Synthesis of Isoquinolines. XI. Dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes and 4-Phenyl-1,2,3,4-tetrahydroisoquinolines[1]

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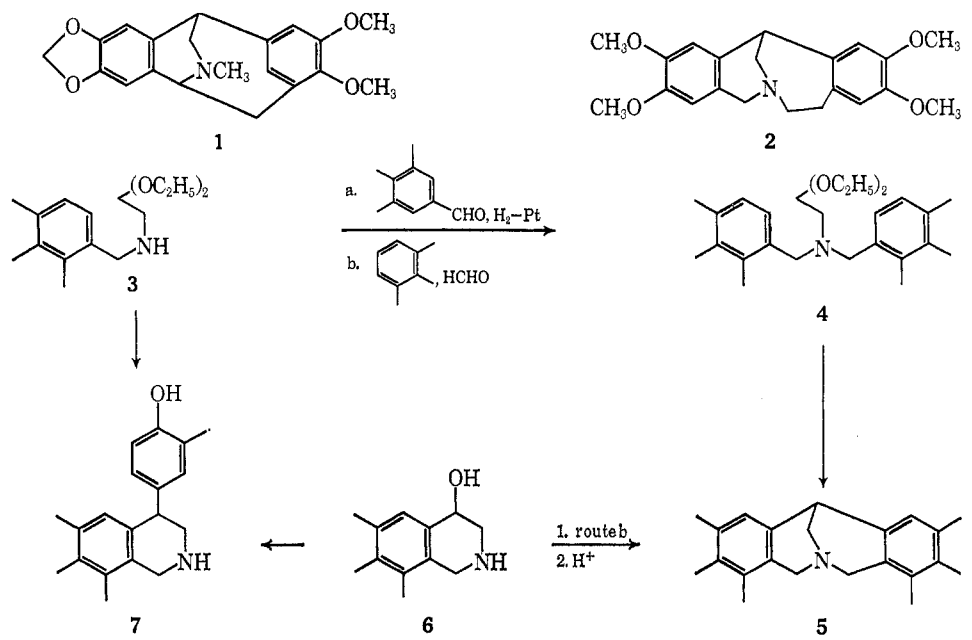
The facile syntheses of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines[2] appears to have made available a versatile intermediate for the preparation of a number of interesting compounds. In addition to the conversions reported in papers II–VIII of this series, they have been converted into 4-benzylisoquinolines,[3] 4-alkoxy-1,2,3,4-tetrahydroisoquinolines,[4] and 4-alkylamino-1,2,3,4-tetrahydroisoquinolines.[5] They have been converted into two bicyclic systems, the pavine system (**1**)[6] and the azabicyclodecane (**2**).[7] It would seem that the 4-hydroxy compounds can react in at least three ways: simple nucleophilic displacement (4-alkoxy and 4-alkylamino compounds and bicyclic structures);[4-7] dehydration to an enamine followed by alkylation at the 4 position;[3] and dehydration followed by nucleophilic attack at the 3 position.[8] Furthermore, 4-hydroxy-1,2,3,4-tetrahydroisoquinolines have been suggested[6] as biosynthetic intermediates. In this paper, we would like to report two additional nucleophilic displacement reactions of the hydroxyl group leading to the title compounds.

N,N-Bisbenzylaminoacetals (**4**) were prepared from **3**[9] by reductive benzylation in acetic acid over a platinum catalyst (route a) or by a Mannich reaction (route b).[10] These compounds were cyclized in 6 *N* HCl to yield the azabicyclononanes (**5**). The results are shown in Table I. The yields are based upon crude **3**[9] and were slightly erratic, although never low. The structures of **5** are based upon the mode of formation and the usual spectra and analytical data. The mass spectra showed the correct molecular ions and reasonable cracking patterns. Compounds **5a** and **5b** were methylated with diazomethane to give **5h**, which was the major compound for nmr studies. The spectrum is extremely simple, indicating a highly symmetrical structure. The aromatic protons show up as two sharp singlets (4 protons) at τ 3.5 and 3.29, as do the methoxyl protons (12 protons) at τ 6.21 and 6.19. The protons on the methylene groups between the nitrogen and the rings (5 and 7 positions) appear as an AB pattern (J = 17.5 cps) centered at τ 5.8, and the remaining protons appear in the general region of τ 6.7–6.4. The other compounds in Table I have similar and predictable spectra.



When the appropriately substituted benzylaminoacetals (crude)[9] were allowed to stand in 6 *N* HCl at room temperature in the presence of various phenols, the 4-(*p*-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines (**7**) resulted. These compounds could also be obtained from the purified 4-hydroxy compounds (**6**)[2] as could the azabicyclononanes, but quite satisfactory yields were obtained from the acetals. The results are shown in Table II. The yields are based upon crude **3**.[9]

The structures of the 4-phenyl derivatives are based upon their mode of formation, their predictable nmr spectra, and the synthesis by this method of a known

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(2) J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, **33**, 856 (1968).

(3) Paper IV: W. J. Gensler, K. T. Shamasundar, and S. Marburg, *ibid.*, **33**, 2861 (1968); see also D. W. Brown, S. F. Dyke, and M. Sainsbury, *Tetrahedron*, **25**, 101 (1969), and references cited therein.

(4) B. Umezawa, O. Hoshino, and Y. Yamanashi, *Tetrahedron Lett.*, 933 (1969).

(5) O. Hoshino, Y. Yamanashi, and B. Umezawa, *ibid.*, 937 (1969).

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(7) D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *ibid.*, 2609 (1968).

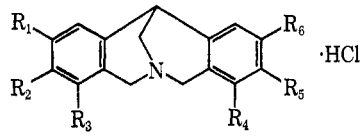
(8) J. M. Bobbitt and T. E. Moore, *J. Org. Chem.*, **33**, 2958 (1968).

(9) J. M. Bobbitt, J. M. Kiely, K. L. Khana, and R. Ebermann, *ibid.*, **30**, 2247 (1965).

(10) J. M. Bobbitt and C. P. Dutta, *ibid.*, **34**, 2001 (1969).

TABLE I

DIBENZO[c,f]-1-AZABICYCLO[3.3.1]-NONANE HYDROCHLORIDES[a]



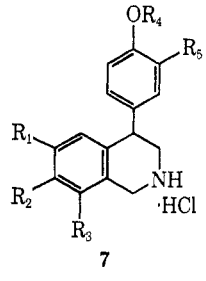
5

Compd	R_1	R_2	R_3	R_4	R_5	R_6	Yield, %	Mp, °C
5a	OCH_3	OH	H	H	OH	OCH_3	70	278–280
5b	OH	OCH_3	H	H	OCH_3	OH	75	170–173
5c	OCH_3	OCH_3	H	OH	OCH_3	OCH_3	60	270–272
5d[b]	OCH_3	OCH_3	H	H	OH	OCH_3	72	118–120
5e	OCH_3	OH	H	OH	OCH_3	OCH_3	70	288–290
5f[c]	H	OCH_3	OH	H	OH	OCH_3	65	265–267
5g	H	OCH_3	OH	OH	OCH_3	H	70	279–281
5h[d]	OCH_3	OCH_3	H	H	OCH_3	OCH_3	95	280–282

[a] Analytical values (±0.35%) for C, H, and N were reported for all compounds except **5c** (C found, 0.46% low) and **5g** (C found 0.55% low) (Ed.). [b] Purified as free base after basification of the hydrochloride. The data given refer to the free base. [c] Crystallized with 1 mol of water. [d] Prepared from **5a** and **5b** by methylation.

TABLE II

4-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES[a]



7

Compd	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C
7a	OCH_3	OCH_3	H	CH_3	OCH_3	10	238–240[b]
7b[c]	OCH_3	OCH_3	H	H	OCH_3	70	131–133
7c	OCH_3	OCH_3	H	H	OH	65	126–128.5
7d	OCH_3	OH	H	H	OCH_3	70	261–263
7e	OCH_3	OH	H	H	CH_3	60	280–281
7f	H	OCH_3	OH	H	CH_3	78	286–288
7g	H	OCH_3	OH	H	OH	75	276–278

[a] Analytical values (±0.30) for C, H, and N were reported for all compounds except **7g**, for which C and N values (found) were 0.5 and 0.4% high (Ed.). [b] Literature (ref 11) mp 240°. [c] The compound was purified as the free base from crude hydrochloride. The data given apply to the free base; analysis indicated 1 mol of water.

compound, 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,-2,3,4-tetrahydroisoquinoline (**7a**).[11] The condensation always appeared to go in the position *para* to the phenol group of the ring destined to be the 4-phenyl group. The reaction does take place on activated systems which contain no phenol group, as for **7a**, but the yields are low.

Experimental Section[12]

Dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes. General Procedure.—Substituted N-benzylaminoacetaldehyde diethyl acetals (**3**) were prepared on 0.02-mol amounts from aminoacetal and the appropriate benyaldehydes as described.[9,13] The acetals, in ethanol over platinum as formed, were combined with 0.02 mol of the second aldehyde and 6 ml of glacial acetic acid and hydrogenated until hydrogen uptake ceased (8–10 hr). The catalyst was removed, the solvent was removed under vacuum, and the residue was taken up in 80 ml of 6 *N* HCl. After 12–15 hr at room temperature, the solvent was evaporated under vacuum. During the evaporation, compounds **5a**, **5b**, **5f**, and **5g** crystallized and were recrystallized from ethanol–ether to give the final products. Compound **5d** was obtained by basifying the solid from the evaporation and extracting with $CHCl_3$. The analytical sample was crystallized from ethanol–ether.

Compound 5e.—N-Isovanillylominoacetaldehyde diethyl acetal (1 g, 0.0037 mol) in 30 ml of ethanol was allowed to stand with 1.4 ml (0.18 mol) of 40% HCHO and 0.41 g (0.0037 mol) of 2,3-dimethoxyphenol for 24 hr at room temperature. The solvent was removed and the residue was taken up in 50 ml of 6 *N* HCl and allowed to stand at room temperature for 12 hr. Evaporation of solvent under vacuum and crystallization from ethanol–ether yielded 0.98 g (70%) of **5e** hydrochloride.

Compound 5c.—Crude 6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.5 g, 0.002 mol), prepared by the reported procedure,[2] was allowed to stand for 24 hr at room temperature in 20 ml of ethanol with 1 ml (0.01 mol) of 40% HCHO and 0.27 g (0.002 mol) of 2,3-dimethoxyphenol. The solvent was removed and the residue was allowed to stand for 15 hr at room temperature in 20 ml of 6 *N* HCl. Evaporation of the solvent under vacuum and crystallization from ethanol gave 0.48 g (60%) of **5c**.

Methylation of 5a and 5b to 5h.—Compounds **5a** and **5b** (0.3 g), converted into the free bases, were methylated with an excess of distilled ethereal diazomethane (*ca.* 100 ml, from 5 g

(11) R. Quelet, M. Mansouri, and R. Pineau, *Compt. Rend.*, **245**, 537 (1957).

(12) Melting points were taken on a Kofler hot-stage apparatus and are corrected. The analyses were carried out by Baron Consulting Co., Orange, Conn. The nmr spectra were measured on a Varian A-60 instrument using tetramethylsilane as a standard.

(13) Actually, this means that the yields are based upon the benzaldehydes originally used to prepare the benzylaminoacetals,[9] since the acetals are not purified.

of N,N′-dimethyl-N,N′-dinitrosoterrephthalamide) in 20 ml of methanol–ether (1:2). The reaction was allowed to stand for *ca.* 36 hr. Evaporation and purification through the hydrochloride (prepared with HCl in ethanol) gave **5h** in *ca.* 95% yield from both compounds.

4-Phenyl-1,2,3,4-tetrahydroisoquinolines. General Procedure.—Crude substituted N-benzylaminoacetaldehyde diethyl acetals[9,13] (**3**, 0.01 mol) were allowed to stand with 0.011 mol of the appropriate phenols in 20 ml of 6 *N* HCl at room temperature for 12–15 hr. The product (**7**) precipitated. Concentration of the reaction mixtures yielded additional amounts of product. They were combined and recrystallized from ethanol or ethanol–ether.

Registry No.—**5a**, 23230-67-3; **5b**, 23282-29-3; **5c**, 23230-68-4; **5d**, 23230-69-5; **5e**, 23230-70-8; **5f**, 23230-71-9; **5g**, 23230-72-0; **5h**, 23230-73-1; **7a**, 23230-74-2; **7b**, 23263-77-6; **7c**, 23263-78-7; **7d**, 23230-75-3; **7e**, 23230-76-4; **7f**, 23230-77-5; **7g**, 23230-78-6.

Rearrangement of a 2,3-Alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-Substituted Benzoxazole

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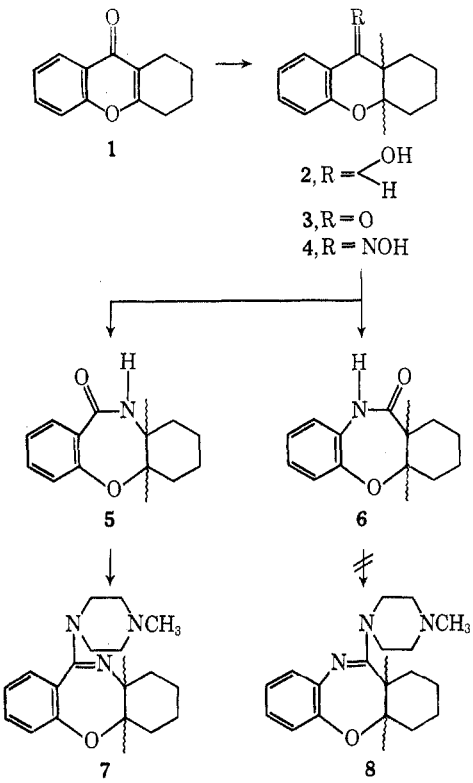
Discussion

Laboratory[1] studies have suggested that 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine[1c,2] possesses potential psychotropic utility. In view of the interest of our laboratories in this agent,[1b–d] we undertook the preparation of partially saturated congeners of this compound. During this study we observed a facile rearrangement of a 2,3-alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-substituted benzoxazole, which is the subject of this report.

1,2,3,4-Tetrahydroxanthone (**1**)[3] served as the starting material for this investigation (see Scheme I). Catalytic reduction of **1** gave the hexahydro alcohol **2**, which afforded ketone **3** on treatment with chromium trioxide–pyridine.[4] Beckmann rearrangement of the derived oxime **4** furnished a separable mixture of lactams **5** and **6**. Consonant with earlier studies,[5] lactam **6**, the product of aryl migration, predominated. Treatment of **5** with phosphorus oxychloride gave a chloroimidate, which reacted with 1-methylpiperazine to give 5a,6,7,8,9,9a-hexahydrodibenz[*b,f*][1,4]oxazepine (**7**).

SCHEME I



Application of this sequence to the isomeric lactam **6** failed to afford hexahydrodibenz[*b,f*][1,4]oxazepine (**8**); instead a product with composition $C_{13}H_{13}NO$ was isolated. This material appeared to result from a skeletal rearrangement in view of its distinctive ultraviolet spectrum (λ_{max} 265, 285, and 290 mμ). In contrast, the spectrum of **7** shows only weak end-absorption. The identity of the ring system present in the $C_{13}H_{13}NO$ substance was indicated by dehydrogenation in boiling decalin with palladium on carbon, which afforded the known 2-phenylbenzoxazole.[6] Although thermally induced rearrangement under the stringent conditions of dehydrogenation could not yet be eliminated from consideration, this observation suggested that the $C_{13}H_{13}NO$ substance was 2-(1-cyclohexenyl) benzoxazole (**11**). Thus the formation of **11** from the intermediate chloroimidate **9** could be interpreted as proceeding *via* a base-induced elimination to give phenoxide **10**, which then undergoes intramolecular displacement of chloride to afford **11** (see Scheme II). The well-known intermolecular reaction of phenoxides with chloroimidates constitutes ample precedent for this last stage.[7]

The 2-substituted benzoxazole **11** was synthesized independently by ring closure of anilide **12** with phosphorus pentachloride.[8] The identity of **11** prepared in this manner with the $C_{13}H_{13}NO$ product established the structure of the latter material and confirmed that base treatment of chloroimidate **9** results in rearrangement of the 2,3-dihydro-1,5-benzoxazepine system into a benzoxazole.

(1) (a) G. Stille, H. Lauener, E. Eichenberger, F. Hunziker, and J. Schmutz, *Arzneim.-Forsch.*, **15**, 841 (1965); (b) C. N. Latimer and L. C. Malone, *Fed. Proc.*, **27**, 438 (1968); (c) C. F. Howell, N. Q. Quinones, E. N. Greenblatt, A. C. Osterberg, and R. A. Hardy, Jr., Abstracts of Papers, 1st Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968; (d) C. N. Latimer, *J. Pharmacol. Exp. Ther.*, **166**, 151 (1969).

(2) J. Schmutz, F. Künzle, F. Hunziker, and R. Gauch, *Helv. Chim. Acta*, **50**, 245 (1967).

(3) Prepared by the procedure of L. A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).

(4) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(5) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 17 (1960).

(6) H. L. Wheeler, *Amer. Chem. J.*, **17**, 400 (1895).

(7) J. W. Schulenberg and S. Archer, *Org. React.*, **15**, 38 (1965).

(8) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 420.