

SYNTHESIS OF 10,11-DIMETHOXYAPORPHINE - d<sub>8</sub>.

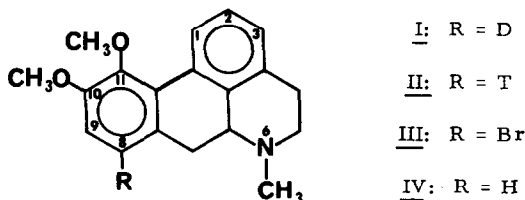
USE OF Eu(FOD)<sub>3</sub> REAGENT IN STRUCTURE DETERMINATION

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In a continuing study of the metabolism of aporphine alkaloids,<sup>1,2,3</sup> 10,11-dimethoxyaporphine-d<sub>8</sub> (I) was required for model studies leading to the synthesis of 10,11-dimethoxyaporphine-t<sub>8</sub> (II). Preparation of I was proposed via III. The synthesis of III is believed to be the first direct bromination of an aporphine to be reported. Catalytic hydrogenation of III led to I. Structure elucidation of I was confirmed by a novel application of NMR spectroscopy employing Eu(fod)<sub>3</sub> shift reagent.



10,11-Dimethoxyaporphine<sup>2</sup> (IV) was allowed to react with Br<sub>2</sub> in acetic acid following the method of Harley-Mason.<sup>4</sup> The resulting solution was neutralized with 5% NaOH, then repeatedly extracted with ether. After drying, the ether solution was taken to dryness, giving a dark brown oil. The oil, dissolved in chloroform, was applied to preparative tlc plates (1 mm; Woelm neutral alumina). Following development in chloroform-benzene (9:1), III was isolated by elution of scraped alumina (R<sub>f</sub> 0.4) with ether in a continuous extractor. Crystallization of III was carried out in *n*-pentane, giving a 15% yield. Melt. pt., 83-84°C (uncorrected). NMR (in CDCl<sub>3</sub>); loss of AB quartet (8, 9H) at 7.01 δ<sup>5</sup>, with a downfield shift of one

aromatic proton to 7.11  $\delta$ . Mass spec.;  $m/e$ , 373, 375 ( $M^+$ ). Anal., calcd for III: C, 60.92; H, 5.39; N, 3.74. Found: C, 60.85; H, 5.46; N, 3.78.

Compound I was prepared by treating a mixture of 0.25 mmole of III, 0.03 mole triethylamine, and 30 mg 5% Pd/C in 1.5 ml ethyl acetate with deuterium gas. The mixture was stirred in a deuterium atmosphere for 4 hours, keeping the pressure between 870 to 880 mm Hg. The catalyst was filtered off and continuously extracted with ethyl acetate for 12 hours. The solvent was removed under reduced pressure and the remaining residue was crystallized from *n*-pentane, giving a 83% yield of I. NMR (in  $CDCl_3$ ); singlet at 6.81  $\delta$  (one proton). IR (2%,  $CHCl_3$ );  $\nu$  C-D 2325  $cm^{-1}$ . Mass spec.;  $m/e$ , 296 ( $M^+$ ). Anal., calcd for I: C, 77.00; H, 7.48; N, 4.73. Found: C, 77.24; H, 7.23; N, 4.43.

The NMR spectrum of I (Fig. 1) indicates that the deuterium is located on 8C. Preliminary experiments with IV, however, revealed that this assignment might unequivocally be made through use of  $Eu(fod)_3$  reagent. When IV is measured in the presence of increasing quantities of  $Eu(fod)_3$ , a large downfield shift of its 10-OCH<sub>3</sub> protons is observed (Table 1). Studies relating the angular and radial dependencies of lanthanide induced shifts (LIS)<sup>6,7</sup> suggested that the downfield doublet of the AX quartet observed at  $R/S \approx 0.11$  (Table 1; Fig. 2) should be assigned to the 9H with the upfield doublet assigned to the 8H.<sup>8</sup> The chemical shifts of the 8 and 9 H's of IV were plotted vs.  $R/S$  (Fig. 3). When extrapolated to the Y-axis, these lines cross, signifying that in the absence of  $Eu(fod)_3$ , 9H should appear upfield from 8H. This is

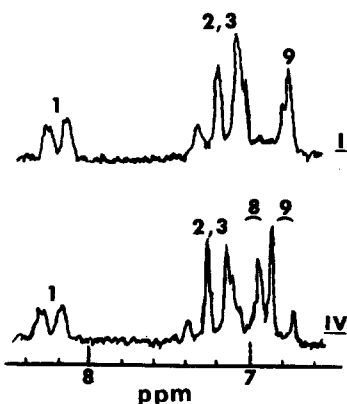


Fig. 1 NMR,  $CDCl_3$

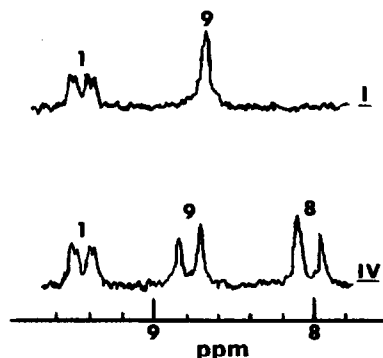


Fig. 2 NMR,  $CDCl_3$ - $Eu(fod)_3$ ,  $R/S$  0.28.

expected because of the shielding effect of the 10-OCH<sub>3</sub> and verified through assignments made in similar systems.<sup>5</sup> I was studied by NMR in the same fashion as IV. Shifts of the 10-OCH<sub>3</sub> and its neighboring proton (Table I; Fig. 4) are in accord with assignment of a proton at 9C (Fig. 2) and the deuterium at 8C.

Nuclear Overhauser effects (nOe) between ortho-substituted aromatic and methoxyl protons have been reported in a number of systems.<sup>9</sup> An noe of 16 ± 1% was observed for signals at 6.83 δ and 6.84 δ in compounds IV and I respectively, upon irradiation of their 10-OCH<sub>3</sub> protons. These data corroborate the chemical shift assignments made for the signals noted (Table 1) and confirm the assignment of a proton in I to 9C. Assignment of the deuterium in I establishes 8C as the location of the bromo atom in III.

At the highest R/S studied (0.56), the 2H in I and IV appear as well resolved triplets (J = 7.5 Hz) while the 3 H's are observed as apparent doublets (J = 8Hz). It is noteworthy, then, that Eu(fod)<sub>3</sub> can be employed to resolve all the aromatic protons of IV.

TABLE 1.

		<u>Compound IV, Chemical Shift δ (ppm)</u>							
<u>(R/S)</u>	<u>protons</u>	<u>(1)</u>	<u>(2)</u>	<u>(3)</u>	<u>(6)</u>	<u>(8)</u>	<u>(9)</u>	<u>(10)</u>	<u>(11)</u>
0.		8.25	-	-	2.57	7.00	6.83	3.90	3.72
0.11		8.75	-	-	2.82	7.47	7.68	5.43	4.07
0.28		9.47	-	-	3.33	8.04	8.68	7.56	4.36
0.56		10.67	7.17	7.63	4.28	9.08	10.70	11.47	4.75

		<u>Compound I, Chemical Shift δ (ppm)</u>							
<u>(R/S)</u>	<u>protons</u>	<u>(1)</u>	<u>(2)</u>	<u>(3)</u>	<u>(6)</u>	<u>(8)</u>	<u>(9)</u>	<u>(10)</u>	<u>(11)</u>
0.		8.27	-	-	2.57	-	6.84	3.91	3.73
0.11		8.62	-	-	2.83	-	7.51	5.01	4.03
0.28		9.47	-	-	3.27	-	8.65	7.50	4.35
0.56		10.50	7.17	7.63	4.13	-	10.53	11.07	4.70

R = conc. of Eu(fod)<sub>3</sub>: 9.6, 24, 48 μmole in 0.5 ml CDCl<sub>3</sub>; S = conc. of IV and I: 86 μmole in 0.5 ml CDCl<sub>3</sub>/TMS internal stand; Varian T-60; Temp. = 38° C.

Fig. 3. Effects of  $\text{Eu}(\text{fod})_3$  on 8H and 9H of IV

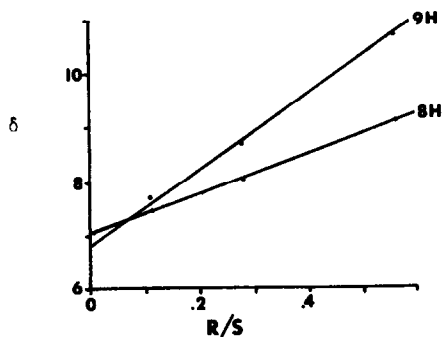
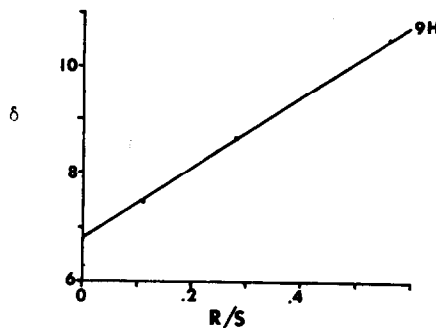


Fig. 4. Effect of  $\text{Eu}(\text{fod})_3$  on 9H of I.



### ACKNOWLEDGEMENT

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