dry THF. The mixture was refluxed for 2 h, cooled, and treated sequentially with 1.8 mL of water, 1.8 mL of 15% NaOH, and 5.4 mL of water. Solids were filtered and washed well with ether, and the filtrates were combined and concentrated in vacuo. The resulting oil was dissolved in ether and extracted with dilute HCl. The acidic extract was made basic by addition of dilute NaOH and extracted with ether. Ether extracts were dried ($MgSO_4$), concentrated, and bulb to bulb distilled [90 °C bath (0.1 mm)], to give 2.3 g (73%) of colorless **4**. The free amine was dissolved in ether and treated with an ethereal solution of oxalic acid to provide a white precipitate, which was recrystallized from methanol–acetone to give 3.4 g (68%) of 4 oxalate: mp 229–231 °C; IR (KBr) 2300–3300, 1755, 1650, 1415 cm^{-1}; NMR (D_2O) δ 1.9–2.2 (2 H, m, bridging methylene), 3.0–3.3 (6 H, m, benzylic and methylene), 7.2 (4 H, m, aromatic). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

3-Methyl-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4a) Oxalate. A mixture of 0.40 g (2.5 mmol) of 4, 0.46 mL of formic acid, and 0.46 mL of 40% formaldehyde was heated at 100 °C for 3 h, cooled, treated with 13.8 mL of 15% NaOH, and extracted with four 15-mL portions of CH_2Cl_2. Combined organic extracts were dried ($MgSO_4$), concentrated, and distilled [70–80 °C bath (0.1 mm)] to give white solid 4a (0.31 g, 71%), which was converted to the oxalate: mp 204–206 °C (MeOH–acetone). Anal. ($C_{14}H_{17}NO_4$) C, H, N.

3-(2-Phenylethyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4b) Oxalate. To 0.50 g (3.1 mmol) of 4 and 1.07 g (7.7 mmol) of K_2CO_3 in 15 mL of dry DMF (distilled from CaH_2) was added 0.60 g (3.2 mmol) of 2-phenylethyl bromide, and the mixture was stirred overnight at 100 °C. After cooling the mixture, the DMF was removed in vacuo, and the residue was treated with 35 mL of $CHCl_3$ and 16 mL of water. The organic layer was

separated, washed with five 30-mL portions of water, dried ($MgSO_4$), concentrated, dissolved in ether, filtered, and treated with ethereal oxalic acid solution to provide **4b** oxalate (0.75 g, 68%): mp 223–225 °C (MeOH–CCl_4). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

3-(Cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine. Cyclopropylcarbonyl chloride (1.58 g, 15.1 mmol) was added dropwise to a stirred, ice-cooled mixture of 1.0 g (6.3 mmol) of **4**, 20 mL of methanol, 3 mL of water, and 2.0 g (14.5 mmol) of K_2CO_3. The mixture was stirred for 3 h, concentrated in vacuo, and treated with 42 mL of water, 28 mL of benzene, and 14 mL of 1-butanol. The organic layer was separated, washed with two 40-mL portions of 3 N HCl and two 40-mL portions of water, concentrated, dissolved in benzene, dried ($MgSO_4$), concentrated, and distilled [180 °C bath (0.1 mm)], to provide 0.60 g (42%) of 3-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine: IR (thin film) 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.4–2.5 (7 H, m, bridge methylene and cyclopropyl), 2.8–3.7 (4 H, m, methylene), 3.9–4.5 (2 H, m, benzylic), 7.2 (4 H, s, aromatic). Anal. ($C_{15}H_{17}NO$) C, H, N.

3-(Cyclopropylmethyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4c) Oxalate. A solution of 0.50 g (2.2 mmol) of 3-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine in 6 mL of dry THF (distilled from CaH_2) was added dropwise to 0.26 g (6.9 mmol) of LAH in 10 mL of dry THF. The mixture was refluxed 3 h, cooled, hydrolyzed with 0.5 mL of water in 9.5 mL of THF, filtered, dried ($MgSO_4$), concentrated, and bulb to bulb distilled [150 °C (0.2 mm)]. Anal. ($C_{15}H_{19}N$) C, H, N. The free amine was converted to the oxalate (0.49 g, 74%): mp 147–148 °C (MeOH–acetone); NMR (D_2O) δ 0.3–0.9 (5 H, m, cyclopropyl), 1.9–2.5 (2 H, m, bridging methylene), 2.9–3.0 (2 H, m, CH_2 cyclopropyl), 3.3–3.7 (6 H, m, methylene and benzylic), 7.4 (4 H, s, aromatic).

3-Propyl-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4d) Oxalate. To 0.50 g (3.1 mmol) of **4** and 1.1 g (7.9 mmol) of K_2CO_3 in 8 mL of dry DMF (distilled from CaH_2) was added 0.41 g (3.3 mmol) of *n*-propyl bromide. The mixture was refluxed 2 h, cooled, and filtered. Solids were washed with $CHCl_3$ and the combined filtrates concentrated in vacuo. The resulting oil was bulb to bulb distilled [150 °C (0.2 mm)]. Anal. ($C_{14}H_{19}N$) C, H, N. The free amine was converted to the oxalate (0.41 g, 45%): mp 170.5–172.0 °C (MeOH–CCl_4).

3-Allyl-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4e) Oxalate. To 0.90 g (4.5 mmol) of **4** and 1.44 g (17.1 mmol) of $NaHCO_3$ in 30 mL of absolute EtOH was added 0.70 g (5.8 mmol) of 3-bromopropene. The mixture was stirred at reflux for 24 h, cooled, and filtered. Solids were washed with EtOH, and combined filtrates were concentrated and bulb to bulb distilled [150 °C (0.2 mm)]. Anal. ($C_{14}H_{17}N$) C, H, N. The free amine was converted to the oxalate (1.18 g, 72%): mp 135–136 °C (MeOH–acetone).

3-(3-Methyl-2-butenyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (4f) Oxalate. To 0.50 g (3.1 mmol) of **4** in 25 mL of dry DMF (distilled from CaH_2) were added 0.47 g (3.2 mmol) of 1-bromo-3-methyl-2-butene and 0.40 g (4.7 mmol) of $NaHCO_3$. The mixture was refluxed 4 h, cooled, and filtered through Celite. The filter cake was washed with EtOH, and the combined filtrates were concentrated and converted to the oxalate (0.54 g, 54%): mp 190–191.5 °C (MeOH–CCl_4). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

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