The Synthesis of Some Benzo[4,5]cyclohept[1,2,3-*ij*]isoquinolines

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A facile synthesis and spectroscopic properties of various oxidation states of the novel benzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline system are described. The synthesis involves the condensation of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, or of its 10,11-dihydro derivative, with aminoacetaldehyde diethylacetal, followed by treatment of the resultant imines with polyphosphoric acid to afford the novel tetracyclic system in high yields.

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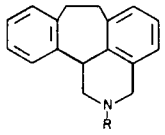
Previous reports from this Laboratory have described the syntheses and some biological properties of compounds containing the benzo[1,2]cyclohept[3,4,5-*de*]isoquinoline ring system **1** (1,2).



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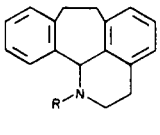

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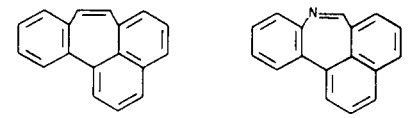
The *N*-ethyl derivative (**1**, R = Et) was of particular interest, exhibiting in animals, the profile of a minor tranquilizer (3) and we therefore wished to investigate the synthesis of compounds containing the hitherto unknown isomeric benzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline system (**2**).

A facile synthesis of various oxidation states of this novel system was ultimately achieved as illustrated in Scheme I. Condensation of 10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-5-one (**3**) with aminoacetaldehyde diethylacetal in refluxing toluene with boron trifluoride-etherate as catalyst afforded, in 48% yield, the Schiff's base **4**. Heating **4** with polyphosphoric acid gave 86% of the 7,8-dihydro form of the tetracyclic system, **5**. Ethylation of **5** produced the quaternary salt **6** which, on reduction with sodium borohydride gave the 1-ethyl-1,2,3,7,8,12b-hexahydro form of the system (**7**) in high yield.

The facile synthesis of the 7,8-dihydro derivative **5** prompted us to investigate the preparation of the fully unsaturated benzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline (**10**), in view of recent interest in the syntheses and properties of the analogous systems **11** (4-6) and **12** (7). Compound **10** was readily obtained (see Scheme 1) by the condensation of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**8**) with aminoacetaldehyde diethylacetal to afford **9** which was cyclized to **10** with polyphosphoric acid. The nmr spectrum of **10** is similar to that of the recently reported (4-6) carbon analog, benzo[4,5]cyclohepta[1,2,3-*de*]naphthalene (**11**). Thus the protons at positions 7 and 8 of **10** absorb as a singlet at 7.0 δ, while the similar non-aromatic



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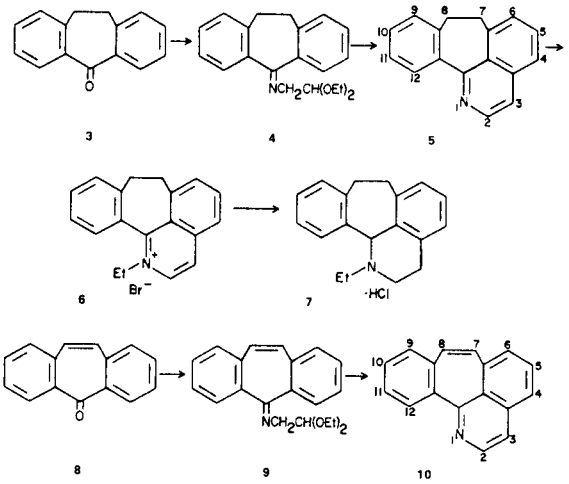
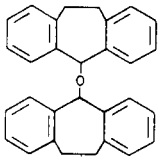
Scheme I



protons of **11** appear as a singlet at 6.5 δ (4,6).

A number of unsuccessful approaches to the synthesis

of the benzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline systems were investigated, based on acid-catalysed condensations of the 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylamine derivatives **15, 17** and **19** (see Scheme 2). Thus the reaction of **15**, and of **19**, with either concentrated sulfuric acid at 22° for 1 hour, or with polyphosphoric acid at 100° gave quantitative yields of the known ether **20** (8), while similar treatments of **17** afforded high yields of the primary amine **13**. Of the compounds illustrated



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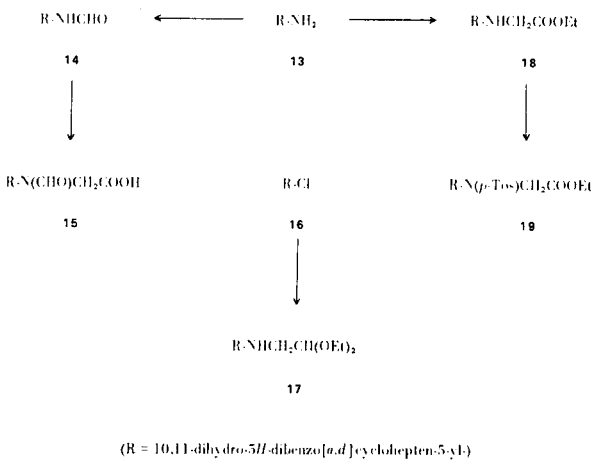
in Scheme 2, **15** and **17-19** are new compounds while the amine **13** (9), the formamide **14** (10) and the chloro derivative **16** (11) have been described previously.

Scheme 2



(R = 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl-)

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by the Ayerst Analytical Laboratory under the direction of Dr. G. Schilling. The nmr spectra were recorded on a Varian A-60-A instrument.

(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)acetaldehyde Diethylacetal (**4**).

To a refluxing solution of 10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5-one (**3**) (20.8 g., 0.1 mole) in toluene, in an apparatus fitted with a Dean-Stark trap, was added during 36 hours, a mixture of aminoacetaldehyde diethylacetal (40 g., 0.3 mole) and boron trifluoride etherate (14.1 g., 0.1 mole). The solution was washed with 10% aqueous sodium bicarbonate then with water. The toluene was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with benzene:ether (9:1) gave the product (15.5 g., 48%) as an oil, homogeneous by tlc; nmr (deuteriochloroform): δ 1.15 (6, t, J = 7 Hz, $(CH_3)_2$), 3.1 (4, m, CH_2CH_2), 3.6 (6, m, $(CH_2CH_3)_2$ and NCH_2), 4.9 (1, t, J = 5 Hz, $CH(OEt)_2$), 7.2-7.6 (8, m, benzene H's).

7,8-Dihydrobenzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline Hydrochloride (**5**·HCl).

The acetal **4** (13.0 g., 0.04 mole) was added to polyphosphoric acid (20 g.) and the mixture was stirred at 100° for 2 hours, then poured into a cold ammonium hydroxide solution. Extraction with ether gave a solid which was converted to the hydrochloride salt. Crystallization from ethanol-ether gave the product (8.0 g., 86%) as yellow crystals, m.p. 241-243°; λ max (ethanol): 340 mμ (ε = 7,600), 331 mμ (ε = 7,800), 302 mμ (ε = 6,460), 290 mμ (ε = 6,840), 228 mμ (ε = 32,400); nmr (deuteriochloroform): δ 3.33 (4, m, CH_2CH_2), 7.5 (8, m, aromatic H's at positions 3-6 and 9-12), 8.8 (1, m, aromatic H at position 2).

Anal. Calcd. for $C_{17}H_{13}N$·HCl: C, 76.25; H, 5.28; Cl, 13.23. Found: C, 76.43; H, 5.30; Cl, 13.23.

1-Ethyl-7,8-dihydrobenzo[4,5]cyclohept[1,2,3-*ij*]isoquinolinium Bromide (**6**).

To a solution of the isoquinoline **5** (6.0 g., 0.026 mole) in acetonitrile (100 ml.) was added ethyl bromide (12.0 g., 0.11 mole) and the mixture was heated at reflux for 48 hours. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with chloroform:methanol (85:15) gave the product (2.0 g., 23%), m.p. 175-176° (acetone-ether); λ max (ethanol): 294 mμ (ε = 7,300), 248 mμ (ε = 33,600); nmr (deuteriochloroform): δ 1.6 (3, t, J = 7 Hz, CH_2CH_3), 3.4 (4, m, CH_2CH_2), 5.0 (2, m, CH_2CH_3), 7.6-8.1 (7, m, aromatic H's at positions 4-6 and 9-12), 8.5 (1, d, J = 6.5 Hz, aromatic H at position 3), 9.4 (1, d, J = 6.5 Hz, aromatic H at position 2).

1-Ethyl-1,2,3,7,8,12b-hexahydrobenzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline Hydrochloride (**7**).

To the quaternary bromide **6** (6.0 g., 0.017 mole), dissolved in a mixture of methanol (200 ml.) and water (2 ml.), was added sodium borohydride (3.0 g.). The mixture was stirred at 22° for 18 hours, then the methanol was removed *in vacuo*. The residue was dissolved in 5% aqueous hydrochloric acid and washed with ether. The aqueous acidic phase was made alkaline with 10% aqueous sodium bicarbonate and extracted with ether to give a residue which was transformed to the product with hydrogen chloride. It was crystallized from methanol-acetone and had m.p. 230-232° (4.4 g., 95%); λ max (ethanol): 270 mμ (ε = 522), 264 mμ (ε = 613).

Anal. Calcd. for $C_{19}H_{21}N$·HCl: C, 76.11; H, 7.40; N, 4.67. Found: C, 75.93; H, 7.25; N, 4.44.

N-(2,2-Diethoxyethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-imine (**9**).

To a refluxing solution of 5*H*-dibenzo[*a,d*]cyclohepten-5-one (**8**) (2.0 g., 0.01 mole) in toluene (30 ml.), in an apparatus fitted with a Dean-Stark trap, was added during 24 hours, a mixture of aminoacetaldehyde diethylacetal (3.0 g., 0.022 mole) and boron trifluoride etherate (1 ml.). The solution was washed with 10% aqueous sodium bicarbonate, then with water. The toluene was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with benzene:ether (9:1) gave the product (1.65 g., 53%) as an oil, homogeneous by tlc; nmr (deuteriochloroform): δ 1.08 (3, t, J = 7 Hz, CH_3), 1.25 (3, t, J = 7 Hz, CH_3), 3.45 (2, q, J = 7 Hz, CH_2CH_3), 3.73 (2, q, J = 7 Hz, CH_2CH_3), 3.67 (2, m, NCH_2), 4.91 (1, t, J = 5.5 Hz, $CH(OEt_2)$), 6.91 (2, s, CH=CH), 7.35 (8, m, benzene H's).

Benzo[4,5]cyclohept[1,2,3-*ij*]isoquinoline Hydrobromide (**10**·HBr).

The diethylacetal **9** (2.0 g., 0.006 mole) was stirred with polyphosphoric acid (20 g.) at 100° for 2 hours, then poured onto crushed ice. The mixture was made alkaline with ammonium hydroxide and extracted with ether to give an oil which was treated with ethereal hydrogen bromide to give the product. It was crystallized from methanol to afford yellow crystals (1.3 g., 90%), m.p. 250-252°; λ max (ethanol): 238 mμ (ε = 38,000), 278 mμ (ε = 8,750), 301 mμ (ε = 8,880), 313 mμ (ε = 6,900), 322 mμ (ε = 5,150); nmr (DMSO): δ 7.0 (2, s, H's at positions 7 and 8), 8.33 (7, m, benzene H's), 9.26 (2, m, NCH=CH), 10.25 (1, m, $^{+}$NH).

Anal. Calcd. for $C_{17}H_{11}N$·HBr: C, 65.82; H, 3.90; N, 4.52; Br, 25.76. Found: C, 65.57; H, 4.21; N, 4.44; Br, 25.76.

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-*N*-formylglycine (**15**).

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)formamide (**14**) (10) (0.47 g., 0.0019 mole) was dissolved in benzene (40 ml.) and sodium hydride (90 mg. of a 57% suspension in mineral oil; 0.002 mole) was added. The mixture was heated at reflux for 12 hours, then ethyl bromoacetate (0.5 g., 0.003 mole) in benzene (5 ml.) was added and the heating was continued for 24 hours. The benzene was removed *in vacuo* and the residue was dissolved in a mixture of methanol (30 ml.), potassium hydroxide (225 mg.) and water (5 ml.). After heating at 100° for 1 hour, the methanol was removed and water was added. After removing neutral material by chloroform extraction, the aqueous solution was acidified with 10% aqueous hydrochloric acid and extracted with chloroform to afford a residue which was crystallized from benzene to give the product, m.p. 176-178° (280 mg., 48%); ir (chloroform): 1723 cm^{-1} (COOH), 1656 cm^{-1} (NCHO); nmr (deuteriochloroform): δ 3.2 (4, m, CH_2CH_2), 4.0 (2, s, NCH_2), 5.6 (1, s, NC*H*), 7.2 (8, m, benzene H's), 8.1 (1, s, NCOH), 11.0 (1, s, COOH).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.03; H, 5.81; N, 4.81.

(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylamino)acetaldehyde Diethylacetal Hydrochloride (**17**).

A solution of 5-chloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (**16**) (11) (20 g., 0.087 mole) and aminoacetaldehyde diethylacetal (11.7 g., 0.087 mole) in pyridine (75 ml.) was kept at 22° for 2 hours. The pyridine was evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with benzene:ether (9:1) afforded an oil which was treated with hydrogen chloride in ether to give the product (8.7 g., 32%), m.p. 218° dec. (absolute ethanol-ether).

Anal. Calcd. for $C_{21}H_{27}NO_2$·HCl: C, 69.69; H, 7.80; Cl, 9.80. Found: C, 69.44; H, 7.48; Cl, 9.86.

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-*N*-(*p*-toluenesulfonyl)glycine Ethyl Ester (**19**).

Treatment of compound **18** (500 mg., 0.002 mole) in pyridine (2 ml.) with *p*-toluenesulfonyl chloride (425 g., 0.0026 mole) at 22° for 48 hours afforded, after the usual work-up procedure, the product (550 mg., 72.5%), m.p. 141-142° (ether); ir (chloroform): 1748 cm^{-1} (COOEt), 1150 and 1340 cm^{-1} (SO_2).

Anal. Calcd. for $C_{26}H_{27}NO_4S$: C, 69.45; H, 6.05; N, 3.11. Found: C, 69.23; H, 6.10; N, 3.44.

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)glycine Ethyl Ester Hydrochloride (**18**·HCl).

To a solution of 5-amino-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (**13**) (9) (4.0 g., 0.019 mole) in dimethylformamide (150 ml.) was added ethyl bromoacetate (3.2 g., 0.019 mole) and potassium carbonate (1.4 g., 0.01 mole). The mixture was stirred at 80° for 13 hours, the precipitate discarded and the remaining solution evaporated to give a residue which was chromatographed on silica gel. Elution with benzene:ether (9:1) gave an oil which was treated with hydrogen chloride in ether to afford the product (3.6 g., 64%), m.p. 158-160° (2-propanol-ether); nmr (deuteriochloroform): δ 1.05 (3, t, J = 7 Hz, CH_2CH_3), 2.2 (1, s, NH), 3.27 (2, s, CH_2CO), 4.15 (2, q, J = 7 Hz, CH_2CH_3), 4.8 (1, s, NCH), 7.2 (8, m, benzene H's).

Anal. Calcd. for $C_{19}H_{21}NO_2$·HCl: C, 68.77; H, 6.68; Cl, 10.93. Found: C, 68.48; H, 6.54; Cl, 10.64.

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