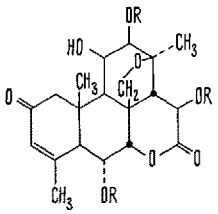
Bruceines from *Brucea sumatrana*: The Structure of Bruceine G

Brucea sumatrana has long been known to contain a number of bitter principles[1] but none of these substances were ever fully characterized. Recent work has clarified the structure of one of these principles[2]; it has been named brusatol and has been shown to be related to bruceine A which has been found in the seeds of *Brucea amarissima*[3].

We have investigated the seeds of *B. sumatrana* Roxb.[4] and have isolated 2 other principles by the extraction of a concentrated 50% aqueous-alcoholic extract of defatted seeds with chloroform:95% ethanol 3:2 and chromatography of this extract on a water-impregnated cellulose column using toluene:*n*-butanol 1:1 as eluting solvent. One of the substances isolated by this method proved to be identical with a substance called bruceine D, recently isolated from *B. amarissima*[5]. A mixed melting point of our substance with authentic bruceine D showed no depression and in addition, the IR-spectrum, mass-spectrum and Rf on thin-layer chromatography were identical. The other substance which we were able to isolate has not yet been described in the literature; we have named it bruceine G thus following the nomenclature in use for the majority of the other bitter principles found in *Brucea* species[6].

Bruceine G (Ia) ($C_{20}H_{26}O_8$[7]; m.p. 254–258°, $[\alpha]_D^{25}$ + 58.9 Py. $[\alpha]_D^{25}$ + 85.4 W) exhibits an alkali-stable peak at 230 nm in the UV (ε = 14,600 W) which is good evidence for a β-alkyl substituted α,β-unsaturated cyclic ketone in ring A as shown. The IR-spectrum showed 2 carbonyl bands at 1701 and 1724 cm^{-1}(KBr), the former given by the unsaturated ketone and the latter by the δ-lactone. In addition, bruceine G gave an intense violet colouration on treatment with concentrated sulphuric acid[8].



Ia) R=H, bruceine G
Ib) R=Ac, bruceine G triacetate

Bruceine G formed a triacetate with Ac_2O/Py (Ib) ($C_{26}H_{32}O_{11}$[7]; anal. found[9] C, 57.48%; H, 6.26%; calc. as monohydrate: C, 57.98%; H, 6.36%; m.p. 243–248°, $[\alpha]_D^{25}$ + 89.0 EtOH). The IR-spectrum (KBr) showed a band at 3448 cm^{-1}, evidence for a remaining unacetylated hydroxyl group. The NMR-spectrum of bruceine G triacetate (see Table) provided information which defined most of the structural features of the molecule as shown in Ib. The signal at 4.08 ppm could be assigned to the 2 methylene protons in the 13,30 oxide bridge[3] while other methyl and methylene proton signals occurred at 1.43, 1.53, 1.78 and 2.35 ppm. The signal at 2.35 ppm integrated for 3 protons and we have reason to believe that the C-5 proton signal occurs at this position along with the 2 C-1 protons. Other assignments were in good agreement with data reported for this or related classes of compounds[3,10–12]. In addition to the NMR data, bruceine G gave no red colouration with triphenyltetrazolium chloride, proof that a hydroxyl was lacking at position 1. It also gave no colour with ferric chloride but was positive with periodate, evidence for the glycol at 11 and 12 and also evidence that the 2 hydroxyls are *cis* to one another. Due to the difficulty we encountered in acetylating bruceine G completely, it would appear that the configuration of the 11 hydroxyl is β (axial). If this is so, the results with periodate would seem to indicate that the configuration of the 12 hydroxyl is also β (equatorial).

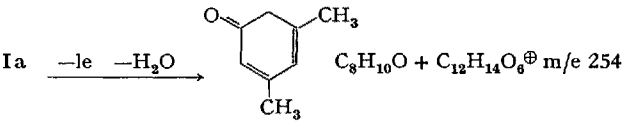
NMR assignments for bruceine G triacetate[a]

ppm	No. of protons	Assignment
1.43 (s) 1.53 (s)	6	CH_3–C–[3,10]
1.78 (s)	3	CH_3–C=C<[3,10,11]
2.10 (s)	9	CH_3–CO_2–
2.35 (broad)	1	CH–C=C< (C-5 proton)
	2	–CH_2–C=O
2.78 (s)	2	H–C– (C-9 proton)[11,12]
2.90 (s)		H–O–C–H
3.40 (s)	1	CH_3–O– (impurity)
4.08	2	–CH_2–O–C–[3]
4.70	2	H–C–O_2C–R (lactone)
4.95		H–C–CO_2–CH_3 (C-14)[11,12]
5.30	1	H–C–O–H
5.60	3	H–CO_2–CH_3[11]
6.30 (s)	1	H–C–C=O[12]

[a] Spectrum in $DCCl_3$ using a Varian A60 Spectrometer with TMS as internal standard.

[1] C. K. LIANG, J. Chinese chem. Soc., Peiping *16*, 53 (1949).
[2] K. Y. SIM, J. J. SIMS and T. A. GEISSMAN, J. org. Chem. *33*, 429 (1968).
[3] J. POLONSKY, Z. BASKEVITCH, A. GAUDEMER and B. C. DAS, Experientia *23*, 424 (1967).
[4] The seeds were purchased from S. B. Penick and Co., N.Y. 4.5 kg were used for this study.
[5] Private communication, Mme. J. POLONSKY, CNRS, Gif-sur-Yvette, France. The authors would like to express their appreciation to Mme. POLONSKY for a sample of authentic bruceine D.
[6] At the time of publication, bruceines have been named up to and including the letter F[5].
[7] The molecular ion in the mass spectrum appeared at m/e 394. High resolution mass spectrometry on the triacetate by Dr. B. C. DAS, CNRS, Gif-sur-Yvette, France, yielded the mass of 520.1952 thereby firmly establishing the formula shown for bruceine G. The authors would like to thank Dr. DAS for the assistance he gave us in this problem.
[8] One of the substances previously isolated from this plant by LIANG[1] and presumably the active principle, also gives a violet colouration with sulphuric acid. LIANG called his substance 'Yatanoside' believing it to be a glycoside. Our compound appears to be similar to 'Yatanoside' in some aspects but differs in melting point and specific rotation.
[9] Analysis by Mr. H. Thommen, Basel, Switzerland.
[10] C. G. CASINOVI and P. CECCHERELLI, Tetrahedron Lett. *52*, 3991 (1964).
[11] J. POLONSKY, C. FOUQUEY and A. GAUDEMER, Bull. Soc. chim. Fr. 1827 (1964).
[12] A. GAUDEMER, J. L. FOURREY and J. POLONSKY, Bull. Soc. chim. Fr. 1678 (1967).

The remaining hydroxyl groups were readily acetylated and are therefore secondary hydroxyls attached at positions 6 and 15 in the molecule as shown. Additional evidence for the attachment of 1 of the hydroxyls at position 6 was obtained by analysis of the mass spectrum of bruceine G. An abundant peak at m/e 254 could be assigned to the fragment $C_{12}H_{14}O_6^{\oplus}$ which forms by the fragmentation of the molecule across the 5–6 and 9–10 bonds as shown.



This is very similar to the fragmentation found for other bruceines[3] however occurs closer to ring A due to the presence of the hydroxyl at position 6. (The lactone at 7 in other bruceines promotes cleavage of the 6–7 bond.)

We have no direct evidence which proves that the stereochemistry of the ring junctions is as shown, however it is reasonable to assume that these related compounds (bruceines) arise via similar biogenetic routes[13] and that their gross stereochemistry is alike. Also, it is reasonable to assume that the configuration of the hydroxyls at 6 and 15 is equatorial due to their facile acetylation with acetic anhydride/pyridine[14].

Zusammenfassung. Aus den Samen von *Brucea sumatrana* wurden die beiden neuen Stoffe Brucein D und G isoliert. Für die letztere Verbindung wird eine Strukturformel vorgeschlagen.

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29 April 1968.

[13] For a review see J. Polonsky, Planta med., Suppl. 107 (1966).

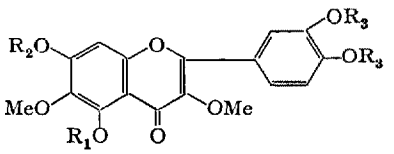
[14] The authors would like to thank the National Research Council of Canada (grant No. A-1863) and Poulenc Ltd. for their support of this research.

The Syntheses of Axillarin and its Related Compounds

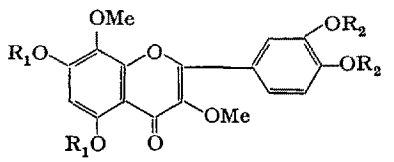
Axillarin (quercetagetin 3,6-dimethyl ether) was first isolated from the leaves of cocklebur (*Xanthium pensylvanicum*)[1] and later from the flowers and leaves of *Iva axillaris* Pursh. ssp. *robustor*[2]. Its structure was assigned to 5,7,3′,4′-tetrahydroxy-3,6-dimethoxyflavone (I)[1,2]. Axillarin 7-methyl ether (II) was also isolated from the leaves of *Cyanoestegia microphylla*[3]. The synthetic approaches to those compounds, however, had remained unsuccessful. 5,7,3′,4′-Tetrahydroxy-3,8-dimethoxyflavone (III), an isomer of I was isolated from *Ricirocarpus muricatus* Muell. Arg.[4] and was synthesized[5]. The present paper deals with the first syntheses of I and II, and a new synthesis of III from 2,4,6-trihydroxy-3,ω-dimethoxyacetophenone (IV) in a manner similar to that described earlier[6,7].

According to the Allan-Robinson's flavone synthesis, the ketone (IV) with 3,4-dibenzyloxybenzoic anhydride and potassium 3,4-dibenzyloxybenzoate gave a mixture of flavones, which was used for next acetylation step without purification. After usual acetylation, the reaction products were purified by recrystallization from methanol to give 5,7-diacetoxy-3′,4′-dibenzyloxy-3,6-dimethoxyflavone (V) (m.p. 135–136.5°, UV λ_{max}^{EtOH} nm (log ε): 252 (4.32), 350 (4.21). Found: C, 69.08; H, 4.80. $C_{35}H_{30}O_{10}$ requires: C, 68.84; H, 4.95%) in 26% yield from IV. Treatment of V with dilute alkali gave 3′,4′-dibenzyloxy-5,7-dihydroxy-3,6-dimethoxyflavone (VI) (m.p. 147.5 to 148.5°, UV λ_{max}^{EtOH} nm (log ε): 255 (4.27), 273 (4.23), 347 (4.35). Found: C, 70.66; H, 4.76. $C_{31}H_{26}O_8$ requires: C, 70.71; H, 4.98%). The residue, obtained from the methanolic filtrate, hydrolyzed its acetoxy groups with alkali to phenolic compounds, from which 3′,4′-dibenzyloxy-5,7-dihydroxy-3,8-dimethoxyflavone (VII) (m.p. 180 to 181.5°, UV λ_{max}^{EtOH} nm (log ε): 258 (4.28), 277 (4.32), 339 (4.21), 355 (4.20). Found: C, 70.99; H, 4.97. $C_{31}H_{26}O_8$ requires: C, 70.71; H, 4.98%) was isolated by repeated recrystallization from ethyl acetate in 18% yield from IV.

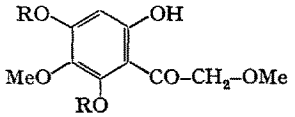
Debenzylation of VI with hydrogen yielded axillarin (I) (m.p. 207–208° and 217–218° (208–209° sinter), IR 3380, 3130, 1652, 1602 cm^{-1} (Nujol), UV λ_{max}^{EtOH} nm (log ε): 259 (4.25), 295 (3.91), 358 (4.32). Found: C, 58.86; H, 3.96.



I $R_1 = R_2 = R_3 = H$
II $R_1 = R_3 = H$ $R_2 = Me$
V $R_1 = R_2 = Ac$ $R_3 = C_6H_5CH_2$
VI $R_1 = R_2 = H$ $R_3 = C_6H_5CH_2$
VIII $R_1 = R_2 = R_3 = Et$
X $R_1 = R_2 = Ac$ $R_2 = Me$



III $R_1 = R_2 = H$
VII $R_1 = H$ $R_2 = C_6H_5CH_2$



IV R = H
IX R = Et