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TECLEANONE: A NEW ALKALOID FROM TECLEA GRANDIFOLIA (Engl.)[1,2]

Adria C. Casey* and Ashwani Malhotra

New England Institute, Ridgefield, Connecticut 06877

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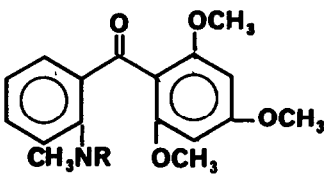
Crude extracts from the bark of Teclea grandifolia (Engl.) Rutaceae have been reported to exhibit antitumor activity.[3-5] In the course of our studies of the components of T. grandifolia for tumor inhibitory substances we have isolated a new alkaloid tecleanone (1).[6]

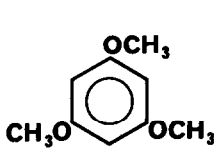
1; R=H

2; R=CH_3



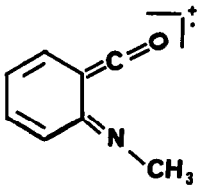
The dried bark of the plant was extracted exhaustively with cold ethanol and the residue from these extracts was treated with 10% HCl. The filtrate was made to pH 8 with conc. ammonia and the solid that precipitated was continuously extracted with $CHCl_3$ after drying. Thin layer chromatography of the

yellow residue from the $CHCl_3$ extract (silica gel, 20 X 20 cm prewashed plates; benzene-ethyl acetate 1:1 as solvent) and extraction of the yellow band at R_f0.65 gave a yellow solid. Repeated tlc (silica gel, benzene-ethyl acetate 1:1) followed by fractional crystallization from a) acetone (white unidentified solid separated) and b) hexane (lupeol obtained[3]) gave tecleanone (1) as a yellow crystalline solid in 0.006%, mp 190-1°. Anal.[7] calculated for $C_{17}H_{19}O_4N$: C, 67.64; H, 6.34; N, 4.65. Found C, 67.77; H, 6.36; N, 4.65. The infrared spectrum of 1 showed absorption bands at 3330 (NH), 2950, 1650 (CO), 1590, 1575, 1520 and 1460 cm^{-1}. Methoxyl group determination[7] indicated that 1 contained three OCH_3 groups.



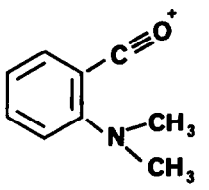
A

m/e 168



B

m/e 133



C

m/e 148

The structure of tecleanone was elucidated from its mass and nmr spectra.[7] High-resolution mass spectral analysis of 1 gave, in addition to the M^+ peak at m/e 301.1329 (calcd. for $C_{17}H_{19}O_4N$, m/e 301.1313) two main fragments at m/e 168 ($C_9H_{12}O_3$, A) and at m/e 133 (C_8H_7ON, B) indicating that the molecule consisted of two parts, one containing the nitrogen and the other containing three oxygens with the fourth oxygen near the point of attachment of the two parts. These fragments, probably formed by intramolecular hydrogen transfer, suggested an ortho substituted bis-aryl compound.[8]

The position of the methoxy groups was determined by the nmr spectrum of 1 (60 MHz, $CDCl_3$, TMS). Singlets at δ 3.76 (6H) and 3.87 (3H) confirmed the presence of three OCH_3, a broad peak at δ 9.0 (NH) disappeared when exchanged with D_2O; a doublet at δ 2.97 (3H) was in agreement with a methylamino group. The chemical shift for the 3- and 5-protons in 2,4,6-trimethoxybenzophenone have been reported as 6.23 δ ($CDCl_3$ TMS).[9] The equivalent 3- and 5-protons in 1 gave a peak at δ 6.20 (s,2H). The four aromatic protons in the other ring gave signals at δ 6.6 (m,1H); 6.8 (m,1H); 7.27 (m,1H) and 7.40 (m,1H), in good agreement with the position of the four aromatic protons in o-aminoacetophenone.[12] The latter, together with the mass spectral fragmentation pattern data rules out the possibility of meta or para substitution in that ring.

In agreement with the assigned structure N-methylation of 1 with MeI in anh. acetone containing 1% K_2CO_3 gave 2, mp 128°, M^+ at m/3 315.1467, (calcd. for $C_{18}H_{21}O_4N$ m/e 315.1470) indicating that only one additional CH_3 had been added to 1. The decreased intensity of the fragment A (m/3 168) and the shift of the peak from m/e 133 (B) to m/e 148 (C) in the high-resolution mass spectrum of 2 indicated that the CH_3 was attached to N.

Tecleanone is the first o-aminobenzophenone alkaloid ever reported. Its structure is very similar to an intermediate, derived from anthranilic acid and three acetate units, proposed to be involved in the biosynthesis of the acridone alkaloids.[11] Since T. grandifolia (bark) contains evoxanthine and norevoxanthine[5,10], both acridone alkaloids, the presence of tecleanone provides experimental evidence for this pathway.

ACKNOWLEDGMENT

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REFERENCES

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2. The authors thank J. Brookman-Amissah, Silviculturist, Department of Forestry, Kumasi Ghana and Dr. R. Perdue, Agricultural Research Service, U.S.D.A., Beltsville, Md. for collection and identification of the plant material.

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6. Tecleanone did not exhibit any cytotoxicity (ED_{50}) against KB cell culture at 10 μg/ml nor LE1210 activity at 50 mg per kilogram level. Cytotoxicity and in vivo studies were carried out under the auspices of the National Cancer Institute by the protocols described in Cancer Chemotherapy Reports, 25, 1 (1962). The authors thank Dr. J. L. Hartwell for assistance in having the extracts screened.

7. Elemental analysis and group determination performed by Gailbraith Laboratories, Knoxville, Tenn. Nmr and mass spectral analysis by Shrader Analytical Co., Detroit, Michigan.

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12. The authors are indebted to the referee for helpful comments.