Dehydroaporphines. An Acylation Study

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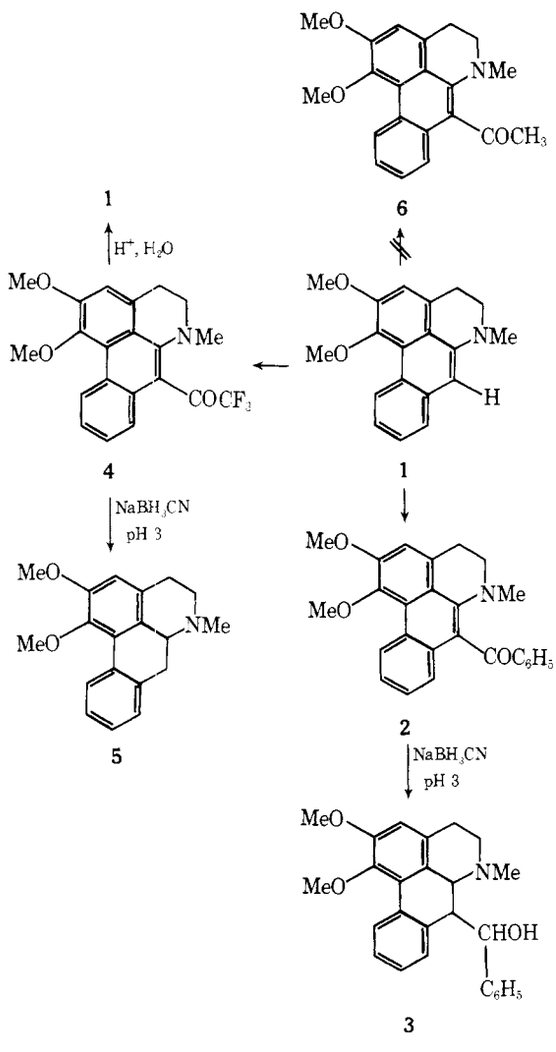
The representative dehydroaporphine, dehydronuciferine (1), is acylated by benzoyl chloride and by trifluoroacetic anhydride to give the 7-benzoyl and 7-trifluoroacetyl derivatives **2** and **4**, respectively. Dehydronuciferine (1) and dehydroapomorphine dimethyl ether (**13**) undergo direct acylative cyclization on treatment with oxalyl chloride to give the condensed isatins **8** and **14**, respectively. Some chemical transformations of the acyl derivatives **2** and **4** and the isatins **8** and **14** are described.

Previous studies from our laboratory have shown that dehydroaporphines possess a certain degree of enamine-type character, as evidenced by their behavior on protonation,[1] as well as their participation in a Reimer–Tiemann type formylation reaction.[2] We now report the first examples of dehydroaporphine acylations, and a simple route to some previously unavailable and pharmacologically interesting 7-substituted aporphine derivatives.

Results

Dehydronuciferine (1) was found to react smoothly with benzoyl chloride in pyridine at room temperature to give the yellow crystalline 7-benzoyldehydronuciferine (**2**) (Scheme I). Attempts to convert **1** into 7-acetyldehydronuciferine (**6**) in a similar manner failed, however, the starting material being converted into a complex mixture, as evidenced by TLC analysis. This failure was attributed to the possibility that **6** was in fact initially formed, but subsequently converted into secondary reaction products by way of reactions involving the acetyl methyl group. In accord with this idea, dehydronuciferine (1) was found to react cleanly with trifluoroacetic anhydride in pyridine to give 7-trifluoroacetyldehydronuciferine (**4**) as an orange oil.

Scheme I



The two ketones **2** and **4** differed markedly in their behavior toward acids as well as sodium cyanoborohydride. Whereas the benzoyl compound **2** was stable under both basic and acidic conditions (solutions or adsorbants), the trifluoroacetyl compound **4** was stable only in the absence of acid. A dilute acid wash, or even chromatography on ordinary silica, brought about a reverse acylation with the formation of dehydronuciferine (1). Sodium cyanoborohydride reduction of the benzoyl compound **2** took place readily at pH 3 to give an apparently homogeneous 7-(α-hydroxybenzyl)nuciferine (**3**), characterized as its crystalline hydrochloride. Under the same experimental conditions, the trifluoroacetyl compound **4** afforded only nuciferine (**5**).

Dehydronuciferine (1) reacted readily with oxalyl chloride under mild conditions (Scheme II). Unlike the case of the corresponding reaction with indole,[3] the initially formed glyoxalyl chloride **7** was not isolable, and cyclized with the loss of methyl chloride to give the wine-red isatin derivative **8**. In accord with the assigned structure, isatin **8** showed two carbonyl bands in the infrared at 5.75 and 5.90 μm, and no *N*-methyl singlet in its NMR spectrum.

Isatin **8** was used as the starting material for the synthesis of several unusual representative dehydroaporphines. Reaction of **8** with excess diazomethane gave the condensed pyridone **9**, a process analogous to the known conversion of isatin itself into 3-methoxycarbostyril.[4] The infrared spectrum of **9** showed a single carbonyl band at 6.10 μm, while its NMR spectrum showed the presence of three aromatic methoxyls (δ 3.86, 3.91, and 3.98) and two aromatic singlets (δ 7.01 and 7.51). Oxidation of **8** with *m*-chloroperbenzoic acid gave the isatoic anhydride **10**, characterized by its anhydride carbonyl doublet in the infrared at 5.59 and 5.88 μm. Finally, reduction of **8** with lithium aluminum hydride in tetrahydrofuran[5] afforded the indole derivative **11** as the major product (ca. 60%); a minor reaction product (12%) was lysicamine (**12**), which may have been formed from **11** as a photooxidation product during workup.

In a similar manner, dehydroapomorphine dimethyl ether (**13**) was successfully transformed into the corresponding isatin (**14**), pyridone (**15**), and anhydride (**16**). In view of the considerable pharmacological interest in apomorphine and its derivatives,[6] these compounds should be of value for the synthesis of various novel C-7 substituted apomorphines.

Discussion

The striking difference in the chemical behavior of the two ketones **2** and **4** must be attributed to the contrasting elec-

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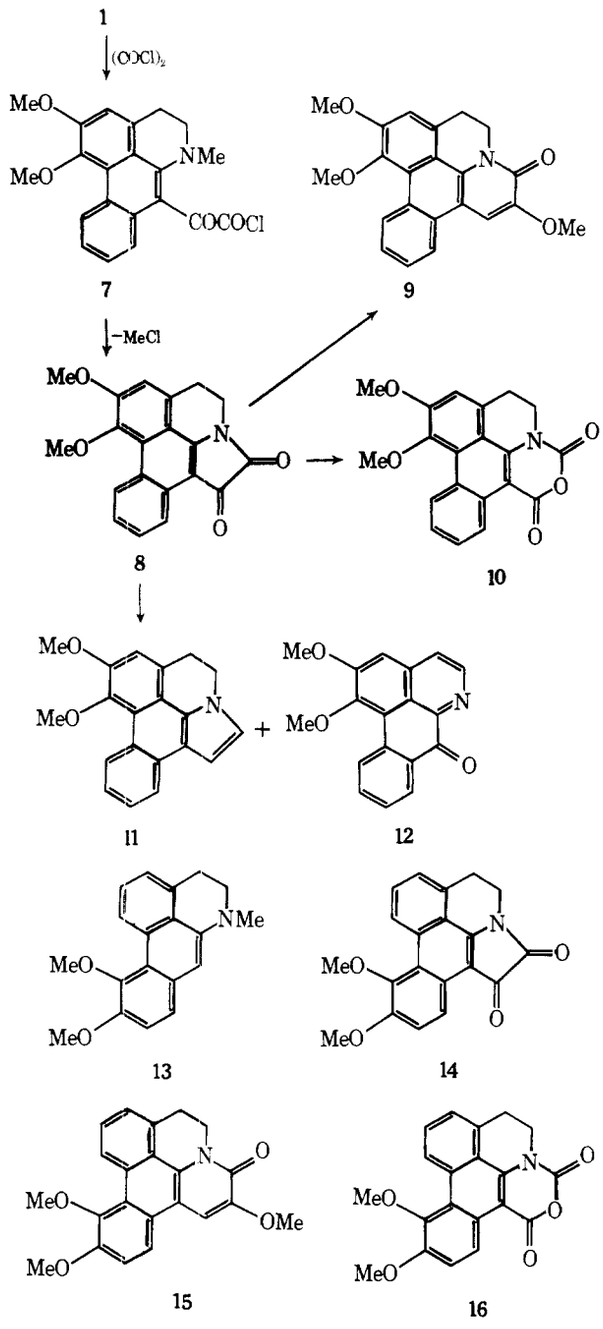
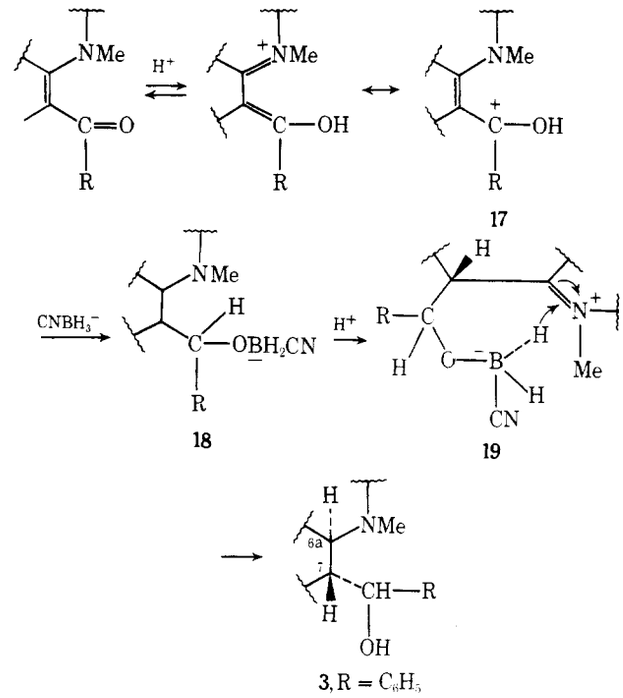
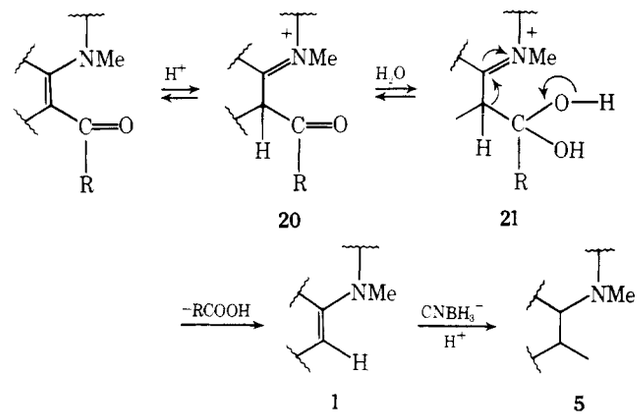
Scheme II



Scheme III



Scheme IV



tronic nature of their acyl substituents. In the case of the benzoyl compound **2**, a reversible protonation would be expected to occur readily at the carbonyl oxygen (Scheme III), the resulting cation being resonance stabilized by the phenyl substituent (R = C_6H_5). The rapid reduction of **2** to alcohol **3** by sodium cyanoborohydride in an acid medium is in accord with this view, since the reagent is known to be almost inert to ketonic carbonyls, but a good reducing agent for immonium ions.[7] 1,4-Reduction of the conjugated immonium ion **17** would give the dehydroaporphine borate ion **18**, protonation of which would give a new immonium ion **19**. If the latter process is followed by a rapid intramolecular hydride transfer as shown below, the ring hydrogens at C-6a and C-7 would be in a trans-diaxial arrangement, and the C-7 hydroxybenzyl substituent of **3** would have the more stable equatorial configuration.

In the case of the trifluoroacetyl compound **4**, carbonyl protonation on oxygen would be unfavorable, since the above ion **17** (R = CF_3) would be destabilized by the strongly electron-withdrawing trifluoromethyl substituent. As a result, the alternative process shown below (Scheme IV) could take place. Protonation of the ketone at C-7 would result in an immonium ion (**20**), which could be in equilibrium with its ketone hydrate **21**, especially if R is a strongly electron-withdrawing group. Rapid collapse of **21** would afford the deacylated dehydroaporphine (**1**). In the case of ketone **4**, collapse of the immonium ion **21** to **1** must occur more rapidly than its attack by cyanoborohydride ion, since treatment of **4** with acidic cyanoborohydride yields only nuciferine (**5**), shown to be the reduction product of dehydroaporphine **1** under the same experimental conditions.

Experimental Section

Melting points are uncorrected. Chromatography was carried out using silica. NMR spectra ($CDCl_3$ containing tetramethylsilane as internal standard), ultraviolet spectra (ethanol), infrared spectra (KBr), and mass spectra were determined using JEOL-JNH-PS-100 and Perkin-Elmer 202, 137, and 270 spectrometers, respectively. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana.

7-Trifluoroacetyldehydronuciferine (4). Excess trifluoroacetic anhydride (0.3 mL) was added to a cooled solution of dehydronucif-

erine[8] (1, 0.400 g) in dry pyridine (4 mL). After standing overnight at room temperature the orange solution (which showed the absence of 1 by TLC) was poured into water. The mixture was made slightly acidic and quickly extracted with chloroform, and the extract was washed with 5% $NaHCO_3$ followed by water. Evaporation of the extract gave crude 4 (~0.4 g) as an oil which was purified by chromatography over basic alumina (grade I), using a benzene–chloroform eluant. The orange oil, which could not be crystallized, showed UV maxima at 260, 321, and 370 nm; NMR δ 2.93 (s, 3 H, NMe), 3.88 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 7.08 (s, 1 H, C-3), 7.43–7.95 (m, 3 H), 9.48–9.65 (m, 1 H); IR 5.80, 5.85 μm; mass spectrum *m/e* (rel intensity) 389 (M^+, 56) 320 (100), 293 (13), 276 (24), 194.5 (2).

A chloroform solution of 4 (0.100 g) was shaken three times with 5% HCl and then water. Evaporation of the dried solvent gave dehydronuciferine (1, 0.090 g), mp 129–130 °C, identical (IR, UV, NMR, mmp) with authentic material.[8] In contrast, neutral or basic methanolic solutions of 4 were found (TLC) to be stable for weeks.

A freshly prepared solution of 4 (0.100 g) in methanol was acidified to pH 3 with 1% HCl, and excess $NaCNBH_3$ was added. After 15 min, workup (basification and chloroform extraction) afforded, after ethanol crystallization, racemic nuciferine (5), mp 133–135 °C (lit.[9] 134–135 °C), identical (IR, UV, TLC, mmp) with authentic material.

7-Benzoyldehydronuciferine (2). Benzoyl chloride (0.2 mL) was added to a solution of dehydronuciferine (1, 0.200 g) in dry pyridine (1 mL). After standing overnight, the solution was poured into water, the mixture was made slightly acidic, and the product was extracted into chloroform. Chromatography on silica (chloroform eluant) afforded 2 (0.190 g, 71%), which crystallized from EtOH as yellow prisms: mp 154–155 °C; IR 5.97 μm; UV λ_{max} 257 nm (ϵ 46 000), 323 (11 000), 373 sh (3200); NMR δ 2.80 (s, 3 H, NMe), 3.08 (s, 4 H), 3.92 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.06 (s, 1 H), 6.96–9.38 (m, 9 H); mass spectrum *m/e* (rel intensity) 397 (M^+, 100), 380 (90), 198.5 (1). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.58; H, 5.79; N, 3.52. Found: C, 78.30; H, 5.93; N, 3.37.

7-(α-Hydroxybenzyl)nuciferine (3). Reduction of ketone 2 (0.200 g) by $NaCNBH_3$ was carried out as in the case of the trifluoroacetyl analogue 4 (see above). The resulting oil (0.150 g, 3) was converted into colorless plates of the hydrochloride: mp 225–227 °C; UV λ_{max} 243 (sh) nm (ϵ 23 000), 275 (32 000); NMR δ 2.68 (s, 3 H, NMe), 3.35 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 5.21 (d, 1 H, J = 5 Hz, CH(OH)-C_6H_5), 5.43 (br, 1 H, OH, vanishes with D_2O), 6.56 (s, 1 H, C-3), 6.60–7.43 (m, 8 H), 8.30–8.50 (m, 1 H, C-11); mass spectrum *m/e* (rel intensity) 391 (M^+, 14), 385 (28), 384 (100), 370 (18), 294 (24), 278 (12), 263 (13), 252 (84). Anal. Calcd for $C_{26}H_{28}NO_3Cl$: C, 71.31; H, 6.40; N, 3.20. Found: C, 71.30; H, 6.24; N, 3.19.

Isatin 8. Oxalyl chloride (3 mL) was added to a solution of dehydronuciferine (1, 2.00 g) in a mixture of dry ether (80 mL) and tetrahydrofuran (30 mL). After stirring for 2 h, the precipitated product was filtered, washed with ether, and crystallized from chloroform to give wine-red needles (2.09 g): silica chromatography of the mother liquors afforded a further 0.22 g of crystalline 8: mp 233–234 °C; IR 5.75, 5.90 μm; UV λ_{max} 257 nm (ϵ 68 000), 324 sh (21 000), 336 (25 000), 357 sh (14 000), 510 (6000); NMR (Me_2SO + $CDCl_3$) δ 3.36 (t, 2 H, J = 6 Hz), 3.90 (t, 2 H, J = 6 Hz), 3.90 (s, 3 H, OMe), 4.09 (s, 3 H, OMe), 7.43 (s, 1 H), 7.53(–9.40 (4 H, m); mass spectrum *m/e* (rel intensity) 333 (M^+, 100), 305 (52), 277 (21), 166.5 (1). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.07; H, 4.50; N, 4.20. Found: C, 71.91; H, 4.77; N, 4.15.

Pyridone 9. Excess ethereal diazomethane was added to a solution of isatin 8 (0.050 g) in chloroform–methanol. After standing overnight, the mixture was worked up in the usual manner to give, after crystallization from ethyl acetate, pyridone 9 (0.040 g): mp 152–153 °C; IR 6.10 μm; UV λ_{max} 247 (sh) nm (ϵ 30 000), 267 (50 000), 320 (13 000), 344 (14 000), 360 (14 000), 379 (16 000); NMR δ 3.11 (t, 2 H, J = 6.5 Hz), 4.43 (t, 2 H, J = 6.5 Hz), 3.86 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.01 (s, 1 H), 7.51 (s, 1 H), 7.45–9.66 (m, 4 H); mass spectrum *m/e* (rel intensity) 361 (M^+, 100), 346 (28), 331 (25), 318 (46), 108.5 (5). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.87. Found: C, 73.13; H, 5.46; n, 3.81.

Anhydride 10. An excess of *m*-chloroperbenzoic acid in methylene chloride was added dropwise with cooling and stirring to a solution of isatin 8 (1.00 g) in methylene chloride (100 mL) containing an excess of powdered sodium bicarbonate. After 4 h at room temperature, the yellow solution contained no detectable starting material (TLC). The organic phase was shaken with 10% sodium sulfite until a starch-iodide test showed that all peracid was destroyed and was then washed (sodium bicarbonate then water), dried, and evaporated. Crystallization from chloroform–ethanol afforded yellow plates of anhydride 10 (0.750 g): mp 219–220 °C; IR 5.59, 5.88 μm; UV λ_{max} 262 nm (ϵ 38 000), 310 (8900), 324 (9300), 378 (4100); NMR δ 3.30 (t, 2 H, J = 6 Hz), 4.35 (t, 2 H, J = 6 Hz), 3.91 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 7.13 (s, 1 H), 7.52–9.55 (m, 4 H). Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.29; N, 4.01. Found: C, 68.47; H, 4.32; N, 3.93.

Indole 11. Lithium aluminum hydride (0.400 g) was added in small portions to a solution of isatin 8 (1.300 g) in dry tetrahydrofuran (75 mL). After refluxing for 4 h, excess hydride was destroyed by the careful addition of saturated sodium sulfate solution. Evaporation of the filtered solution yielded a gum which was chromatographed on silica ($CHCl_3$ eluant) to give, after crystallization from ethanol, prisms of indole 11 (0.520 g): mp 134–135 °C; UV λ_{max} 254 (sh) nm (ϵ 47 000), 263 (70 000), 296 (13 000), 317 (9300), 360 sh (28 000), 376 (3500); NMR δ 3.43 (t, 2 H, J = 6.8 Hz), 4.31 (t, 2 H, J = 6.8 Hz), 3.97 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 6.91 (d, 1 H, J = 2.8 Hz), 7.03 (d, 1 H, J = 2.8 Hz), 7.16 (s, 1 H), 7.46–9.62 (m, 4 H); mass spectrum *m/e* (rel intensity) 303 (M^+, 100), 288 (54), 260 (24), 151.5 (5). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.20; H, 5.61; N, 4.62. Found: C, 79.11; H, 5.35; N, 4.83.

A minor reaction product (12%) was isolated by elution of the silica column and proved to be lysicamine (12), as shown by comparison (TLC, IR, mmp) with authentic material.

Isatin 14. Oxalyl chloride (0.600 g) was added dropwise to a solution of dehydroapomorphine dimethyl ether (13, 0.500 g) in a mixture of dry ether (35 mL) and tetrahydrofuran (10 mL). After 90 min, the solvent was evaporated and the residue was taken up in chloroform and washed with 5% sodium bicarbonate and then water. Evaporation of the solvent and crystallization from methanol afforded, in two crops, wine-red prisms of isatin 14 (0.320 g): mp 183–184 °C; IR 5.70, 5.83 μm; UV λ_{max} 215 nm (ϵ 11 000), 255 (33 000), 320 (6600), 525 (1200); NMR δ 3.21 (t, 2 H, J = 6 Hz), 3.78 (t, 2 H, J = 6 Hz), 3.85 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 7.05 (d, 1 H, J = 9 Hz), 7.95 (d, 1 H, J = 9 Hz), 7.31 (m, 1 H), 7.56 (m, 1 H), 9.11 (m, 1 H); mass spectrum *m/e* (rel intensity) 333 (M^+, 100), 319 (20), 305 (92), 290 (32), 277 (14), 262 (32), 234 (21), 219 (35), 190 (25), 166.5 (4). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.07; H, 4.50; N, 4.20. Found: C, 71.63; H, 4.60; N, 4.05.

Pyridone 15. Excess ethereal diazomethane was added to a solution of isatin 14 (0.070 g) in chloroform–methanol. After standing overnight, the mixture was worked up in the usual manner and the product chromatographed on silica (chloroform eluant) and crystallized from ethyl acetate–ether to give needles of pyridone 15 (0.060 g): mp 153–154 °C; IR 5.96 μm; UV λ_{max} 257 (sh) nm (ϵ 41 000), 268 (50 000), 302 (16 000), 320 (12 000), 346 (8300), 365 (1900), 384 (10 000); NMR δ 3.28 (t, 2 H, J = 6 Hz), 4.51 (t, 2 H, J = 6 Hz), 3.96 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 7.31 (s, 1 H), 7.13 (d, 1 H, J = 9 Hz), 7.70 (d, 1 H, J = 9 Hz), 7.36 (m, 1 H), 7.20 (m, 1 H), 9.33 (m, 1 H); mass spectrum *m/e* (rel intensity) 361 (M^+, 100), 346 (15), 318 (27), 303 (10), 274 (10), 260 (9), 180.5 (11). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.86. Found: C, 72.91; H, 5.18; N, 3.77.

Anhydride 16. Isatin 14 (0.060 g) was oxidized by *m*-chloroperbenzoic acid as described above for the oxidation of the isomeric isatin 8. The anhydride 16 (0.050 g) crystallized from acetone as yellow needles: mp 194–195 °C; IR 5.59, 5.87 μm; UV λ_{max} 240 nm (ϵ 17 000), 261 (25 000), 284 sh (8100), 309 sh (7100), 323 (8400), 358 (3900), 387 (3400); NMR δ 3.23 (t, 2 H, J = 6 Hz), 4.25 (t, 2 H, J = 6 Hz), 3.88 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.23 (d, 1 H, J = 9 Hz), 7.78 (d, 1 H, J = 9 Hz), 7.45 (m, 1 H), 7.31 (m, 1 H), 9.25 (m, 1 H); mass spectrum *m/e* (rel intensity) 349 (M^+, 100), 321 (37), 306 (35), 281 (10), 278 (16), 263 (16), 234 (15), 174.5 (1). Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.29; N, 4.01. Found: C, 68.10; H, 4.35; N, 3.87.

Cyanoborohydride Reduction of 1. A methanol–tetrahydrofuran solution of dehydronuciferine (1, 0.100 g) was acifified to pH 3 with 1% HCl, and excess $NaCNBH_3$ was added. After 30 min, the usual workup afforded (ethanol crystallization) racemic nuciferine (5, 0.090 g), mp 133–135 °C, identical (IR, UV, TLC, mmp) with authentic material.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work and the Fundación Juan March for a supporting fellowship to one of us (J. M. Saá).

Registry No.—1, 7630-74-2; 2, 64938-90-5; 3 HCl, 64938-91-6; 4, 64957-46-6; 8, 64938-92-7; 9, 64938-93-8; 10, 64938-94-9; 11, 64938-95-0; 13, 18605-43-1; 14, 64938-96-1; 15, 64938-97-2; 16, 64938-98-3; trifluoroacetic anhydride, 407-25-0; benzoyl chloride, 98-88-4; oxalyl chloride, 79-37-8; diazomethane, 334-88-3.

References and Notes

(1) A. Venkateswarlu and M. P. Cava, *Tetrahedron*, **32**, 2079 (1976).
(2) J. M. Saá and M. P. Cava, *J. Org. Chem.*, **42**, 347 (1977).

(3) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(4) B. Eistert and H. Selzer, *Chem. Ber.*, **96**, 1234 (1963).
(5) C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, **20**, 1699 (1967).
(6) J. G. Cannon in "Advances in Neurology," Vol. 9, D. Calne, T. N. Chase, and A. Barbeau, Ed., Raven Press, New York, N.Y., 1975, p 177, and references cited therein.
(7) C. F. Lane, *Synthesis*, 135 (1975).
(8) M. P. Cava, D. L. Edie, and J. M. Saá, *J. Org. Chem.*, **40**, 3601 (1975).
(9) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 56. Strychnos Alkaloids[1]

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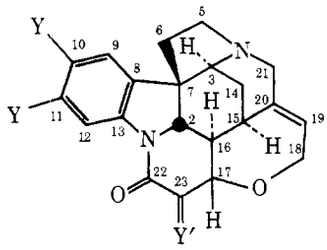
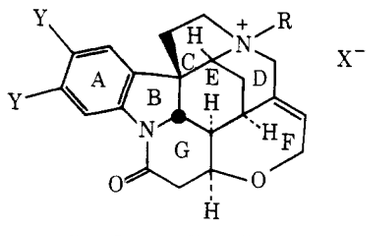
An exhaustive ^1H and ^{13}C NMR analysis of the Strychnos alkaloids strychnine, brucine, Wieland Gumlich aldehyde, diaboline, hemitoxiferin-I, 10-methoxy-*O*-demethyltsilanine, toxiferine-I, and strychnospermine and their derivatives is presented. The data have been used for the solution of a variety of configurational and conformational problems.

The naturally abundant Strychnos alkaloids are characterized by an azabicyclo[3.3.1]nonane system fused to an indoline unit. They vary in structural complexity from the pentacyclic alkaloid tubifolidine (**14** minus the 16β-methyl group) to heptacyclic strychnine (**1a**) and "dimeric" substances such as toxiferine-I (**12**). The present communication presents a composite study of the ^{13}C NMR spectroscopy of the Strychnos and related alkaloids.[3]

The study was initiated by the analysis of the spectra of strychnine (**1a**), its hydrochloride (**2a**), methiodide (**2b**), *N*-oxide (**2c**), and 23-oximino derivative (**1b**), as well as of brucine (**1c**) and its hydrochloride (**2d**).[6] The aromatic carbon resonances of compounds **1** and **2** can be assigned by comparison with indoline shifts of Aspidosperma bases.[7] The aromatic methines can be differentiated from the olefinic ones by the larger residual coupling in the single-frequency off-resonance decoupled (sford) spectra (the decoupler frequency being set at the high-field end of the spectrum and therefore close to the olefinic proton resonances) and the splitting caused by the meta hydrogens ($^3J_{CH}$).[8] Most upfield carbon signals are assigned on the basis of their multiplicities and chemical-shift theory.[9] Being an allylic carbon, C(15) shows larger residual coupling than C(16) and reveals long-range coupling with olefinic H(19). C(18) couples with the same hydrogen. The distinction between the aminomethylenes C(5) and C(21) is founded on the exhibition of second-order coupling by the former but not the latter and unequal residual coupling of the latter to each of its own hydrogens. For further differentiation of the aminomethylenes as well as the methylenes at highest field, C(6) and C(14), individual carbons and their attached hydrogens were related by way of Birdsall plots, a series of sford experiments at various decoupling frequencies.[10] All carbon shifts of compounds **1** and **2** are presented in Table I.

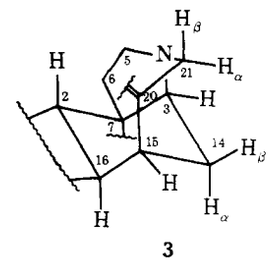


1a, Y = H; Y′ = H_2
b, Y = H; Y′ = NOH
c, Y = OMe; Y′ = H_2



2a, R = Y = H; X = Cl
b, R = Me; X = I; Y = H
c, R = O^-; Y = H
d, R = H; X = Cl; Y = OMe

The above study necessitated a ^1H NMR spectral investigation of the Strychnos alkaloid systems, especially in order to ascertain the conformation of strychnine (**1a**) and its relatives. Even though an analysis of a 250-MHz ^1H NMR spectrum of the alkaloid has been reported,[11] the new measurements (Tables II and III) require a reversal of shift assignment within each pair of geminal hydrogens at C(5), C(14), and C(21). The small vicinal couplings, ca. 2–5 Hz, between the hydrogens of C(3), C(14), C(15), and C(16) and the large H(2)–H(16) coupling, 10.5 Hz, confirm the equatoriality of H(3) and H(15) and the axiality of H(2) and H(16) within a chair conformation of ring E (**3**). It has been shown that H(18α) is coupled with H(15) and H(19) with the low-field hydrogen at C(21).[11] Further double irradiation experiments



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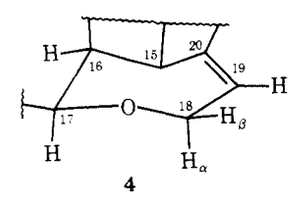

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