Studies on the Syntheses of Heterocyclic Compounds. Part DCXXIX.† A Ready Synthesis of Indeno[2,1-*a*][3]benzazepines

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The 3',4'-dihydrospiro[indan-2,1'(2'*H*)-isoquinoline]-1,3-diones (6)—(9) were transformed into a mixture of *cis*- (10)—(13) and *trans*- (14)—(17) hexahydroindeno[2,1-*a*][3]benzazepines under reductive conditions (zinc and acetic acid). 5-(3,4-Dimethoxybenzoyl)-2,3-dihydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (18) was converted into 12-chloro-5,6,7,7a-tetrahydro-2,3,9,10-tetramethoxy-7-methylindeno[2,1-*a*][3]benzazepine (20) with phosphoryl chloride in hot toluene, and the product was reduced with sodium borohydride to give 5,6,7,12-tetrahydro-2,3,9,10-tetramethoxy-7-methylindeno[2,1-*a*][3]benzazepine (21).

INDENO[2,1-*a*][3]BENZAZEPINES are important key intermediates for total syntheses of rhoeadine-type of alkaloids (1).[1,2] We report here a ready synthesis of these compounds.

Reductive transformation of the 1-benzoyl-1,2,3,4-tetrahydro-2-methylisoquinoline (2) into the benzazepine derivative (3) has been reported,[3] and the berbinium system (4) has been converted into the indolobenzazepine (5) under similar conditions.[4]

We first investigated the transformation of spiroisoquinolines into indenobenzazepines under reductive conditions. Treatment of the spiroisoquinoline (6) with zinc dust and acetic acid under reflux with stirring for 1.5 h gave a diastereoisomeric mixture in 85% yield of compounds A [*m/e* 297 (M^+), δ($CDCl_3$) 4.77 (1H, d, *J* 9 Hz, 7a-H), 2.57 (3H, s, N·CH_3)] and B [*m/e* 297 (M^+), δ ($CDCl_3$) 4.38 (1H, d, *J* 8.5 Hz, 7a-H), 2.36 (3H, s, N·CH_3)] in the ratio 1:3. The mixture was partly separable by column chromatography on silica gel, and the ratio was determined by g.l.c. and from the n.m.r. spectrum of the mixture. Dreiding models of hexahydroindeno[2,1-*a*]-[3]benzazepine show that if the junction between B and C is *cis*, the proton at position 7a is in the same plane as ring A. On the other hand, this proton is above ring A in the *trans*-fused system, and would be expected to resonate at higher field. It was therefore considered from the chemical shifts of the 7a-proton that compound A (δ 4.77) is a *cis*-fused (10) and compound B (δ 4.38) is *trans* (14).

The spiroisoquinolines (7)—(9) were similarly transformed into diastereoisomeric mixtures of *cis*- (11)—(13) and *trans*- (15)—(17) indenobenzazepines in the ratio 1:3. Methylation of the *cis–trans* (12) + (16) and (13) + (17) with 37% formalin and sodium borohydride gave the *cis–trans* mixtures (10) + (14) and (11) + (15), respectively.

The transformation of the benzazepine (18) into an indenobenzazepine was then investigated. The synthesis of the indeno[2,1-*a*][3]benzazepin-12-ol (19) has been reported,[5] but the yield in the cyclization of the benzazepine (18) was very low. However when the benzazepine (18) was treated with phosphoryl chloride in hot toluene, the 12-chloroindeno[2,1-*a*][3]benzazepine (20) was obtained in 89.3% yield. The structure of this compound was confirmed by microanalysis and n.m.r. and mass spectra. Treatment of the indenobenzazepine (20) with sodium borohydride in the presence of sodium hydroxide gave the indenobenzazepine (21), identified by microanalysis and n.m.r. [δ 3.71 (12-H_2)] and mass spectra.

EXPERIMENTAL

N.m.r. spectra were measured with a JNM-PMX-60 spectrophotometer (solutions in deuteriochloroform; tetramethylsilane as internal reference), i.r. spectra with a Hitachi 215 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

Treatment of the Spiroisoquinolines (6)—(9) *with Zinc and Acetic Acid.*—(*a*) A mixture of the spiroisoquinoline [6] (6) (300 mg), zinc dust (2.0 g), and acetic acid (15 ml) was refluxed with stirring for 1.5 h. The acidic solution was separated by decantation from the unchanged zinc dust and evaporated; the residue was diluted with water (30 ml) and basified with 10% ammonia. The resulting mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a syrupy diastereoisomeric mixture (255 mg), which was partly separated by silica gel (10 g) chromatography to give *cis*-5,6,7,7a,12,12a-hexahydro-7-methyl-2,3-methylenedioxyindeno[2,1-*a*][3]benzazepine (10) [δ ($CDCl_3$) 2.57 (3H, s,

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[2] K. Orito, R. H. F. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 1974, **96**, 1944.
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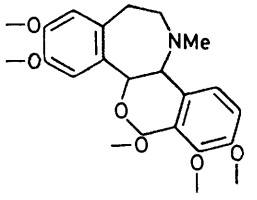
[4] C. Schöpf and M. Schweickert, *Chem. Ber.*, 1965, **98**, 2566.
[5] T. Kametani, S. Hirata, F. Satoh, and K. Fukumoto, *J.C.S. Perkin I*, 1974, 2509.
[6] R. H. F. Manske and Q. A. Ahmed, *Canad. J. Chem.*, 1970, **48**, 1280.

N·CH_3), 4.77 (1H, d, *J* 9 Hz, 7a-H), 5.85 (2H, s, O·CH_2·O), and 6.55 and 6.66 (2H, each s, 1- and 4-H), *m/e* 297 (M^+)] and the *trans*-isomer (14) [δ ($CDCl_3$) 2.36 (3H, s, N·CH_3), 4.38 (1H, d, *J* 8 Hz, 7a-H), 5.86 (2H, s, O·CH_2·O), and 6.59 and 6.78 (2H, each s, 1- and 4-H), *m/e* 297 (M^+)]. A solution of the mixture (50 mg) and methyl iodide (1 ml) in methanol (10 ml) was refluxed for 1 h. Evaporation then afforded the methiodide as a yellow powder (55 mg), m.p. 240—244° (from methanol–ether) (Found: C, 55.35; H, 5.0. Calc. for $C_{20}H_{22}INO_2$: C, 55.2; H, 5.1%).



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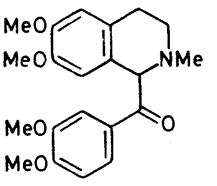
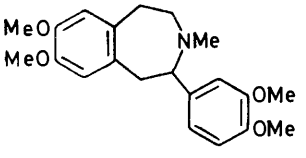
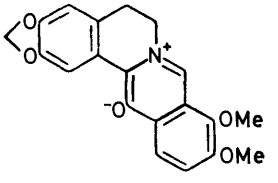


(2)



(3)



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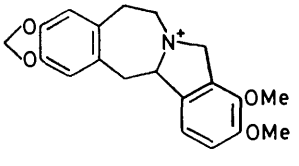
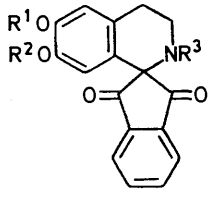
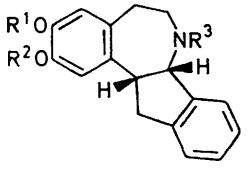


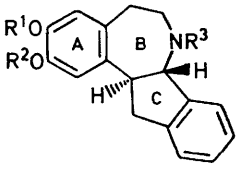
(5)



(6)-(9)



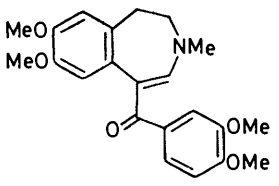
(10)-(13)



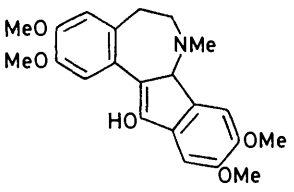
(14)-(17)

(6), (10), (14) $R^1R^2 = CH_2$, R^3 = Me
(7), (11), (15) $R^1 = R^2 = R^3$ = Me
(8), (12), (16) $R^1R^2 = CH_2$, R^3 = H
(9), (13), (17) $R^1 = R^2$ = Me, R^3 = H

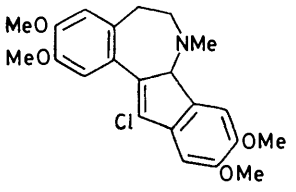
(*b*) A mixture of the spiroisoquinoline [7] (7) (200 mg), zinc dust (1.5 g), and acetic acid (15 ml) was refluxed with stirring for 1.5 h and worked up as above to give a syrupy diastereoisomeric mixture (145 mg), which was partly separated by silica gel (6 g) chromatography to give *cis*-5,6,7,7a,12,12a-hexahydro-2,3-dimethoxy-7-methylindeno[2,1-*a*][3]benzazepine (11) [δ ($CDCl_3$) 2.59 (3H, s, N·CH_3), 4.78 (1H, d, *J* 9.5 Hz, 7a-H), and 6.61 and 6.72 (2H, each s, 1- and 4-H), *m/e* 309 (M^+)] and the *trans*-isomer (15) [δ ($CDCl_3$) 2.41 (3H, s,



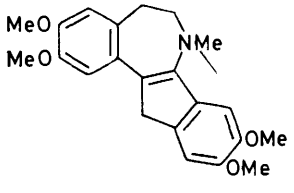
(18)



(19)



(20)



(21)

N·CH_3), 4.54 (1H, d, *J* 9 Hz, 7a-H), and 6.66 and 6.78 (2H, each s, 1- and 4-H), *m/e* 309 (M^+)]. A solution of the mixture (50 mg) and methyl iodide (1 ml) in methanol (10 ml) was refluxed for 1 h and evaporated to give the methiodide as a yellow powder (55 mg), m.p. 175—180° (from methanol–ether) (Found: C, 54.05; H, 5.7. Calc. for $C_{21}H_{26}INO_2$,-H_2O: C, 53.75; H, 6.0%).

(*c*) A mixture of the spiroisoquinoline [6] (8) (1 g), zinc dust (15 g), and acetic acid (50 ml) was refluxed with stirring for 1.5 h and worked up as above to give a syrupy mixture (780 mg) of *cis*-5,6,7,7a,12,12a-hexahydro-2,3-methylenedioxyindeno[2,1-*a*][3]benzazepine (12) and the *trans*-isomer (16), the hydrochloride of which formed prisms, m.p. 225—230° (from methanol) (Found: C, 68.0; H, 5.65. Calc. for $C_{18}H_{17}NO_2$, HCl: C, 68.45; H, 5.75%).

(*d*) A mixture of the spiroisoquinoline [7] (9) (2 g), zinc dust (15 g), and acetic acid (70 ml) was refluxed with stirring for 1.5 h and worked up as above to give a syrupy mixture (1.41 g) of *cis*-5,6,7,7a,12,12a-hexahydro-2,3-dimethoxyindeno[2,1-*a*][3]benzazepine (13) and the *trans*-isomer (17), the hydrochloride of which formed prisms, m.p. 238—245° (from methanol) (Found: C, 69.25; H, 6.75. Calc. for $C_{19}H_{21}NO_2$, HCl: C, 68.75; H, 6.7%).

N-*Methylation of the Isomers* (12) *and* (16).—To a solution of the mixture (100 mg) of (12) and (16) in methanol (15 ml), 37% formalin (1.5 ml) was added. After 20 min, sodium borohydride (0.4 g) was added in small portions with stirring. Stirring was continued for 30 min, the solvent was evaporated off, and water was added to the residue, which was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a mixture of (10) and (14) as a syrup (90 mg), identical with the sample described above.

N-*Methylation of the Isomers* (13) *and* (17).—The mixture (450 mg) of (13) and (17) was similarly treated to give a mixture of (11) and (15) as a syrup (420 mg), identical with the sample described before.

12-*Chloro*-5,6,7,7a-*tetrahydro*-2,3,9,10-*tetramethoxy*-7-*methylindeno*[2,1-a][3]*benzazepine* (20).—A mixture of the benzazepine (18) (300 mg), phosphoryl chloride (400 mg),

[7] T. Kametani, S. Hibino, S. Shibuya, and S. Takano, *J. Heterocyclic Chem.*, 1972, **9**, 47.

and dry toluene (50 ml) was refluxed for 30 min, washed with 10% ammonia and water, dried (Na_2SO_4), and evaporated to afford a syrup, which was chromatographed on silica gel (5 g). Elution with chloroform–methanol (99.5:0.5 v/v) gave a pale yellow syrup (277 mg), δ ($CDCl_3$) 2.09 (3H, s, N·CH_3), 4.52 (1H, s, 7a-H), and 6.54, 6.86, 7.10, and 7.21 (4H, each s, ArH); the hydrochloride formed *needles*, m.p. 197—198° (from methanol) (Found: C, 56.8; H, 5.55. $C_{22}H_{25}Cl_2NO_4$, $1.5H_2O$ requires C, 56.8; H, 6.05%).

5,6,7,12-*Tetrahydro*-2,3,9,10-*tetramethoxy*-7-*methylindeno*-[2,1-a][3]*benzazepine* (21).—To a solution of the indenobenzazepine (20) (90 mg) in methanol (20 ml), sodium borohydride (100 mg) and sodium hydroxide (60 mg) were added. After stirring for 2 h, the solvent was evaporated off and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give *prisms* (70 mg), m.p. 187—188° (from methanol) (Found: C, 72.05; H, 6.8. $C_{22}H_{25}NO_4$ requires C, 71.9; H, 6.85%), δ ($CDCl_3$) 2.97 (3H, s, N·CH_3), 3.71 (2H, s, 12-H_2), and 6.62 and 6.96 (1H and 3H, each s, ArH).

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