Chemical Examination of the Roots of *Cissampelos Pareira* Linn. IV.[1] Structure and Stereochemistry of Hayatin

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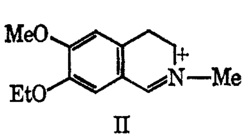
The isolation of hayatin [mp 298–303° dec, $[\alpha]_D$ 0° (pyridine)] from the roots of *Cissampelos pareira* Linn. was described earlier by Bhattacharji, *et al.*[2,3] The reported curariform activity[4–7] of its dimethiodide led to an investigation of its chemical structure.

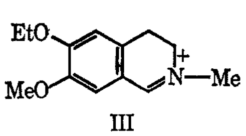
Sodium and liquid ammonia reduction of hayatin diethyl ether was undertaken with a view to establish, from the fragments obtained, the structure of hayatin as well as to determine the stereochemistry at the two asymmetric centers in the molecule.

Hayatin diethyl ether when subjected to sodium and liquid ammonia reduction gave a nonphenolic compound [mp 64°, $[\alpha]_D$ 0° ($CHCl_3$), mass spectrum M^+ 355 ($C_{22}H_{29}NO_3$)] and a phenolic compound, [$[\alpha]_D$ 0° (methanol)] which could not be crystallized. However, the R_f value of the phenol on tlc on silica gel (benzene–ethyl acetate–diethylamine, 7:2:1) was identical with that of N-methylcoclaurine. The O,O′-dimethyl methiodide of this compound, mp 131°, and the O,O′-diethyl methiodide derivative, mp 186°, were identical with samples of *dl*-O,O′,N-trimethylcoclaurine methiodide and O,O′-diethyl N-methylcoclaurine methiodide, respectively, in respect to melting point, mixture melting point, and infrared spectra. This establishes the structure of the phenolic fragment as N-methylcoclaurine (I).

The structure of the nonphenolic fragment was determined as follows. Its mass spectrum showed abundant ions at *m/e* 220 (base peak), 204, and 190, a very weak molecular ion peak (M^+) at 355 ($C_{22}H_{29}NO_3$), and a weak peak at *m/e* 354 (M − 1). The base peak corresponded to the ion II or III and *m/e* 204 and 190 ions could presumably be formed by a further loss of a methyl or ethyl, respectively, with hydrogen transfer. That the *m/e* 220 ion was II and not III was proved by the nmr spectrum of the nonphenolic fragment which showed a singlet for three protons at τ 6.18 (6-O*Me*) and four protons in the region 5.93–6.32 (7,4′-(OC*H*$_2$-CH$_3$)$_2$. There were no signals at τ 6.4–6.5 which clearly showed the absence of an OMe at the 7 position of the tetrahydroisoquinoline ring.[8] The other features of the nmr spectrum were as follows: (i) six aromatic protons, four forming an A_2B_2 pattern with doublets centered at τ 2.95 and 3.22 (J = 9 cps) and two as singlets at 3.52 and 3.98, respectively; that the proton at τ 3.98 was the one at C-8 would be in consonance with the shielding by the bottom aromatic ring; (ii) two triplets of three protons each at τ 8.61 and 8.70, respectively [J = 7.0 cps, ($OCH_2CH_3)_2$]; and (iii) three protons for >N·*Me*. All this data led to the formulation of the nonphenolic fragment as 7,4′-O,O-diethyl-N-methylcoclaurine (IV).



II



III

This was confirmed by establishing the identity of the methiodide of IV, mp 186°, with an authentic sample of *dl*-7,4′-O,O-diethyl-N-methylcoclaurine methiodide.

The confirmation of the phenolic and nonphenolic fragments as I and IV, respectively, and the fact that both hayatin and its sodium and liquid ammonia reduction products are optically inactive clearly establish the structure of hayatin as *dl*-bebeerine This structure is fully supported by the nmr and mass spectra of hayatin and its diethyl ether.

It is pertinent to point out that the biological activity reported for hayatin dimethiodide agrees very closely with the computed values for *dl*-bebeerine dimethiodide on the basis of reported activities of the corresponding quaternary compounds of *d*- and *l*-bebeerine.[9]

Experimental Section

Hayatin Diethyl Ether.—Hayatin was ethylated with triethyl anilinium chloride in the usual manner, when a mixture of mono- and diethylated bases was obtained. The two were separated and purified by column chromatography on neutral alumina using benzene–chloroform mixture as the eluent. O,O′-Diethylhayatin was crystallized from methanol, mp 160° (yield 48%). *Anal.* Calcd for $C_{40}H_{46}N_2O_6$: C, 73.84; H, 7.07; N, 4.30. Found: C, 74.08; H, 7.12; N, 4.47.

Monoethylated hayatin was crystallized from methanol, mp 234° (yield 30%). *Anal.* Calcd for $C_{38}H_{42}N_2O_6$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.50; H, 6.90; N, 4.25.

Sodium and Liquid Ammonia Fission of O,O′-Diethylhayatin.—A solution of O,O′-diethylhayatin (500 mg), in a mixture of dry benzene (20 ml) and toluene (20 ml), was added dropwise to stirred liquid ammonia (500 ml) containing sodium (0.5 g). More sodium was added (total 1.5 g) until the blue color persisted. Stirring was continued for 2 hr and the mixture was then allowed to stand overnight and the ammonia was allowed to evaporate. The phenolic and nonphenolic fragments were then separated in the usual way. The latter, obtained in the form of fine plates, was recrystallized from methanol, yield 180 mg, mp 58° rising to 64° on drying at 40° under high vacuum; methiodide (methanol–ether) mp 186°. *Anal.* Calcd for $C_{23}H_{32}NO_3I$: N, 2.81. Found: N, 2.68. Base oxalate (methanol–ether) had mp 188°. *Anal.* Calcd for $C_{24}H_{31}NO_7 \cdot 0.5H_2O$: C, 63.43; H, 7.04; N, 3.08. Found: C, 63.15; H, 7.12; N, 3.24.

The phenolic portion (230 mg) was chromatographed on alumina (neutral). Elution with chloroform–methanol (49:1) gave a product (110 mg) which could not be crystallized. A part of this (70 mg) was methylated with diazomethane and then converted into the methiodide which was crystallized (methanol–ether), mp 131°, $[\alpha]_D$ (0)° (methanol), yield 60 mg. A mixture melting point and infrared spectrum showed it to be identical with O,O′,N-trimethylcoclaurine methiodide.

The rest of the phenolic fraction (40 mg) was ethylated with triethylanilinium chloride and the product after purification on alumina column was converted into the methiodide which was

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crystallized from methanol-ether (yield 20 mg), mp 186°. The methiodide was found to be identical with the methiodide of the nonphenolic fragment in respect to melting poing, mixture melting point, and infrared spectrum.

Registry No.—Hayatin, 1381-51-7.

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A Comparison of the Electron Spin Resonance Spectra of *p*-Nitrotoluene, *p*-Nitroethylbenzene, *p*-Nitrocumene, and 2-Nitrotriptycene Radical Anions in Acetonitrile

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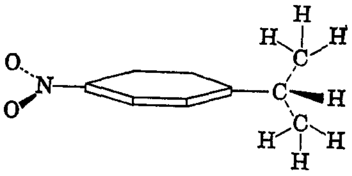
In connection with some studies on the spontaneous, free-radical formation in basic solutions of *o*- and *p*-nitrotoluenes[1] we obtained the esr spectrum of *p*-nitrotoluene, *p*-nitroethylbenzene, and *p*-nitrocumene anion radicals in dimethyl sulfoxide (80%)-*t*-butyl alcohol (20%) containing potassium *t*-butoxide. The spectra are consistent with 3.81-, 2.92-, and 1.73-gauss splitting for the α hydrogens of the methyl, ethyl, and isopropyl groups, respectively.[2] The ring hydrogens compare well with values previously reported for *p*-nitrotoluene radical anion in acetonitrile (Table I).

The observed decrease in α-hydrogen coupling constant with increased substitution in *p*-methyl-, *p*-ethyl-, and *p*-isopropylnitrobenzene radical anion is undoubtedly due to preferred population of certain conformations for the ethyl and isopropyl groups which are unfavorable for maximum interaction of the α hydrogen(s) with the unpaired electron in the aromatic system. Maximum interaction is possible if the dihedral angle (defined as the angle between the H-C-C plane and the axis of the p orbital containing the unpaired electron) is 0. The angular dependence of α-hydrogen coupling constants is expressed in the following relationship[3]

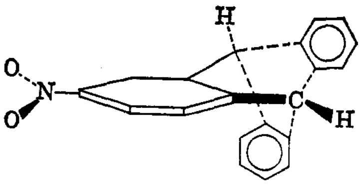
$$A^{H} = B + A\cos^2\theta \qquad (1)$$

where θ is the dihedral angle, $B \cong 0$, and $A \cong 50$ for alkyl radicals. Thus when $\theta = 90°$ no proton coupling (or very small coupling) is expected.

The nonuniform population of all possible conformations for alkyl groups larger than methyl in nitrobenzene radical anions and other similar radicals is due to steric hindrance to free rotation.[4-6] The bulky methyl groups of the isopropyl group in isopropylnitrobenzene radical anion, for example, prevent free rotation of the isopropyl group and orientations which place the methyl groups above and below the aromatic ring are favored. Because such orientations have relatively large dihedral angles for the methine hydrogen the coupling constant for this hydrogen is relatively small.



It was thought that further support for this interpretation could be provided from a study of the esr spectrum of 2-nitrotriptycene radical anion. Because of the restrictions imposed by the bonding to the bridgehead carbon the α hydrogen is essentially fixed at a dihedral angle of 90°. This Note reports our results on a comparison of the esr spectra of 2-nitrotriptycene, *p*-isopropylnitrobenzene, *p*-ethylnitrobenzene, and *p*-nitrotoluene radical anions.



Since more studies of substituted nitrobenzene radical anions have been made in acetonitrile than in any other solvent system this solvent was chosen. Esr spectra for *p*-ethyl- and *p*-isopropylnitrobenzene radical anions have previously been obtained in basic ethanol[7] and aqueous acetone.[8]

The electron spin resonance spectra of *p*-nitroethylbenzene and *p*-nitroisopropylbenzene in acetonitrile can be fitted to coupling constants listed in Table I.[9] Essentially the same values are obtained in acetonitrile as found earlier[1,2] in dimethyl sulfoxide (80%)-*t*-butyl alcohol (20%) containing potassium *t*-butoxide. The spectra in basic *t*-butyl alcohol, ethanol,[7] or aqueous acetone,[8] however, show a sizable increase in the nitrogen coupling constant. This effect has previously been observed in protic solvents and is attributed to solvation and hydrogen bonding of the partially negatively charged nitro group.[10]

2-Nitrotriptycene gave the spectrum in Figure 1. An analysis of the spectrum gives the coupling constants in Table I. The assignment is based on the coupling constants reported for 3,4-dimethylnitro-

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