SYNTHESIS OF (±)-MESEMBRINE†

Osamu Hoshino, Shohei Sawaki, Naomi Shimamura,
Akira Onodera, and Bunsuke Umezawa*
Faculty of Pharmaceutical Sciences, Science University of Tokyo, Shinjuku-ku, Tokyo, 162, Japan

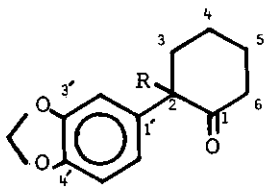
The base-catalyzed reaction of 2-(3',4'-methylenedioxyphenyl)cyclohexanone (1a) and 5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2a) with allyl bromide in the presence of 18-crown-6 afforded the 2-allyl-2-arylcyclohexanones (1b and 2b) in good yields, which was applied to the synthesis of (±)-mesembrine (3).

In the course of our studies[1] on the synthesis of Amaryllidaceae alkaloids, we found that the alkylation of 2-(3',4'-methylenedioxyphenyl)cyclohexanone (1a)[1] and 5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2a) with allyl bromide or acrylonitrile in the presence of a phase transfer catalyst[2] (18-crown-6) took place readily at their benzylic positions to give the corresponding 2-alkyl-2-arylcyclohexanones (1b,c and 2b). The Present paper is concerned with the synthesis of (±)-mesembrine (3)[3]

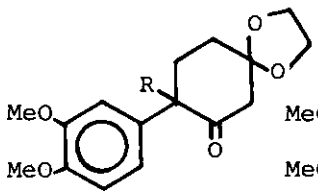
† Dedicated to Prof. Dr. A. Butenandt on the occasion of his seventy-fifth birthday.

starting from 2b.

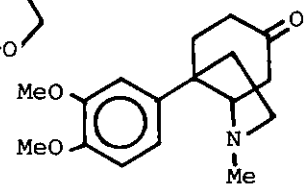
A mixture of 1a (436 mg, 2 mmole), allyl bromide (291 mg, 2.4 mmole) and 50% aq. sodium hydroxide(3 ml) in benzene (3 ml) containing 18-crown-6 (26.5 mg, 0.1 mmole) was heated at 70-75° for 1.25 hr with stirring. Usual work-up of the reaction mixture gave an oil (588 mg), which was chromatographed over silica gel with benzene-ethyl acetate (10:1) to afford 2-allyl-2-(3',4'-methylenedioxyphenyl)cyclohexanone (1b)[4] (495 mg, 96%), bp 140°/0.02 mm. (bath temp.)(mp 46-47°)[IR[5] $\nu(CHCl_3)$:1710 cm^{-1}(C=O);NMR[6] δ:5.76-4.60(m, 3H, CH_2=CH-);MS[7] m/e:258(M^+)]. Similar reaction (room temp., 0.5 hr) of 1a with acrylonitrile produced the 2-cyanoethylcyclohexanone (1c)(60%), bp 170°/0.05 mm.(bath temp.). On the other hand, the reaction of 1a with chloroacetonitrile yielded two kinds of glycidonitriles (4)(36%), though their stereochemistry was not determined yet.



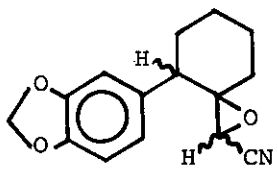
1a R= H
b R= $CH_2CH=CH_2$
c R= CH_2CH_2CN
d R= CH_2CN



2a R= H
b R= $CH_2CH=CH_2$



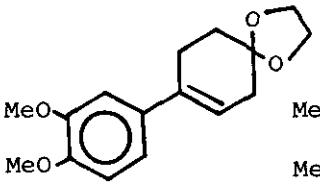
3



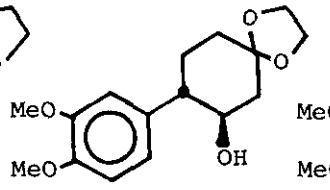
4

Then, the above reaction of 1a was extended to 2a.

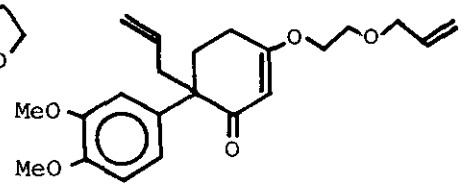
The starting material (2a) was synthesized as follows. The annelation (benzene, room temp., 22 hr) via a pyrrolidine enamine of homoveratraldehyde[8] with methyl vinyl ketone followed by heating (8 hr) in acetic acid gave a mixture of two cyclohexenones depending on the position of double bond, which was treated with ethylene glycol to furnish 4,4-ethylenedioxy-(3',4'-dimethoxyphenyl)-cyclohex-1-ene (5) (42% from the aldehyde), mp 77.5-78°(n-hexane-ether). Hydroboration-oxidation of 5 gave the cyclohexanol (6) (88%), mp 118-118.5°(ether), which was oxidized with chromic trioxide-pyridine in methylene chloride to afford 2a (91%), mp 94-95.5°(MeOH) [IR[9] $\nu(CHCl_3)$:1710 cm^{-1}(C=O);NMR δ:3.95(s, 4H, OCH_2CH_2O), 3.65-3.35(m, 1H, 2-H), and 2.70(s, 2H, 6-H);MS m/e:292(M^+)].



5



6

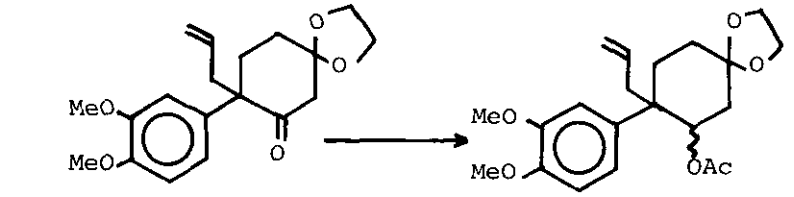


7

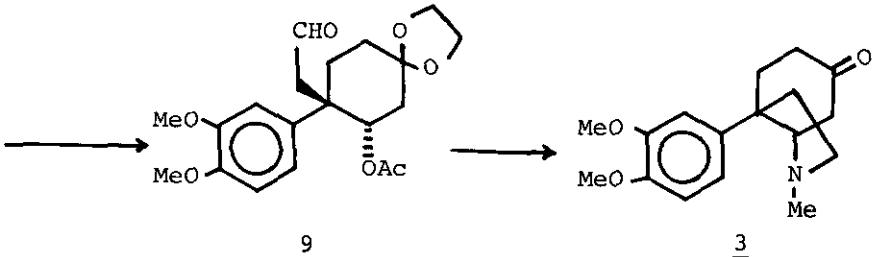
The base-catalyzed reaction (room temp., 0.5 hr) of 2a (1 mmole) with allyl bromide (1.2 mmole) yielded an oil, which was chromatographed over silica gel with benzene-ethyl acetate (10:1) to give 2-allyl-5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2b) (oil, 69%) [IR $\nu(CHCl_3)$:1710 cm^{-1}(C=O);NMR δ:5.73-4.70 (m, 3H, CH_2=CH-) and 3.90(s, 4H, OCH_2CH_2O);MS m/e:332(M^+)] accompanied by a small amount of an oil (7) [IR $\nu(CHCl_3)$:1650 cm^{-1}(C=CHC=O);

NMR δ:6.20-4.75(m, 7H, 2 x CH_2=CH- and 6-H);MS m/e:372(M^+)].

The conversion of 2b into 3 was achieved in the following manner. Sodium borohydride reduction of 2b in methanol followed by acetylation (Ac_2O-pyridine) yielded the acetate (8)(95% from 2b), mp 85.5-86°(ether)[IR[9] ν(KBr):1730 cm^{-1}($OCOCH_3$);NMR δ:5.40-4.65(m, 4H, CH_2=CH- and 1-H) and 1.95(s, 3H, $OCOCH_3$);MS m/e:376(M^+)]. Oxidation of 8 with osmium tetroxide-sodium metaperiodate in aq. dioxane[3a] gave the aldehyde (9)(oil, 75%)[IR ν(film):1750($OCOCH_3$) and 1720 cm^{-1}(CHO);NMR δ:8.15(t, J=4 Hz, 1H, CHO), 5.11(t, J=8 Hz, 1H, 1-H), 2.60(d, J=4 Hz, 2H, $\underline{CH_2}CHO$), and 2.02(s, 3H, $OCOCH_3$);MS m/e:378(M^+)]. Reductive amination[10] (room temp., 3 days) of the crude aldehyde (9) with methylamine hydrochloride and sodium cyanoborohydride in methanol followed by heating (0.5 hr) with 10% hydrochloric acid gave, on purification by the preparative thin layer chromatography, (±)-mesembrine (3)(oil, 49%)[picrate, mp 173-175°



2b 8



9 3

(EtOH-EtOAc)(lit.[3c] mp 171.5-172.5°)]. The spectral data (IR, NMR) of 3 were identical with those of the natural alkaloid described in the literature.[3b]

ACKNOWLEDGEMENTS We are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind gift of the starting material. Thanks are also due to Misses N. Sawabe and K. Odachi of this Faculty for NMR and MS spectral measurements and to Sankyo Co., Ltd. for elemental analysis.

REFERENCES

1. B. Umezawa, O. Hoshino, S. Sawaki, S. Sato, and N. Numao, J. Org. Chem., 1977, 42, 4272.
2. Cf. E.V. Dehmdow, Angew. Chem. Internat. Ed., 1974, 13, 170.
3. a) M. Shamma and H.R. Rodriguez, Tetrahedron Letters, 1965, 4847; Tetrahedron, 1968, 24, 6583;b) T. Oh-ishi and H. Kugita, Tetrahedron Letters, 1968, 5445; Chem.Pharm. Bull. (Tokyo), 1970, 18, 299;c) R.V. Stevens and M.P. Wentland, J. Am. Chem. Soc., 1968, 90, 5580;d) T.J. Curphey and H.L. Kim, Tetrahedron Letters, 1968, 1441;e) S.L. Keely and F.C. Tahk, J. Am. Chem. Soc., 1968, 90, 5584;f) S. Yamada and G. Ohtani, Tetrahedron Letters, 1971, 1133;G. Ohtani and S. Yamada, Chem. Pharm. Bull. (Tokyo), 1973, 21, 2130 for the synthesis of (+)-mesembrine;g) J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron Letters, 1975, 3963;h) R.V. Stevens, P.M. Lesko, and R. Lapalme, J. Org. Chem., 1975, 40, 3495.
4. Satisfactory analytical data were obtained for all new com-

pounds described.

5. IR spectra were taken with a Hitachi Model 215 spectrometer, unless otherwise noted.
6. NMR spectra were measured on a Japan Electron Optics Lab. JNM-FX-100 spectrometer in $CDCl_3$ solution using Me_4Si as internal standard.
7. MS spectra were run on a Hitachi Model RMU-7M mass spectrometer at 70 ev.
8. Y. Ban and T. Oishi, Chem. Pharm. Bull. (Tokyo), 1958, 6, 574.
9. A Hitachi Perkin-Elmer 225 spectrometer was used.
10. R.F. Borch, M.D. Bernstein, and H.D. Durst, J. Am. Chem. Soc., 1971, 93, 2897.

Received, 16th September, 1978