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-aryl-cyclohexanones (1b and 2b) in good yields, which was applied to the synthesis of (†)-mesembrine (3).

In the course of our studies on the synthesis of Amaryllidaceae alkaloids, we found that the alkylation of 2-(3',4'-methyleneedioxyphenyl)cyclohexanone (1a) and 5,5-ethylenedioxy-2-(3',4'-dimethoxyphenyl)cyclohexanone (2a) with allyl bromide or acrylonitrile in the presence of a phase transfer catalyst (18-crown-6) took place readily at their benzylic positions to give the corresponding 2-alkyl-2-aryl-cyclohexanones (1b, c and 2b). The present paper is concerned with the synthesis of (†)-mesembrine (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'-methylene-dioxyphenyl)cyclohexanone \(1b\) (495 mg, 96%), bp 140°/0.02 mm. (bath temp.) (mp 46-47°) \(\text{IR}^5 \nu(\text{CHCl}_3):1710 \text{ cm}^{-1}(\text{C=O})\); \(\text{NMR}^6 \delta:5.76-4.60(\text{m, 3H, } \text{CH}_2=\text{CH}-); \text{MS}^7 m/e:258(\text{M^+})\). Similar reaction (room temp., 0.5 hr) of \(1a\) with acrylonitrile produced the 2-cyanoethyl-cyclohexanone \(1c\) (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.

![Chemical structures](image-url)

\(1a\) R= H
\(b\) R= CH\(_2\)CH=CH\(_2\)
\(c\) R= CH\(_2\)CH\(_2\)CN
\(d\) R= CH\(_2\)CN

\(2a\) R= H
\(b\) R= CH\(_2\)CH=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 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 ν(CHCl₃): 1710 cm⁻¹ (c=O); NMR δ: 3.95 (s, 4H, OCH₂CH₂O), 3.65-3.35 (m, 1H, 2-H), and 2.70 (s, 2H, 6-H); MS m/e: 292 (M⁺)].

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(CHCl₃): 1710 cm⁻¹ (c=O); NMR δ: 5.73-4.70 (m, 3H, CH₂=CH⁻) and 3.90 (s, 4H, OCH₂CH₂O); MS m/e: 332 (M⁺)] accompanied by a small amount of an oil (7) [IR ν(CHCl₃): 1650 cm⁻¹ (C=CHC=O);
NMR δ: 6.20-4.75 (m, 7H, 2 x CH₂=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 (Ac₂O-pyridine) yielded the acetate (8) (95% from 2b), mp 85.5-86° (ether) [IR₉ ν(KBr): 1730 cm⁻¹ (OCOCH₃); NMR δ: 5.40-4.65 (m, 4H, CH₂=CH- and 1-H) and 1.95 (s, 3H, OCOCH₃); MS m/e: 376 (M⁺)]. Oxidation of 8 with osmium tetroxide-sodium metaperiodate in aq. dioxane gave the aldehyde (9) (oil, 75%) [IR ν(film): 1750 (OCOCH₃) 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, CH₂CHO), and 2.02 (s, 3H, OCOCH₃); MS m/e: 378 (M⁺)]. Reductive amination (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°]
(EtOH-EtOAc) (lit. 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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REFERENCES
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 CDCl₃ solution using Me₄Si as internal standard.

7. MS spectra were run on a Hitachi Model RMU-7M mass spectrometer at 70 ev.


9. A Hitachi Perkin-Elmer 225 spectrometer was used.


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