alkane), 2.1 (m, 4 H, CH_2CO_2H, CH_2CH_2I), 3.0 (t, 2 H, CH_2I), 11.9 (s, 1 H, CO_2H).

22-Iododocosanoic Acid. 21-Docosenoic acid (55 mg, 0.16 mmol) was hydroborated with dicyclohexylborane (0.32 mmol) at 0 °C. The organoborane was iodinated with a mixture of sodium acetate (0.32 mmol), sodium iodide (0.16 mmol), and chloramine-T (0.32 mmol). The product was isolated by column chromatography on silica gel (10% ethyl acetate–hexane): yield 68 mg (91%); mp 71–72 °C; mass spectrum, *m/e* 466.5 (calcd for 466.5); NMR ($CDCl_3$) δ 1.2 (s, 36 H, alkane), 2.1 (m, 4 H, CH_2CO_2H and CH_2CH_2I), 3.0 (t, 2 H, CH_2I, 11.9 (s, 1 H, CO_2H).

Iodobenzene. Triphenylborane was prepared according to a published procedure.[12] The triphenylborane (247 mg 1.02 mmol) was placed in a 5-mL, dry, nitrogen-flushed flask containing 1.5 mL of THF. Sodium acetate, sodium iodide, and chloramine-T (1.02 mmol) were added at room temperature. The yield of iodobenzene (100%) was determined via GLC analysis (yield based on the migration of one phenyl group per organoborane molecule).

(12) Koster, R.; Binger, P.; Fenzye, W. *Inorg. Synth.* 1941, *15*, 134.

Acknowledgment. We thank the National Institutes of Health (1-R01-GM-25187-02) for support of this research.

Registry No. 1-Hexene, 592-41-6; 1-iodohexane, 638-45-9; cyclohexene, 110-83-8; iodocyclohexane, 626-62-0; 5-benzoxy-1-pentene, 29264-40-2; 1-benzoxy-5-iodopentane, 74203-20-6; 3-(*p*-tolylthio)-2-methylpropene, 54844-24-5; 3-(*p*-tolylthio)-2-methyl-1-iodopropane, 74203-21-7; safrole, 94-59-7; 3-[3,4-(methylenedioxy)phenyl]-1-iodopropane, 74203-22-8; methyl 10-undecenoate, 111-81-9; methyl 11-iodoundecanoate, 929-33-9; 18-nonodecenoic acid, 76998-87-3; 19-iodononodecanoic acid, 76998-88-4; 21-docosenoic acid, 53821-23-1; 22-iododocosanoic acid, 76998-89-5; iodobenzene, 591-50-4; triphenylborane, 960-71-4; methyl 10-undecynoate, 2777-66-4; (*E*)-11-iodo-10-undecenoic acid, 76998-90-8; catecholborane, 274-07-7; (*E*)-11-(1,3,2-benzodioxaborol-2-yl)-10-undecenoic acid, 76998-91-9; iodine monochloride, 7790-99-0; dicyclohexylborane, 1568-65-6; sodium iodide, 7681-82-5; BH_3–THF, 14044-65-6.

Notes

Dehydroaporphines. Enamine-Type Michael Additions

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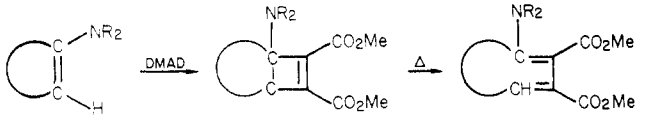
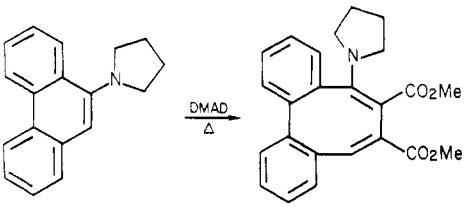
We have shown previously that dehydroaporphines show a certain degree of enamine-type character, as evidenced by their behavior on protonation,[1] Reimer–Tiemann formylation,[2] and acylation.[3] We now report the first study of the reactions of a typical dehydroaporphine, dehydronuciferine (1), with Michael acceptors and the resulting synthesis of some new types of 7-substituted aporphines of potential pharmacological interest.

Results and Discussion

Enamines derived from cyclic ketones are known to undergo [2 + 2] cycloadditions to dimethyl acetylenedicarboxylate (DMAD) to give thermally labile cyclobutenes which, on heating, are transformed into diene diesters; the overall process affords a simple bishomologation of the carboxylic ring of the original enamine.[4]



This process has been carried out successfully even in the case of 9-(dialkylamino)phenanthrenes. For example, a dibenzocyclooctatetraene derivative was produced smoothly when 9-pyrrolidinophenanthrene was heated in dioxane with DMAD, as shown below.[5]



The analogous reaction of dehydronuciferine (1) with DMAD in refluxing dioxane proceeded very sluggishly and required over 5 days for the consumption of the original alkaloid. Chromatographic separation afforded none of the *C*-dihomoaporphine **2**; the isomeric diesters **3** and **4** were produced in good yield in hot benzene–methanol, the reaction going largely to completion in 30 min. The stereochemistry of esters **3** and **4** was clearly revealed by their NMR spectra. As predicted by molecular models, one of the ester methoxyls of the trans isomer **4** lies over the lower aromatic ring of the phenanthrene system and appears at the rather shielded position of δ 3.43. In addition, the olefinic proton of **4** is deshielded by the adjacent carbomethoxyl and appears δ 7.20, as compared to the more normal value of δ 6.43 in the cis isomer **3**. The esters **3** and **4** were slowly interconverted in refluxing benzene–methanol. After 4 days of heating, the cis isomer **3** yielded a mixture of **3** and **4** containing about 35% **4**; after 4 days of similar treatment, the far more stable trans isomer **4** was converted to **3** to an extent of only about 1%.

The mechanism of formation of **3** and **4** merits some comment. The initial product of addition of dehydronuciferine to DMAD may be formulated as the dipolar species **5**. Cyclization of **5** to the cyclobutene **6** involves no unusual steric problems, but ring opening of **6** to the strained tetracyclic diene **2** is a process of high enough energy that ring cleavage back to **5** occurs instead (Scheme

(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) J. M. Saá and M. P. Cava, *J. Org. Chem.*, **43**, 1096 (1978).
(4) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).
(5) D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans 1*, 1674 (1977).

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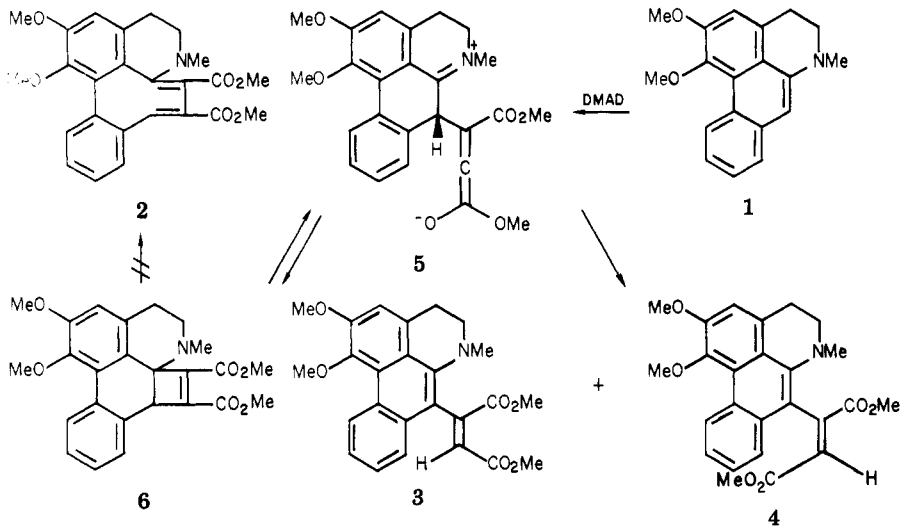
Scheme I

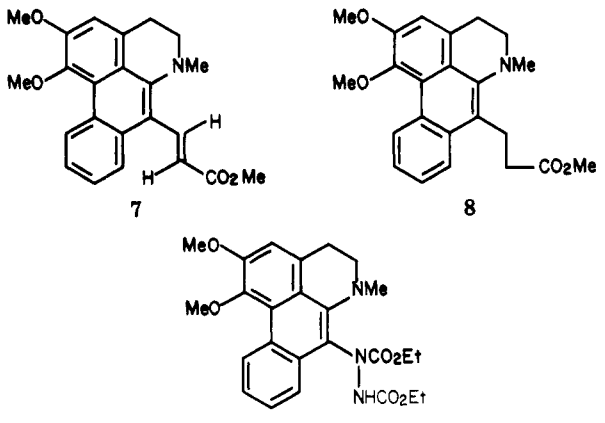


I). A prototropic shift of the C-7 proton to the anionic side chain results in the formation of **3** and **4**. Although this process occurs much more readily in a methanolic solvent mixture than in an aprotic solvent, proton transfer from methanol to the product does not take place. Thus, when the addition of **1** to DMAD is carried out in CD_3OD, no deuterium enters the products, proving that the proton transfer from C-7 is intramolecular.

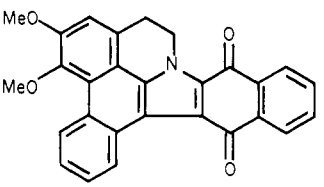
The reaction of dehydronuciferine (**1**) with methyl propiolate in hot methanolic benzene was slower than that of DMAD but afforded a fairly good yield of a single crystalline adduct. This compound was assigned structure **7**, in accord with the coupling constant (J = 16 Hz) of its two olefinic protons.

The corresponding reaction of **1** with methyl acrylate was very sluggish and afforded only a poor yield of the oily addition product **8** after 1 week of reflux time. No adduct of **1** with acrylonitrile could be obtained.

The addition of simple enamines to diethyl azodicarboxylate (DEAD) has been reported.[6] Similarly, **1** reacted slowly with DEAD in hot toluene to give the crystalline adduct **9**.



The reaction of **1** with excess 1,4-naphthoquinone in refluxing methanol afforded a complex mixture from which the major red crystalline component was isolated in 27% yield. The spectroscopic properties of this compound, which no longer contained an N-methyl group, were in good accord with the heptacyclic structure **10**. The loss of the N-methyl group of a dehydroaporphine in the course of a reaction at C-7 is not without precedent.[3]



Experimental Section

Melting points are uncorrected. NMR spectra ($CDCl_3$ containing tetramethylsilane as internal standard), ultraviolet spectra (ethanol), infrared spectra (KBr), and mass spectra were determined by using Varian A-60, Bruker 250, and Perkin Elmer 202, 137, and 270 spectometers, respectively. High-resolution mass spectra were determined on a Hitachi Perkin-Elmer RMH-2 instrument.

Reaction of 1 with Dimethyl Acetylenedicarboxylate. A. In Methanol. To a solution of dehydronuciferine (**1**; 0.30 g, 1.02 mmol) in benzene–methanol was added a benzene solution of dimethyl acetylenedicarboxylate (0.16 g, 1.13 mmol) and the reaction mixture was heated on a steam bath for 30 min. The solvent was removed in vacuo and the residue was subjected to chromatography over silica gel with 25% ethyl acetate in hexane. The more mobile spot was collected and recrystallized from ethyl acetate to give the trans isomer **4** (0.23 g) as orange prisms: mp 142.5–143.5 °C; UV max (EtOH) 253 nm (log ϵ 4.48), 263 (4.49), 323 (3.95), 357 (3.85), 376 (3.70); NMR ($CDCl_3$) δ 9.76–9.46 (m, 1 H), 7.76–7.33 (m, 3 H), 7.20 (s, 1 H), 7.06 (s, 1 H, C_3-H), 4.00, 3.93, 3.66, and 3.43 (s, 3 H each, OCH_3), 2.70 (s, 3 H, NCH_3); IR (KBr) 1742, 1724 cm^{-1}; mass spectrum, m/e (relative intensity) 435 (100), 420 (19), 388 (31), 376 (42), 361 (35), 344 (29), 316 (54); high-resolution mass spectrum calcd for $C_{25}H_{25}NO_6$ 435.1674, found 435.1693.

The less mobile spot from the above reaction was collected and recrystallized from ethyl acetate to give yellow crystals of **3** (0.18 g): mp 160–161 °C; UV max (EtOH) 253 nm (log ϵ 4.49), 263 (4.49), 323 (3.95), 357 (3.60), 375 (3.58); IR (KBr) 1742, 1724 cm^{-1}; NMR ($CDCl_3$) δ 9.83–9.66 (m, 1 H), 8.20–8.05 (m, 1 H), 7.60–7.43 (m, 2 H), 7.10 (s, 1 H), 6.43 (s, 1 H), 4.00 (s, 3 H), 3.88 (s, 6 H), 3.73 (s, 3 H), 2.78 (s, 3 H, NCH_3); mass spectrum, m/e (relative intensity) 435 (100), 420 (19), 388 (28), 376 (46), 361 (35), 344 (31), 316 (54); high-resolution mass spectrum calculated for $C_{25}H_{25}NO_6$ 435.1674, found 435.1670.

B. In Dioxane. A solution of dehydronuciferine (**1**; 0.2 g, 0.68 mmol) and dimethyl acetylenedicarboxylate (0.099 g, 0.70 mmol) in dry dioxane (3.2 mL) was refluxed under nitrogen for 3 days. More acetylenic ester was added (0.099 g, 0.70 mmol) and heating was continued for 2 more days. Removal of the solvent under

(6) G. Pitacco, C. P. Francesco, C. Russo, and E. Valentin. *Gazz. Chim. Ital.*, **105**, 1137 (1975).

reduced pressure and separation by column chromatography over silica gel with 25% ethyl acetate in hexane gave the trans isomer **4** (0.063 g) and the cis isomer **3** (0.018 g).

Thermal Isomerization of *cis*-3 and *trans*-4 Esters. A solution of the cis ester **3** (0.05 g, 0.11 mmol) in benzene (2 mL) and methanol (1 mL) was refluxed under nitrogen for 4 days. Evaporation of the solvents under reduced pressure, followed by column chromatography over silica gel with 25% ethyl acetate in hexane, gave the trans ester **4** (0.012 g) and the cis ester **3** (0.020 g). After 4 days of similar treatment, the trans ester **4** was converted to the cis ester **3** to an extent of only about 1%.

Reaction of 1 with Methyl Propiolate. A solution of dehydronuciferine (**1**; 0.092 g, 0.314 mmol) in methanol (1 mL)–benzene (1 mL) containing excess methyl propiolate was refluxed under nitrogen for 2 days. Evaporation under reduced pressure, followed by column chromatography over silica gel with 25% ethyl acetate in hexane, gave the Michael adduct **7** in 56% yield. Crystallization from ethyl acetate gave yellow-orange crystals: mp 157.5–158.5 °C; UV max (EtOH) 240 nm (sh, log ϵ 5.15), 253 (sh, 5.13), 260 (5.17), 300 (4.70), 356 (4.35), 373 (sh, 4.30), 450 (4.11); IR (KBr) 1739, 1667, 1626 cm^{-1}; NMR ($CDCl_3$) δ 9.63–9.58 (dd, 1 H, J = 8, 2 Hz), 8.26–8.22 (dd, 1 H, J = 8, 2 Hz), 7.58–7.44 (m, 2 H), 7.08 (s, 1 H, C_3-H), 8.40 and 6.40 (d, 1 H each, J = 16 Hz), 4.02 (s, 3 H, OCH_3), 3.86 and 3.84 (s, 3 H each, OCH_3), 3.42 (t, 2 H), 3.16 (t, 2 H), 2.88 (s, 3 H, NCH_3); mass spectrum, m/e (relative intensity) 377 (100), 362 (13), 330 (17), 318 (14), 304 (100), 288 (22), 273 (63); high-resolution mass spectrum calcd for $C_{23}H_{23}NO_4$ 377.1620, found 377.1633.

Reaction of 1 with Methyl Acrylate. Excess methyl acrylate was added to a solution of dehydronuciferine (**1**; 0.10 g, 0.34 mmol) in methanol (1 mL) and the solution was refluxed under nitrogen for 7 days. After evaporation of the solvent, the residue was chromatographed over silica gel with 50% ethyl acetate in hexane to give recovered **1** (0.079 g) and 0.014 g of the Michael adduct **8** as a greenish yellow oil: UV max (EtOH) 230 nm (log ϵ 4.18), 256 (4.22), 275 (sh, 3.93), 312 (3.60), 354 (2.93), 373 (2.93); IR (film) 1724 cm^{-1}; NMR ($CDCl_3$) δ 9.72 (dd, 1 H, J = 8, 2 Hz), 8.02 (dd, 1 H, J = 8, 2 Hz), 7.63–7.50 (m, 2 H), 7.12 (s, 1 H, C_3-H), 4.03, 3.88, and 3.74 (s, 3 H each, OCH_3), 3.60 (t, 2 H), 3.34 (t, 2 H), 3.19 (t, 2 H), 2.79 (s, 3 H, NCH_3), 2.69 (t, 2 H); mass spectrum, m/e (relative intensity) 279 (5), 306 (17), 149 (19); high-resolution mass spectrum, calcd for $C_{23}H_{25}NO_4$ 379.1776, found 379.1778. Acrylonitrile failed to react under the same conditions.

Reaction of 1 with Diethyl Azodicarboxylate. To a solution of dehydronuciferine (**1**; 0.23 g, 0.785 mmol) in anhydrous toluene (5 mL) was added diethyl azodicarboxylate (0.15 mL, 0.952 mmol), and the mixture was refluxed for 24 h. More diethyl azodicarboxylate (0.2 mL) was added and the heating continued for 48 h. Evaporation of the solvent under reduced pressure and separation by column chromatography over silica gel with 25% ethyl acetate in hexane gave the crystalline adduct **9** (0.152 g, 41%). Crystallization from ethyl acetate gave green yellow crystals: mp 167–169 °C; UV max (EtOH) 230 nm (log ϵ 4.15), 250 (4.69), 258 (4.65), 277 (sh, 4.23), 320 (4.11), 350 (sh, 3.64), 367 (3.43); IR (KBr) 3333, 1770, 1724 cm^{-1}; NMR ($CDCl_3$) δ 9.76–9.56 (m, 1 H), 8.53–8.23 (m, 2 H), 7.66–7.53 (m, 2 H), 7.13 (s, 1 H, C_3-H), 4.40–4.08 (m, 4 H), 4.03 and 3.70 (s, 3 H each, OCH_3), 2.80 (s, 3 H, NCH_3), 1.33–1.10 (t, 6 H); mass spectrum, m/e (relative intensity) 467 (16), 379 (41), 335 (24), 334 (100), 319 (18), 306, (52), 305 (76); high-resolution mass spectrum calcd for $C_{25}H_{29}N_3O_6$ 467.2046, found 467.2058.

Reaction of 1 with Naphthoquinone. Excess naphthoquinone (0.19 g, 1.2 mmol) was added to a solution of dehydronuciferine (**1**; 0.015 g, 0.051 mmol) in methanol (2 mL) and the mixture was refluxed under nitrogen for 2 days. The unreacted dehydronuciferine was eluted first from the column with 25% ethyl acetate in hexane. A red band eluted next, which on evaporation, followed by two crystallizations from chloroform, gave red crystals of compound **10** in 27% yield: mp 295–297 °C; UV max (EtOH) 225 nm (sh, log ϵ 4.26), 239 (sh, 4.27), 260 (4.34), 271 (4.39), 282 (4.38), 316 (4.07), 341 (sh, 3.78), 355 (3.59), 490 (3.41); IR (KBr) 1653 cm^{-1}; NMR ($CDCl_3$) δ 10.12 (d, 1 H, J = 8 Hz), 9.65 (dd, 1 H, J = 8, 2 Hz), 8.34 (dd, 1 H, J = 8, 2 Hz), 8.20 (dd, 1 H, J = 8, 2 Hz), 7.80–7.64 (m, 4 H), 7.20 (s, 1 H, C_3-H), 5.06 (t, 2 H), 4.06 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.50 (t, 2 H); mass spectrum, m/e (relative intensity) 433 (100), 418 (39), 390 (14), 375 (17); high-resolution mass spectrum calcd for $C_{28}H_{19}NO_4$ 433.1308, found 433.1322.

Acknowledgment. We thank the National Institutes of Health for a grant (CA 22337-03) in support of this work.

Registry No. **1**, 7630-74-2; **3**, 77027-97-5; **4**, 77027-98-6; **7**, 77027-99-7; **8**, 77028-00-3; **9**, 77028-01-4; **10**, 77028-02-5; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8; methyl acrylate, 96-33-3; diethyl azodicarboxylate, 1972-28-7; naphthoquinone, 130-15-4.

Acid-Catalyzed Hydrolysis of Phenyl Acetate

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Yates and McClelland suggested that the monotonic increase in the rate of hydrolysis of phenyl acetate in 1.0–12.0 M sulfuric acid masked a changeover from an $A_{Ac}2$ to an $A_{Ac}1$ mechanism.[1] They analyzed their kinetic data using Yates' modified hydration parameter treatment (eq 1),[2] where k_ψ is the observed first-order rate coefficient,

$$\log k_\psi + mH_o = r \log a_W + \text{constant} \quad (1)$$

m = 0.62 for acetate esters, and H_o and a_W have their usual meanings. The value of r (1.62) at low acidity (0–70% H_2SO_4) was characteristic of an A2 reaction. At higher acidities the r plot begins to curve and its slope to fall. Unfortunately, sulfonation also begins to occur, and the hydrolysis of phenyl acetate could not be studied in >12.5 M sulfuric acid.

More recently, Rochester and Attiga have studied the hydrolysis of phenyl acetate in 0–9 M perchloric acid.[3] Analysis of the data in terms of the Bunnett w and w^* relationships[4] for a weakly basic substrate (eq 2 and 3) gave

$$\log k_\psi + H_o = w \log a_w + \text{constant} \quad (2)$$

$$\log k_\psi - \log C_{H^+} = w^* \log a_w + \text{constant} \quad (3)$$

values of w and w^* of 2.5 (curved) and −0.3, respectively, again consistent with a bimolecular (A2) mechanism. Evidence for a possible change to an A1 mechanism was adduced from the decreasing slope of the w plot in >9.0 M perchloric acid although this could not be clearly established because kinetic data were not obtained at >9.67 M perchloric acid.

In order to confirm unequivocally the original suggestion[1] that there is a changeover of mechanism in the acid-catalyzed hydrolysis of phenyl acetate, we have extended previous data in perchloric acid to 11.5 M, followed the rate of hydrolysis in concentrated hydrochloric acid, and determined the Arrhenius parameters for hydrolysis under a variety of different acidic conditions in sulfuric and perchloric acids. Values of k_ψ for the hydrolysis of phenyl acetate in a number of mineral acids are shown in Figure 1. The data of Yates and McClelland[1] for sulfuric acid and those of Rochester and Attiga[3] for perchloric acid

(1) K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).
(2) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).
(3) S. A. Attiga and C. H. Rochester, *J. Chem. Soc., Perkin Trans. 2*, 466 (1978).
(4) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).

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