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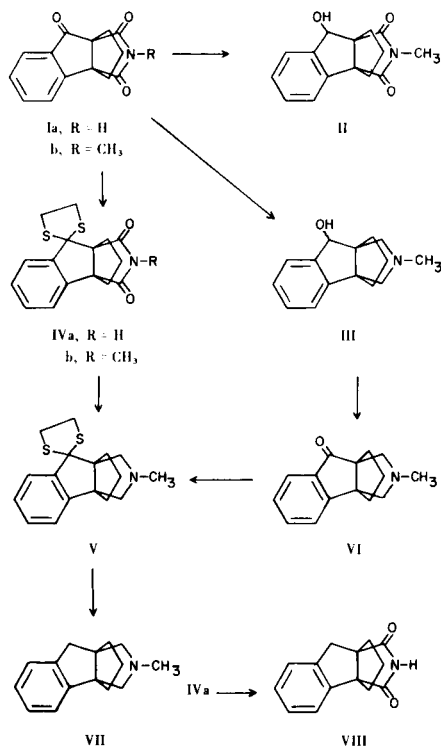
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Sodium borohydride reduction of 3-methyl-2,3-dioxo-7,8-benzo-3-aza[3.3.3]propellane-6-one (Ib) gave 2,4-dioxo-3-methyl-7,8-benzo-3-aza[3.3.3]propellane-6-ol, while lithium aluminum hydride reduction gave 3-methyl-7,8-benzo-3-aza[3.3.3]propellane-6-ol, which on oxidation, gave the corresponding ketone. This ketone formed the corresponding thioketal upon reaction with 1,2-ethanedithiol. Raney nickel desulfurization of the thioketal provided 3-methyl-6,7-benzo-3-aza[3.3.3]propellane. The same compound was also obtained in poor yield by forming the thioketal of Ib followed by lithium aluminum hydride reduction and Raney nickel desulfurization of the product. Desulfurization of the thioketal of Ib gave 2,4-dioxo-6,7-benzo-3-aza[3.3.3]propellane.

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The availability of 2,4-dioxo-7,8-benzo-3-aza[3.3.3]propellane-6-one (Ia) (2) suggested a study of its reduction to related azapropellanes. Compound Ia was prepared in good yields by addition of cyanide ion to 2-carbamoyl-3-(γ -chloropropyl)-1-indenone followed by acid hydrolysis of the resultant imino-pyrrolido derivative. Treatment of Ia under reflux with lithium aluminum hydride (four molar excess) afforded a white solid, the infrared spectrum of which revealed the absence of the succinimide ring, but showed two carbonyl peaks indicating that incomplete reduction of the carbonyl function had occurred. It is well known that the reduction of unsubstituted amides and imides is hindered by complex formation with the lithium aluminum hydride. To avoid this complication, we studied the reduction of the *N*-methyl derivative, Ib, (Scheme I),

Scheme I



since Ginsburg, *et al.*, (3) reduced some keto-*N*-methylsuccinimides of related structure, and found that the ketone function could be reduced.

Reduction of Ib with sodium borohydride in ethanol resulted in a single alcohol, II, in excellent yield. This alcohol could not be converted to its tosylate, probably because of the high degree of steric hindrance. Attention, therefore, was turned to the initial reduction of the succinimide carbonyl functions. Treatment of ketosuccinimide Ib with lithium aluminum hydride afforded the expected aminoalcohol III. Attempts to prepare the tosylate of this alcohol, like II, were unsuccessful and again resulted in quantitative recovery of the starting material. Attempted hydrogenolysis of the benzylic alcohol III over 10% palladium/carbon were also unsuccessful.

Since the alcohol functions in II and III proved resistant to reduction a further approach to the *N*-methylazapropellane VII was formulated. This approach consisted of protecting the ketone function with 1,2-ethanedithiol, reduction of the succinimide and finally treatment of the thioketal with Raney nickel. Further, acid treatment of the reduced thioketal would yield the ketoamine IV, a compound of possible biological interest (4).

Treatment of Ib with 1,2-ethanedithiol yielded the thioketal IVb in high yield as a colorless crystalline compound. Lithium aluminum hydride reduction of IVb afforded a light green oil which showed three constituents by tlc, but without further purification was subjected to Raney nickel desulfurization, and the resultant oil chromatographed on a silica gel column, giving the desired product VII. This azapropellane could also be obtained in improved yield by manganese dioxide oxidation of the aminoalcohol III to the ketone VI, followed by thioketal formation to V and its subsequent treatment with Raney nickel to form VII.

The azapropellane VII represents a new ring system and the first example where a single aromatic ring is fused to an azapropellane system. Thompson (5) reported an example, triptindan, in which three aromatic rings are fused to a carbocyclic propellane system.

Encouraged by the stability of the propellanes described above to the desulfurization conditions, the thioketal IVa was prepared from the ketosuccinimide Ia; desulfurization of IVa afforded the succinimide VIII. Succinimides such as VIII may be expected to exhibit anticonvulsant activity. Wagner and Rudzik (6) have examined the biological activity of succinimides of the [4.4.3]propellane family and have found that 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide is an anticonvulsant of low toxicity. They considered steric hindrance an important factor in the activity of such compounds. Crowding on either or both sides of the succinimide ring resulting in decreased activity. Compounds VIII, VI, and III were submitted to Bristol Laboratories, Syracuse, New York, for biological screening. These compounds were essentially devoid of anticonvulsant activity (7).

EXPERIMENTAL

Melting points were determined in open capillary tubes in a Mel-Temp heating block apparatus and are corrected. A Perkin-Elmer Model 137 infracord Spectrophotometer was used to record all spectra in the range 2.5 to 15 μ . Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505 Recording Spectrophotometer in 95% ethanol. The nuclear magnetic resonance spectra were obtained in specified solvents with a Varian Associates Model A-60 NMR Spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in parts per million downfield from tetramethylsilane. Coupling constants (J) are given in cycles per second. The abbreviations s, d, t, p, and m indicate singlet, doublet, triplet, quartet, and multiplet respectively. The nmr data are given by listing the chemical shift, number of protons (when different from that indicated in the assignment), multiplicity, and coupling constants. Mass spectra were obtained with an AEI MS-9 mass spectrophotometer (ionizing energy 70 ev, 100 μ A). We are indebted to the National Science Foundation for an instrument grant (GP-5234) for the purchase of the mass spectrometer used in this work. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

2,4-Dioxo-3-methyl-7,8-benzo-3-aza[3.3.3]propellan-6-ol (II).

A solution of 255 mg. (1.0 mmole) of Ib (2) in 25 ml. of absolute ethanol was added to a solution of 37.8 mg. (1.0 mmole) of sodium borohydride in 25 ml. of absolute ethanol. The reaction mixture was stirred for 12 hours at room temperature, then 10 ml. of water was added and the solution brought to pH 7 by adding 20% sulfuric acid dropwise. The solution was concentrated and extracted with chloroform (3 x 25 ml.). The combined extracts were washed with 5% sodium hydroxide (3 x 30 ml.), and with saturated salt solution (3 x 30 ml.). Each aqueous layer was washed with an additional portion of chloroform. The combined chloroform extracts (130 ml.) were dried and evaporated yielding 252 mg. (98%) of the product as a colorless oil, which solidified after storing overnight at reduced pressure. Recrystallization from ether-hexane gave a solid, m.p. 52-54° (sublimed at 150°; 0.1 mm. Hg), which showed only one spot on tlc: ir γ max (liquid film): 2.92 (broad, OH), 5.64 and 5.83 μ (imide, asymmetric and symmetric stretch); uv: γ max (nm) 213 (ϵ 7,700), 256 (broad, ϵ 750), 266 (shoulder, ϵ 700), 274 (ϵ 500); nmr (60 Mcps): δ 7.1-7.7 (m, aromatic), 5.37 (s, C₆ proton) 4.72 (broad, OH), 2.9 (s, NCH₃), and 1.1-2.8 ppm (m; methylene protons).

Anal. Calcd. for C₁₅H₁₅NO₃: C, 70.02; H, 5.88. Found: C, 69.90; H, 5.92.

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

A solution of 4.47 g. (0.0176 mole) of Ib in 250 ml. of THF (freshly distilled over LAH) was added slowly to a suspension of 5.21 g. (0.14 mole) of LAH in 200 ml. of THF. The mixture was refluxed for 7 days, cooled in an ice-bath, and 40 g. of sodium sulfate decahydrate was added in portions and stirred overnight. The solution was filtered, dried and evaporated, yielding 4.0 g. (99.7%) of a yellow, viscous oil. The product was chromatographed on neutral alumina (activity IV) and eluted with 50% benzene-ether to afford a colorless oil, b.p. 70-72°/0.01 mm., N_D²⁷ 1.715; ir: γ max 3.0 (OH), 6.24 μ (C=C); nmr (60 Mcps): δ 6.84-7.5 (m, aromatic), 4.88 (s, C₆ proton), 4.1 (broad, OH), 2.33-2.93 (4H, m, NCH₂), 2.17 (s, NCH₃), and 1.2-2.17 ppm (m, methylene protons).

Anal. Calcd. for C₁₅H₁₉NO: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.56; N, 6.28.

The hydrochloride was formed by bubbling dry hydrogen chloride gas into ethereal solution of the amine. Recrystallization (with difficulty) from ethyl acetate-methanol gave white microcrystals of III hydrochloride, m.p. 223-224°.

Anal. Calcd. for C₁₅H₂₀ClNO: C, 67.81; H, 7.59. Found: C, 67.76; H, 7.74.

Spiro[1',3'-dithiolane-2',6-(2,4-dioxo-3-methyl-7,8-benzo-3-aza[3.3.3]propellane)] (IVb).

A solution of 280 mg. (1.1 mmoles) of Ib in 1 ml. of boron trifluoride-etherate and 0.5 ml. of 1,2-ethanedithiol was stirred for 24 hours at room temperature. A white solid precipitated after 2 hours, then 0.5 ml. of 5% sodium hydroxide was added, the solution stirred for 5 minutes and then 5 ml. of water added. The clear solution was extracted with chloroform (8 x 8 ml.), the combined extracts washed with water (3 x 60 ml.), dried and evaporated yielding 333 mg., (91.5%) of a white solid. Two recrystallizations from ethyl acetate gave white hexagonal plates, m.p. 177.2-178°; ir: λ max 2.88 (overtone of bands in carbonyl region), 5.64 and 5.87 μ (imide, asymmetric and symmetric stretch); nmr (60 Mcps): 7.16-7.57 (m; aromatic), 3.33-3.7 (4H, m, SCH₂), 2.99 (s, NCH₃), and 1.4-2.75 ppm (m; methylene protons).

Anal. Calcd. for C₁₇H₁₇NO₂S₂: C, 61.63; H, 5.17; N, 4.23; S, 19.35. Found: C, 61.71; H, 5.14; N, 4.51; S, 19.02.

3-Methyl-7,8-benzo-3-aza[3.3.3]propellan-6-one (VI).

A solution of 1.5 g. (6.5 mmoles) of III in 150 ml. chloroform was stirred with 15 g. of manganese dioxide, b (active) (Winthrop Laboratories, New York, N. Y.) at room temperature for 44 hours. The solution was filtered, dried and evaporated to yield 1.5 g. (100%) of a light-yellow oil; ir: λ max 5.84 μ (carbonyl); nmr (60 Mcps; carbon tetrachloride): δ 7.2-7.8 (m; aromatic), 2.24-3.17 (4H, m, NCH₂), 2.16 (s, NCH₃), and 1.4-2.08 ppm (m, methylene protons). The hydrochloride, made by passing dry hydrogen chloride into an ethereal solution of the aminoketone, was recrystallized from methanol as hygroscopic white prisms, m.p. 212° (sublimes). The sublimation is complete at 274°, however, the sublimation range depends on the rate at which the temperature is raised. The same hydrochloride was prepared (99%) by manganese dioxide oxidation of III-HCl using the above procedure: uv (of hydrochloride): λ max (nm) 210 (ϵ , 17,000), 251 (ϵ , 8,400), 295 (ϵ , 1,450). Addition of a drop of 5% sodium hydroxide solution to the solution resulted in the disappearance of the absorption at 210 μ ; the rest of the spectrum remained unaltered.

Anal. Calcd. for $C_{15}H_{18}ClNO$: C, 68.31; H, 6.88; Cl, 13.44; N, 5.31. Found: C, 68.38; H, 7.00; Cl, 13.54; N, 5.46. Spiro[1',3'-dithiolane-2',6-(3-methyl-7,8-benzo-3-aza[3.3.3]propellane)] (V).

A solution of 422 mg. (1.86 mmoles) of VI (dried overnight over phosphorus pentoxide) in 3 ml. of boron trifluoride-etherate and 1 ml. of 1,2-ethanedithiol was stirred for 48 hours at room temperature. To the reaction mixture was added 40 ml. of water and the solution immediately made basic (pH 10) by adding sodium hydroxide pellets in portions. The aqueous solution was extracted with chloroform (5 x 25 ml.), and the combined extracts dried and evaporated, yielding 395 mg. (70.3%) of the product as a white solid. Repeated recrystallizations from 2-propanol gave white crystals of V, m.p. 119.5-120.5°; nmr (60 Mcps): δ 6.84-7.5 (m; aromatic), 3.15-3.67 (4H, m; SCH₂), 2.4-3.1 (4H, m; NCH₂), 2.25 (s; NCH₃), and 1.0-2.1 ppm (m; methylene protons).

Anal. Calcd. for $C_{27}H_{21}NS_2$: C, 67.44; H, 6.98. Found: C, 67.26; H, 7.13.

3-Methyl-6,7-benzo-3-aza[3.3.3]propellane (VII).

A. A solution of 330 mg. (1.0 mmole) of IVb in 15 ml. of THF (freshly distilled over LAH) was added slowly to a suspension of 300 mg. (8 mmoles) of LAH in 10 ml. of THF. The mixture was refluxed for 7 days, cooled with ice and 5 g. of sodium sulfate monohydrate added. The white precipitate was filtered and the filtrate dried and evaporated, yielding 306 mg. of a light green oil, which showed three spots on tlc (silica plates; 1:9 methanol-chloroform). This crude product was dissolved in 10 ml. of methanol and the solution added to a suspension of ca. 5 g. of previously well washed Raney nickel (W. R. Grace and Co., Chattanooga, Tenn.) in 50 ml. of methanol. The reaction mixture was refluxed with stirring for 2 days. The hot reaction mixture was carefully filtered and the solvent removed to yield 150 mg. of a light green oil. Column chromatography (neutral alumina, activity IV; eluant: hexane) of the oil provided 41 mg. of the product as a colorless oil; ir: λ max 3.4, 3.6 (methylene), 6.7 (benzene ring), 6.9 (methylene) and 8.6 μ (tertiary amine); nmr (60 Mcps; carbon tetrachloride) δ 6.75-7.25 (m; aromatic), 2.3-3.1 (6H, m; C₂C₄, C₈ protons), 2.15 (s; NCH₃), and 1.3-2.0 ppm (m; C₉, C₁₀, C₁₁ protons); M⁺, 213.1509, C₁₅H₁₉N requires 213.1517. In the mass spectrum the parent peak at m/e 213 was also the base peak of spectrum.

The picrate was made by the usual method (8). Recrystallization from methanol afforded yellow needles, m.p. 210-211.5°.

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 57.25; H, 5.25; N, 12.74.

B. Three g. of commercially available Raney nickel (W. R. Grace and Co., Chattanooga, Tenn.) was weighed into 95% ethanol, washed well and suspended in 30 ml. of ethanol. A solution of 130 mg. (0.43 mmole) of V in 5 ml. of 95% ethanol was added, and the suspension refluxed with vigorous stirring for 48 hours. The hot reaction mixture was carefully filtered and the solvent removed to yield 113 mg. of a mixture of a white solid and a colorless oil. The mixture of reaction products was extracted with pentane (2 x 20 ml.). Evaporation of the dried extracts yielded 60 mg. (65.5%) of the product as a colorless oil, which was further purified by chromatography (neutral alumina, activity IV; eluant: hexane). The oil was identical in all respects to that obtained above, including an identical picrate.

Spiro[1',3'-dithiolane-2',6-(2,4-dioxo-7,8-benzo-3-aza[3.3.3]propellane)] (IVa).

A mixture of 1.45 g. (6.0 mmoles) of Ia, 1.5 ml. of 1,2-ethanedithiol, and 5 ml. of boron trifluoride-etherate was stirred for 24 hours at room temperature. The ketosuccinimide dissolved as the reaction progressed and a clear solution was obtained after 1 hour. Further stirring for 2 hours resulted in a white precipitate. Stirring was stopped after 24 hours and 50 ml. of 5% sodium hydroxide solution added to the reaction mixture. The aqueous suspension was immediately extracted into chloroform (5 x 25 ml.), the organic layer dried and evaporated to yield 1.90 g. (100%) of a white solid. Two recrystallizations from methanol gave long white needles of IVa, m.p. 212.5-213°; ir: λ max 2.7-3.0 (NH), 5.65 and 5.83 μ (imide carbonyl).

Anal. Calcd. for $C_{16}H_{15}NO_2S_2$: C, 60.53; H, 4.76; N, 4.41; S, 20.20. Found: C, 60.72; H, 4.81; N, 4.59; S, 20.26.

2,4-Dioxo-6,7-benzo-3-aza[3.3.3]propellane (VIII).

Twenty g. of commercial Raney nickel was weighed into absolute ethanol, washed well and suspended in 125 ml. of absolute ethanol. To the above suspension was added 1.9 g. (6.0 mmoles) of IVa and the reaction mixture refluxed for 36 hours. The hot reaction mixture was carefully filtered and the solid washed with additional absolute ethanol (6 x 40 ml.). Evaporation of the solvent afforded 1.04 g. (76%) of a hygroscopic white solid, which was recrystallized with difficulty from methanol to yield white microcrystals of VIII, m.p. 180.5-181.5°. Repeated recrystallizations raised the m.p. to 183.2-184°; ir: λ max 2.86-3.14 (NH), 5.65 and 5.85 μ (imide, asymmetric and symmetric stretch); uv: λ max (nm) 214 (ϵ , 9,300), 256 (shoulder, ϵ , 1,000), 263 (ϵ , 1,250), 269 (ϵ , 1,700), 275 (ϵ , 1,750); nmr (60 Mcps): δ 8.88-9.33 (m; NH), 7.0-7.7 (m; aromatic), 3.33 (2H, AB quartet, J_{AB} = 17 cps; C₈ protons), and 1.6-3.0 ppm (m; C₉, C₁₀, C₁₁).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.24; H, 6.07; N, 6.44.

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REFERENCES AND NOTES

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