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SHORT COMMUNICATION

NEW DITERPENOIDS WITH CLERODANE SKELETON

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Abstract—The structure of two diterpenoids with clerodane skeleton isolated from bulbs of *Annona coriacea* have been established as (1) and (2).

A SHRUB from Brazil classified as *Annona coriacea* (identified by M. Kuhlmann[1]) (Annonaceae) contains some terpenoids which we have isolated. Now we propose for two of them the structures (I) and (II), while the elucidation of the structure of the other unknown products is still in progress.

The acid (I) which was separated from the crude acetonic extract by silica gel column chromatography has m.p. 117°, $[\alpha]_D$ −57° ($CHCl_3$) and gave a cyclohexylamine salt melting at 176–178°. The IR spectrum of (1) in nujol showed the absorption of the carboxylic group at 1705 cm^{-1}; its NMR spectrum showed resonances indicative of two tertiary methyl groups (3H each, s at 0·72 and 1·06 δ), one secondary methyl group (3H, d at 0·84 δ, $J = 7$ Hz) and one β-substituted furan ring (6·27, 7·25 and 7·38 δ, 1H each).

With diazomethane (I) gave the corresponding methylester (3) as an oil with $[\alpha]_D$ −56° ($CHCl_3$) which was also present in the crude extract. Mass spectrum allowed us to assign the formula $C_{21}H_{32}O_3$ (M^+ at *m/e* 332) to the ester (III). The IR spectrum of (III) showed an absorption at 1740 cm^{-1} and its NMR spectrum showed a three protons singlet at 3·6 δ (CH_3O—) for the ester group. The highest peaks of the mass spectrum of (3) were at *m/e* 237, 95, 81 and corresponded to the cleavage of the C-9, C-11 and C-11, C-12 bonds. On dehydrogenation with selenium, 1,2,5-trimethylnaphthalene and 1,2-dimethylnaphthalene were obtained. No trace of 1,5-dimethylnaphthalene was detected. These data allowed us to hypothesize the structure (I) with a clerodane[2] skeleton and the secondary carboxyl group at C-4.

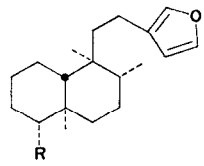
On reduction with LAH (I) gave the alcohol (IV). The NMR spectrum showed that methylene protons at C-18 were the part AB of an ABX system (3·83 δ_A, 3·23 δ_B, $J_{AB} = 10{\cdot}5$ Hz, $J_{AX} = 2{\cdot}5$ Hz, $J_{BX} = 7$ Hz) in accordance with the presence of one proton at C-4. On acetylation a monoacetate with a singlet at 2·0 δ (3H, CH_3COO—) was obtained. When oxidized according to Fetizon[3] (IV) afforded the aldehyde (V).

With TsCl in Py (IV) yielded a tosylate which on treatment with Al_2O_3 (activity I) in benzene eliminated TsOH affording the olefine (VI); this olefine absorbed one mole of

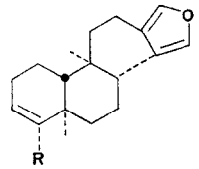
[1] M. Kuhlmann, Sao Paolo, Brazil, personal communication.

[2] J. W. ROWE, *The Common and Systematic Nomenclature of Cyclic Diterpenoids*, Third Revision, Madison, Wisconsin (October 1968).

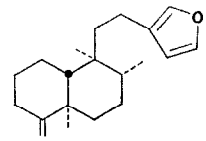
[3] M. FETIZON and M. GOLFIER, *C.R. Acad. Sci., Paris* **267C**, 900 (1968).



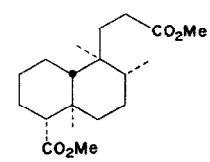
(I) R = CO_2H
(III) R = CO_2Me
(IV) R = CH_2OH
(V) R = CHO



(II) R = CH_3
(VIII) R = CO_2H



(VI)



(VII)

hydrogen with subsequent disappearance of the signal at 4·5 δ for the exocyclic methylene. The above data reported confirmed the secondary nature of the carboxyl group at C-4.

The ozonolysis of (I) followed by oxidation with alkaline hydrogen peroxide and treatment with diazomethane afforded the diester (VII). When treated with tert-BuOK in benzene diester (VII) did not undergo the Dieckmann condensation and was recovered unchanged. The failure of the two ester functions to undergo condensation and the behaviour of (I) on dehydrogenation supported the presence of the carboxyl group at the position 4.

The structure of (I) was confirmed by comparison (GLC, TLC, IR, MS, $[\alpha]_D$) with the methylated product of sodium-propanol reduction of (−)-hardwickiic acid (8)[4] and by LAH reduction of (I) which gave a product identical (m.p., mixed m.p., IR, $[\alpha]_D$) with the alcohol (IV) of established structure.[5] The stereochemistry at C-4 is consistent with the expected course of sodium-propanol reduction of (VIII) and with the resistence of (III) to epimerization. However, hydrolysis of the ester functionality of (III) required conditions which were more vigorous than expected for an equatorial configuration of the ester functionality.

The compound (II) which can be isolated from the first fractions of the chromatography of the crude extract is an oil showing $[\alpha]_D$ −32° ($CHCl_3$). Its mass spectrum agrees with the formula $C_{20}H_{30}O$; the highest peaks were at *m/e* 191, 95 and 81. The NMR spectrum of (II) showed two tertiary methyl groups (3H each, s at 0·75 and 1·0 δ), one secondary methyl group (3H, d at 0·85 δ, J = 7 Hz), one methyl group on double bond (3H, broad singlet at 1·57 δ), one vinylic proton (m at 5·18 δ) and one β-substituted furan ring (6·24, 7·18 and 7·32 δ, 1H each). On dehydrogenation with selenium the 1,2,5-trimethylnaphthalene was obtained.

The structure (II) which could be hypothesized besides the isomeric structure with the double bond between C-7 and C-8, was confirmed by correlation to the olefin (VI). In fact the latter isomerized to (II) on treatment with *N*-lithioethylenediamine.[6]

EXPERIMENTAL

Extraction and isolation of (I), (II) and (III). Crude acetonic extract of dry bulbs (96 kg) of *Annona coriacea*, after removal of a crystalline insoluble compound (which we are studying), was evaporated. The residue (800 g) was chromatographed on silica gel (16 kg) with benzene containing increasing quantities of Et_2O. The first fractions contained fats and the compound (II), then ester (III) together with acid (I) was eluted. The following fractions contain no more substances with positive Ehrlich test. Olefin (II) was purified by Al_2O_3 (act.III) chromatography using light petroleum as eluent with a 0·01% yield. Ester (III) was by the same way purified with 0·03% yield. Acid (I) was chromatographated on silica gel with a 0·2–0·3% yield.

Dehydrogenation of (I) with selenium. The acid (*I*) (250 mg) was mixed with Se dust (575 mg) and the mixture was heated at 120° for 1 hr and at 280° for 30 hr. It was then cooled and extracted with Et_2O and

[4] R. MISRA, R. C. PANDAY and SUKH DEV, *Tetrahedron Letters* 3751 (1964), *ibid.* 2681 (1968).
[5] P. R. JEFFERIES, J. R. KNOX and B. SCAF, to be published.
[6] L. REGGEL, S. FRIEDMAN and I. WENDER, *J. Org Chem.* **23**, 1136 (1958).

n-pentane. The solution was washed with H_3PO_4 (85%) and H_2O. The solvent was removed and the product (100 mg) was chromatographed on Al_2O_3 (3 g, act.I) with *n*-pentane as eluent. 1,2-dimethyl- and 1,2,5-trimethylnaphthalene were isolated and identified by comparison with authentic samples (GLC–MS).

Reduction of (I) with LAH. The acid (I) (1 g) and LAH (400 mg) in dry dioxan were heated at 70° for 3 hr and then were kept at room temp. overnight. The reduction was terminated by usual workup. The crude product (700 mg) was crystallized from *n*-pentane: m.p. 80–81°; $[\alpha]_D$ − 30·5°; MS *m/e* 304 (M^+), highest peaks at *m/e* 191, 95 and 81; NMR signals at δ 0·70 (3H, s), 0·75 (3H, d, J = 7 Hz), 0·82 (3H, s), 3·23 (1H, dd), 3·83 (1H, dd), 6·25, 7·20 and 7·32 (3H, furan). The treatment of (IV) with Ac_2O in Py afforded a monoacetate: NMR signal at δ 2·0 (3H, s).

Oxidation of (IV) according to fetizon. The alcohol (IV) (600 mg) in toluene (200 ml) was mixed with an excess of Ag_2CO_3 over celite. The mixture was fully dried by azeotropic distillation of 50 ml of solvent. After refluxing for 4 hr the soln was filtered and evaporated. The crude residue was chromatographed on Al_2O (act.II) with *n*-hexane-Et_2O as eluent. 250 mg of pure aldehyde (V) were isolated: $[\alpha]_D$ −52°; IR 2730, 1715 cm^{-1}; MS *m/e* 302 (M^+), highest peaks at *m/e* 274, 179, 95 and 81; NMR signals at δ 0·65 (3H, s), 0·75 (3H, d, J = 7 Hz), 0·93 (3H, s), 6·15, 7·1, 7·22 (3H, furan) and 9·73 (lH, d, J = 2 Hz).

Dehydration of (IV) with p-toluensulfonylchloride and alumina. TsCl (10 ml) was added to an ice cooled soln of alcohol (IV) (3 g) in Py (50 ml). The mixture was kept overnight at 0°. H_2O and ice were added and the product extracted into Et_2O. Workup gave a crude tosylate. This tosylate (2·6 g) was stirred overnight with Al_2O_3 (act.I) in Et_2O. The soln was filtered, evaporated and chromatographed on Al_2O_3 (act.I) with benzene as eluent. Olefin (VI) (1·3 g) was obtained: $[\alpha]_D$ +10°; MS *m/e* 286 (M^+), highest peaks at *m/e* 191, 95 and 81; NMR signals at δ 0·76 (3H, s), 0·85 (3H, d, J = 7 Hz) 1·06 (3H, s), 4·5 (2H), 6·21, 7·19 and 7·29 (3H, furan).

Catalytic hydrogenation of (VI). The olefin (VI) (100 mg) in AcOEt (10 ml) was hydrogenated for 1 hr over PtO_2 (3 mg). Filtration and removal of solvent gave a crude product: in its NMR disappears the signal at 4·5 δ for exocyclic methylene.

Ozonolysis of (III). The ester (III) (1·2 g) was dissolved in AcOH (10 ml) and AcOEt (10 ml) and ozonized at 0° for 2 hr. The solution was shaken with H_2O (1·2 ml) and H_2O_2 35% (0·5 ml) and kept at room temp. overnight. H_2O and Et_2O were then added and the organic layer evaporated. The crude product was oxidized with Jones's reagent (0·5 hr at 0°), followed by usual workup. The acid (0·8 g) was esterified with CH_2N_2 and the ester (VII) was obtained: IR 1720 cm^{-1}; MS *m/e* 324 (M^+), highest peaks at *m/e* 237, 205 and 177; NMR signals at δ 0·85 (3H, s), 0·95 (3H, d, J = 7 Hz), 1·24 (3H, s), 3·70 (3H, s) and 3·75 (3H, s).

Dieckmann reaction of (*VII*). The ester (VII) (75 mg) in benzene (5 ml) was refluxed under N_2 for 4 hr with tert-BuOK (310 mg) and kept at room temp. for 8 hr. The reaction was terminated in the usual manner and from the organic layer the unchanged ester (VII) was recovered.

Reduction of Hardwickiic acid (VIII). Sodium wires (230 mg) were added over 3 hr to a refluxing solution of acid (VIII) (40 mg) in *n*-PrOH (5 ml). After cooling the solvent was distilled and the product dissolved in water, the solution was acidified with H_2SO_4 M/10 and extracted with Et_2O and CH_2N_2 was added. The ester was purified by preparative TLC and identified as (III) (MS, IR (0·1 M) $[\alpha]_D$).

Isomerization of (VI). To a solution of *N*-lithioethylenediamine prepared according to Reference 4 from Li (200 mg) and ethylenediamine (10 ml), the olefin (VI) (250 mg) was added. The mixture was stirred and refluxed under N_2. The solution was then cooled in ice and H_2O added. The product was extracted and chromatographed on Al_2O_3 (act. I) and was identified as (2) (IR, NMR, $[\alpha]_D$).

Hydrolysis of ester (III). After refluxing for 2 hr with 3N EtOH–NaOH (100 ml) ester (3) (500 mg) was recovered unchanged. In another experiment ester (3) (500 mg) was refluxed with 10% NaOH in diethylene glycol (100 ml) for 2 hr. The alkaline solution was concentrated under reduced pressure, cooled, acidified and extracted with Et_2O. Acid (I) was obtained with 80% yield.

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