

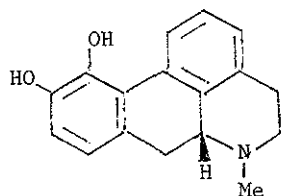
SYNTHESIS OF A BENZO[a]PHENANTHRIDINE
ISOMERIC WITH APOMORPHINE[†]Chung-Chen Wei and Sidney Teitel^{*}Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110, U. S. A.

The synthesis of the benzo[a]phenanthridine (2), an isomer of apomorphine (1) with the identical rigid spatial arrangement of the dopamine moiety, is described. Conversion of the β -tetralone (9) into the N-benzoyl enamine (10) followed by photolysis furnished the trans-lactam (11) which was reduced, N-methylated and O-demethylated to afford the target compound (2).

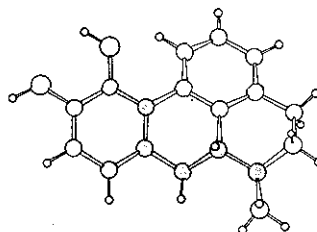
Although apomorphine (1) has been known for over a century¹ and has been used clinically as an emetic agent,² it was not until 1970 when Cotzias and co-workers³ reaffirmed the dopamimetic activity reported by Schwab⁴ and indicated its potential as an antiparkinson agent that structure-activity studies were undertaken. As a result, modifications of (1) have been synthesized which encompassed variation of the aromatic substitution pattern,⁵ enlargement of the heterocyclic ring,⁶ as well as the

[†]Dedicated to Professor Emeritus Shigehiko Sugawara on the occasion of his eightieth birthday.

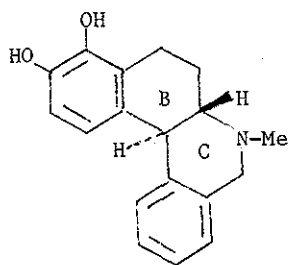
dissection of (1) into 2-aminotetralins^{7,8} and benzo[f]quinolines.⁹ In this connection, based on the concept that an isomer of (1) such as the benzo[a]phenanthridine (2) which retains the dopamine moiety in the same rigid spatial arrangement [shown by the shading in the stereomodels (1a) and (2a)] might also exhibit some dopaminergic activity, it was of interest to synthesize and evaluate this novel isomer (2).



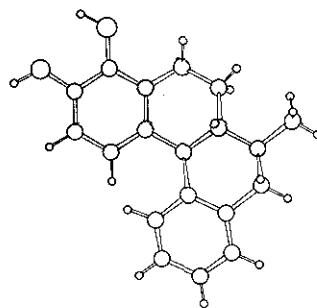
(1)



(1a)



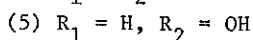
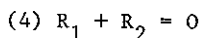
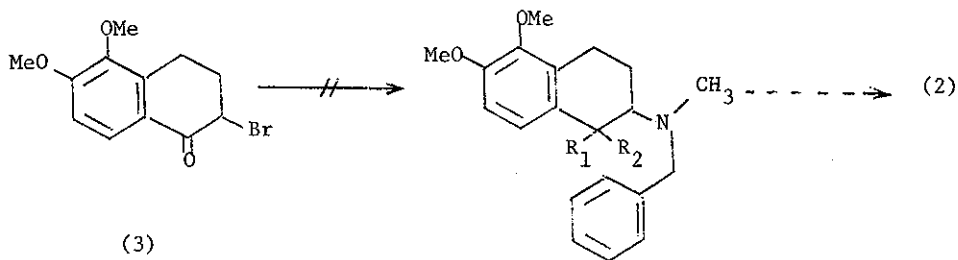
(2)



(2a)

Initially, the route chosen for the synthesis of (2) envisioned the construction of the C-ring by acid-catalyzed cyclization of (5) (Scheme I). However, since 5,6-dimethoxy-2-bromotetralone (3), obtained by treating 5,6-dimethoxy-1-tetralone¹⁰ with Br_2 in CHCl_3 , could not be annelated with N-methylbenzylamine by the procedure given for the unsubstituted 2-bromotetralone,¹¹ this approach was abandoned.

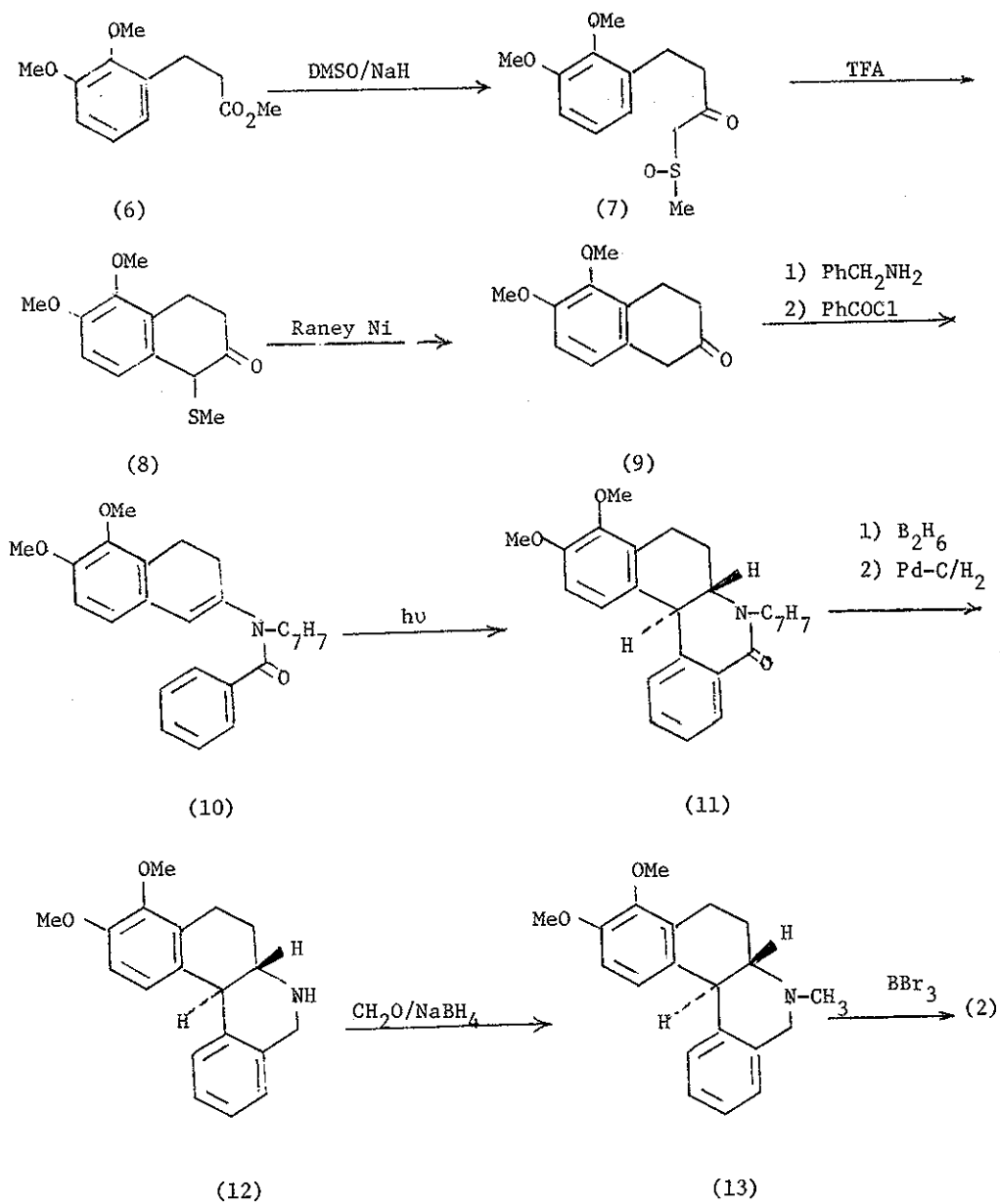
Scheme I



Alternatively, closure of the C-ring in the substituted enamine (10) by the photocyclization procedure of Ninomiya and co-workers¹² furnished the tetracycle (11), the key precursor of the benzo[a]phenanthridine (2) (Scheme II). For this purpose, the dimethoxy- β -tetralone (9), previously prepared by a multi-step synthesis involving the epoxidation of 5,6-dimethoxy-3,4-dihydronaphthalene,¹³ was conveniently obtained via cyclization of the β -keto sulfoxide (7). By adapting the procedure of Oikawa and Yonemitsu,¹⁴ treatment of methyl 2,3-dimethoxyphenylacetate (6)¹⁵ with methylsulfinyl carbanion gave the β -keto sulfoxide (7) [84% yield, mp 46 - 48°] which was cyclized with trifluoroacetic acid to the methylthio-2-tetralone (8) [75% yield, mp 38 - 41°]. Reductive desulfurization of (8) with Raney Ni,¹⁶ deactivated by refluxing in acetone for 1.5 hrs, then afforded the β -tetralone (9) [85% yield, mp 60 - 61° (lit.⁸ mp 61 - 63°)].

Successive treatment of the β -tetralone (9) with benzylamine¹⁷ and benzoyl chloride provided the N-benzoyl enamine (10) [72% yield; mp 96 - 97.5°; m/e 399 (M^+); δ (CDCl₃) 2.04-2.55 (4H, m, CH₂CH₂), 3.66 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 4.94 (2H, s, CH₂Ph), 6.05 (1H, s, CH=N), 6.54 (2H, s, ArH), 7.35 (5H, m, ArH)]. Irradiation of (10) at 256 m μ in ether effected

Scheme II



cyclization to the trans-B/C fused lactam (11) [74% yield; mp 168-170°; m/e 399 (M^+); δ ($CDCl_3$) 3.77 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.35 (1H, d, $J = 11$ Hz, 12b-H), 5.06 (2H, q, NCH_2Ph), 6.91 (1H, d, $J = 9$ Hz, ArH), 7.21 (1H, d, $J = 9$ Hz, ArH), 7.30 (9H, m, ArH), 8.19 (1H, m, ArH)].

Reduction of the amide function in (11) with B_2H_6 in THF followed by catalytic debenzoylation furnished the phenanthridine (12) [65% yield, m/e 295 (M^+), mp of HCl 261-262°]. Reductive condensation of (12) with CH_2O and $NaBH_4$ then gave the N-methyl derivative (13) as the HCl salt [75% yield; mp 155-157°; m/e 309 (M^+); δ (CD_3OD) 2.98 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.45 (3H, m, $PhCHPh$ and NCH_2Ph), 7.00 (2H, q, ArH), and 7.43 (4H, m, ArH). De-etherification of (13) with BBr_3 in CH_2Cl_2 furnished the desired product, rac. trans - 9, 10-dihydroxy-5,6, 6a, 7, 8, 12b-hexahydro-6-methylbenzo[a]phenanthridine hydrobromide (2) [76% yield, mp 268-271°, m/e 281 (M^+)].

On preliminary evaluation, the benzo[a]phenanthridine (2) was devoid of any noteworthy dopamimetic activity. Studies are now in progress to prepare other "rigid-dopamine" isomers of apomorphine (1).

ACKNOWLEDGEMENT: We are indebted to our Physical Chemistry Department, in particular Drs. W. Benz, F. Scheidl, V. Toome, and T. Williams for providing the analytical and spectral data. We are also grateful to Mr. J. Borgese and K. Deitcher for technical assistance.

REFERENCES AND NOTES

- 1 A. Matthiessen and C. R. A. Wright, Proc. Roy. Soc. (London), 1869, 17, 455.
- 2 L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics" 2nd Ed., MacMillan, New York, 1960, p. 1064.
- 3 G. C. Cotzias, P. S. Papavasiliou, C. Fehling, B. Kaufman, and I. Mena, N. Engl. J. Medicin., 1970, 282, 31.
- 4 R. S. Schwab, L. V. Amador, and J. Y. Lettrín, Trans. Amer. Neurol. Assoc., 1951, 76, 251.
- 5 M. K. Menon, W. G. Clark, and J. G. Cannon, J. Pharm. Pharmacol., 1976, 28, 778 and references cited therein.
- 6 D. Berney, T. J. Petcher, J. Schmutz, H. P. Weber and T. G. White, Experientia, 1975, 31, 1327.
- 7 J. G. Cannon, J. C. Kim, M. A. Aleem, and J. P. Long, J. Medicin. Chem., 1972, 15, 348.
- 8 J. D. McDermid, G. M. McKenzie, and A. P. Phillips, J. Medicin. Chem., 1975, 18, 362.
- 9 J. G. Cannon and G. J. Hatheway, J. Medicin. Chem., 1976, 19, 987.
- 10 N. F. Elmore and T. J. King, J. Chem. Soc., 1961, 4425.
- 11 C. F. Barfknecht and D. B. Rusterholz, J. Medicin. Chem., 1974, 17, 308.
- 12 I. Ninomiya, T. Naito, and T. Mori, J. Chem. Soc., 1973, 505.
- 13 J. G. Cannon, J. P. O'Donnell, J. P. Rosazza, and C. R. Hoppin, J. Medicin. Chem., 1974, 17, 564. Subsequent to our investigation, McDermid and co-workers reported the preparation of (9) by Birch reduction of 2,5,6-trimethoxynaphthalene (see Ref. 8).
- 14 Y. Oikawa and O. Yonemitsu, Tetrahedron, 1974, 30, 2653.
- 15 R. K. Callow, J. M. Gulland, and R. D. Hawroth, J. Chem. Soc., 1929, 662.
- 16 Y. Oikawa and O. Yonemitsu, J. Org. Chem., 1976, 41, 1118 used NaBH₄ for this type of desulfurization.
- 17 Benzylamine was used instead of methylamine in order to have access to the secondary amine which was required for other purposes.

Received, 25th April, 1977