Tetrahedron Letters No.27, pp. 2273-2279, 1965. Pergamon Press Ltd.
Printed in Great Britain.

OCCURRENCE OF BITTER SUBSTANCES RELATED TO QUASSIN IN AILANTHUS GLANDULOSA(+)

C.G. Casinovi
Laboratori di Chimica Biologica, Istituto Superiore di Sanità
Rome
V. Bellavita, G. Grandolini
Istituto di Chimica Farmaceutica e Tossicologica
dell'Università, Perugia
P. Ceccherelli
Centro di Chimica del Farmaco e delle Sostanze Biologicamente
attive del C.N.R., Università del S.Cuore,
Rome

(Received 7 May 1965)

The present paper deals with the structure of substance $C_{22}H_{30}O_7$ (m.p. 264-265°) (I) and substance $C_{20}H_{28}O_6$ (m.p. 253-255°) (II) whose isolation from A. glandulosa has been recently reported elsewhere by us (1).

Both compounds are obtained after silica-gel chromatography of an alcoholic extract of the bark, previously defatted with petroleum ether and diethyl ether, using as eluent chloroform containing

(+) Unless otherwise stated, all elemental analyses were in agreement with the formula given; U.V. spectra were taken in 95% ethanol, I.R. spectra in $CHCl_3$ and NMR spectra in $CDCl_3$ (tetramethylsilane as internal standard).

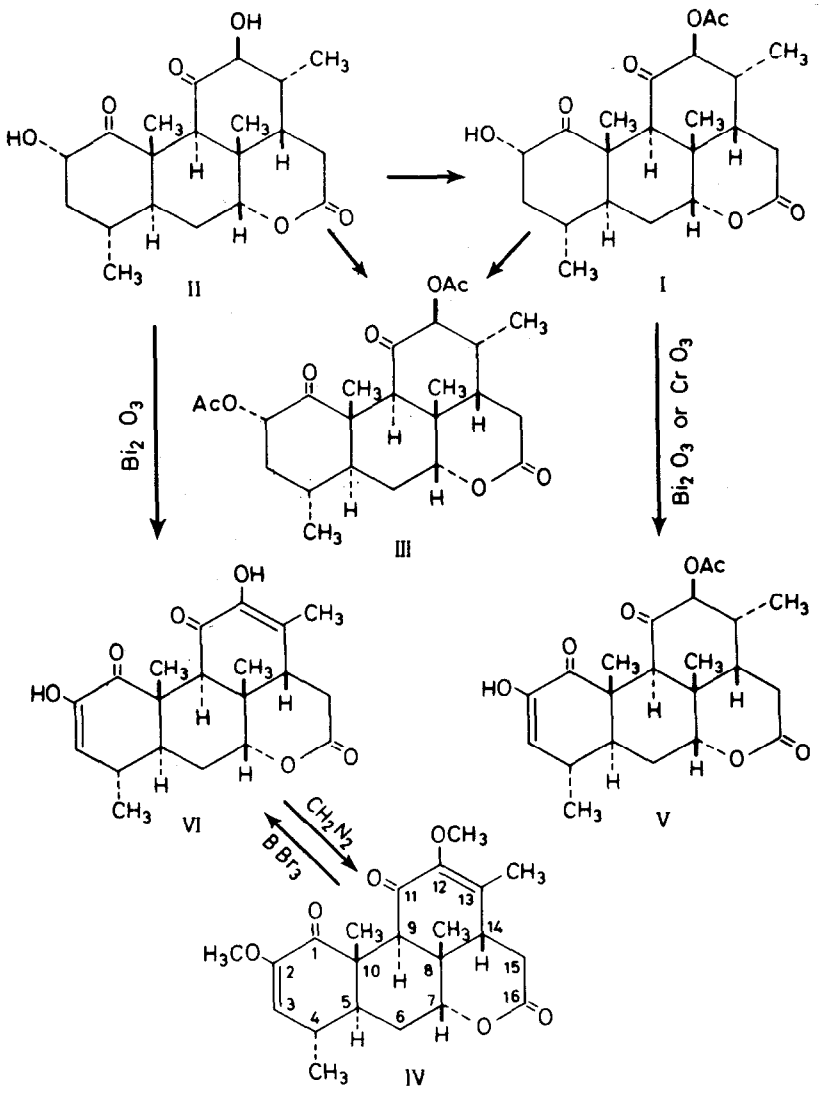
1% methanol. Acetic anhydride converts them into the same diacetyl derivative $C_{24}H_{32}O_8$ (m.p. 269-270°)(III): this fact and the presence in the NMR spectrum of (I) of a singlet at δ= 2.03 (corresponding to three protons) (CH_3-COO-) demonstrate that compound (I) is a monoacetylderivative of (II), for which we propose the name of amarolide.

Amarolide is a saturated compound (lack of notable U.V.absorbtion, absence of ethylenic protons in the NMR spectrum, negative results on catalytic hydrogenation), insoluble in weak alkaline solution, slightly soluble in sodium carbonate, easily dissolved by sodium hydroxide.

From such solution, amarolide can be recovered upon acidification(+): this behaviour, the strong absorption at 1722 cm^{-1} and the characteristic triplet-like signal at δ= 4.25 (one proton) are indicative of the presence of a lactone in a six-membered or larger ring.

Although the limited solubility of amarolide in deuterochloroform precludes detailed interpretation of minor peaks in its 60 Mc NMR spectrum, nevertheless the resemblances with those of the other bitter constituents of Simarubaceae (1,2,3,4) can be safely assumed as suggestive of the presence of the same basic skeleton of quassin (IV) (4). The most prominent peaks at δ= 0.90 (doublet, J=6 cps)

(+) Standing in acidic solution results however in a decomposition of amarolide: the reasons of such a decomposition are as yet not fully understood.


OH
OAc
HO
AcO
CH3
O
H
II
I
III
Bi2 O3
Bi2 O3 or Cr O3
VI
V
CH2N2
BBr3
OCH3
H3CO
IV
QUASSIN

and 1.03 (doublet, J=6.5 cps) are assigned to two secondary methyls, while the singlets at δ= 1.48 and 1.50 are assigned to two tertiary methyls.

The two acetylable functions in amarolide are secondary alcoholic groups, and they can be easily traced owing to the lower field shift caused by acetylations one is a doublet, having the same chemical shift (δ= 5.25) both in (I) and in (III), whose splitting (J=12.5 cps) indicates an axial-axial relationship with one vicinal proton, while the other is a multiplet, partially hidden by the former in (III), but appearing at δ= 4.67 in (I) as an axial proton coupled with two neighbouring non-equivalent protons pertaining to a methylene group.

The magnitudes of these chemical shifts suggest the protons in question are part of alpha-ketol systems, a conclusion which is strenghtened by the presence in the I.R. spectrum of (I), when taken in nujol, of three bands in the carbonyl region. In this way, all oxygens of amarolide are accounted for and its tetracyclic backbone is confirmed.

Bearing in mind the multiplicities of the >CH-O- protons referred to above, and the substitution pattern in the skeleton of (IV), we are now able to deduce the structures of rings A and C. The proton responsible of the doublet with J=12.5 cps must be placed in ring C, at C_{12}; (since the C_9-H appears in (I) as a singlet at δ= 3.15), the C_{13}-methyl being equatorial; the proton

coupled to a neighbouring CH_2 must in turn lie, axially, on C_2 (otherwise a singlet would be expected).

In the hypothesis that all the ring fusions are the same as in ailanthone, the principal bitter constituent of Ailanthus glandulosa (1,2), as consideration of the magnitude of the chemical shift of the C_{10} methyl group may confirm, we can propose formula (II) for amarolide, where the quasi-equatorial conformation of the C_4-methyl is chosen for reasons to be seen later.

The presence of an acetoxy function in (I) is confirmed by oxidation, with chromium trioxide or Bi_2O_3 in acetic acid, to a triketone (V)($C_{22}H_{28}O_7$, m.p.253-255°). Its NMR spectrum shows the presence of two secondary (δ=1.08, J=6.5 cps and δ=1.27, J=7.5 cps), two tertiary (δ=1.20 and 1.53) methyls and of one acetyl group (δ=2.05), A one-proton doublet (J=2 cps) at δ=5.62, the absence of allylic methyls, the persistence of the one-proton doublet (J=12.5 cps) at δ=5.28 and its U.V.spectrum (λ_{max}=267 mμ, ε=2.400) are in agreement with formula(V)and support the correctness of the assumption sustaining formula (I)(+).

In order to demonstrate our conclusions, we have oxidized amarolide by means of Bi_2O_3, a reagent known to be able to transform alpha-ketols into diosphenols; the product obtained in this way possesses the right analytical data ($C_{20}H_{24}O_6$, m.p.207-208°)

(+) Although a direct comparison was not possible, all the evidence available points out to an identity or a strict similarity of (I) with the substance $C_{22}H_{30}O_7$ isolated by Geissman and Chandorkar from Castela Nicholsoni (5).

and physical properties (U.V.: λ_{max}=272 mμ (ε=9.360), shifting at 320 mμ in alkaline solution; I.R.: ν_{max}=1722 (lactone), 1680, 1652 (conj. >C=O) and 1620 cm^{-1} (conj. >C=C<); NMR: 1.12 (doublet, J=6.5 cps; >CH-CH_3), 1.23 (>C-CH_3), 1.55 (>C-CH_3), 1.89 (>C=C-CH_3), 5.75 (doublet, J=2 cps, >C=C<u>H</u>-CH) for the expected bisdiosphenol (formula VI). Under the validity of the expressed suppositions about stereochemistry of the ring junctions, such a formula would represent the product of demethylation of quassin. Compound (VI) indeed is easily methylated by diazomethane to give a diether, which, after purification by silica gel chromatography (eluent 1% methanol in chloroform) was shown to be in every respect identical to quassin. Moreover, since the procedure adopted by Robertson et al. (6) for demethylating quassin (HCl in acetic acid at 100°C) is accompanied by a rearrengement, we have used BBr_3 in CH_2Cl_2 at room temperature(+). The product obtained in this way was shown to be identical to (VI) by thin layer chromatography and comparison of their U.V., I.R. and NMR spectra. Since the stereochemistry depicted in (IV) is the most probable for quassin (4), we may conclude that amarolide is represented by formula (II).

The simultaneous occurrence in the same plant of ailanthone, amarolide and acetyl amarolide, constitutes the best available

(+)As a by-product, a monoether is formed which differs from the known norquassin (6); since it gives quassin upon methylation, we can logically suppose to be the alternative isomer.

evidence of the same biogenetical pathway occurring in Quassia, Ailanthus and Castela.

REFERENCES

(1) C.G.Casinovi, P.Ceccherelli, G.Grandolini and V.Bellavita, Tetrahedron Letters, no.52, 3991 (1964).

(2) J.Polonsky and J.L.Fourrey, Tetrahedron Letters, no. 52, 3983 (1964).

(3) T.A.Geissman and G.A.Ellestad, Tetrahedron Letters, no.23, 1083 (1962); T.A.Davidson, T.R.Hollands and P.de Mayo, Tetrahedron Letters, no. 23, 1089 (1962); J.Polonsky, C.Fouquey and M.A.Gaudemer, Bull.Soc.Chim.Fr., 1827 (1964); J.Zylber and J.Polonsky, Bull.Soc.Chim.Fr., 2016 (1964) and earlier papers.

(4) Z.Valenta, A.H.Gray, D.E.Orr, S.Papadopoulos and C.Podevsva, Tetrahedron, 18, 1433 (1962) and earlier papers; R.M.Carman and A.D.Ward, Tetrahedron Letters, no.10, 317 (1961) and Australian J.of Chem., 15, 867 (1962).

(5) T.A.Geissman and M.R.Chandorkar, J.Org.Chem., 26, 1217 (1961).

(6) H.R.Hanson, D.B.Jaquiss, J.A.Lamberton, A.Robertson and W.E. Savige, J.Chem.Soc., 4238 (1954).