Tetrahedron Vol 24, pp 2527 to 2531 Pergamon Press 1968 Printed in Great Britain

THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—VII[1]

STEREOCHEMICAL STUDIES IN THE FUJENAL SERIES

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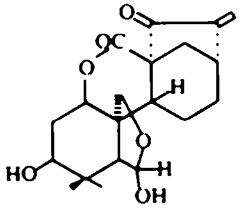
(*Received in the UK* 10 *September* 1967; *accepted for publication* 19 *September* 1967)

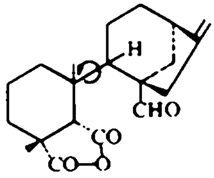
Abstract—Spectroscopic and chemical evidence is discussed in favour of rotamer (II) for some compounds derived from fujenal.

RECENTLY the bitter principles of the *Isodon* species have been shown[2] to be kauranoid diterpenes. Included amongst these are a number of compounds of which enmein (I) is the best known, where ring B of the kaurene skeleton has been cleaved. Fujenal (II)[3] from *Gibberella fujikuroi*, represents another example of this series. Cleavage between C-6 and C-7 permits rotation about the 9–10 bond. Molecular models suggest that this rotation is probably hindered and hence with partial synthesis in mind, it was of interest to distinguish between the two possible rotamers of fujenal (II and III). In this paper we present evidence for the prevalence of the rotamer (II) in the ground state of fujenal.

Initially we represented[3] fujenal as the rotamer (II) because of its relationship to the kaurenolides. Furthermore two groups of reactions demonstrated a ready reconstruction of ring B which would not be expected from the alternative III.



I



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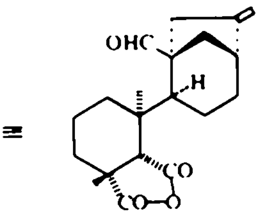

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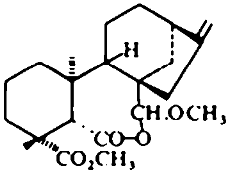

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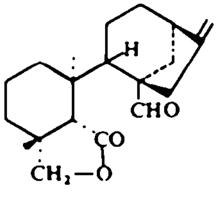

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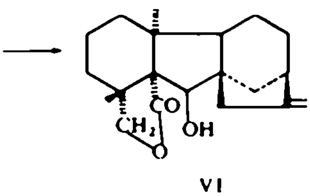


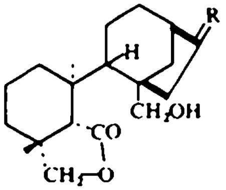
VI

These were the formation of the pseudo-ester IV with methanolic hydrogen chloride and the gibbane VI by treatment of the aldehyde-lactone V with base.[4] The position of the C-5 proton in the NMR spectra of this series was shown to be sensitive to the oxidation level of substituents at C-7—a feature which requires these two centres to be close together in space. Further evidence comes from the IR spectra of a number of C-7 alcohols containing a 6 → 19 lactone ring. These show (Table 1) marked evidence of intramolecular hydrogen bonding between the C-7 OH and the lactone CO at C-6.

TABLE 1. HYDROXYL FREQUENCIES DETERMINED IN DIOXAN SOLUTION

Compound	Free OH	Bonded OH cm^{-1}
VII; R = CH_2	3570	3500
VII; R = O	3570	3490
VII; R = CH_3, H (in CS_2)	3620	3560

Molecular models indicated that such bonding cannot occur in the rotamer III. Furthermore they suggested that the CO of the lactone ring was oriented in such a manner as to form a restraining feature on the position of a C-7 substituent relative to the rest of the molecule. Hence a number of attempts were made to hydrolyse the lactone.



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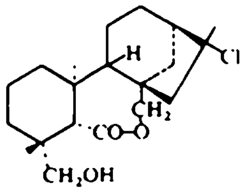

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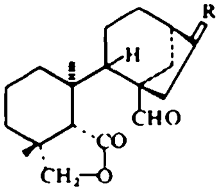
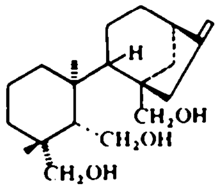


IX



X

Hydrolysis with alkali gave an unstable hydroxy acid which readily relactonized. Treatment of the lactone VII (R = CH_2) with aqueous methanolic sulphuric acid merely led to hydration of the terminal methylene. The product, $C_{20}H_{32}O_4$ (VII; R = CH_3, OH) showed an additional C-CH_3 resonance (τ 8·61) in the NMR spectrum whilst resonances due to the terminal methylene protons had disappeared. The IR spectrum (ν_{max} 1760 cm^{-1}) indicated that the molecule retained a γ-lactone ring. Treatment of the lactone VII (R = CH_2) with methanolic hydrogen chloride gave a gummy product from which a chloro-lactone, $C_{20}H_{31}O_3Cl$, was isolated by chromatography. This was assigned the ε-lactone structure VIII on the basis of the following evidence. Firstly the lactone CO absorption appeared at 1720 cm^{-1} (cf. IV ν_{max} 1726 cm^{-1}) rather than in the range 1750–1760 cm^{-1} characteristic of the γ-lactones in this series. Secondly examination of the NMR spectrum revealed differences in the position of the C-7 and C-19 protons.

The assignment of the protons in the lactones VII (Table 2) was made by preparing a C-7-deutero derivative by reduction of the aldehyde IX (R = CH_2) with sodium borodeuteride. The signal at τ 6·74 was almost absent whilst the resonance at 5·83 appeared as a singlet indicating very marked hindered rotation in the —CDH·OH grouping.

TABLE 2

NMR SPECTRA OF SOME LACTONES OF THE STRUCTURE VII DETERMINED IN $CDCl_3$ AT 60 MC

Compound	C-7 τ	J c/s	C-19 τ	J c/s	C-20 and C-18 τ	C-17 τ
VII; R = CH_2	5·83, 6·74	11	6·01, 6·27	9	8·89, 8·72	5·26
d-VII; R = CH_2	5·83		6·01, 6·27	9	8·89, 8·72	5·26
VII; R = CH_3, H	5·94, 6·82	11	6·04, 6·30	9	8·93, 8·77	9·04 (6 c/s)
VII; R = CH_3, OH	5·94, 6·56	11	5·96, 6·24	9	8·85, 8·72	8·61
VII; R = O	5·88, 6·60	11	6·04, 6·28	9	8·89, 8·71	—
IX; R = CH_2	0·29	—	6·02, 6·32	9	9·10, 8·92	5·20
IX; R = CH_3, H	0·28	—	6·02, 6·32	9	9·12, 8·93	8·98 (6 cps)
VIII	5·26, 5·99	11	5·63, 6·15	13	8·95, 8·89	8·27

In the chloro-lactone VIII the C-7 protons have moved downfield to τ 5·26 and 5·99 consonant with their acylation. The C-19 protons now appear at τ 5·63 and 6·15 with a different coupling constant. This change in coupling constant is in accord with the difference between a strained γ-lactone ring and the free alcohol. This rearrangement of 6 → 19 lactone to 6 → 7 lactone is again a reaction which would be expected of the rotomer II.

Reduction of the pseudo-ester IV with LAH furnished a crystalline triol (X). However, it was not possible to individually modify and thus to distinguish between the three primary alcohols of this compound.

Despite this an attempt was made to introduce functionality at C-20 photolysis of a C-7 substituent. In the kaurene series photolysis of a 7α-nitrite leads to activation of C-20.[5] The alcohol VII (R = CH_3, H) was prepared from fujenal by reduction with LAH[4] and catalytic hydrogenation over Pd-C. Reversal of the order of these steps was unsatisfactory due to the ready autoxidation of the aldehyde of dihydrofujenal. Photolysis of the nitrite of VII (R = CH_3, H)[6] gave a gummy product from which the corresponding C-7 aldehyde IX (R = CH_3, H) was isolated. It was identical to the product of brief chromium trioxide oxidation of the alcohol. Photolysis of this alcohol with iodine and lead tetraacetate gave similar results.

EXPERIMENTAL

General details are described in part I.[3]

Ozonolysis of the lactone (VII; R = CH_2)

Ozonized O_2 (38 mg. O_3/min) was passed through a soln of the lactone (85 mg) in AcOH (10 ml) for 2 min. Zn dust was added and after 45 min the soln was filtered, neutralized with $NaHCO_3$aq and the organic material recovered in AcOEt. Chromatography on Al_2O_3 gave, in the fraction eluted with 20% AcOEt–light petroleum, the *nor-ketone* VII (R = O; 80 mg) which crystallized from AcOEt–light petroleum as plates, m.p. 150·5–151·5°, $[\alpha]_D^{21}$ −79° (c, 0·5 in EtOH). (Found: C, 71·3; H, 8·8. $C_{19}H_{28}O_4$ requires: C, 71·2; H, 8·8%); ν_{max} 3450, 1755, 1722 cm^{-1}.

Hydration of the lactone VII (R = CH_2)

The lactone (150 mg) in MeOH (20 ml) and 2N H_2SO_4 (20 ml) was refluxed for 2 hr. The MeOH was evaporated and the organic material recovered in ethyl acetate. The residual gum slowly deposited crystals of the *hydroxy-lactone* VII (R = CH_3, OH; 40 mg) which crystallized from acetone–light petroleum as prisms, m.p. 278–281°. (Found: C, 71·6; H, 9·2. $C_{20}H_{32}O_4$ requires: C, 71·4; H, 9·6%); ν_{max} 3550, 3280 (br), 1760 cm^{-1}.

Hydrolysis of the lactone VII (R = CH_2)

(a) The lactone (400 mg) in MeOH (100 ml) was refluxed with 6N KOH (100 ml) for 3 hr. The MeOH was removed *in vacuo* and the soln acidified at 0°. The organic material was recovered with AcOEt and rapidly methylated with CH_2N_2. The lactone, m.p. 154–155°, however, was recovered on several occasions.

(b) A gentle stream of dry HCl gas was bubbled through a soln of the lactone (500 mg) in MeOH (50 ml) for 2 hr. The MeOH was evaporated, water was added and the organic material recovered in AcOEt. Chromatography on silica gel and elution with 10% Et_2O–light petroleum gave the *chloro-lactone* VIII (194 mg) which crystallized from petrol as plates, m.p. 167° or needles, m.p. 176°. (Found: C, 67·3; H, 8·4. $C_{20}H_{31}O_3Cl$ requires: C, 67·6; H, 8·75%); ν_{max} 1720 and 705 cm^{-1}.

Reduction of the aldehyde IX (R = CH_2)

The aldehyde[4] (48 mg) in MeOH-d (0·5 ml) was treated with $NaBD_4$ (10 mg) for 2 hr. D_2O (0·5 ml) was added and the crystalline product (34 mg) filtered and recrystallized, m.p. 145–146°.

Reduction of the pseudo-ester IV

The pseudo-ester (250 mg) in Et_2O (50 ml) was refluxed with LAH (250 mg) for 4 hr. The soln was cautiously acidified and the organic material recovered in Et_2O. The *triol* X crystallized from acetone–light petroleum as needles, m.p. 178–180°. (Found: C, 74·4; H, 10·6. $C_{20}H_{34}O_3$ requires: C, 74·5; H, 10·6%); ν_{max} 3300 (br) 1654, 875 cm^{-1}; NMR τ 8·88, 8·53 (2-O—CH_3), 6·68, J = 4, 12 c/s, 6·11, 5·83, J = 5, 10 c/s, (3-CH_2OH) 5·37, 5·19 (C=CH_2). Attempts to prepare an acetate and a toluene-*p*-sulphonate gave gummy products.

Hydrogenation of the lactone VII (R = CH_2)

The lactone (1·5 g) in EtAc (50 ml) was shaken with 10% Pd-C (400 mg) under an atmosphere of H_2 until uptake ceased. Filtration and evaporation of the solvent gave a crystalline residue which was chromatographed on Al_2O_3. Elution with 20% AcOEt–light petroleum gave the *dihydro-lactone* VII (R = CH_3, H; 950 mg) which crystallized from acetone–light petroleum as needles, m.p. 145–148°, $[\alpha]_D^{21}$ −63° (c. 0·5 in EtOH). (Found: C, 74·7; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 74·95; H, 10·1%); ν_{max} 3500, 1750 cm^{-1}.

Photolysis of the nitrite of the alcohol VII (R = CH_3, H)

The alcohol (500 mg) in pyridine (3 ml) was treated with excess NOCl at −10° for 20 min. The soln was poured into ice–water and the organic material cautiously recovered in ether. The residue in benzene (100 ml) was irradiated under N_2 with 125 watt UV lamp through a SiO_2 sleeve for 30 min. The benzene was evaporated and the residue refluxed in isopropanol (10 ml) for 1 hr. The solvent was evaporated and the residual gum subjected to preparative TLC on silica. Apart from starting material the sole crystalline product was the aldehyde, IX (R = CH_3, H; 15 mg) m.p. 159–161°.

Oxidation of the dihydro-lactone VII (R = CH_3, H)

The dihydro-lactone (300 mg) in acetone (10 ml) was treated with the 8N CrO_3 reagent (0·37 ml) for 1 hr. MeOH was added, the soln concentrated and poured into H_2O. Recovery with AcOEt and chromatography on silica gel gave the *aldehyde* IX (R = CH_3, H) which crystallized from acetone–light petroleum as needles, m.p. 160–162°, $[\alpha]_D^{23}$ −42° (c. 0·5 in EtOH). (Found: C, 75·25; H, 9·5. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%); ν_{max} 2700, 1750 cm^{-1}.

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Acknowledgements We thank Dr. R. H. B. Galt for a gift of fujenal and the Medical Research Council for a studentship for one of us (A. W.)