Communications

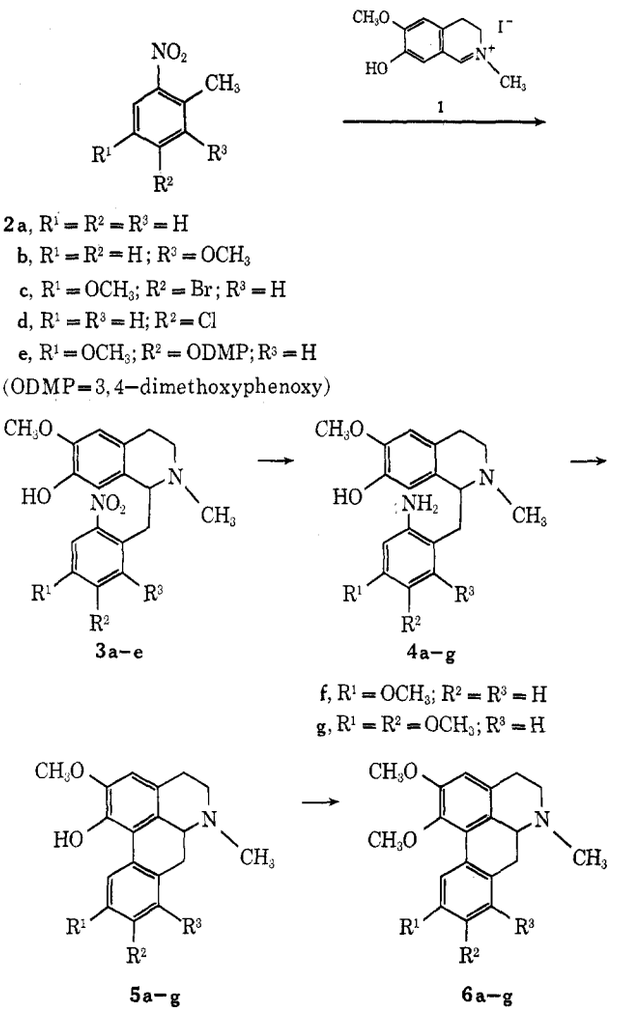
See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

Aporphine Synthesis by Pschorr Cyclization of Aminophenols. An Improved Synthesis of a Thalicarpine Precursor[1,2]

Summary: An improved general synthesis of aporphines *via* Pschorr cyclization of 1-(2′-aminobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines has been developed and successfully applied to the synthesis of thalicmidine (**5g**), nuciferine (**6a**), glaucine (**6g**), and the thalicarpine precursor **6e**, in the highest yields reported to date.

Sir: In an earlier communication,[3] we have described a total synthesis of the tumor inhibitory alkaloid thalicarpine.[4,5] The synthesis suffered from a single low-yield (15%) step, cyclization to the intermediate **6e**. Similar problems have been encountered in the synthesis of most aporphines, and, in general, the cyclization yield decreases as the oxygenation level of the precursor increases.[6,7] This communication reports an improved synthesis of aporphines. We believe this synthesis to be of general synthetic utility.

The key step in our synthesis is the Pschorr cyclization of 1-(2′-aminobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines of type **4**. Earlier studies have demonstrated the yield enhancement by the 7-hydroxy group in mechanistically different aporphine cyclizations, but the overall synthetic sequences were not of general practicality.[8,9] In contrast, condensation of the appropriate *o*-nitrotoluenes **2a–e** with 6-methoxy-7-hydroxy-3,4-dihydroisoquinolinium methiodide[10] (1.2 mol equiv) in the presence of KO-*t*-Bu (2.2 mol equiv) in *N*,*N*-dimethylacetamide gave the 1-(2′-nitrobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines **3a–e** in yields of 88–95% (Table I).[11,12] Reduction of **3a,b,e** with 5% Pd/C gave the corresponding aminophenols **4a,b,e** in yields of 87–98%. Catalytic reduction of **3c** was accompanied by hydrogenolysis to **4f**. The halogenated aminophenols **4c,d** were consequently obtained by Zn–H_2SO_4 reduction. Aminophenols **4a–f** were cyclized to the corresponding 1-hydroxyaporphines **5a–f** (35–50% yield) by diazotization in 1:1 20% H_2SO_4 and HOAc, and cyclization with copper powder. Aporphines **5a–d,f** were separated directly as crystalline salt derivatives. Hydroxyaporphine **5e** was separated as free base by chromatography, and methylation with diazomethane gave the thalicarpine precursor **6e** in 90% yield. For aporphines **6a–d,f**, it was found advantageous to proceed with diazomethane methylation of the crude hydroxyaporphines **5a–d,f**. Thus, *e.g.*, the most efficient synthesis of *dl*-nuciferine (**6a**) reported to date proceeds *via* **3a** (90%) and **4a** (87%) and cyclization–methylation to **6a** (48%).



An improved synthesis of *dl*-glaucine was effected *via* hydrogenation with 5% Pd/C of 1-(2′-nitro-4′,5′-dimethoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-

(1) Tumor Inhibitors. LXXVIII. Part LXXVII: R. J. Restivo, R. F. Bryan, and S. M. Kupchan, *J. Chem. Soc., Perkin Trans. 2*, in press.

(2) This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (T-275).

(3) S. M. Kupchan and A. J. Liepa, *Chem. Commun.*, 599 (1971).

(4) *Chem. Eng. News*, **44**, 64 (1966); J. L. Hartwell and B. J. Abbott, *Advan. Pharm. Chemother.*, **7**, 117 (1969).

(5) Clinical investigation of thalicarpine is underway, in the program of the Division of Cancer Treatment, National Cancer Institute.

(6) For a brief review of the synthesis of aporphines up to 1960, see A. R. Pinder in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier, New York, N.Y., 1960, Chapter 24.

(7) S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, *J. Org. Chem.*, **36**, 2413 (1971), and references cited therein.

(8) B. Franck and L.-F. Tietze, *Angew. Chem., Int. Ed. Engl.*, **6**, 799 (1967).

(9) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971).

(10) A. Brossi, J. O'Brien, and S. Teitel, *Org. Prep. Procedures*, **2**, 281 (1970).

(11) *Cf.* S. Narayanaswami, S. Prabhakar, B. R. Pai, and S. Shanmugasundaram, *Indian J. Chem.*, **7**, 755 (1969), and references cited therein.

(12) All new compounds were characterized by concordant analytical and spectral data.

TABLE I

YIELDS (PER CENT) AND MELTING POINTS (°C)

	3	4	5	6[a]
a	90[b,c]	87, 210–112 dec[d]	44, 269–271 dec[e]	48, 259–261 dec[e]
b	88, 167–168	93, 161–162[f]	45, 239–241 dec[e]	40, 186–187[f]
c	95, 146–147	83[b,g]	43, 241–243 dec[h]	
d	94, 127–129	77, 118–119[f,g]	50, 244–246 dec[h]	43, 260–261 dec[h]
e	92, 173–174	98[b,f]	35, 150–151[f]	23, 212–214 dec[e]
f		81, 137–138[e]	46, 219–223 dec[e]	36, 223–225 dec[e]
g		81, 177–179[d]	43, 190–192[f]	46, 191–192 dec[i]

[a] Combined yields for direct two-step conversion from 4 to 6. [b] Amorphous. [c] Characterized as the *N*-methiodide, mp 218–219°. [d] Dihydrochloride. [e] Hydrobromide. [f] Free base. [g] Reduction with Zn–H_2SO_4. [h] Hydrochloride. [i] Picrate.

1,2,3,4-tetrahydroisoquinoline[13] to aminophenol **4g** (81%). Cyclization of the diazonium salt of **4g** using copper powder gave *dl*-thalicmidine[13,14] (**5g**) in 43% yield. Cyclization–methylation gave *dl*-glaucine (**6g**) in 46% yield from **4g** (which was isolated as the picrate salt[15]).

(13) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).

(14) S. Yunosov and N. N. Progressov, *Zh. Obshch. Khim.*, **22**, 1047 (1952); *Chem. Abstr.*, **47**, 8084 (1953); M. Shamma, M. J. Hillman, R. Charubala, and B. R. Pai, *Indian J. Chem.*, **7**, 1056 (1969).

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

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA 22901

S. MORRIS KUPCHAN*
V. KAMESWARAN
J. W. A. FINDLAY

OCTOBER 11, 1972