A Novel Pschorr Reaction in the Papaverine Series

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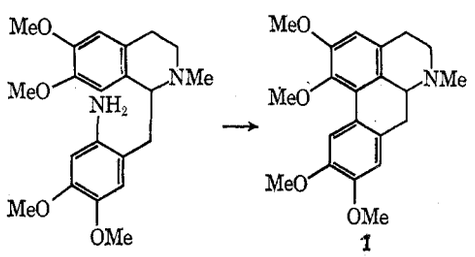
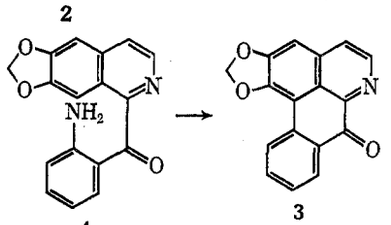
Diazotization of 6′-aminopapaverine (**5**) in dilute sulfuric acid, followed by treatment with copper, gave the indazole **7** as the major product; the oxoaporphine **8**, derived from the normal Pschorr product **9**, was the minor product. In contrast, diazotization of **5** in 46% sulfuric acid, followed by Pschorr cyclization, gave papaverine (**10**, 4.3%), the 1-oxoaporphine **12** (2.4%), and the indenoisoquinoline **11** (30%). Acid treatment of **11** affords **12** almost quantitatively. Chemical conversions of **11** and **12** to the known aporphine bases glaucine (**1**) and thaliporphine (**18**), respectively, are described.

The classical Pschorr synthesis of aporphine alkaloids consists of the copper-catalyzed decomposition of the diazonium salt derived from a 6′-amino-1,2,3,4-tetrahydroisoquinoline.[1] The original Gadamer synthesis of glaucine (**1**) from 6′-aminolaudanosine (**2**) exemplifies this synthesis.[2] The Pschorr procedure also takes an unexceptional course when applied to 6′-aminobenzoylisoquinolines, and affords a straightforward route to oxoaporphine alkaloids, *i.e.*, liriodenine (**3**) from amino ketone **4**.[3]



2 **1**



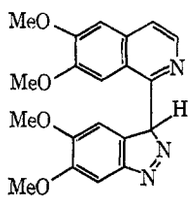
4 **3**

In 1904, Pschorr reported a very different result when he diazotized a typical 6′-aminoisoquinoline, 6′-aminopapaverine (**5**). Loss of nitrogen did not occur, and Pschorr isolated the stable "diazopapaverine," which he formulated as the isoindazole **6**. No aporphine-related substance was obtained.[4]

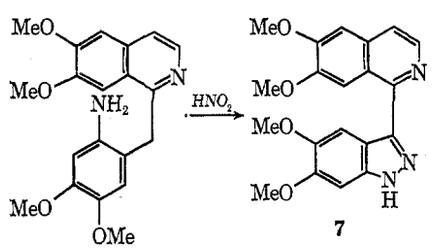
In this paper, we report a reinvestigation of the diazotization of 6′-aminopapaverine, including the conversion of this amine to a novel and hitherto unknown type of Pschorr reaction product.

Results

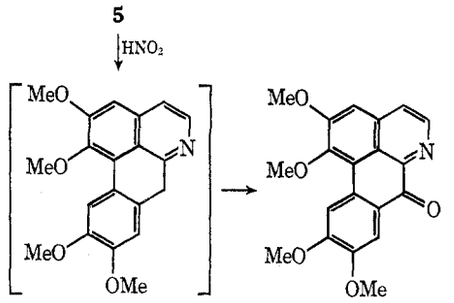
Diazotization of 6′-aminopapaverine in dilute sulfuric acid–methanol, followed by treatment with copper, gave Pschorr's "diazopapaverine" as the major product. Since this compound shows an NH band in the infrared at 3.0 μ, and no nmr signal in the benzylic region, it may be reassigned the indazole structure **7**. The residues afforded as a minor product (11%) the known 1,2,9,10-tetramethoxydibenzo[*de*,*g*]quinolin-7-one (**8**).[5] The oxoaporphine **8** presumably arises by the facile air oxidation of the unknown B-aromatic aporphine **9** during the work-up.[6]



6



5 **7**



9 **8**

In an attempt to suppress the formation of indazole **7**, 6′-aminopapaverine (**5**) was diazotized in 46% sulfuric acid. Decomposition of the diazonium salt with copper in the cold, followed by the usual work-up, gave none of indazole **7**, but a mixture of the deamination product papaverine (**10**, 4.3%), a pale yellow compound $C_{20}H_{19}NO_4$ (30%), and an orange compound $C_{19}H_{15}NO_4$ (2.4%). The latter compounds were assigned the novel structures **11** and **12**, respectively, on the basis of the evidence presented below.

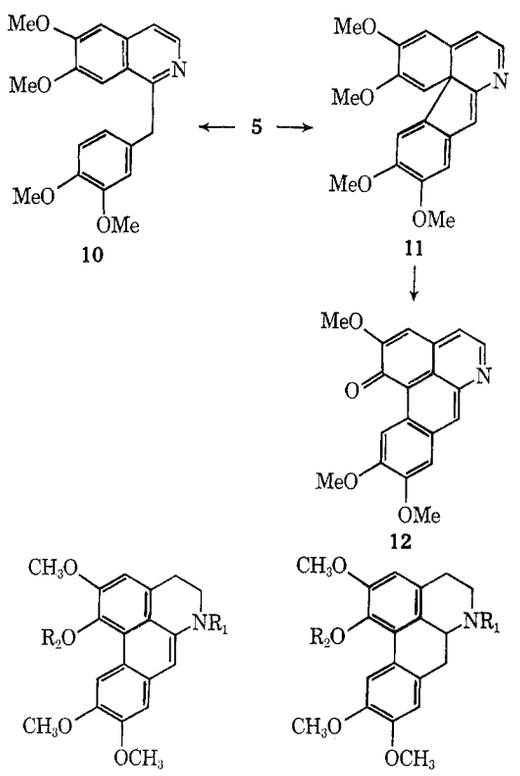
The yellow compound corresponds in composition to the B-aromatic aporphine **9**, but nmr analysis immediately eliminated this structure in favor of the angular-coupled isomer **11**. Whereas the planar molecule **9** should show a two-proton benzylic singlet and four methoxyls close to δ 4.0, the yellow compound

(1) D. F. DeTar, *Org. React.*, **9**, 409 (1957).
(2) J. Gadamer, *Arch. Pharm. (Weinheim)*, **249**, 680 (1911).
(3) W. I. Taylor, *Tetrahedron*, **14**, 42 (1961).
(4) R. Pschorr, *Ber.*, **37**, 1926 (1904).
(5) J. Cohen, W. Von Langenthal, and W. I. Taylor, *J. Org. Chem.*, **26**, 4143 (1961).
(6) A similar observation was reported recently in the synthesis of the oxoaporphine imenine: M. P. Cava and I. Noguchi, *J. Org. Chem.*, **38**, 60 (1973).

actually showed four methoxyls at δ 3.98, 3.67, 3.50, and 3.08. This is reasonable for structure **11**, in which two methoxyls are nonaromatic, and one of these is considerably shielded by the aromatic ring. In further accord with structure **11**, unsplit olefinic protons appeared at δ 4.97, 4.75, and 3.76; the latter proton represents that corresponding to C-8 of the original isoquinoline system, since a Dreiding model of **11** predicts this proton to be highly shielded by the aromatic nucleus below it.

Catalytic reduction of **11** under neutral conditions gave a dihydro derivative which proved to be the rearranged aporphine 6a,7-dehydronorglaucine (**13**). Ethyl chloroformate acylation of **13** afforded a product identical with synthetic *N*-carbethoxy-6a,7-dehydronorglaucine (**14**).[7] Furthermore, reduction of **13** by amalgamated zinc and acid afforded (±)-norglaucine (**16**), converted by formaldehyde and sodium borohydride to (±)-glaucine (**1**).

Reaction of the indenoisoquinoline **11** with warm 65% sulfuric acid brought about its conversion in high yield (94%) to the minor orange product originally isolated from the Pschorr reaction of 6′-aminopapaverine (**5**). The orange compound showed a conjugated carbonyl at 6.15 μ in the infrared; its nmr showed three similar methoxyls at δ 4.01, 4.08, and 4.13, all other protons falling into the aromatic region between δ 6.75 and 9.60. The formulation of this substance as the 1-oxoaporphine **12** followed from its chemical correlation with (±)-thaliporphine (**18**). Thus, catalytic reduction of **12** gave 6a,7-dehydronorthaliporphine (**15**), which was reduced by amalgamated zinc and acid to northaliporphine (**17**). Methylation of **17** by diazomethane gave (±)-norglaucine (**16**), whereas methylation of **17** by formaldehyde and sodium borohydride gave (±)-thaliporphine (**18**), identical with authentic synthetic material.[8]

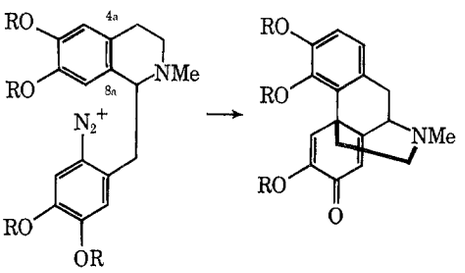


13, $R_1 = H$; $R_2 = CH_3$
14, $R_1 = CO_2Et$; $R_2 = CH_3$
15, $R_1 = R_2 = H$
16, $R_1 = H$; $R_2 = CH_3$
17, $R_1 = R_2 = H$
18, $R_1 = CH_3$; $R_2 = H$

(7) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).

Discussion

The Pschorr synthesis of the indenoisoquinoline **11** appears to be the first example of the formation of this unusual system, and involves a cyclization into the 8a position of an isoquinoline. Angular Pschorr cyclization into the 4a position of a 1,2,3,4-tetrahydroisoquinoline is, however, well documented and results in the formation of a morphinandienone, as shown below.[9] In the case of 6′-aminopapaverine (**5**), the



planarity of the aromatic isoquinoline system prevents attack at 4a for steric reasons and attack at 8a occurs instead.

The acid conversion of the indenoisoquinoline **11** to the 1-oxoaporphine **12** must involve selective demethylation at C-1, skeletal rearrangement to the aporphine system, and air oxidation to the quinone-like **12**; at present, the exact sequence of events cannot be specified. It may be noted, however, that **12** represents the first known 1-oxoaporphine. The stability of **12** suggests that compounds of this type will be found in nature.

Experimental Section

All melting points are uncorrected. Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Nmr spectra were measured on a Varian A-60A and a Varian HA-100 instrument in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise noted. Low-resolution mass spectra were measured on a Perkin-Elmer Model 270 instrument. Ultraviolet spectra were measured on a Perkin-Elmer 202 spectrophotometer.

6′-Aminopapaverine (5).—6′-Nitropapaverine[4] (6.7 g) was dissolved in tetrahydrofuran (300 ml) and hydrogenated below 10 psi pressure in the presence of 5% Pd/C (4.0 g) for 2 hr. Evaporation of the filtered solution followed by crystallization from ether gave colorless needles of **5** (5.8 g, 94%), mp 136–138° (lit.[4] mp 143°).

Pschorr Reaction of 6′-Aminopapaverine (5). A.—6′-Aminopapaverine (**5**) hydrochloride (400 mg) was dissolved in MeOH (30 ml) and 2 *N* H_2SO_4 (1.8 ml), and diazotized with 10% $NaNO_2$ (1.2 ml) at 0–5°. After the solution was stirred for 20 min at 0–5°, copper[10] (80 mg) was added and the mixture was stirred for 20 min at room temperature, warmed to 40° for 1 hr, and then basified (ammonia) to give a precipitate, which was extracted into $CHCl_3$. Usual work-up of the extract and crystallization from $CHCl_3$ gave 1-[3′-(5′,6′-dimethoxyindazolyl)]-6,7-dimethoxyisoquinoline (**7**) (156 mg, 42%), as colorless needles:

(8) (a) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967); (b) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971).

(9) The synthesis of morphinandienones by the Pschorr reaction has been reviewed: T. Kametani and K. Fukumoto, *J. Heterocycl. Chem.*, **8**, 341 (1971).

(10) Prepared from zinc dust and excess copper sulfate solution and stored under H_2O.

mp 271–273°; ir (KBr) 3.00 (NH), 6.10 μ (C=N); nmr (DMSO-d_6) δ 9.02 (1 H, s, C_7 H), 8.58 (1 H, d, J = 6.0 Hz, C_3 H), 8.00 (1 H, s, C_4 H), 7.68 (1 H, d, J = 6.0 Hz, C_4 H), 7.44 (1 H, s, C_8 H), 7.08 (1 H, s, C_5 H), 3.98, 3.94, 3.88, 3.84 (each 3 H, s, 4 OCH_3); uv λ_{max}^{EtOH} 245 nm (log ε 4.36), 307 (3.72), 341 (3.82); mass spectrum m/e 365 (M^+, base peak), 350 (M − 15), 334 (M − 31).

Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 66.00; H, 5.45; N, 11.72.

The residue from evaporation of mother liquors was purified by preparative tlc [silica gel, benzene–acetone (1:1) eluent] to give 1,2,9,10-tetramethoxydibenzo[*de,g*]quinolin-7-one (8) (42 mg, 11%) as yellow needles (from MeOH): mp 226° dec (lit.[1] mp 227–229°); ir (KBr) 6.10 μ (C=O); nmr δ 8.79 (1 H, d, J = 6.0 Hz, C_5 H), 8.69 (1 H, s, C_{11} H), 7.94 (1 H, s, C_8 H), 7.67 (1 H, d, J = 6.0 Hz, C_4 H), 7.10 (1 H, s, C_3 H), 4.03 (9 H, s, 3 OCH_3), 3.98 (3 H, s, OCH_3).

B.—6′-Aminopapaverine (5) (4.0 g) was dissolved in a precooled mixture of H_2SO_4 (65 ml) and H_2O (130 ml) and diazotized with a solution of $NaNO_2$ (760 mg) in H_2O (10 ml) at −5 to 0°. After the solution was stirred for 5 min at −5 to 0°, sulfamic acid (800 mg) and copper[10] were added to the mixture. The reaction was stirred for 30 min at 0–5° and then poured into cooled 20% NH_4OH and the precipitate was extracted into $CHCl_3$. Washing (10% NaOH and H_2O), work-up as usual, and crystallization from acetone (8 ml) yielded 2,3,10,11-tetramethoxyindeno[1,2-*j*]-isoquinoline (11) (1.12 g, 30%) as yellowish needles: mp 215° dec; ir (KBr) 6.15 μ (C=N and C=C); nmr δ 8.63 (1 H, d, J = 6.0 Hz, C_6 H), 8.04 (1 H, s, C_9 H), 7.41 (1 H, d, J = 6.0 Hz, C_5 H), 6.91 (1 H, s, C_{12} H), 4.97 (1 H, s, C_8 H), 4.75 (1 H, s, C_4 H), 3.76 (1 H, s, C_1 H), 3.98, 3.67 (each 3 H, s, 2 aromatic OCH_3), 3.50, 3.08 (each 3 H, s, 2 vinylic OCH_3); uv λ_{max}^{EtOH} 246 nm (log ε 4.17), 265 (sh, 4.00), 308 (sh, 3.33), 335 (sh, 3.28), 359 (3.38); mass spectrum m/e 337 (M^+), 322 (M − 15, base peak), 306 (M − 31).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; m/e 337.1313. Found: C, 71.01; H, 5.55; N, 4.14; m/e 337.1301.

The residue from the mother liquors was purified by preparative tlc [silica gel, benzene–acetone (1:1 eluent)] to yield the following compounds.

2,9,10-trimethoxydibenzo[*de,g*]quinolin-1-one (12) was collected from the polar zone as orange needles (89 mg, 2.4%): mp 214° dec (from $CHCl_3$–ether); ir (KBr) 6.15 μ (C=O); nmr δ 9.60 (1 H, s, C_{11} H), 8.96 (1 H, d, J = 6.0 Hz, C_5 H), 8.76 (1 H, s, C_3 H), 7.43 (1 H, d, J = 6.0 Hz, C_4 H), 7.23 (1 H, s, C_8 H), 6.75 (1 H, s, C_7 H), 4.13, 4.08, 4.01 (each 3 H, s, 3 OCH_3); uv λ_{max}^{EtOH} 232 nm (log ε 4.54), 245 (sh, 4.49), 273 (sh, 4.22), 285 (sh, 4.13), 295 (sh, 4.04), 402 (3.98), 463 nm (3.92); mass spectrum m/e 321 (M^+), 306 (M − 15), 290 (M − 31, base peak).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36; m/e 321.1010. Found: C, 70.80; H, 4.76; N, 4.44; m/e 321.0972.

Work-up of the less polar zone gave papaverine (10) (164 mg, 4.3%), mp 146–147°.

6a,7-Dehydronorglaucine (13).—A solution of the spiro compound 11 (120 mg) in tetrahydrofuran (20 ml) was hydrogenated in the presence of platinum (from 120 mg of PtO_2) at atmospheric pressure for 20 hr. After filtration and the usual work-up, crystallization from ether afforded **13** (101 mg, 84%) as plates: mp 182° dec; ir (KBr) 3.05 (NH), 6.10 μ (C=C); nmr δ 9.05 (1 H, s, C_{11} H), 6.97, 6.92 (each 1 H, s, C_3 and C_8 H), 6.58 (1 H, s, C_7 H), 4.00 (6 H, s, 2 OCH_3), 3.98, 3.90 (each 3 H, s, 2 OCH_3), 3.60–3.20 (4 H, m, methylene protons): mass spectrum m/e 339 (M^+, base peak), 324 (M − 15); uv λ_{max}^{EtOH} 259 nm (log ε 4.81), 335 (3.89), 380 (3.35).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.77; H, 6.12; N, 4.18.

***N*-Carbethoxy-6a,7-dehydro-*N*-norglaucine (14).**—A solution of ethyl chloroformate (0.1 ml) in $CHCl_3$ (1 ml) was added dropwise to a stirred solution of **13** (50 mg) in $CHCl_3$ (10 ml) and triethylamine (0.1 ml) at 0–5°. After stirring for 2.5 hr at room temperature, the reaction mixture was washed (10% $NaHCO_3$ and H_2O) and dried ($MgSO_4$). Evaporation and crystallization of the residue from ether–hexane gave **14** (42 mg, 70%) as plates, mp 159–160° (lit. mp 162–163°[7], 156–157°[11]), ir (KBr), melting point, and mixture melting point identical with those of an authentic sample.

Norglaucine (16).—To a stirred mixture of zinc amalgam [prepared from 2 *N* HCl (10 ml), 2% $HgCl_2$ (10 ml), and zinc dust (1.0 g) as usual] was added a suspension of **13** (100 mg) in EtOH (10 ml). After the solution was heated at 60–70° for 30 min, 6 *N* HCl (5 ml) was added and heating was continued for an additional 30 min. The mixture was filtered and the filtrate was basified with ammonia. The free base was extracted with $CHCl_3$. The usual work-up of the extract gave **16** (78 mg, 79%) as an off-white gum: nmr δ 8.12 (1 H, s, C_{11} H), 6.77, 6.61 (each 1 H, s, C_3 and C_8 H), 3.89 (6 H, s, 2 OCH_3), 3.87, 3.67 (each 3 H, s, OCH_3). Amine **16** formed a colorless hydrochloride, mp 214° dec (from MeOH–ether), ir (KBr) 3.60–4.00 μ (≡NH^+). Its picrate had mp 218° dec (EtOH); uv λ_{max}^{EtOH} 280 nm (log ε 4.17), 303 (4.20), 315 (sh, 4.16), 356 (4.14).

Anal. Calcd for $C_{26}H_{26}N_4O_{11}$: C, 54.73; H, 4.59; N, 9.82. Found: C, 54.69; H, 4.77; N, 10.00.

(±)-Glaucine (1).—A solution of **16** (50 mg) in MeOH (5 ml) and 37% HCHO (1 ml) was warmed to 40–50° for 30 min. $NaBH_4$ (100 mg) was added portionwise to the mixture. The solvent was evaporated and the residue was extracted with benzene. The organic layer was washed with water and worked up as usual. Crystallization of the residue from ether afforded **1** (42 mg, 81%) as pale yellowish needles: mp 127–129°; ir (KBr) 3.70 μ (NMe); nmr δ 8.10 (1 H, s, C_{11} H), 6.80, 6.61 (each 1 H, s, C_3 and C_8 H), 3.93, 3.92, 3.90, 3.68 (each 3 H, s, 4 OCH_3), 2.55 (3 H, s, NCH_3); mass spectrum m/e 355 (M^+), 354 (M − 1, base peak), 324 (M − 31); uv λ_{max}^{EtOH} 280 nm (log ε 4.04), 301 (3.97). The picrate of **1** formed yellow needles, mp 199–200° dec (from EtOH) (lit.[7] mp 197–199°). The ir (KBr), melting point, and mixture melting point of **1** picrate were identical with those of an authentic sample.

2,9,10-Trimethoxydibenzo[*de,g*]quinolin-1-one (12).—A solution of 11 (1.4 g) in 65% H_2SO_4 (40 ml) was heated at 65° for 20 min. The reaction mixture was poured into ice–water and neutralized with ammonia. Extraction with $CHCl_3$ and the usual work-up gave **12** (1.25 g, 94%) as orange needles, mp 214° dec (from $CHCl_3$–ether), melting point and spectral properties identical with those of the authentic sample described above.

6a,7-Dehydronorthaliporphine (15).—A solution of **12** (1.1 g) in tetrahydrofuran (200 ml) was hydrogenated in the presence of platinum (from 1.1 g of PtO_2) at atmospheric pressure for 48 hr. Work-up as usual and crystallization from ether afforded **15** (850 mg, 77%) as gray plates: mp 197–199°; ir (KBr) 2.90, 3.00 (NH and OH), 6.10 μ (C=C); nmr (acetone-d_6) δ 9.26 (1 H, s, C_{11} H), 7.06, 7.00 (each 1 H, s, C_3 and C_8 H), 6.64 (1 H, s, C_7 H), 3.98 (3 H, s, OCH_3), 3.89 (6 H, s, 2 OCH_3); mass spectrum m/e 325 (M^+, base peak), 310 (M − 15); uv λ_{max}^{EtOH} 257 nm (sh, log ε 4.33), 266, (4.34), 310 (3.70), 335 (3.57), 380 (3.10).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.88; H, 5.88; N, 4.51.

Northaliporphine (17) from 15.—A suspension of **15** (530 mg) in tetrahydrofuran (40 ml) was added to a stirred suspension of zinc amalgam [prepared from zinc dust (6.0 g), 2% $HgCl_2$ (60 ml), and 2 *N* HCl (60 ml)]. The reaction was completed and worked up as for the reduction of **13**.

Crystallization from MeOH afforded **17** (450 mg, 85%) as colorless needles: mp 214–216° dec; ir (KBr) 3.00 μ (NH); nmr δ 8.13 (1 H, s, C_{11} H), 6.77 (1 H, s, C_3 H), 6.58 (1 H, s, C_8 H), 3.91 (9 H, s, 3 OCH_3); mass spectrum m/e 327 (M^+), 326 (M − 1, base peak), 310 (M − 17); uv λ_{max}^{EtOH} 279 nm (log ε 4.04), 302 (4.07).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.56; H, 6.45; N, 4.36.

Norglaucine (16).—A solution of excess diazomethane in ether was added to **17** (27 mg) in MeOH (3 ml) and dioxane (0.5 ml) and the mixture was allowed to stand at room temperature for 20 hr. The excess diazomethane was decomposed with 2 *N* HCl, and the solvent was evaporated. Basification with 10% NaOH followed by usual work-up of the extract gave **16** as a colorless syrup, characterized as the hydrochloride (19 mg, 63%), mp 214° dec, ir (KBr) superimposable on that of the authentic sample prepared above.

(±)-Thaliporphine (18).—A solution of **17** (100 mg) in MeOH (20 ml), tetrahydrofuran (5 ml), and 37% HCHO (4 ml), was warmed to 65° for 30 min. $NaBH_4$ (500 mg) was added portionwise to the mixture. Work-up as for the methylation of **13** and crystallization from MeOH afforded **18** (64 mg, 64%) as color-

(11) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).

less needles: mp 188–190° (lit.[8] mp 190–192°); ir (KBr) 2.80 (OH), 3.60 μ (NMe); nmr δ 8.09 (1 H, s, C_{11} H), 6.80 (1 H, s, C_8 H), 6.55 (1 H, s, C_3 H), 3.91 (6 H, s, 2 OCH_3), 3.90 (3 H, s, OCH_3), 2.55 (3 H, s, NCH_3); mass spectrum *m/e* 341 (M^+), 340 (M − 1, base peak), 326 (M − 15), 310 (M − 31); uv λ_{max}^{EtOH} 279 nm (log ε 4.04), 304 (4.04). The spectral properties and mixture melting point of **18** were identical with those of authentic (±)-thaliporphine.

Northaliporphine (17) from 12.—A suspension of the oxoaporphine **12** (40 mg) in tetrahydrofuran (10 ml) was added to a stirred suspension of zinc amalgam [prepared from 2% $HgCl_2$ (15 ml), zinc dust (1.5 g), and 2 *N* HCl (15 ml)].

The reaction was completed and worked up as for the reduction of **15** to give a reddish residue. Purification by preparative tlc [silica gel, $CHCl_3$–MeOH (5:1) eluent] afforded **17** (21 mg, 52%) as colorless needles, mp 212–214° (from $CHCl_3$–ether–hexane), identical by spectral properties and mixture melting point with the sample prepared by reduction of **15**.

Registry No.—**1**, 5630-11-5; **5**, 39945-32-9; **5** HCl, 39945-33-0; **7**, 39945-34-1; **8**, 5574-24-3; **10**, 58-74-2; **11**, 39945-36-3; **12**, 39945-37-4; **13**, 39945-38-5; **15**, 39945-39-6; **16**, 39945-40-9; **16** HCl, 39945-41-0; **16** picrate, 39945-42-1; **17**, 39945-43-2; $NaNO_2$, 7632-00-0; formaldehyde, 50-00-0; sodium borohydride, 16940-66-2; diazomethane, 334-88-3.

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Purine *N*-Oxides. XLVII. Photochemistry of 1-Hydroxy- and 1-Methoxyhypoxanthines[1]

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The photochemistry of the cations, neutral species, and anions of 1-hydroxyhypoxanthine and 1-hydroxy-7-methylhypoxanthine is reported. Two types of reactions, rearrangement and reduction, occur upon uv excitation of these *N*-hydroxypurines. The influence of tautomeric structure and ionic state on the type and the extent of these two reactions is examined. 1-Methoxy-7-methylhypoxanthine, which undergoes photoreduction only, was used as a model for the un-ionized *N*-hydroxy species. It is deduced that deoxygenation is the primary reaction of the neutral *N*-hydroxy species, while rearrangement occurs from an excited state of the enolate anions of these 1-hydroxyhypoxanthines. Studies with triplet sensitizers in dioxane demonstrated that photoreduction of the neutral species of 1-hydroxy-7-methylhypoxanthine occurs through the triplet state, while in acetonitrile photoreduction of it takes place by a combination of triplet energy transfer and chemical sensitization. Photoreduction of 1-methoxy-7-methylhypoxanthine occurs from the excited singlet but it can also be accomplished by chemical sensitization with aromatic ketones. The enolate anions can also be photoreduced with aqueous acetone as sensitizer. Syntheses of the requisite 1-hydroxy-7-methyl- and 1-methoxy-7-methylhypoxanthines are described.

The photochemical sensitivity of purine *N*-oxides in solution has been reported[2–7] and products resulting from deoxygenation, rearrangement, and ring opening have been isolated. Study of a series of *N*-hydroxyxanthines showed that free radicals can be induced by ultraviolet irradiation of the dry solids.[8] These radicals are stable in the solid state, but are immediately reduced to the parent purines when dissolved in protic solvents. Irradiation of the same *N*-hydroxypurines in solution gave the deoxygenated derivatives as the primary photoproducts.[8] We have now studied the mechanism of photochemical reduction of *N*-hydroxypurines in solution, with consideration of the influence of the ionic and the tautomeric state on the photochemical behaviors of the irradiated compounds.

For initial study 1-hydroxyhypoxanthine[9] (**1**) and derivatives of it were selected. This system has the desired cyclic hydroxamic acid moiety, only one additional ionizable proton, and a minimal number of ionic species and tautomeric forms to be considered. In addition, the availability of 1-hydroxyinosine[9] (**12**) presented a route to the desired selectively methylated derivatives of **1**.

Results

Irradiations of 1-Hydroxyhypoxanthine (1).—The neutral species of **1** was studied at pH 3, which is more than 2 pH units from the first ionization p*K* of 5.65,[9] but above the protonation p*K* of 1.77 ± 0.05. Irradiation of **1** at pH 3 in the presence of O_2 resulted in rapid destruction of uv-absorbing components (expt 1–2, Table I); by 2 hr only 6% of the starting material could be accounted for, all as hypoxanthine (**8**). This loss could be greatly diminished by flushing with N_2 and all subsequent irradiations were done under N_2.

Irradiation of the neutral species of **1** under N_2 with a Corex filter (260-nm cutoff) for 30 min or more gave three isolable products (Scheme I): hypoxanthine (**8**) (40%), 2,6-dihydroxypurine (xanthine) (**10**) (9%), and 6,8-dihydroxypurine (**7**) (1%) (expt 8–10, Table I). Even under N_2 there was still a decrease in the total recovery of these products, based on uv absorption, as the photolysis proceeded (expt 5–10). The cation of **1**, irradiated in 3 *N* CF_3CO_2H (pH ~0) (expt 3–4), re-

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