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Studies on the Benzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline Ring System

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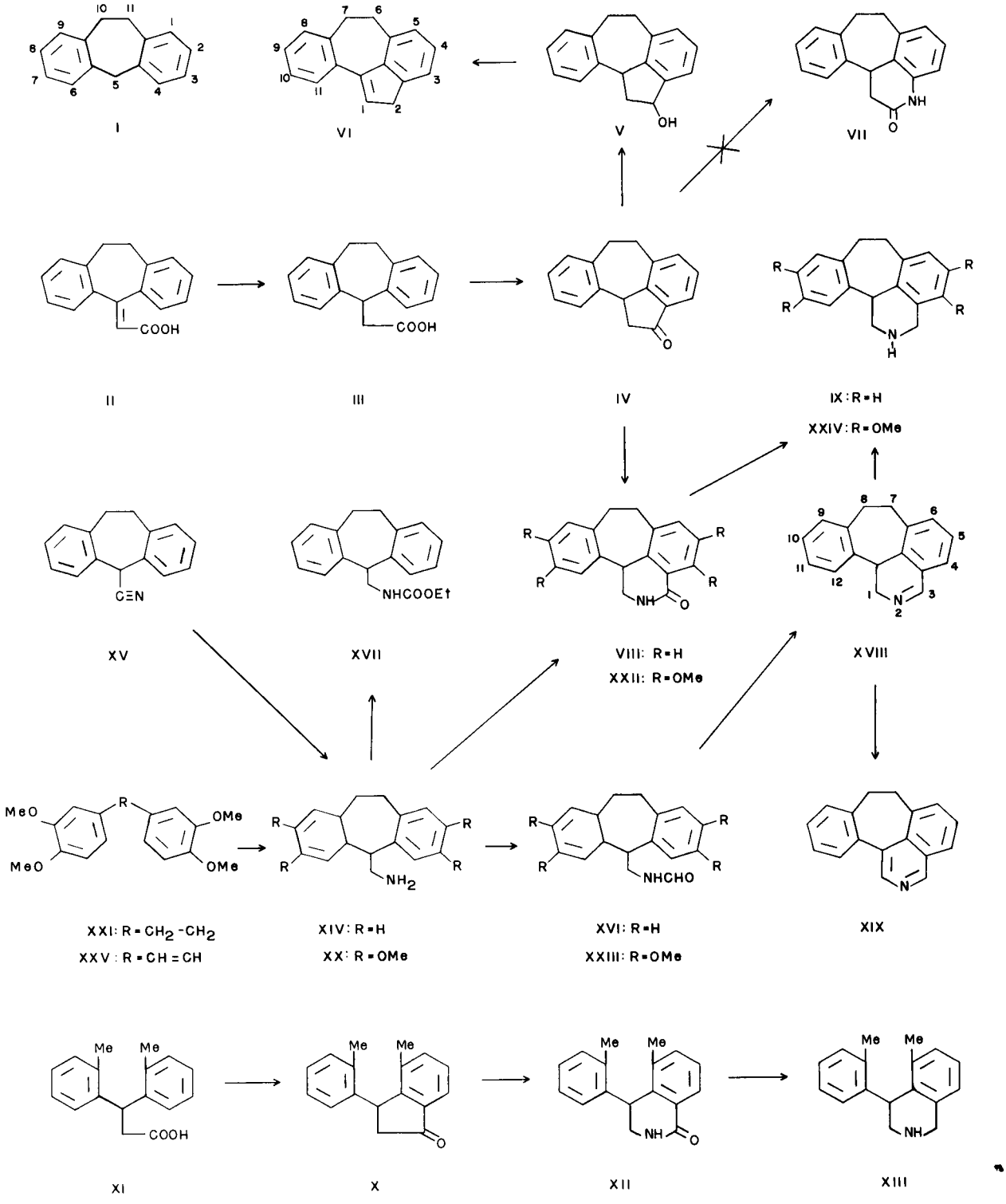
The syntheses of various oxidation states of the novel benzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline ring system is described. The ring system was obtained by the Schmidt rearrangement, with exclusive alkyl migration, of 1,6,7,11b-tetrahydro-2*H*-dibenz-[cd,h]azulen-2-one and by a Bischler-Napieralski reaction of suitable derivatives of 10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine. 4,5,10,11-Tetramethoxy derivatives of the new ring system were best prepared by a Pictet-Spengler reaction of the appropriate amine.

The 10,11-dihydrobenzo[a,d]cycloheptene ring system (I) is present in several compounds with interesting biological properties (1) and it was considered useful to elaborate this into other systems by fusing an additional ring, *e.g.*, between positions 4 and 5. We chose as starting material for this investigation, 10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-ylideneacetic acid (II) (2) which was smoothly hydrogenated to the saturated acid (III) using Raney Nickel and this latter compound cyclized with anhydrous hydrogen fluoride to give 1,6,7,11b-tetrahydro-2*H*-dibenz[cd,h]azulen-2-one (IV). It was converted to the oxime in high yield. Reduction of IV with lithium aluminum hydride, or preferably with sodium borohydride, gave 2-hydroxy-1,6,7,11b-tetrahydro-2*H*-dibenz[cd,h]azulene (V). Dehydration of this alcohol was accomplished by the elegant method of Traynelis, *et al.*, (3) giving the hydrocarbon (VI) in 96% yield. The 1,11b-position of the double bond was assigned on the basis of the n.m.r. spectrum which showed one vinylic proton as a triplet centered at 3.23 τ. The benzylic proton at the 2-position showed up as a doublet centered at 6.55 τ, and the four equivalent (4) protons of the ethylene bridge gave a sharp singlet at 6.91 τ. Since this work was completed, the synthesis of IV has been reported by van der Stelt, *et al.*, (5) from the acid chloride of III, and Galantay, *et al.*, (6) have reported the synthesis of the fully unsaturated 2*H*-dibenz[cd,h]azulen-2-one.

Attempts to realize the Beckmann rearrangement of the oxime of IV under various conditions were without success, but treatment of IV with sodium azide in molten trichloroacetic acid at 70° gave a single lactam in 80% yield. It was the isocarbostyril (VIII) rather than the expected carbostyril derivative (VII). The structure of VIII was assigned by examination of the ultra-violet spectra of its lithium aluminum hydride reduction product IX which was unchanged when taken as the hydrochloride salt, or, in the presence of sodium hydroxide. The formation of this isocarbostyril was not anticipated in view of the expected behaviour of cyclic aryl alkyl ketones in the Schmidt rearrangement (7) where aryl migration is usually observed. We considered that the high yield of the isocarbostyril (VIII) might have been due to the ridigity of the system (IV) imposing a configurational preference on an assumed iminodiazonium ion intermediate. Thus, the Schmidt rearrangement of the indanone (X) formally derived from IV by cleavage of the 6,7-bond and prepared from the acetic acid (XI) with anhydrous hydrogen fluoride, was studied using conditions analogous to those used for the rearrangement of IV. The isocarbostyril (XII) was obtained in 45% yield as the only isolable product, its structure being assigned on the basis of the ultra-violet spectra of its reduction product XIII. The Schmidt rearrangement of 3-phenyl-1-indanone, using different conditions from those above, has been reported (8) to proceed normally giving a 25% yield of 3,4-dihydro-4-phenylcarbostyril. The reaction of IV to give an isocarbostyril may be due to the non-sterospecific rearrangement of an iminium cation intermediate (9,10) where aryl migration would impose a high degree of strain in the transition state (11).

The Schmidt rearrangement of the azulenone (IV) represents the first synthesis of the benzo[1,2]-cyclohepta[3,4,5-d,e]isoquinoline nucleus and while the reaction proceeds in high yield it was apparent that the ring system would be more readily accessible through the Bischler-Napieralski reaction on a suitable substrate. The methylamine derivative (XIV) was thus prepared from the carbonitrile (XV)

by Raney Nickel catalyzed hydrogenation, or, by lithium aluminum hydride - aluminum chloride reduction (12). Attempts to prepare XIV by lithium aluminum hydride reduction of 10,11 - dihydro-5*H*-dibenzo[a,d]cycloheptene - 5 - carboxamide were unsuccessful due to an unusual dehydrating action of this reagent (13). The methylamine (XIV) was readily converted to the *N*-formyl (XVI) and *N*-carbethoxy (XVII) derivatives with formic - acetic anhydride (14) and with ethyl chloroformate, respectively. Cyclization of the *N*-formyl derivative (XVI) was best achieved with polyphosphoric acid, yielding the Schiff base (XVIII) which was reduced with sodium borohydride to give the tetrahydroiso-



quinoline derivative (IX) which had been obtained previously by reduction of the isocarbostyril (VIII). Cyclization of the *N*-carbethoxy derivative (XVII) gave the isocarbostyril (VIII), alternatively obtained by treating the methylamine (XIV) with phosgene and cyclizing the crude isocyanate with polyphosphoric acid. Attempts to obtain IX directly from XIV by the Pictet-Spengler reaction were unsuccessful.

The Schiff base (XVIII) was dehydrogenated with palladium on charcoal to yield the isoquinoline (XIX) whose ultra-violet spectrum was similar to that of 4-phenylisoquinoline (15) suggesting that a double bond had not been introduced into the 7,8-position. This was confirmed by the following sequence: the dehydrogenation product (XIX) was converted to its quaternary methiodide and this reduced with formic acid-triethylamine (16) to yield the corresponding *N*-methyltetrahydroisoquinoline derivative whose ultra-violet spectrum was virtually identical with that of the des-methyl derivative (IX).

Two methoxylated analogs of the novel ring system were prepared from 2,3,7,8-tetramethoxy-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XX), which was obtained in good yield from 3,3'-4,4'-tetramethoxydibenzyl (XXI) using a modification of the published procedure (17). Treatment of the isocyanate derived from XX with polyphosphoric acid gave the tetramethoxyisocarbostyril (XXII) in low yield. Attempted cyclizations of the formamide (XXIII) to the tetramethoxy Schiff base corresponding to XVIII using polyphosphoric acid, phosphorus oxychloride, or polyphosphoric ester (18) under a variety of conditions were unsuccessful. The tetramethoxylated ring system (XXIV) was best obtained, taking advantage of the activating effect of the 3-methoxyl group, through a Pictet-Spengler reaction of XX, in 39% yield. The required starting material for the tetramethoxy series, the dibenzyl (XXI) was obtained by catalytic hydrogenation of the stilbene (XXV) as described (19), or alternatively, by the hydrogen-transfer method of Braude, *et al.*, (20) (see Experimental). The dibenzyl (XXI) has also been prepared by a two-stage reduction of veratroin (17,21) but the method is impractical on a large scale. We have investigated the preparation of XXI by a direct Wurtz-type coupling of 3,4-dimethoxybenzyl chloride. The use of sodium, magnesium with ferric chloride (22), or phenyl lithium (23) as catalyst gave none of the desired product. Using magnesium alone (24), traces of XXI were obtained, and with sodium and tetraphenylethylene (22), a 37% yield was obtained, but this could not be reproduced on a large scale. Attempted preparation of the 10,11-dehydro analog of XX by the reaction of the stilbene (XXV) with aminoacetal was unsuccessful.

Further chemical and biological properties of compounds containing this ring system are under study.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of our Laboratories.

10,11-Dihydro-5*H*-dibenzo[a,d]cycloheptene-5-acetic acid (III).

10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-ylideneacetic acid (II) (2) (29.0 g.) was dissolved in anhydrous ethanol (125 ml.) and 10% palladium on charcoal (2.0 g.) was added. The mixture was hydrogenated at 40° and 50 p.s.i. for 9 hours. The catalyst was removed by filtration and the filtrate evaporated. Crystallization of the residue from benzene yielded III, m.p. 163-164° (21.8 g., 75%) λ max (EtOH), 266 mμ (ε, 620). Lit. m.p. 159-161° (5).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.62; H, 6.37.

1,6,7,11b-Tetrahydro-2*H*-dibenz[cd,h]azulen-2-one (IV).

The acetic acid derivative (III) (92.0 g.) was dissolved in anhydrous hydrogen fluoride (500 ml.). After 48 hours, the remaining hydrogen fluoride was removed by distillation and the residue was distributed between 10% aqueous sodium hydroxide and chloroform. The chloroform phase yielded a solid residue which on crystallization from a chloroform-methanol mixture gave compound IV, m.p. 219-220° (65.1 g., 75.5%), λ max (EtOH), 247 (ε, 10,050), 297 mμ (ε, 2,670); ν max ($CHCl_3$), 1700 cm^{-1}. Lit. m.p. 213-215° (5).

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.86; H, 5.86.

The oxime was prepared with hydroxylamine hydrochloride in refluxing pyridine and had a melting point of 186-188° (ethyl acetate-benzene).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.9; H, 6.06; N, 5.62. Found: C, 82.12; H, 6.25; N, 5.67.

2-Hydroxy-1,6,7,11b-tetrahydro-2*H*-dibenz[cd,h]azulene (V).

The ketone (IV) (1.0 g.) was dissolved in methanol (20 ml.) containing sodium borohydride (500 mg.) and the mixture refluxed for 16 hours. The methanol was removed *in vacuo* and the residue distributed between water and chloroform. The organic phase yielded the product m.p. 161-162° (benzene) (950 mg., 95%).

Anal. Calcd. for $C_{17}H_{15}O$: C, 86.77; H, 6.43. Found: C, 86.72; H, 6.42.

This product was also obtained in 37% yield by lithium aluminum hydride reduction of the ketone in tetrahydrofuran.

6,7-Dihydro-2*H*-dibenz[cd,h]azulene (VI).

2-Hydroxy-1,6,7,11b-tetrahydro-2*H*-dibenz[cd,h]azulene (V) (5.3 g.) was dissolved in anhydrous dimethylsulfoxide (55 ml.) and the mixture heated at 160° under nitrogen for 34 hours. At the end of this period thin layer chromatography showed that no starting material was present. The dark red reaction mixture was poured into water (300 ml.) and extracted with benzene to give a red oil which was chromatographed on activity II, neutral alumina. Elution with hexane gave a colorless oil (4.7 g., 96%) which solidifies on standing. Crystallization from hexane gave the pure product, as colorless prisms, m.p. 90-90.5°, λ max (EtOH), 240, 269, 291, 302 mμ (ε, 2,360, 3,590, 6,215, 23,270 resp.).

Anal. Calcd. for $C_{17}H_{14}$: C, 93.53; H, 6.47. Found: C, 92.96; H, 6.37.

The compound is sensitive to light and on standing the color changes to pink.

1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolin-3-one (VIII).

(a) The ketone (IV) (4.5 g.) was dissolved in molten trichloroacetic acid (45 g.) and sodium azide (2.4 g.) was added. The mixture was heated and stirred on the steam bath for 30 minutes, allowed to remain at room temperature for 24 hours, then poured into iced water, made alkaline with ammonium hydroxide and extracted with chloroform to yield a solid (2.4 g.). Crystallization from a chloroform-hexane mixture yielded compound VIII, m.p. 173-175°, ν max ($CHCl_3$), 1672 cm^{-1}, λ max (EtOH), 235 mμ (ε, 10,220).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.9; H, 6.06; N, 5.62. Found: C, 82.2; H, 5.89; N, 5.73.

(b) The *N*-carbethoxy derivative (XVII) (1.0 g.) was dissolved in polyphosphoric acid (20 g.) and heated at 120-150° for 2 hours. The reaction mixture was distributed between aqueous 10% sodium hydroxide and chloroform. The chloroform phase yielded the title compound, m.p. 173-175°, (750 mg.).

(c) The hydrochloride of the methylamine (XIV) (9.2 g.) was suspended in toluene (200 ml.) and a slow stream of phosgene was bubbled through the stirred solution until the mixture was homogenous (*ca.* 1.5 hours). The cooled solution was evaporated *in vacuo* to yield the crude isocyanate derivative ν max ($CHCl_3$), 2250 cm^{-1} (NCO), which was heated with polyphosphoric acid (75 g.) for 2 hours at

150 ± 10° to yield the lactam (VIII) (4.5 g.), m.p. 170-173°.

1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline (IX).

(a) The lactam (VIII) (2.1 g.) and lithium aluminum hydride (1.0 g.) were combined in tetrahydrofuran and refluxed for 16 hours to yield the compound IX (2.0 g.), m.p. 88-90° (ethyl acetate-petroleum ether). The hydrochloride had a melting point of 280-284° (ethanol-ether), λ max (EtOH), 273 (ε, 684), 266 mμ (ε, 768) unchanged on addition of sodium hydroxide.

Anal. Calcd. for $C_{17}H_{18}ClN$: N, 5.15; Cl, 13.05. Found: N, 5.16; Cl, 13.11.

(b) To the Schiff base (XVIII) (50.0 g.) in ethanol (300 ml.) was added sodium borohydride (20.0 g.) and the mixture refluxed for 16 hours. The ethanol was removed *in vacuo* and the residue was distributed between water and chloroform. The chloroform phase yielded compound IX (43.5 g., 86%), m.p. 83-84° (benzene-hexane). The *N*-acetyl derivative had a melting point of 120-123° (methanol).

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 81.72; H, 6.71; N, 5.14.

10,11-Dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XIV).

(a) 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-carbonitrile (XV) (109.5 g.) dissolved in ether (1500 ml.) was added over 3 hours to a mixture of lithium aluminum hydride (20.9 g.) and aluminum chloride (73.3 g.) in ether (1250 ml.). The mixture was refluxed for 2 hours then allowed to remain at 22° for 16 hours. Concentrated hydrochloric acid (200 ml.) and water (1500 ml.) were added and the ether was removed by distillation. The remaining aqueous mixture was heated until all solids were dissolved, filtered and cooled to yield the hydrochloride salt of compound XIV, m.p. >295° (96.2 g., 74%). The analytical sample was crystallized from a methanol-ethyl acetate mixture.

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; Cl, 13.65; N, 5.39. Found: C, 73.81; H, 6.92; Cl, 13.66; N, 5.71.

(b) The carbonitrile (XV) (2.0 kg.) was dissolved in methanol (8 l.) containing anhydrous ammonia (765 g.). Raney Nickel (200 g.) was added and the mixture hydrogenated at 1100 p.s.i. for 7 hours at 70-75°. The catalyst was removed by filtration and the filtrate was fractionally distilled to yield compound XIV (1.56 kg. 78%), b.p. 127° (0.15 mm.), n_D^{23} 1.6122.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.08; H, 7.51; N, 6.16.

N-Formyl 10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XVI).

Formic acid (476 ml.) and acetic anhydride (1126 ml.) were heated together for 2 hours at 60°. To this mixture at 22° was added the amine (XIV) (1243 g.) over 1 hour with stirring. After remaining at 22° for 16 hours the mixture was poured onto cracked ice and the resultant precipitate extracted with chloroform to yield compound XVI (1158 g., 82.5%), m.p. 109-110° (benzene-hexane), λ max (EtOH), 264 mμ (ε, 586), ν max ($CHCl_3$), 1690 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.77. Found: C, 81.39; H, 6.88; N, 5.88.

N-Carbethoxy 10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XVII).

The amine (XIV) (6.7 g.) was added to a mixture of ethylene dichloride (80 ml.) and 1 *N* sodium hydroxide (33 ml.). Ethyl chloroformate (3.58 g.) was added over 30 minutes with vigorous stirring at 0°. The reaction mixture was kept at 22° for 3 hours, the organic phase was separated, to yield compound XVII, m.p. 77-79°, (5.6 g., 63.5%) from ethyl acetate-hexane); ν max ($CHCl_3$), 1715 cm^{-1}, λ max (EtOH), 263 mμ (ε, 589).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.54; H, 7.39; N, 4.67.

1,7,8,12b-Tetrahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline (XVIII).

The *N*-formyl derivative (XVI) (1155 g.) was added to polyphosphoric acid (5 kg.) and the mixture stirred and heated at 160° for 4 hours. It was poured into water (80 l.) containing sodium hydroxide (5 kg.) and extracted with chloroform to yield compound XVIII (875 g., 81.5%), m.p. 108-109° (benzene), λ max (EtOH), 253 mμ (ε, 10,200), ν max ($CHCl_3$) 1638 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.50; H, 6.65; N, 6.09.

The hydrochloride salt was prepared with ethereal hydrogen chloride and had a melting point of 205-207° (methanol-ether), λ max (EtOH), 298 mμ (ε, 10,120) ν max (Nujol), 1663 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}ClN$: Cl, 13.14. Found: Cl, 13.53.

7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline (XIX).

The Schiff base (XVIII) (1.17 g.) and 10% palladium on charcoal (500 mg.) were heated together for 45 minutes at 240° then cooled, diluted with benzene and filtered. The filtrate was fractionally distilled to yield compound XIX (1.05 g., 89%), b.p. 148-160° (0.08-0.10 mm.). The hydrochloride salt was obtained as a hydrate and had a melting point of 199-201° (acetonitrile) λ max (EtOH), 231.5 (ε, 38,700), 306 (ε, 8,970); 340 mμ (ε, 9,070).

Anal. Calcd. for $C_{17}H_{14}ClN \cdot H_2O$: C, 71.45; H, 5.64; Cl, 12.41; H_2O, 6.3. Found: C, 71.83; H, 5.76; Cl, 12.41; H_2O, 6.4.

2-Methyl-1,7,8,12b-hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline.

The isoquinoline derivative (XIX) (3.0 g.) was dissolved in acetone (15 ml.) and treated with methyl iodide (5 g.). After 2 hours at room temperature a solid precipitate was obtained which was crystallized from methanol to give 2-methyl-7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolinium iodide (2.7 g., 56%), m.p. 228-231°, λ max (EtOH), 290 mμ (ε, 14,250).

Anal. Calcd. for $C_{18}H_{18}NI$: I, 34.01. Found: I, 34.06.

The isoquinolinium iodide (1.3 g.) was mixed with triethylamine (1.4 ml.) and 90% formic acid (1.5 ml.) and heated on a steam bath for 3 hours (16). Ten percent aqueous sodium hydroxide (50 ml.) was added and the mixture extracted with ether to yield the compound indicated in the heading above (500 mg.), m.p. 90-91° (hexane); λ max (EtOH), 262 mμ (ε, 569). The hydrochloride had a melting point of 266-270° (methanol-ether).

Anal. Calcd. for $C_{18}H_{20}ClN$: C, 75.65; H, 7.06; Cl, 12.41. Found: C, 75.95; H, 6.81; Cl, 12.41.

3,3-Di-(*o*-tolyl)-2-propenoic Acid.

Ethyl magnesium bromide prepared from ethyl bromide (6.54 g., 0.06 mole) and magnesium (1.47 g., 0.06 mole) in tetrahydrofuran (100 ml.) was treated with diethylamine (4.3 g., 0.06 mole) at 0° and the mixture was refluxed for 30 minutes (25). A mixture of *t*-butyl acetate (3.45 g., 0.03 mole) and di-(*o*-tolyl)-ketone (26) (4.2 g., 0.02 mole) was added in tetrahydrofuran (40 ml.) at 0° and the mixture refluxed for 4 hours, poured into ice cold saturated aqueous ammonium chloride and extracted with benzene to yield *t*-butyl 3-hydroxy-3,3-di-(*o*-tolyl)propionate as an oil (2.7 g.), ν max ($CHCl_3$), 3450, 1700 cm^{-1}. This *t*-butyl ester was dissolved in glacial acetic acid (50 ml.) and hydrogen bromide was bubbled in for 15 minutes. The solution was poured into iced water and extracted with chloroform to yield the title compound (2.5 g.), m.p. 142-144° (benzene), λ max (EtOH), 270 mμ (ε, 9,700).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.91; H, 6.46.

3,3-Di-(*o*-tolyl)-propionic acid (XI).

3,3-Di-(*o*-tolyl)-2-propenoic acid (22.0 g.) in ethanol (150 ml.) was hydrogenated at 50 p.s.i. for 90 minutes at 40° in the presence of 10% palladium on charcoal (2.0 g.). Filtration and concentration of the filtrate yielded the title compound (20.0 g., 91.8%), m.p. 125-127° (benzene) λ max (EtOH), 263 mμ (ε, 688).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13. Found: C, 79.60; H, 6.73.

4-Methyl-3-(*o*-tolyl)-1-indanone (X).

3,3-Di-(*o*-tolyl)propionic acid (XI) (18.0 g.) was dissolved in hydrogen fluoride (200 ml.) and allowed to stand for 20 hours. The residue after evaporation was distributed between chloroform and aqueous sodium hydroxide solution. The organic phase yielded compound X (12.8 g., 86%), m.p. 131-133° (benzene-hexane), ν max ($CHCl_3$), 1710 cm^{-1}, λ max (EtOH), 251 (ε, 12,470), 298 mμ (ε, 2,710).

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.04; H, 6.59.

5-Methyl-4-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline-1-one (XII).

The indanone (X) (4.6 g.) was dissolved in molten trichloroacetic acid (46 g.) at 70° and sodium azide (2.3 g.) was added. The mixture was stirred at 70° for 5 hours, diluted with water and extracted with chloroform to yield the title isoquinoline-1-one (2.0 g.), m.p. 246-250° (acetonitrile), ν max ($CHCl_3$) 1675 cm^{-1} and 3420 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.49; H, 6.95; N, 5.60.

5-Methyl-4-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline (XIII).

The isoquinoline-2-one (XII) (1.05 g.) was dissolved in tetrahydrofuran (40 ml.) and refluxed for 6 hours with lithium aluminum hydride (1.0 g.). Addition of water (4.5 ml.) and filtration yielded compound XIII (900 mg.) m.p. 68-74° (hexane). The hydrochloride had a melting point of 239-240° (methanol-ether); λ max (EtOH), 264 mμ (ε, 526),

unchanged on addition of sodium hydroxide.

Anal. Calcd. for $C_{17}H_{20}ClN$: N, 5.12; Cl, 12.95. Found: N, 5.19; Cl, 12.89.

Cis-3,3',4,4'-Tetramethoxystilbene (XXV).

Powdered α-(3,4-dimethoxyphenyl)-3,4-dimethoxycinnamic acid (27) (150 g.) was added in portions over 20 minutes to a stirred suspension of copper bronze powder (19.1 g.) in quinoline (600 ml.) at 210°. The temperature was raised to 220° and held there for 25 minutes. The cooled mixture was diluted with benzene (2000 ml.) stirred well and filtered through Celite. The filtrate was washed successively with 4 *N* hydrochloric acid (insoluble material was removed by filtration) followed by 5% sodium carbonate solution and then water; this procedure avoids the formation of troublesome emulsions. Removal of the solvent and recrystallization of the residue from methanol-chloroform gave 95 g. (73%) of the stilbene, m.p. 119-120° (reported (19), m.p. 117-118°).

3,3',4,4'-Tetramethoxydibenzyl (XXI).

(a) To a solution of *sym*-tetraphenylethylene (3.0 g.) in dry tetrahydrofuran (1000 ml.) kept under nitrogen was added a 50% sodium dispersion in paraffin (Gray Chemical Inc., 20 g., 0.43 g.-atom). When a deep red colour had developed, the mixture was cooled in an acetone-dry ice bath and a solution of 3,4-dimethoxybenzyl chloride (28) (18.7 g., 0.1 mole) in tetrahydrofuran (100 ml.) was added dropwise over 4 hours. The excess of sodium was destroyed by the addition of 2-propanol and the mixture was filtered. The solvent was removed *in vacuo*, replaced with benzene and the solution was washed with dilute hydrochloric acid. The crude product was triturated with pentane and recrystallized from methanol to give 5.6 g. (37%) of product, m.p. 106-108°, undepressed on admixture with material prepared by hydrogenation of tetramethoxystilbene (18).

(b) A mixture of the stilbene (XXV) (2.0 g., 0.007 mole) cyclohexene (4.4 g., 0.054 mole) and 10% palladium-on-charcoal (0.7 g.) in absolute ethanol (30 ml.) was heated under reflux with slow stirring for 18 hours. There was obtained 1.6 g., (80%) of the dibenzyl, m.p. 108-109° (methanol).

2,3,7,8-Tetramethoxy-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XX).

Concentrated sulfuric acid (330 ml.) was added dropwise to a solution of 3,3',4,4'-tetramethoxydibenzyl (XXI) (55.0 g., 0.18 mole) and 2,2-diethoxyethylamine (27.5 g., 0.21 mole) in glacial acetic acid (1100 ml.) maintained in an ice-salt bath; the internal temperature was not allowed to rise over 15°. The mixture was then kept for 20 hours at 0°, poured onto cracked ice and extracted with benzene. The aqueous solution was made alkaline with 50% sodium hydroxide solution, again keeping the temperature below 20°. The amine was collected giving 44.0 g. (70%) of material, m.p. 122-126°, raised to 129-131° on one recrystallization from benzene-hexane (reported (17) m.p. 129-130°). Carrying out the reaction at these low temperatures considerably decreased the attendant decomposition. The hydrochloride had a melting point of 243-246° (dec.) (from methanol).

Anal. Calcd. for $C_{20}H_{26}ClNO_4 \cdot 0.5CH_3OH$: C, 62.20; H, 7.14; Cl, 8.95. Found: C, 62.04; H, 7.35; Cl, 8.93.

N-Formyl 2,3,7,8-tetramethoxy-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene-5-methylamine (XXIII).

The amine (XX) (20.0 g.) was formylated with formic-acetic anhydride derived from formic acid (5.2 ml.) and acetic anhydride (12.1 ml.); the reaction temperature was kept below 40°. There was obtained 10.0 g. (47%) of product, m.p. 147-148°.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.14; H, 6.80; N, 3.69.

4,5,10,11-Tetramethoxy-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolin-3-one (XXII).

Phosgene was bubbled over a 2 hour period into a stirred suspension of the amine (XX)-hydrochloride (9.0 g., 0.02 mole) in nitromethane. The precipitate gradually dissolved if the mixture was warmed slightly from time to time. It was kept overnight at room temperature and evaporated to give the isocyanate, ν max ($CHCl_3$), 2275 cm^{-1}. Cyclization with polyphosphoric acid (25 g.) for 30 minutes at 100° afforded the crude lactam. It was triturated with ethyl acetate to remove tarry material and recrystallized from acetonitrile to give 0.9 g. (10%) of product, m.p. 247-248° (dec.).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.55; H, 6.41; N, 3.84.

4,5,10,11-Tetramethoxy-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinoline (XXIV).

The amine (XX) (10.0 g., 0.03 mole) and 37% formaldehyde (3 g.) were heated together on the steam-bath for 1 hour. Hydrochloric acid (2:1; 10 ml.) was added and the mixture was stirred and heated for a further 2 hours. It was poured into water and made alkaline with sodium hydroxide. The product was extracted into dichloromethane to give 4.0 g. (39%), m.p. 191-193° (chloroform-methanol).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.73; H, 6.86; N, 3.75.

The hydrochloride had a melting point of 244-247° (dec.) (ethanol).

Anal. Calcd. for $C_{21}H_{26}ClNO_4$: Cl, 9.05. Found: Cl, 9.05.

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