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SYNTHESIS OF (±)-MESEMBRINE[†]

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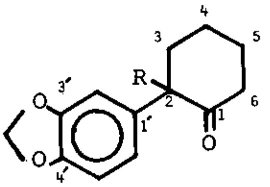
The base-catalyzed reaction of 2-(3',4'-methylenedioxyphenyl)cyclohexanone (1a) and 5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2a) with allyl bromide in the presence of 18-crown-6 afforded the 2-allyl-2-arylcyclohexanones (1b and 2b) in good yields, which was applied to the synthesis of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

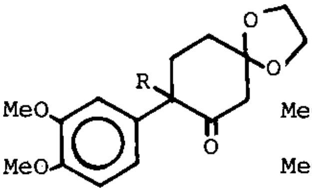
[†] Dedicated to Prof. Dr. A. Butenandt on the occasion of his seventy-fifth birthday.

starting from 2b.

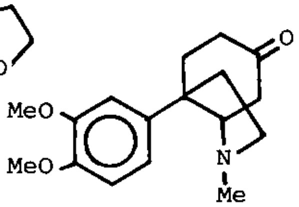
A mixture of 1a (436 mg, 2 mmole), allyl bromide (291 mg, 2.4 mmole) and 50% aq. sodium hydroxide(3 ml) in benzene (3 ml) containing 18-crown-6 (26.5 mg, 0.1 mmole) was heated at 70-75° for 1.25 hr with stirring. Usual work-up of the reaction mixture gave an oil (588 mg), which was chromatographed over 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= $CH_2CH=CH_2$



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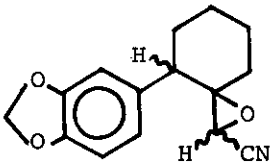

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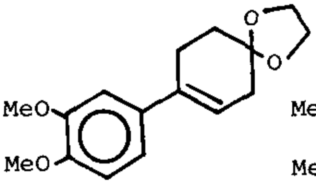
Then, the above reaction of 1a was extended to 2a.

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] ν(CHCl$_3$):1710 cm^{-1}(C=O);NMR δ:3.95(s, 4H, OCH$_2$CH$_2$O), 3.65-3.35(m, 1H, 2-H), and 2.70(s, 2H, 6-H);MS m/e:292(M$^+$)].



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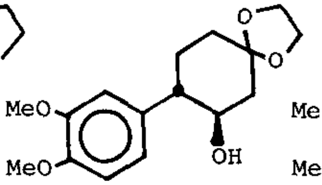

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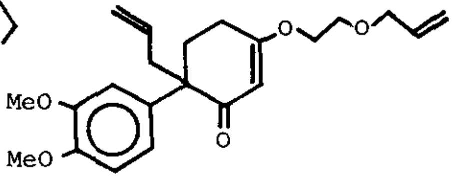

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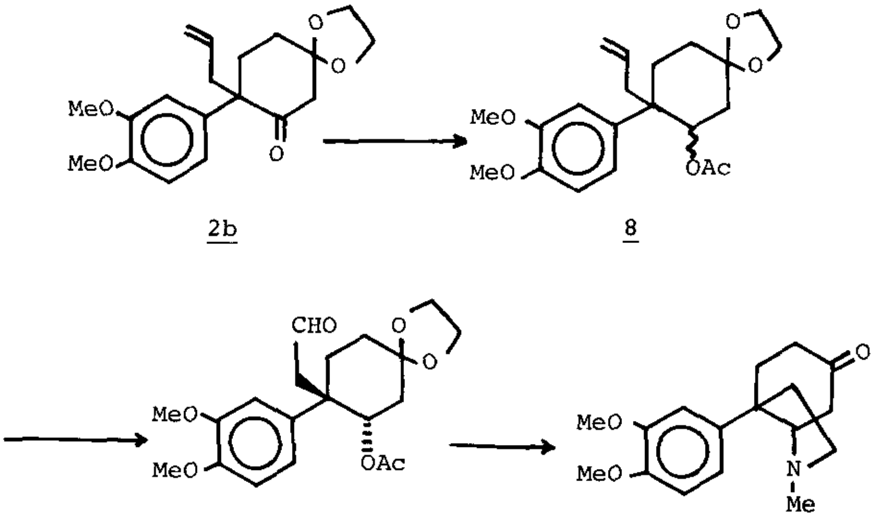
The base-catalyzed reaction (room temp., 0.5 hr) of 2a (1 mmole) with allyl bromide (1.2 mmole) yielded an oil, which was chromatographed over silica gel with benzene-ethyl acetate (10:1) to give 2-allyl-5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2b)(oil, 69%) [IR ν(CHCl$_3$):1710 cm^{-1}(C=O);NMR δ:5.73-4.70 (m, 3H, CH$_2$=CH-) and 3.90(s, 4H, OCH$_2$CH$_2$O);MS m/e:332(M$^+$)] accompanied by a small amount of an oil (7) [IR ν(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, CH_2CHO), 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]

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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.
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