HETEROCYCLES. Vol. 9. No. 8. 1978

GILLETINE, A NEW BISBENZYLISOQUINOLINE ALKALOID FROM TRICLISIA GILLETII [1]

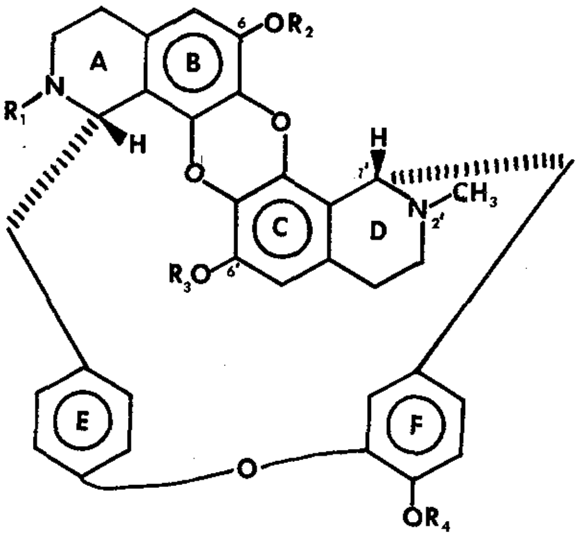
Daniel Dwuma-Badu, John S.K. Ayim and Albert N. Tackie[2]
Department of Pharmaceutical Chemistry
Faculty of Pharmacy
University of Science and Technology
Kumasi, Ghana
and
Philip D. Owusu, Joseph E. Knapp,
David J. Slatkin and Paul L. Schiff, Jr.*
Department of Pharmacognosy
School of Pharmacy
University of Pittsburgh
Pittsburgh, PA 15261, U.S.A.

Gilletine (1), a new alkaloid from extracts of the leaves of Triclisia gilletii (Menispermaceae), was characterized as a dibenzodioxin bisbenzylisoquinoline base by physicochemical data and conversion to O,O-dimethylcocsulinine (3).

Gilletine was first isolated in small quantities in 1973 from extracts of the leaves of Triclisia gilletii (Menispermaceae) and was simply designated as alkaloid TGL-4 at that time.[3] Recently, an additional small quantity of this alkaloid was reisolated from the same source.

Gilletine (1) crystallized as rosettes of needles from $CHCl_3$-Et_2O, mp 174-176°; $[\alpha]_D^{28}$ +294.29° (c0.56, MeOH); uv λ_{max}^{MeOH} nm (log ε); 237 (4.34), 274(sh)(3.33), 290 (3.41) and 301 (sh)(3.36); ir ν_{max}^{KBr} (cm^{-1}): 3520 (br) and 1505. The nmr spectrum (60MHz, $CDCl_3$, TMS, δ in ppm) indicated the presence of one N-methyl function as a singlet at δ2.42, two O-methyl functions as singlets at δ3.91 and 3.95, nine aromatic protons as three singlets at δ6.11 (1H), 6.53 (2H), 6.82 (2H), and two multiplets at 6.90-7.07 (2H) and 7.59-7.68 (2H), with one broad proton singlet at δ4.35 for a N-H function and δ5.16 (D_2O exchanged) for a phenolic hydroxy group. The ms showed M^+ at m/e 578 (33%) for $C_{35}H_{34}N_2O_6$, 352(21), 351(100), 337(21) and 176(27) with metastable ions at m/e 322.5 for the transition 352 → 337 (m^*_{calc} 322.64) and 214.0 for the transition 578 → 352 (m^*_{calc} 214.37). Finally, the base afforded a blue color on treatment with a mixture of conc. H_2SO_4-HNO_3 (1:1). The spectral data[4-7] and color reaction[8] was suggestive of a dibenzo-1,4-dioxin type monophenolic, bisbenzylisoquinoline alkaloid which contained one secondary amino group.

Treatment of gilletine with formaldehyde (37%) and sodium borohydride afforded N-methylgilletine (2) as needles from MeOH, mp 156-157°; $[\alpha]_D^{30}$ + 309.76° (c0.41, $CHCl_3$); uv λ_{max}^{MeOH} nm (log ε): 237(sh)(4.39), 277(sh)(3.39), 289 (3.44) and 304(sh)(3.37); ir ν_{max}^{KBr} (cm^{-1}): 3480(br) and 1505. The nmr spectrum indicated the presence of two N-methyl groups as singlets at δ2.39 and 2.57, two O-methyl groups as singlets at δ3.90 and 3.93, nine aromatic protons as three singlets at δ6.16 (1H), 6.55(2H), 6.87(2H) and two multiplets at 6.97-7.08 (2H) and 7.50-7.65 (2H), with one broad proton singlet at δ5.30 (D_2O exchanged) for a phenolic hydroxy group. The ms showed M^+ at



1 $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$

2 $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$

3 $R_1 = R_2 = R_3 = R_4 = CH_3$

7 $R_1 = R_3 = CH_3$; $R_2 = R_4 = C_2H_5$

8 $R_1 = R_3 = CH_3$; $R_2 = R_4 = COCH_3$

9 $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$

10 $R_1 = R_3 = R_4 = CH_3$; $R_2 = C_2H_5$

m/e 592(45%) for $C_{36}H_{36}N_2O_6$, 366(25), 365(100), 351(33) and 183(57) with metastable ions at m/e 336.5 for the transition 366 → 351 (m^*_{calc} 336.61) and 225.9 for the transition 592 → 366 (m^*_{calc} 226.28).

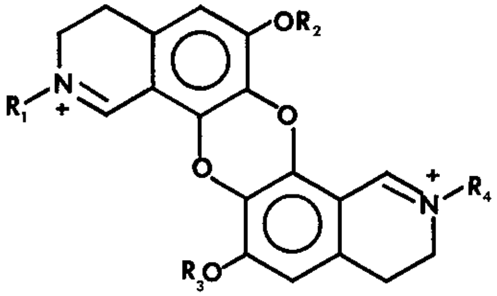
Treatment of N-methylgilletine (2) with ethereal diazomethane gave N,O-dimethylgilletine (3) as needles from MeOH, mp 201-203°; $[\alpha]_D^{24}$ +193.06° (c1.73, $CHCl_3$); uv, λ_{max}^{MeOH} nm (log ε): 237(sh)(4.57), 276(sh)(3.46), 291 (3.51) and 301(sh)(3.45); cd (MeOH):[9] $[\theta]$ 233 +97,700 and $[\theta]$ 288 +20,400; ir, λ_{max}^{KBr} cm^{-1}: 1503. The nmr spectrum indicated the presence of two N-methyl groups as singlets at δ2.38 and 2.58, three O-methyl groups as singlets at δ3.82, 3.90 and 3.95, nine aromatic protons as three singlets at δ6.17 (1H), 6.59 (2H), 6.88 (2H) and two multiplets at 7.00-7.10 (2H) and 7.52-7.58 (2H). The ms showed M^+ at m/e 606 (41%) for $C_{37}H_{38}N_2O_6$, 380(30), 379(100), 365(30) and 190(53) with metastable ions at m/e 350.0 for the transition 380 → 365 (m^*_{calc} 350.59) and 238.0 for the transition 606 → 380 (m^*_{calc} 238.28). A direct comparison (ir, uv, nmr, ms) of the N,O-dimethylgilletine (3) and O,O-dimethylcocsulinine (3) from Cocculus pendulus[10,11] showed them to be identical, thus establishing the skeletal structure of gilletine and fixing positions of oxygenation and nitrogenation. Furthermore, the mp of N,O-dimethylgilletine dimethiodide (260-63° dec.) (prepared by adding methyl iodide to a solution of the alkaloid in acetone) was identical to that of O,O-dimethylcocsulinine dimethiodide (mp 261-63° dec.)[10] Finally, a determination of the cd spectrum (MeOH) of reference O,O-dimethylcocsulinine ($[\theta]$ 236 +100,800 and $[\theta]$ 291 +19,800)[12] showed close agreement with that of N,O-dimethylgilletine ($[\theta]$ 233 +97,700 and $[\theta]$ 288 +20,400) and since the configuration of the asymmetric centers in O,O-dimethylcocsulinine has been determined to S,S,[10,11] the configuration of these centers in N,O-dimethylgilletine should likewise be S,S.

The positions of the secondary amine and that of the single phenol of gilletine remained to be deduced. Prominent doubly changed fragment ions at m/e 176(27%)(4), 183(57)(5), and 190(53)(6) in the ms of gilletine, N-methylgilletine and N,O-dimethylgilletine, respectively, indicate that the phenolic group must be in either ring B at C-6 or ring C at C-6'[4]. Since the methoxy resonances of gilletine are at δ3.91 and 3.95 and those of N-methylgilletine at δ3.90 and 3.93, it is apparent that the methoxy resonance at δ3.82 in N,O-dimethylgilletine (δ3.82, 3.90 and 3.95) was introduced via O-methylation. Since O,O-diethylcocsulinine (7) has only one methoxy group (C-6') (δ3.95)[10] and O,O-diacetylcocsulinine (8) likewise has only one methoxy group (C-6') (δ3.90),[10] the signal at δ3.82 in N,O-dimethylgilletine must be in ring B at C-6 and thus the phenolic hydroxy of gilletine at the same position.

Molecular models (Dreiding) of N-methylgilleine (2) and cocsulinine (9) show that the N-2' in ring D is shielded by ring F and thus methyl groups on N-2' will resonate at a higher field than N-2 in ring A. The N-methyl signal is found at δ2.42 in gilletine while the same signals are found at δ2.39 and 2.57 in N-methylgilletine and δ2.38 and 2.58 in N,O-dimethylgilletine. Therefore, the lower field signals (δ2.57 in N-methylgilletine and δ2.58 in N,O-dimethylgilletine), which have been introduced by N-methylation, must be at N-2 and in turn the secondary amino group at N-2.

Reductive cleavage of N-methyl-O-ethylgilletine (10) under Birch conditions will be undertaken for further confirmation of structure as additional quantities of gilletine become available.

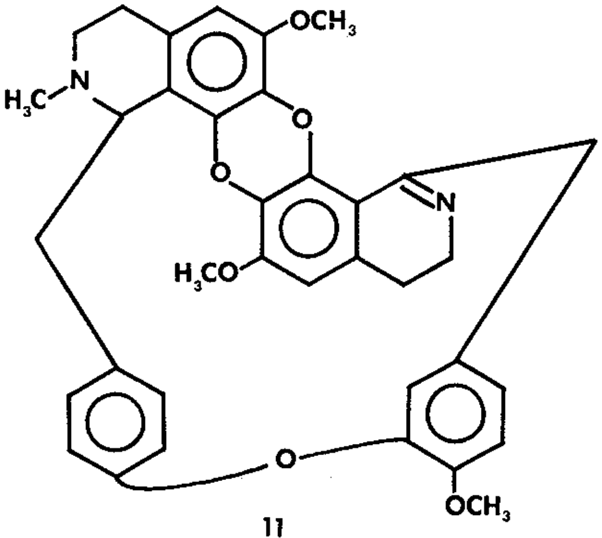
Gilletine is not only the first example of menisarine (11 or 12) type alkaloid to be isolated from Triclisia species, but is also the first example of an alkaloid of this type to be found outside of the genus Cocculus. The other biscoclaurine bases of this type include menisarine (11 or 12)



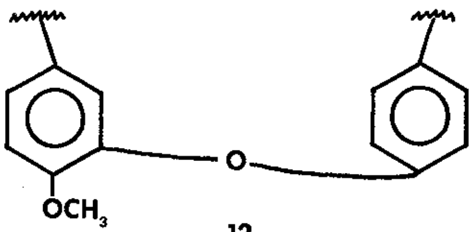
4 $R_1=R_2=CH_3$; $R_3=R_4=H$
or
$R_1=R_3=CH_3$; $R_2=R_4=H$
or
$R_1=R_2=H$; $R_3=R_4=CH_3$
or
$R_1=R_3=H$; $R_2=R_4=CH_3$

5 $R_1=R_2=R_4=CH_3$; $R_3=H$
or
$R_1=R_3=R_4=CH_3$; $R_2=H$

6 $R_1=R_2=R_3=R_4=CH_3$



11



12

from Cocculus sarmentosus (Menispermaceae),[13-15] normenisarine (a partially characterized O-demethylmenisarine) from Cocculus trilobus[13] and cocsulinine (9) from Cocculus pendulus.[10] Finally, the occurrence of these four alkaloids appears to be restricted to the family Menispermaceae and this in itself may be of chemotaxonomic significance.

ACKNOWLEDGMENTS

This investigation was supported in part by Grant R-15 from the Health Research Services Foundation and by Research Grant 5S01RR05455-10 from the National Institutes of Health, Education and Welfare, Bethesda, Maryland 20014. The authors are grateful to Mr. John Naworal, Graduate School of Public Health, University of Pittsburgh for determining the mass spectra. The mass spectrometry facility was supported by Research Grant RR-00273 to the University of Pittsburgh from the National Institutes of Health.

REFERENCES

1. This paper is Part XXII of the series "Constituents of West African Medicinal Plants." For Part XXI, see J.S.K. Ayim, D. Dwuma-Badu, N.Y. Fiagbe, A.M. Ateya, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, Jr., *Lloydia*, 1977, **40**, 561.

2. Present address: Executive Chairman, Council for Scientific and Industrial Research, Accra, Ghana.

3. A.N. Tackie, D. Dwuma-Badu, T. Okarter, J.E. Knapp, D.J. Slatkin and P.L. Schiff, Jr., *Lloydia*, 1974, **37**, 1.

4. J. Baldas, I.R.C. Bick, T. Ibuka, R.S. Kapil and Q.N. Porter, *J. Chem. Soc.* (Perkin I), 1972, 592.

5. M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, 1972, pp. 146-150.

6. K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, 1962, pp. 30-41.

7. A.I. Scott, "Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, pp. 91-97.

8. I.R.C. Bick and A.R. Todd, *J. Chem. Soc.*, 1950, 1606.

9. The authors express their appreciation to Professor Raymond W. Doskotch, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210 for determining the cd spectra.

10. P.P. Joshi, D.S. Bhakuni and M.M. Dhar, *Indian J. Chem.*, 1974, **12**, 517.
11. D.S. Bhakuni and P.P. Joshi, *Tetrahedron*, 1975, **31**, 2575.

12. The authors are grateful to Dr. D.S. Bhakuni, Central Drug Research Institute, Lucknow, INDIA for a reference sample of O,O-dimethylcocsulinine.

13. H. Kondo and M. Tomita, *J. Pharm. Soc. Japan*, 1935, **55**, 911; *Chem. Abstr.*, 1936, **30**, 726.

14. H. Kondo and M. Tomita, *J. Pharm. Soc. Japan*, 1935, **55**, 637; *Chem. Abstr.*, 1939, **33**, 626.

15. M. Tomita, S. Ueda, and A. Taraoka, *Tetrahedron Lett.*, 1962, 635.

Received, 9th May, 1978