Iminoethanophenanthridines by the Pictet-Spengler Reaction

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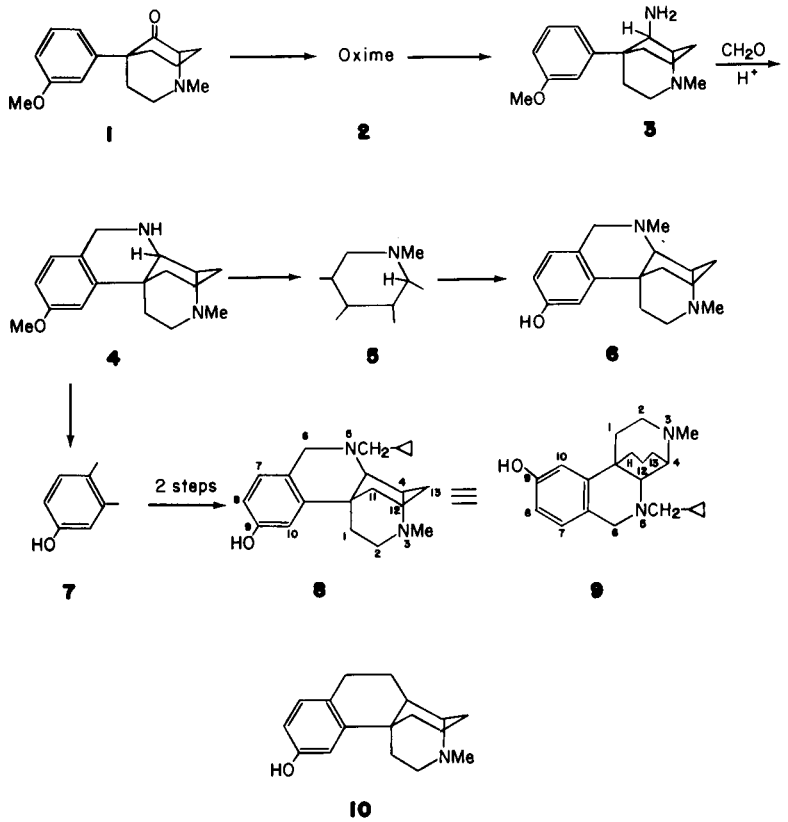
In 1958, the synthesis of 1,2,3,9,10,10a-hexahydro-6-hydroxy-1-methyl-1,4a(4*H*)iminoethanophenanthrene (**10**) (1) was reported. This paper is concerned with phenanthridine isosteres, prepared for comparison with **10** (a relatively weak analgesic in mice) by Pictet-Spengler cyclization of 9-*cis*-amino-5-(*m*-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (**3**) and appropriate subsequent operations.

The synthesis of aminoketone **1** was carried out by a modification of the general method of May and Murphy (2) using 2-(*m*-methoxyphenyl)cyclohexanone as the starting material. The latter was more conveniently prepared from the reaction of *m*-methoxyphenylmagnesium bromide with 2-chlorocyclohexanone (3,4,5) followed by thermal rearrangement of the adduct prior to hydrolysis than as previously described (2).

Hydrogenation of the oxime, **2** over platinum in acetic acid gave **3** in over 95% purity. The amino group in **3** is assigned the *cis* (to the aromatic ring) configuration, because it has been well documented that "steric approach control" (6,7), not "product development control" (8), is operative in the acidic hydrogenation of 2-substituted cyclohexanones or their oximes. An additional factor which contributes to the extremely high degree of stereospecificity in the conversion of **2** to **3** is the rigidity of the alicyclic ring in **2**. The 1,3-fusion of an iminoethano bridge to the cyclohexane frame is only possible through *cis*, diaxial linkages; once fused, both the cyclohexane and the piperidine ring are no longer capable of flipping to their alternative chair conformations.



Pictet-Spengler reaction of **3** with formalin and hydrochloric acid yielded **4** as the only product, which was demethylated to **7** with 48% hydrobromic acid. Although *para*-ring closures have generally been observed for Pictet-Spengler condensations involving a *m*-methoxyphenyl nucleus (9) the structure of **4**, as well as that of **7**, was unambiguously confirmed by nmr spectroscopy, (10), particularly with regard to the direction of cyclization. A 100 MHz spectrum of **7** taken in DMSO-d_6 – deuterium oxide (10:1) showed the presence of three aromatic protons distributed in a 1,2,4- pattern. Two of these protons, H_a at δ 6.75 and H_b at δ 6.52, are ortho-coupled to each other with J_{ab} = 8.0 Hz; H_b is further split into a quartet by the third proton H_c, located *meta* to H_b, while H_c appeared as a doublet centered at δ 6.59. The two single peaks at δ 3.90 (2H) and δ 2.37 (3H) are due to the α-methylene and *N*-methyl groups, respectively.

An alternative route from **3** to **4** was thought to be *via* the Bischler-Napieralski reaction. Although the *N*-formyl derivative of **3** could be readily prepared by refluxing **3** with ethyl formate, the subsequent conversion of the amide to **4** was not achieved.

Methylation of **4** with a mixture of formic acid and formalin afforded **5** in good yield, and demethylation of **5** to **6** was effected by 48% hydrobromic acid. The *N*-cyclopropylmethyl compound, **8**, was prepared by treatment of the phenolic amine, **7**, with an excess of cyclopropyl carbonyl chloride in the presence of triethylamine to yield the *N,O*-diacylated compound (ν max 1770, 1665 cm^{-1}) and lithium aluminum hydride reduction of the crude amido ester in THF.

Amine **3** and phenanthridines **6**, **7**, and **8** were tested for analgesic activity by the hot-plate method, as modified by Eddy and Leimbach (11,12). The first two were essentially inactive to 100 mg/kg (subcutaneous administration) and the last two were about 1/7 as potent as codeine, 1/4 as strong as the isosteric **10**.

EXPERIMENTAL (13)

5-(*m*-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one (**1**).

This compound was prepared in an overall yield of 14% from *m*-methoxyphenylcyclohexanone (3,4,5) following the directions of May and Murphy (2); b.p. 155-158° (0.1 mm.). Compound **1**·HCl crystallized from acetone-ether, m.p. 202° (lit. (2) 203-205°).

The oxime (**2**), recrystallized from benzene-hexane, gave (83% yield) needles, m.p. 159-160°; m/e 274 (M^+), 257 (base); nmr (deuteriochloroform, 60 MHz) δ 6.80-7.30 (m, 4, aromatic protons), 6.65 (s, 1, NH), 4.28 (m, 1, -CH-), 3.75 (s, 3, $-OCH_3$), 3.10 (m, 2, $-NCH_2$), 2.42 (s, 3, NCH_3), 1.3-2.7 (m, 8, alicyclic methylene protons).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 8.01; N, 9.93.

9-*cis*-Amino-5-(*m*-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonane (**3**).

The oxime, **2**, (274 mg., 1 mmole) in 5 ml. of acetic acid was hydrogenated over 100 mg. of platinium oxide (8) at 1 atm. until the theoretical amount of gas was taken up (1 hour). The catalyst was filtered and the filtrate concentrated *in vacuo* to give an oily residue which, upon warming with 10 ml. of 2 *N* sodium hydroxide afforded 200 mg. of a thick oil, b.p. 160-165° (0.2 mm.); m/e 260 (M^+), 243, 230, 217 (base). Although a crystalline hydrochloride or picrate salt of **3** was not obtained, the homogeneity of **3** was demonstrated by tlc in a variety of solvent systems (Rf 0.22, butanol-acetic acid-water 4:1:1; Rf 0.60, 2-propanol-water-ammonia (16:3:1).

The *N*-formyl derivative of **3** was prepared by refluxing **3** with excess ethyl formate overnight. Recrystallization from ether-petroleum ether afforded silky needles, m.p. 116-117°; m/e 288 (M^+); ν max (potassium bromide) 3300 and 1680. cm^{-1}, nmr (deuteriochloroform, 60 MHz), δ 8.00 (s, 1, HCO), 6.55-7.35 (m, 4, aromatic protons), 5.62 (d, 1, -NH-), 4.70 (m, 1, -C*H*-NH-), 3.15 (m, 1, -C*H*-NCH_3), 2.85 (m, 2, $-CH_2N$-), 2.49 (s, 3, NCH_3), 1.30-2.40 (m, 8, alicyclic methylene protons).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.85; H, 8.34; N, 9.68.

2,3,4,4a,5,6-Hexahydro-9-methoxy-3-methyl-1*H*-4,10b-propanobenzo[*c*][1,7]naphthyridine (**4**) Dihydrochloride.

The method of Kametani *et al.* (14) was used. A solution of 630 mg. (2.3 mmoles) of **3**, 6 ml. of ethanol and 6 ml. of 38% formaldehyde was acidified with 0.5 ml. of concentrated hydrochloric acid and refluxed for four hours. Evaporation *in vacuo* left an oily residue which crystallized upon triturating with 1 ml. of ethanol. Recrystallization from ethanol-ether gave colorless prisms, m.p. 233-236° dec.; 660 mg. (82%), m/e 272 (M^+), 241, 229 (base).

Anal. Calcd. for $C_{17}H_{26}Cl_2N_2O$: C, 59.13; H, 7.59; N, 8.11. Found: C, 59.20; H, 7.78; N, 8.31.

The dihydrochloride sublimed readily in high vacuum (10^{-4} mm.) at 150°.

2,3,4,4a,5,6,-Hexahydro-3,5-dimethy-9-methoxy-1*H*-4,10b-propano[*c*][1,7]naphthyridine (**5**) Dihydrochloride.

To an aqueous solution of 430 mg. (1.2 mmoles) of **4**·2HCl was added 40% potassium carbonate to *p*H 9. The liberated oil was extracted with ether, dried and evaporated. To the residual oil was added 1 ml. of formic acid (90%) and 0.94 ml. of 38% formaldehyde, the mixture was refluxed overnight. The cooled solution was then treated with 5 ml. of 1 *N* hydrochloric acid and concentrated to a syrup which crystallized (after addition of ethanol and ether) to give 390 mg. (82% of **5**·2HCl; rosettes, m/e 286 (M^+), 271, 243, 228; m.p. 241-242°.

Anal. Calcd. for $C_{18}H_{28}Cl_2N_2O$: C, 60.17; H, 7.85; N, 7.79. Found: C, 60.00; H, 8.00; N, 7.73.

2,3,4,4a,5,6-Hexahydro-3-methyl-1*H*-4,10b-propanobenzo[*c*]-[1,7]naphthyridine-9-ol (**7**).

A mixture of 400 mg. (1.1 mmoles) of **4**·2HCl in 5 ml. of 48% hydrobromic acid was refluxed under nitrogen for 20 minutes. The cooled solution was concentrated *in vacuo* to a syrup and the residue was dissolved in water. Basification with 40% potassium carbonate gave 315 mg. (76%) of **7** which was recrystallized from acetone-hexane to give prisms, m.p. 227-229°; m/e 258 (M^+), 215 (base), 200; nmr (DMSO-d_6-deuterium oxide, 100 MHz) δ 6.75 (d, 1, aromatic H, J = 8.0 Hz), 6.59 (d, 1, aromatic H, J = 2.4

Hz), 6.52 (q, 1, aromatic H, J = 8.0 and 2.4 Hz), 3.90 (s, 2, $ArCH_2N$-), 2.37 (s, 3, $-NCH_3$); the remaining alicyclic protons were not clearly resolved.

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.36; H, 8.59; N, 10.84. Found: C, 74.58; H, 8.96; N, 10.84.

The dihydrobromide prepared in ether gave (from 80% ethanol) colorless prisms. It decomposed gradually at 250°.

Anal. Calcd. for $C_{16}H_{24}Cl_2N_2O$: C, 58.01; H, 7.30; N, 8.45. Found: C, 57.73; H, 7.52; N, 8.24.

2,3,4,4a,5,6-Hexahydro-3,5-dimethyl-1*H*-4,10b-propanobenzo[*c*]-[1,7]naphthyridin-9-ol (**6**).

A mixture of 230 mg. (0.64 mmole) of **5**·2HCl and 5 ml. of 48% hydrobromic acid was refluxed under nitrogen for 15 minutes. The solution was cooled, evaporated to dryness, and the residue dissolved in 5 ml. of hot water. Basification with 40% potassium carbonate gave 150 mg. (86%) of **6** which was recrystallized from acetone-petroleum ether, m.p. 214-216°; m/e 272 (M^+), 257, 229, 214 (base).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.95; H, 8.80; N, 10.28. Found: C, 75.07; H, 8.83; N, 10.42.

The dihydrobromide prepared in anhydrous ether gave (from ethanol-ether) prisms, m.p. 264-267° dec.

Anal. Calcd. for $C_{17}H_{26}Br_2N_2O$: C, 47.02; H, 6.03; N, 6.45. Found: C, 47.16; H, 6.09; N, 6.52.

2,3,4,4a,5,6-Hexahydro-5-cyclopropylmethyl-3-methyl-1*H*-1,10b-propanobenzo[*c*][1,7]naphthyridin-9-ol (**8**) Dihydrochloride.

To a solution of 258 mg. (1 mmole) of **7** in 20 ml. of methylene chloride was added 2 ml. of triethylamine and 280 mg. (2.7 mmoles) of freshly distilled cyclopropylcarbonyl chloride. The mixture was stirred and refluxed for 18 hours. Evaporation *in vacuo* left a semi-solid residue which was triturated with methylene chloride. The methylene chloride solution was washed with sodium bicarbonate, dried and evaporated to a syrup whose infrared spectrum (nujol) indicated it was the diacylated derivative of **7**. Reduction of the amide-ester with 10 ml. of 1.6 M of lithium aluminum hydride in THF gave 280 mg. of essentially pure **8** which was converted to its dihydrochloride in ether, 294 mg. (76%). Recrystallization from ethanol-acetone-ether gave wart-like crystals, m.p. 228°; m/e 312 (M^+), 269.

Anal. Calcd. for $C_{20}H_{30}Cl_2N_2O$: C, 62.32; H, 7.84; N, 7.27. Found: C, 62.22; H, 8.06; N, 7.14.

REFERENCES

(1) E. L. May, *J. Org. Chem.*, 23, 947 (1958).

(2) E. L. May and J. G. Murphy, *ibid.*, 20, 1197 (1955).

(3) A. S. Hussey and R. R. Herr, *ibid.*, 24, 843 (1959).

(4) W. E. Bachmann, G. I. Fujimoto and L. B. Wick, *J. Am. Chem. Soc.*, 72, 1995 (1950).

(5) The 2-*m*-(methoxyphenyl)cyclohexanone so obtained was badly contaminated and could be brought to no better than 85% purity by ordinary distillation. Two distillations in a Nester-Faust column (24", 28 theoretical plates) raised the purity to 95%. For the synthesis of **1**, the material of 85% purity was satisfactory.

(6) This generalization is sometimes called the von Auwers-Skita hydrogenation rule; E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison in "Conformational Analysis", Interscience, publishers - a division of John Wiley and Sons, Inc., New York, Sydney, London, 1965, pp. 115-119.

(7) 2-Phenylcyclohexanone oxime was found to yield mainly the *cis* isomer; T. Masamune, M. Ohno, M. Koshi, S. Ohuchi and T. Iwadare, *J. Org. Chem.*, 29, 1419 (1964).

(8) Sodium-ethanol reduction of **2** gave a 70:30 mixture of *trans* and *cis* amines, respectively; H. H. Ong, unpublished results.

(9) M. W. Whaley and T. V. Govindachari in "Organic Reactions", Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 157.

(10) This seemed warranted because the amino group of **3** is attached to a rigid bicyclic system in this instance.

(11) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, 107, 385 (1965).

(12) A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965).

(13) Melting points (uncorrected) were determined on a Kofler hot-stage, infrared spectra were recorded with a Perkin-Elmer Grating spectrophotometer, Model 257, mass spectral data on a Hitachi RMR-6E double-focusing spectrometer at 80eV, and proton magnetic resonance spectra on a Varian HA-100 or HA-60 instrument using tetramethyl silane ($\delta = 0$) as internal standard.

(14) T. Kametani, K. Kigasawa, M. Hiragi, N. Wagatzuma, K. Wakisaki, F. Satoh and S. Saito, *J. Med. Chem.*, 13, 1064 (1970).