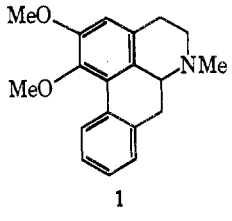
Table I
Dehydrogenation of Some Aporphines to Dehydroaporphines[a]

Aporphine used	(wt, mg)	10% Pd/C, mg	Product	Reaction time, min	Yield,[b] %
Nuciferine (1)	(100)	100	(4)	15	90
Dicentrine (2)	(140)	140	(5)	15	85
Ocopodine (3)	(150)	150	(6)	15	80
Thalicarpine (7)	(140)	140	(8)	60	55

[a] Acetonitrile solvent (10 ml) in all cases. [b] Yields of crystalline products, identical with authentic samples (melting point, ir).[1]

are indicated in Table I. The selective dehydrogenation of the aporphine moiety of thalicarpine (7) is worthy of note. In accord with this result, the simple benzylisoquinoline base laudanosine (9) was recovered unchanged after being subjected to the general dehydrogenation procedure.

The method described here would appear to displace chemical oxidations as the method of choice for the conversion of a nonphenolic aporphine to the corresponding dehydroaporphine. Preliminary dehydrogenation experiments using noraporphines or phenolic aporphines indicate the formation of products which are rapidly attacked by air during work-up, as might be expected from the results of chemical oxidation of similar substrates.[1]



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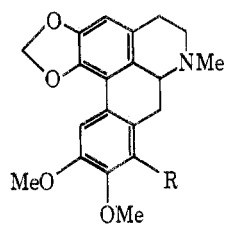
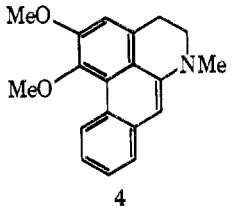


2, R = H
3, R = OMe



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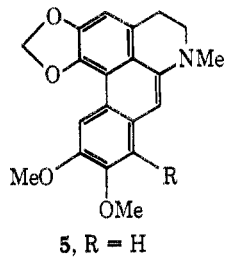
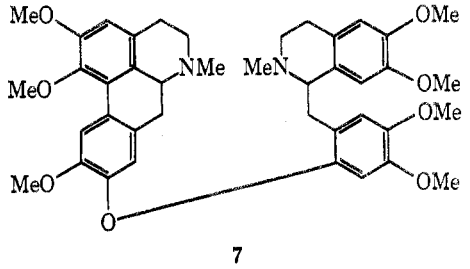


5, R = H
6, R = OMe



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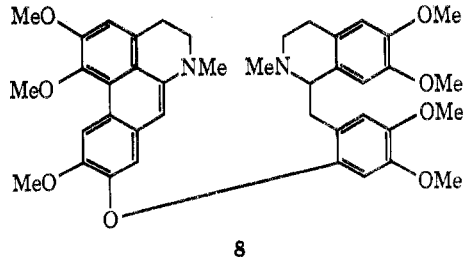

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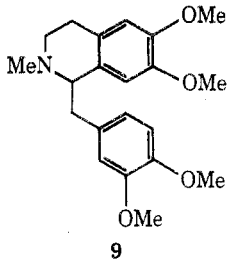

9

Experimental Section

In a typical experiment, a mixture of the aporphine (see Table I) and 10% Pd/C in acetonitrile was refluxed under nitrogen for 15 min. The catalyst was filtered off and the solvent was removed in vacuo. The yellow-green residue was crystallized from acetone or methanol. Dehydrothalicarpine (8) was isolated by PLC (silica gel plates, $CHCl_3$ + 10% MeOH), followed by crystallization.

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

Registry No.—1, 475-83-2; 2, 517-66-8; 3, 19893-95-9; 4, 7630-74-2; 5, 19843-03-9; 6, 33117-76-9; 7, 5373-42-2; 8, 7224-94-4.

References and Notes

(1) M. P. Cava, A. Venkateswarlu, M. Srinivasan, and D. L. Edie, *Tetrahedron*, **28**, 4299 (1972).

Novel Rearrangements of Morphanthridines

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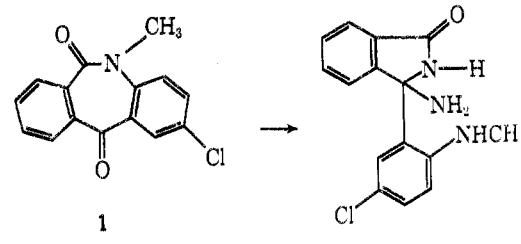
During the course of our investigations toward the synthesis of 9,13b-dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-6-one[1] it was reported that 2-chloro-5-methylmorphanthridine-6,11(5*H*)-dione (1), in the presence of ammonia and NH_4Cl, rearranged in good yield to 3-amino-3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (2). This observation

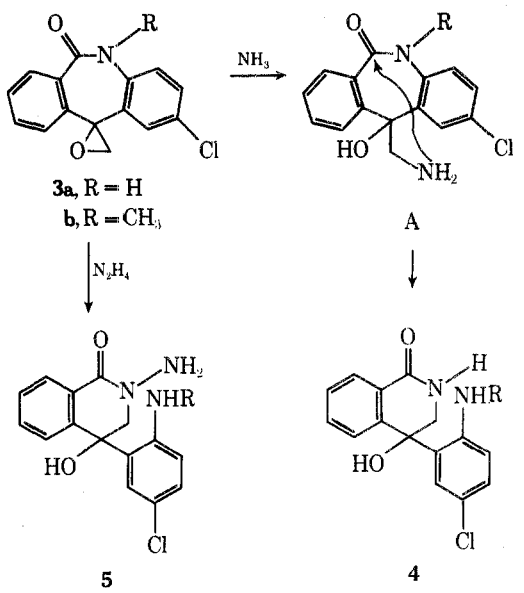


1 2

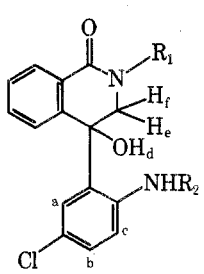
prompted further investigations into the possible rearrangements of other morphanthridines functionalized at the 11 position. We now wish to report several successful examples of such rearrangements.

When 2-chlorospiro[morphanthridine-11,2′-oxirane]-6-one (3a) was allowed to react with ammonia in a steel vessel at 120°, it rearranged to form 4-(2-amino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4a) in 30% yield (Scheme I). If the morphanthridine was substituted on the nitrogen, e.g., 3b, the reaction proceeded in much higher yield to 4b. Similarly, the treatment of 3a with hydrazine afforded 4-(2-amino-5-chlorophenyl)-3,4-dihydro-4-hydroxy-(2-amino)isocarbostyril (5a) in 50% yield.

Scheme I



The structures of 4 and 5 were established by their characteristic NMR spectra. The aromatic proton b in the angular phenyl group of **4a** appears as a multiplet at δ 7.00, proton c, a doublet, appears at δ 6.74, but proton a, also a doublet, is strongly shifted upfield to δ 6.08. This shift is caused partly by the influence of the nuclear substituents but mainly it is due to the geometry of the molecule. Models indicate that the phenyl group is aligned almost 90° to the plane of the isoquinoline nucleus and the proximity of the a proton to the shielding cone of the condensed aromatic ring causes the shift. When $R_1 = NH_2$ in formula D, the



D

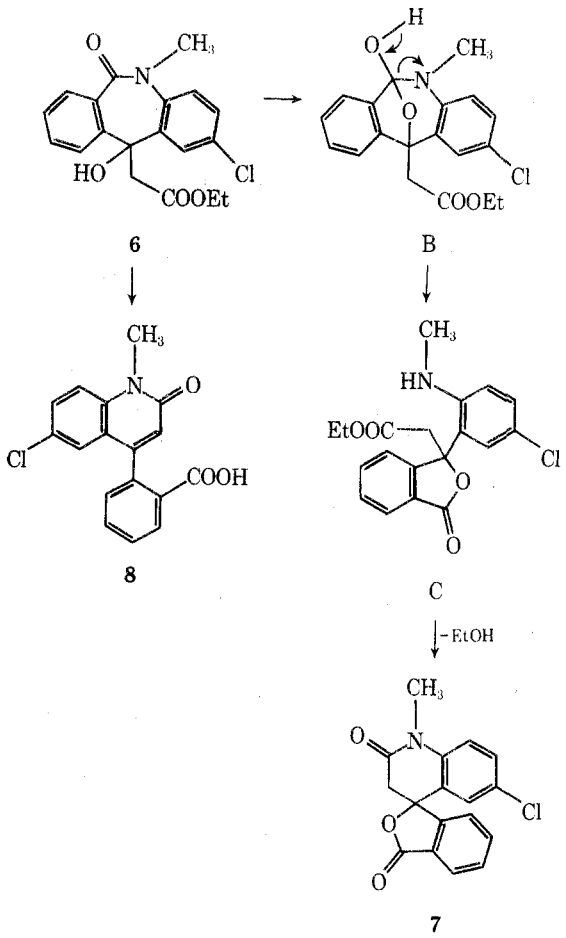
methylene protons H_e and H_f, which are magnetically nonequivalent owing to the asymmetric center at carbon 4, appear as an AB quartet and their chemical shifts are δ 4.36 and 3.42. When R_1 = H and R_2 = H or CH_3 it is observed that further coupling of the farther downfield geminal proton (H_e or H_f) to the amide proton occurs and, instead of the doublet, a multiplet is seen.

It is believed that the rearrangement proceeds by attack of ammonia (or hydrazine) on the epoxide ring to form the intermediate amino alcohol A followed by a nucleophilic attack of the amine on the amide carbonyl at the 6 position with concomitant ring opening.

We observed further that at 180°, **6** rearranged to form spiro compound **7** in 47% yield. The structure of **7** was confirmed based on the following spectral evidence. In the infrared two carbonyl absorptions at 1772 (lactone) and 1680 cm^{-1} (cyclic lactam) were observed. In the NMR spectrum, two separate aromatic regions were observed. The phthalan protons appeared between δ 8.10 and 7.60 while the quinoline protons were shifted slightly upfield, probably owing to the shielding effect of the other aromatic ring. Two methylene protons appeared as a singlet at δ 3.16.

The rearrangement (Scheme II) is believed to proceed by

Scheme II



a nucleophilic attack of the hydroxy on the amide carbonyl possibly forming the bridged intermediate B which then opens to the intermediate C. This in turn spontaneously cyclizes with loss of ethanol to form product **7**.

Treatment of **6** with hydrazine leads to the carbostyril **8** isolated as the hydrazine salt.[2] The assignment of structure **8** was based on comparison of its NMR spectrum with that of 1-methyl-4-phenylcarbostyril[3] (**9**).

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. All pure materials were run as Nujol or halocarbon mulls. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Mass spectra were determined on an LKB 9000 spectrometer. All elemental analyses were performed by Mr. William Bonkoski and associates at Sandoz, Inc.

2-Chlorospiro[morphanthridine-11,2'-oxirane]-6-one (3a). A mixture of 10.0 g (0.039 mol) of 2-chloromorphanthridine-6,11(5*H*)-dione[1] and 5.1 g (0.120 mol) of 57% sodium hydride in 150 ml of Me_2SO was stirred at room temperature for 30 min. To the resulting red solution was added 12.0 g (0.059 mol) of trimethylsulfonium iodide in two equal portions after which the mixture was stirred at room temperature for 4 hr. The reaction mixture was poured onto 1500 ml of cold water and the resulting precipitate was filtered, washed twice with water, and dried, yielding 6.2 g of **3a** (60%). The material was found pure enough for further use. A sample was recrystallized from methylene chloride–ether: mp 204–207°; ir ($CHCl_3$) 3480, 3180, 1660, 1370 cm^{-1}; NMR ($CDCl_3$ + Me_2SO) δ 10.43 (s, broad, 1), 8.20–7.20 (m, 7), 3.06 (s, 2).

4-(2-Amino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4a). The spirooxirane **3a** (4.0 g, 0.015 mol) was added to 15 ml of anhydrous liquid ammonia containing 0.1 ml of methanol. The mixture was heated in a steel cylinder at 120° for 24 hr. The

cylinder was cooled to room temperature and the ammonia was evaporated. The resulting solid was crystallized from methanol, yielding 1.3 g of **4a** (30%): mp 271–274°; ir (Nujol) 3440, 3390, 3360, 3210 (broad), 1670, 1650 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.80 (s, 1), 7.00 (m, 1), 6.74 (d, 1), 6.54 (s, 1), 6.08 (d, 1), 5.42 (s, 2), 4.10 (m, 1), 3.48 (d, 1).

Anal. Calcd for $C_{15}H_{13}N_2O_2Cl$: C, 62.4; H, 4.5; N, 9.7; Cl, 12.3. Found: C, 62.5; H, 4.4; N, 9.8; Cl, 12.5.

4-(2-Methylamino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4b). The reaction was performed as in the previous example (**3b**) and **4b** was isolated in 71% yield: mp 238–240°; ir (Nujol) 3380, 3190 (broad), 1670, 1460 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.82 (s, 1), 7.15 (m, 1), 6.75 (s, 1), 6.64 (d, 1), 6.02 (q, 1), 5.98 (d, 1), 4.20 (m, 1), 3.46 (d, 1), 2.75 (d, 3).

Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.5; H, 5.0; N, 9.3; Cl, 11.7. Found: C, 63.3; H, 5.3; N, 9.0; Cl, 11.5.

4-(2-Amino-5-chlorophenyl)-3,4-dihydro-4-hydroxy-(2-amino)isocarbostyril (5a). A suspension of 0.4 g of **3a** in 5 ml of anhydrous hydrazine was refluxed for 2.5 hr. The resulting solution was poured onto 150 ml of cold water. The mixture was extracted into ethyl acetate and the organic phase dried over sodium sulfate. The solvent was removed under reduced pressure to yield 300 mg of solid which was successively washed with methylene chloride, methanol, and ether to yield 225 mg of **5a** (50%): mp 266–268°; ir (Nujol) 3440, 3360, 3295 (broad), 1650, 1625, 1465 cm^{-1}; NMR (Me_2SO) δ 8.08 (m, 1), 7.80–7.30 (m, 3), 7.01 (m, 1), 6.74 (d, 1), 6.58 (s, 1), 6.36 (d, 1), 5.26 (s, 2), 5.03 (s, 2), 4.36 (d, 1), 3.42 (d, 1).

Anal. Calcd for $C_{15}H_{14}N_3O_2Cl$: C, 59.3; H, 4.7; N, 13.8; Cl, 11.7. Found: C, 59.0; H, 4.8; N, 14.0; Cl, 11.7.

2-Chloro-5-methyl-5,6-dihydro-11-hydroxy-6-oxomorphanthridine-11-acetic Acid Ethyl Ester (6). To a suspension of 14.0 g (0.215 mol) of zinc (activated, 10 mesh) in 75 ml of benzene was added a solution of 10.0 g (0.06 mol) of ethyl bromoacetate and 11.0 g (0.041 mol) of **1** in 75 ml of benzene. When the reaction started, the mixture was refluxed for 5 hr and then poured onto 400 ml of 20% acetic acid and extracted with ethyl acetate. The organic phase was washed twice with water and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 10.4 g of **6** (72%): mp 151–154°, recrystallization from ether raised the melting point to 162–165°; ir ($CHCl_3$) 3450 (broad), 1705, 1630 cm^{-1}; NMR ($CDCl_3$) δ 8.10–7.10 (m, 7), 5.46 (s, 1), 4.04 (q, 2), 3.64 (s, 3), 3.26 (d, 1), 3.02 (d, 1), 1.04 (t, 3).

Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.4; H, 5.0; N, 3.9; Cl, 9.9. Found: C, 63.5; H, 4.9; N, 3.8; Cl, 10.3.

6′-Chloro-1′-methylspiro[phthalan-1,4′(3*H*)-quinoline]-2′,3(1′*H*)-dione (7). Twelve grams of **6** was heated at 140°. The temperature was then raised to 180° over a period of 20 min and kept there for 1 hr, during which time the material was constantly stirred. The resulting solid was extracted in a Soxhlet apparatus using ether as the solvent. After 5 days, the ether was removed under reduced pressure to afford a solid which was crystallized from methylene chloride–ether to yield 5.0 g of **7** (47%): mp 234–235°; ir ($CHCl_3$) 1775, 1680 cm^{-1}; NMR ($CDCl_3$ + Me_2SO) δ 8.20–7.50 (m, 4), 7.40 (m, 1), 7.10 (d, 1), 6.75 (d, 1), 3.48 (s, 3), 3.16 (s, 2).

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.1; H, 3.9; N, 4.5. Found: C, 65.2; H, 3.8; N, 4.5.

6-Chloro-1-methyl-4-(2-carboxyphenyl)carbostyril Hydrazine Salt (8). A mixture of 1.0 g of **6** and 0.5 ml of anhydrous hydrazine in 10 ml of ethanol was refluxed for 4 hr. The solvent was removed under reduced pressure and the resulting foam was dissolved in 25 ml of methylene chloride. After the solution is formed, immediate crystallization occurs yielding 0.65 g of **8** (68%): the material has no definite melting point; ir (KBr) 1640 (broad), 1580 cm^{-1} (broad); NMR (Me_2SO) δ 8.20–7.00 (m, 12), 6.42 (s, 1), 3.68 (s, 3).

Anal. Calcd for $C_{17}H_{16}N_3O_3Cl$: C, 59.0; H, 4.7; N, 12.2. Found: C, 58.8; H, 4.6; N, 11.9.

The free acid of **8** was isolated by dissolving the hydrazine salt in 2 *N* sodium hydroxide followed by acidification with 2 *N* hydrochloric acid: mp >300°; ir (KBr) 1710, 1635, 1570 cm^{-1}; NMR (Me_2SO) δ 8.05 (m, 1), 7.76 (m, 4), 7.44 (m, 1), 6.96 (m, 1), 6.51 (s, 1), 3.69 (s, 3), exchangeable acid proton falls in with the water peak of the solvent.

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.2 ; H, 3.8; N, 4.5. Found: C, 65.0; H, 4.2; N, 4.3.

Tne values for the *N*-methyl protons and the proton in the 3 position of **9** were δ 3.68 and 6.49, respectively. These chemical shifts were in close accord with those of the free acid of **8** (see above).

Acknowledgment. The authors wish to thank Dr. Sandor Barcza and his associates for ir and NMR spectra, Mr. Robert Clark for mass spectra, and Dr. Renate Coombs for interpreting the mass spectra.

Registry No.—**1**, 16219-18-4; **3a**, 56761-60-5; **3b**, 56761-61-6; **4a**, 56761-62-7; **4b**, 56761-63-8; **5a**, 56761-64-9; **6**, 56761-65-0; **7**, 56761-66-1; **8**, 56761-68-3; **8** free acid, 56761-67-2; 2-chloromorphanthridine-6,11(5*H*)-dione, 786-87-8; ethyl bromoacetate, 105-36-2; hydrazine, 302-01-2.

References and Notes

(1) G. E. Hardtmann and H. Ott, *J. Org. Chem.*, **34**, 2244 (1969).
(2) We thank the reviewers for their suggestions.
(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

Preparation of Diketoheptadecanolides and Cyclohexadecanediones by Thermolysis of a Cyclic Diperoxide

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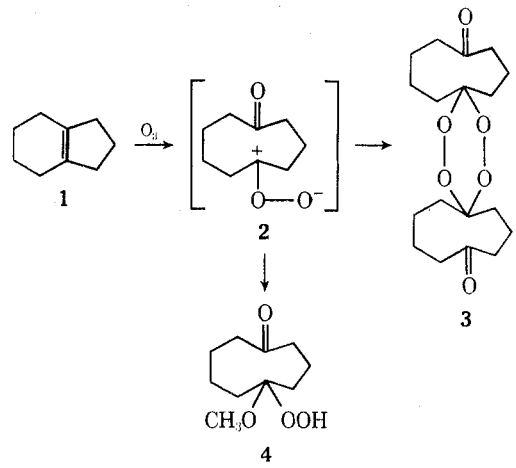
We wish to report the first preparation of four diketoheptadecanolides (**10**). Two known cyclohexadecanediones (**8** and **9**) are also obtained as products of the reaction employed. The method involves the thermolysis of the cyclic diperoxide **3** which is prepared by the reaction of **1** with ozone. The preparation of the diperoxide **3** will first be outlined and then the thermolysis reaction to yield the large-ring products will be discussed.

Criegee first reported[1] the isolation of a solid (<10% yield) upon ozonolysis of 4,5,6,7-tetrahydroindan (**1**) in petroleum ether and proposed that this compound was the cyclic diperoxide **3**, formed by dimerization of the intermediate Criegee zwitterion **2**[2] (Scheme I). In a previous paper[3]

Scheme I



we reported that ozonolysis of **1** in methylene chloride gave, in addition to the expected diketone **6**, a 17% yield of **3**. This product was not formed when the ozonolysis reaction was conducted in methanol, as **2** was converted to the hydroperoxide **4** before it had an opportunity to dimerize. Although our analytical data for diperoxide **3** differ somewhat from that reported by Criegee,[1] our spectral data (ir, NMR, and mass[4]) and molecular weight determination (see