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CYCLEANINE FROM *SYNCLISIA SCABRIDA*: CONFORMATIONAL INFORMATION FROM THE ^{1}H NMR SPECTRUM AT 300 MHz

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Key Word Index—*Synclisia scabrida*; Menispermaceae; alkaloids; cycleanine; ^{1}H NMR.

Abstract—Cycleanine, a bisbenzylisoquinoline alkaloid, has been isolated from the roots of *Synclisia scabrida*. The ^{1}H NMR spectrum at 300 MHz reveals that, in chloroform solution, cycleanine has a conformation whereby ring B partly shields ring C′ and ring C is similarly influenced by ring B′.

INTRODUCTION

West African plants of the Menispermaceae are of medicinal interest and have been shown to contain various bisbenzylisoquinoline alkaloids [1], but there have been no previous reports on extractives from *Synclisia* species. *S. scabrida* is found as a heath straggler at the rubber plantations in the Benin region of Nigeria. It was identified by Professor A. D. Skelding and authenticated by Kew Gardens, London. The plant is used natively as a medicine to treat female lower abdomenal pains, listlessness, and mental strain.

RESULTS

An ethanol extract of the dried roots was acidified with hydrochloric acid and the alkaloid fraction obtained by basifying the aqueous layer with ammonia. Extraction of the organic material gave a bisbenzylisoquinoline alkaloid, mp 268–271°, [α] − 20°, M$^+$ 622. That the alkaloid, from *S. scabrida* was cycleanine was confirmed by MS data which is diagnostic for two head-to-tail ether-linked isoquinoline coclaurine units joined at C-8 and C-12′, and C-8′ and C-12 (Scheme 1) [2]. The ^{1}H NMR spectrum was also identical to that previously published [3], but examination of the aromatic region showed that the chemical shifts and splitting patterns differed from those expected for *p*-alkylphenol derivatives which have AA′ BB′ spin systems with the AA′ signals in the region of ~3τ and BB′ at ~3.3τ [4]. The ^{1}H NMR spectrum of cycleanine was thus examined at 300 MHz (Fig. 1) and the aromatic protons expanded to a sweep width of 500 Hz (Fig. 2). The

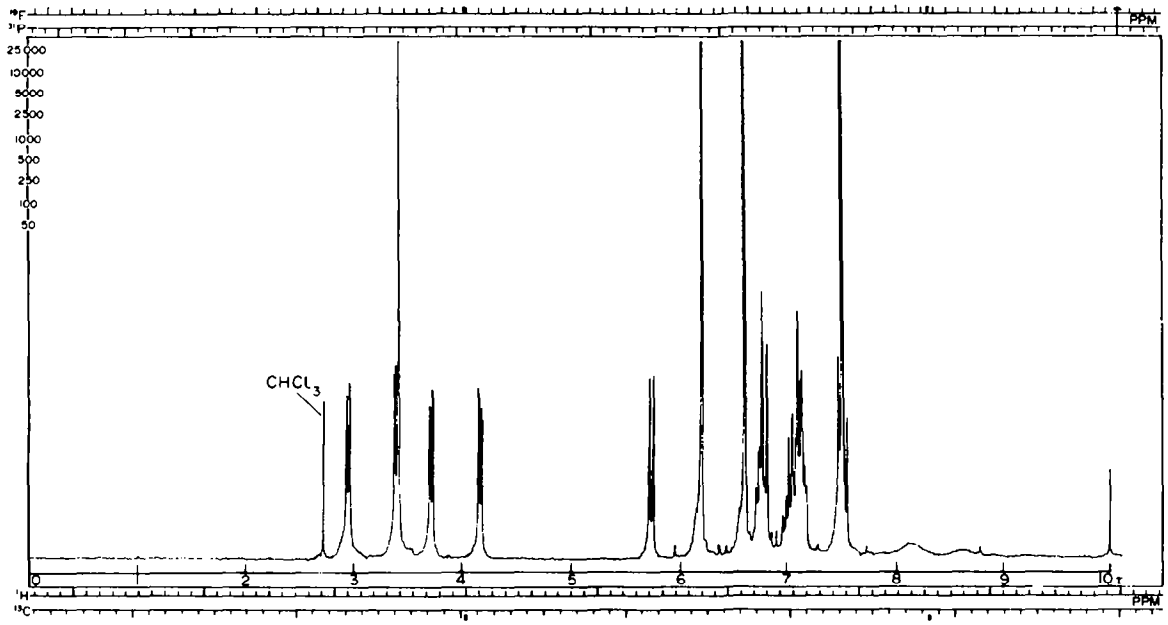
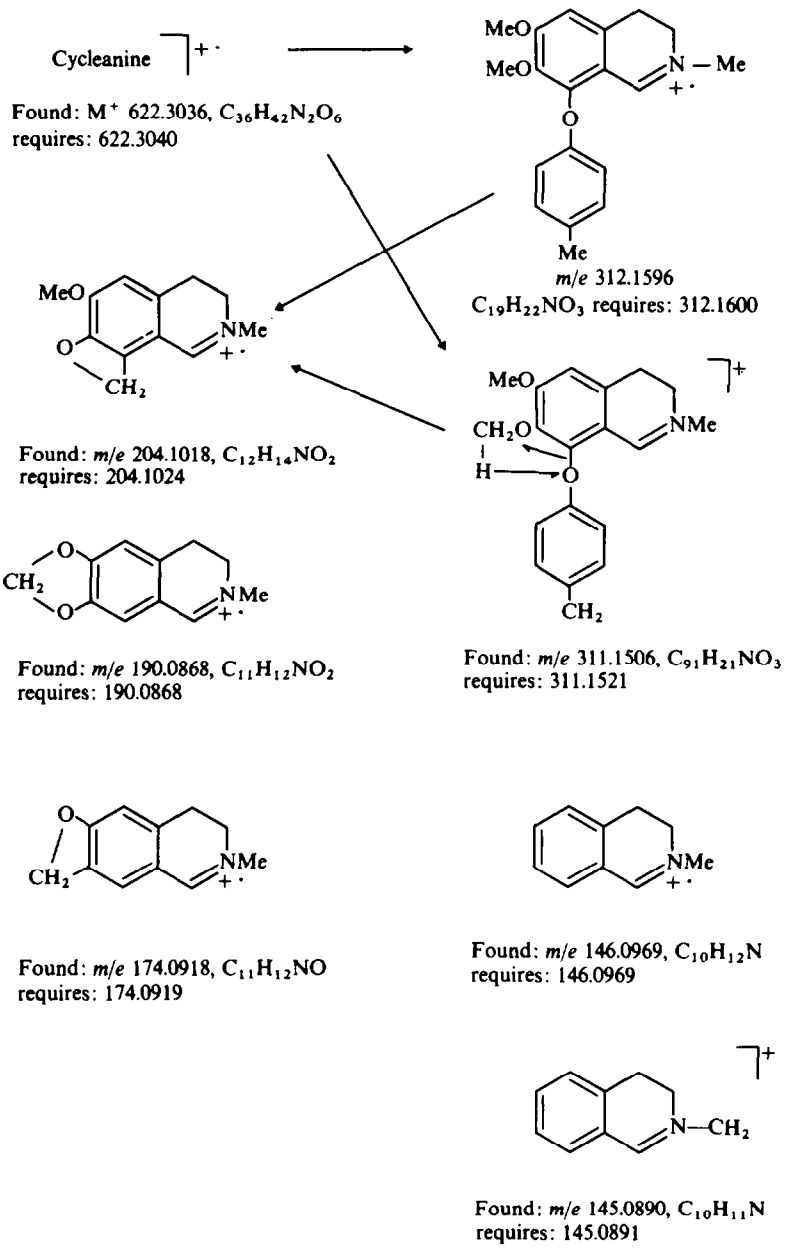


Fig. 1. ^{1}H NMR spectrum of cycleanine measured in $CDCl_3$ at 300 MHz with a sweep width of 3000 Hz.



Scheme 1. MS fragmentation of cycleanine.

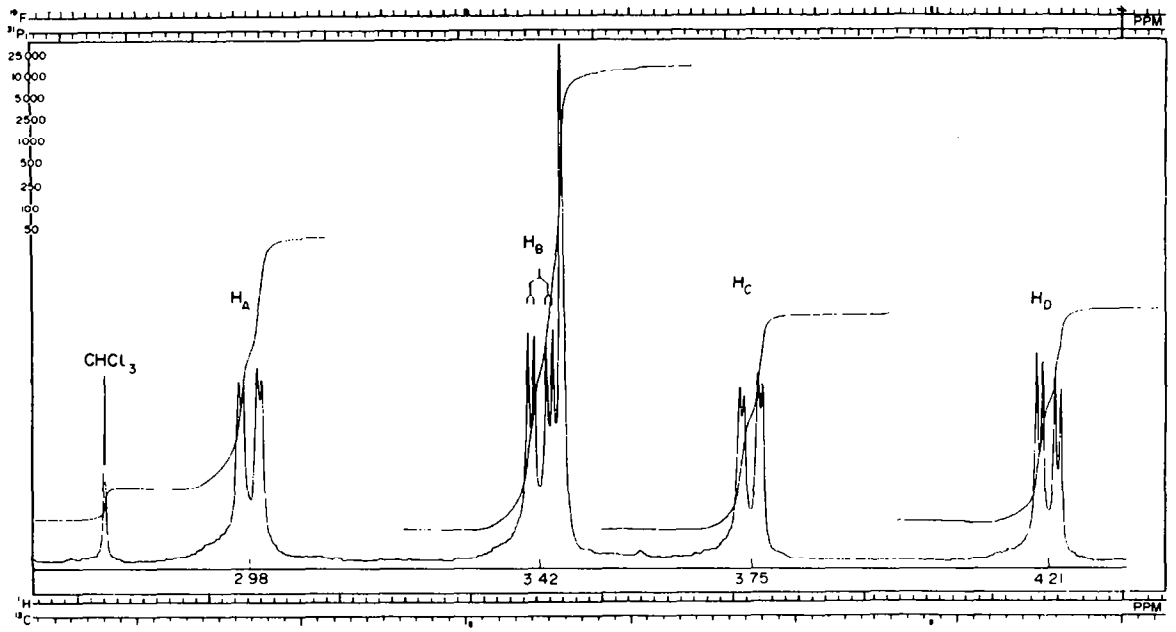
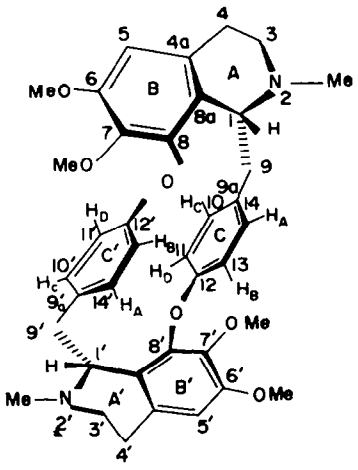


Fig. 2. ^{1}H NMR spectrum of cycleanine measured in $CDCl_3$ at 300 MHz showing the aromatic region at a sweep width of 500 Hz.

aromatic protons of rings C and C′ appear as an ABCD spin-coupled system at τ 2.98 (J = 8.5 and 3 Hz), 3.42 (J = 8.5 and 2 Hz), 3.75 (J = 8.5 and 3 Hz) and 4.21 (J = 8.5 and 2 Hz). Double resonance experiments show that H_D (τ 4.21) at highest field is *ortho* to H_C (τ 3.75) and *meta* to H_B (τ 3.42) while H_A (τ 2.98) is *ortho* to H_B and *meta* to H_C. This suggests that the two protons, H_D and H_C, at highest field are additionally shielded by the induced magnetic field from the ring current of suitably orientated benzene rings. An examination of a Dreiding model of cycleanine (**1**) clearly shows a favourable conformation in which two *ortho* aromatic protons from ring C (H-10 and H-11) would be shielded by the benzene ring B′, and two *ortho* protons from C′ would likewise be shielded by ring B. In agreement with the chemical shift data for H_A and H_B, the model also shows that rings C and C′ each have two adjacent aromatic protons (H-13 and H-14 which are not influenced by the conformational requirements of other parts of the molecule, and their chemical shifts at τ 2.98 and 3.42 are in the expected range. Finally the molecular model also shows that the methoxyl groups at position 7 of rings B and B′ will be shielded respectively by aromatic rings C′ and C whereas those at position 6 should not be influenced. In accordance with these requirements the methoxyl groups appears as two groups of signals at τ 6.20 and τ 6.61. Similar, but smaller chemical shift differences have also been observed in a study of hindered rotation of 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines [5–7].

These conclusions are supported by the ^{13}C NMR data since the methoxyl methyl groups appear at δ 56.0 and 59.8 ppm and the unsubstituted carbons of ring C and C′ resonate at δ 113.9, 117.3, 128.0 and 128.6 ppm [8].



EXPERIMENTAL

The UV spectrum was determined in MeOH and the IR spectrum as a Nujol mull. The ^{1}H NMR spectra were measured at 90 and 300 MHz. TLC was carried out on Si gel using xylene–butanone–MeOH–diethylamine (10:20:5.1) for elution. The mp is uncorr.

Extraction and separation. Roots of *S. scabrida* were collected from rubber plantations. They were washed and dried at 40°. After milling, 900 g of the powder was extracted with petrol (bp 60–80°). This was followed by extraction with 85% EtOH. The alcoholic extract was reduced under pressure to *ca* 500 ml and cooled in ice. The extract was acidified to pH 1 with 2 M HCl. The aq. layer was extracted with petrol, cooled and basified with 18 M NH_4OH to pH 12 at the same temp, left overnight and then extracted with $CHCl_3$. The aq. layer was evapd under red. pres. and the residue extracted with Me_2CO to yield mostly crude cycleanine (2.6 g) which recrystallized from Me_2CO to give off-white needles, mp 268–271°, $[\alpha]_D$ − 20° (*c* 1.0: $CHCl_3$, ref. [9] mp 272–273° $[\alpha]_D^{24}$ −15.1 ($CHCl_3$) [Found: M^+ 622.3036. $C_{36}H_{42}N_2O_6$ requires: 622.3040]. The $CHCl_3$ extract was reduced in vol. and TLC

showed 6 spots R_f 0.2, 0.3, 0.6, 0.7, 0.85, 0.9. The spot at R_f 0.6 was identified as cycleanine. ν_{max}^{Nujol} cm^{-1}: 1616, 1585, 1510, 1493, 1342, 1300, 1225, 1172, 1149, 1120, 1110, 1070, 1020, 1012, 995, 845, 809. λ_{max}^{MeOH} nm: 230, 275, 283 sh. MS *m/e* (%): 622 (27), 312 (100), 311 (54), 204 (73), 190 (46), 176 (14), 174 (51), 159 (45), 146 (42), 145 (46). ^{1}H NMR: See Figs 1 and 2. ^{13}C NMR ($CDCl_3$) ppm: δ 59.5 (C-1); 42.3 (NMe); 44.7 (C-3); 24.8 (C-4); 129.6 (C-4a); 109.3 (C-5); 151.8 (C-6); 139.0 (C-7); 143.6 (C-8); 125.6 (C-8a); 37.7 (C-9); 130.4 (C-9a); 128.0, 128.6, 113.9, 117.3 (C-10, C-11, C-12, C-13); 154.1 (C-14);

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