The Meliacins (Limonoids). Some Transformations and Interconversions of the Meliacins

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The meliacins containing a bicyclo[3,3,1]nonane nucleus have been related to the gedunin–khivorin group by the partial synthesis of mexicanolide from 7-deacetoxy-7-oxokhivorin. 7-Deacetylisogedunin has been converted into 7-oxogedunin; this conversion, together with a previous preparation of isogedunin from khivorin, represents a formal conversion of khivorin into gedunin. A number of new conversion products of the meliacins have been prepared and characterised.

ONE of the main classes of meliacins (limonoids) is a group of compounds which possess a bicyclo[3,3,1]nonane system in their nucleus. Examples are mexicanolide (I), fissinolide, and swietenine (and their derivatives), which occur widely in the genera *Khaya*, *Cedrela*, and *Carapa*, often together with compounds of the gedunin–khivorin and andirobin types.[1] We have now related this class of meliacins to the gedunin–khivorin group by a reaction series similar to that postulated for their biogenesis. This involved cleavage of ring B of a khivorin derivative to give an andirobin derivative, and Michael addition of C-2 to the terminal methylene group on C-8 to afford a bicyclo[3,3,1]nonane system.[2]

Initially the introduction of a 1-hydroxy-group into an andirobin nucleus was attempted. Treatment of methyl angolensate with boron trifluoride in acetic acid, with hot dilute sulphuric acid, or with hydrogen bromide gave deoxyandirobin; when boron trichloride in methylene chloride was used only starting material was recovered. Similar treatment of methyl 3-dihydroangolensate (*i.e.* the 3-hydroxy-compound) afforded only starting material. In contrast to gedunin, which with alkaline hydrogen peroxide (30%) gives a high yield of the 1,2-epoxide, no epoxidation occurred with deoxyandirobin under the same conditions.

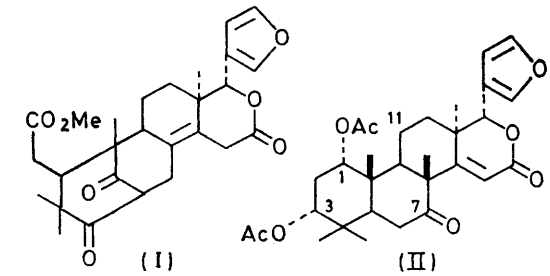
Attention was then turned to the cleavage of ring B in a khivorin derivative which already has acyloxy-functions at the 1- and 3-positions. By analogy with a similar cleavage of limonin, 7-deacetoxy-7-oxo-14,15-deoxygedunin has been treated with dilute alkali to form a B-seco-compound.[3] However with 7-deacetoxy-7-oxo-14,15-deoxykhivorin (II) under similar reaction conditions only hydrolysis was achieved, without cleavage of ring B. The ring was eventually opened with potassium t-butoxide in dimethyl sulphoxide. This led simultaneously to the solvolysis of the 1- and 3-acetoxy-groups and formation of a product formulated as the tetrahydroangolensic acid (III), arising from addition of the 1-hydroxy-group to the double bond generated by the cleavage of ring B. In view of this, the 1- and 3-hydroxy-groups were first oxidised to give the 1,3,7-triketone (IV), which reacted readily with dilute alkali to afford the B-seco-acid (V). Treatment of the acid with diazomethane led to the formation of the enol methyl ether of the 1,3-diketo-system as well as the methyl ester. Attempted esterification of the acid by the Fischer method caused isomerisation of the isolated 8,14-double bond to the conjugated 14,15-position [disappearance of the peak at δ 1·75 (methyl on double bond) and appearance of a vinyl peak at δ 5·83 p.p.m. (H-15) in the n.m.r. spectra of the enol ether methyl esters]. With a view to its oxidation to a diene the acid (V) was treated with *N*-bromosuccinimide. In the product the C-2 position appeared to have been brominated and the 8,14-double bond isomerised to the conjugated position. This material was not further investigated.

[1] For a review see J. D. Connolly, K. H. Overton, and J. Polonsky, *Progr. Phytochem.*, 1970, **2**, 385.

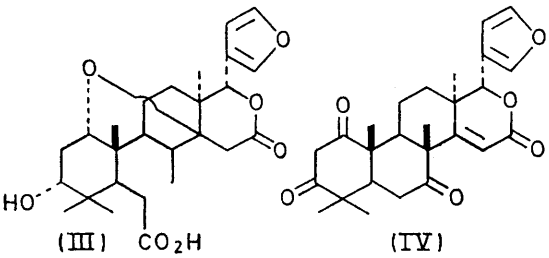
[2] Preliminary communication, M. E. Obasi, J. I. Okogun, and D. E. U. Ekong, *Chem. Comm.*, 1971, 727. A similar but independent correlation has also recently been reported by J. D. Connolly, I. M. S. Thornton, and D. A. H. Taylor, *Chem. Comm.*, 1971, 17.

[3] D. E. U. Ekong and E. O. Olagbemi, *J. Chem. Soc.* (*C*), 1966, 944.

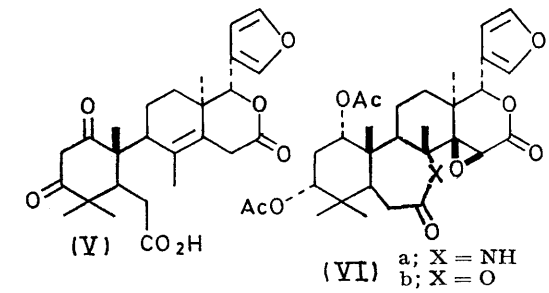
Ring A in a number of triterpenoids has been opened by 'second-order' Beckmann rearrangement of a 3-hydroxyimino-derivative [4] to form a 3-nitrile and a



(I) (II)



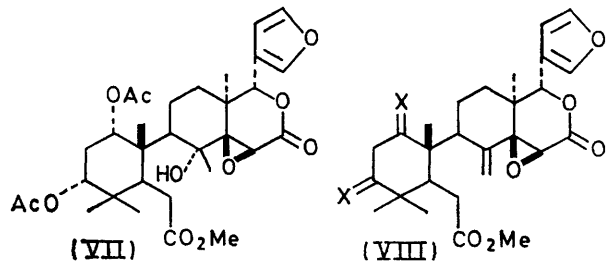
(III) (IV)



(V) (VI) a; X = NH b; X = O

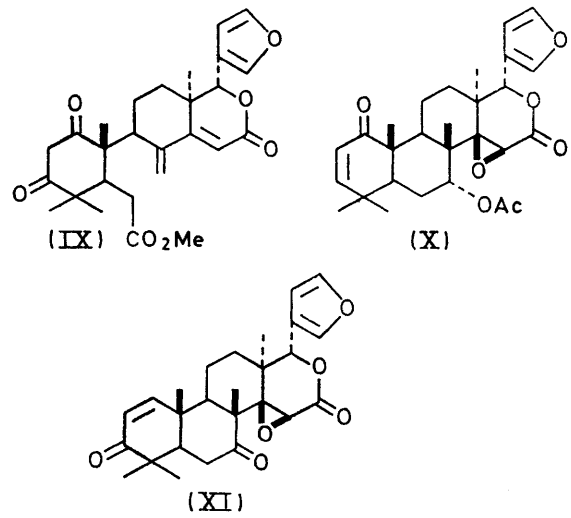
terminal methylene group on C-4. The oxime of 7-deacetoxy-7-oxokhivorin, however, did not react with toluene-*p*-sulphonyl chloride or methanesulphonyl chloride in pyridine, and remained unchanged on treatment with phosphorous pentoxide or phosphorous pentachloride. With acetyl chloride the acetate was formed, which did not react with methanolic sulphuric acid. Thionyl chloride, however, smoothly converted the oxime into the ε-lactam (VIa). Amides have been converted into acids by *N*-nitrosation followed by loss of nitrogen.[5] Following the modification of Bladon and McMeekin,[6] we treated the lactam (VIa) with sodium nitrite in acetic acid–acetic anhydride to obtain the ε-lactone (VIb), which was converted into mexicanolide [2] (see Experimental section).

In an earlier study [7] gedunin and khivorin were related by their conversion into isogedunin (X); we have now reconverted isogedunin into 7-oxogedunin (XI). The reaction of 7-deacetylisogedunin with alkaline hydrogen peroxide gave epoxy-7-deacetylisogedunin. This was treated with hydrazine hydrate to afford a



(VII) (VIII)

rearrangement product which on oxidation gave 7-oxogedunin, identical with an authentic sample. This represents a formal conversion of khivorin into gedunin.



(IX) (X) (XI)

EXPERIMENTAL

Reaction of 14,15-Deoxy-7-oxokhivorin with Potassium t-Butoxide.—14,15-Deoxy-7-oxokhivorin (2·5 g) in dimethyl sulphoxide (22 cm³) was added to potassium t-butoxide (20 g) in a small quantity of t-butyl alcohol containing water (0·2 cm³). The mixture was stirred under nitrogen for 6 h, cooled in ice, acidified with concentrated hydrochloric acid, and diluted with water. A chloroform extract of this material was itself extracted with saturated aqueous sodium hydrogen carbonate. The precipitate obtained on acidifying this aqueous extract was extracted with chloroform, and gave crystals of the *tetrahydroangolensic acid* (III) (200 mg), m.p. 240° (from methanol) (Found: C, 67·6; H, 8·1. $C_{26}H_{36}O_7$ requires C, 67·8; H, 7·9%). Methylation with diazomethane afforded a methyl ester, m.p. 175°; δ 3·7 (CO_2Me) and 3·45 p.p.m. (1H, OH, exchangeable with D_2O); signals due to β-substituted furan and 17-H but no further low-field signals below δ 4 p.p.m.; no vinyl methyl group but δ 1·28 p.p.m. (d, *J* 7 Hz, $H_3C{\cdot}CH$).

Oxidation of 1,3-Dideacetyl-14,15-deoxy-7-oxokhivorin.—1,3-Dideacetyl-14,15-deoxy-7-oxokhivorin (2·5 g) in acetone (450 cm³) was cooled in an ice-bath and oxidised with Jones reagent (4 cm³). After stirring for 30 min methanol (20 cm³)

[4] See for instance R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, 1953, **18**, 1058; C. W. Shoppee, N. W. Hughes, R. E. Lack, and J. T. Pinhey, *J. Chem. Soc.* (*C*), 1970, 1443; G. H. Whitham, *ibid.*, 1960, 2016; R. M. Carman and D. Cowley, *Austral. J. Chem.*, 1965, **18**, 213, and references cited therein.

[5] E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6014; Y. Sato and H. G. Latham, jun., *J. Org. Chem.*, 1957, **22**, 981.

[6] P. Bladon and W. McMeekin, *J. Chem. Soc.*, 1961, 3504.

[7] A. Akisanya, E. O. Arene, C. W. L. Bevan, D. E. U. Ekong, M. N. Nwaji, J. I. Okogun, J. W. Powell, and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1966, 506.

was added; the solution was decanted, neutralised with potassium carbonate, and concentrated under reduced pressure and at low temperature. The chloroform extract of this material gave the triketone (IV), m.p. 290—294° (from methanol), $\lambda_{max.}$ (MeOH) 258 (ε 14,000), $\lambda_{max.}$ (MeOH–NaOH) 285 nm (ε 21,000). With diazomethane the product gave an enol ether, $\lambda_{max.}$ 250 nm (ε 14,000) (no shift in alkali); δ 3·7 p.p.m. (3H, s, C=C–OMe). Oxidation of the 1,3-dideacetyl-14,15-deoxy-7-oxokhivorin at room temperature afforded an acid, m.p. 350°.

Alkaline Cleavage of the Triketone (IV).—The triketone (IV) (1 g) in aqueous sodium hydroxide (10%; 50 cm³) was heated on a steam-bath for 2 h; almost all the material went into solution. The solution was filtered hot through glass wool, cooled, and acidified with hydrochloric acid; the precipitate was chromatographed on silica gel. Elution with ether after washing the column with light petroleum gave the *acid* (V) as a powder (0·5 g) which could not be crystallised but had $\lambda_{max.}$ 257 nm (ε 10,000) [shifted in alkali to 288 nm (ε 20,000)] (Found: C, 67·9; H, 7·0. $C_{26}H_{32}O_7$ requires C, 68·4; H, 7·1%); δ 1·75 p.p.m. (C=C–CH_3).

Treatment with diazomethane afforded the *methoxy-ester* as a gum, $\lambda_{max.}$ 250 nm (ε 12,000) (no shift in base) (Found: C, 69·5; H, 8·0. $C_{28}H_{36}O_7$ requires C, 69·4; H, 7·5%); δ 3·7 (6H, C=C–OCH_3 and CO_2CH_3), 5·25 (1H, CO–C*H*=C–OMe), and 1·75 p.p.m. (3H, C=C–CH_3).

Treatment of the Acid (V) *with Methanolic Sulphuric Acid.*—The acid (V) (200 mg) in methanol (10 cm³) containing conc. sulphuric acid (2 drops) was refluxed on a steam-bath for 4 h; cooling gave the Δ^{14}-*isomer* as crystals (100 mg), m.p. 210°, $\lambda_{max.}$ 256 nm (ε 17,000) [shifted in alkali to 285 nm (ε 23,000)] (Found: C, 67·9; H, 7·0. $C_{26}H_{32}O_7$ requires C, 68·4; H, 7·1%). With diazomethane the product afforded a *methyl ester*, m.p. 220—225°, $\lambda_{max.}$ 250 nm (ε 14,000) (Found: C, 69·0; H, 7·6. $C_{28}H_{36}O_7$ requires C, 69·4; H, 7·5%): δ 1—1·32 (5 × C·CH_3), 3·6 and 3·7 (6H, C=C–OCH_3 and CO_2·CH_3), 5·84 (1H, C=CH·CO·O), and 5·35 p.p.m. (1H, CO·C*H*=C·OMe).

Allylic Bromination of the Acid (V).—The acid (V) (500 mg) in carbon tetrachloride (100 cm³; purified over phosphorus pentoxide) containing freshly recrystallised *N*-bromosuccinimide (250 mg) and benzoyl peroxide (20 mg) was refluxed for 1 h. The solution was evaporated and the product chromatographed over silica gel. Elution with ether gave succinimide, then product that crystallised from chloroform (yield 100 mg), m.p. 225—227°, $\lambda_{max.}$ 260 nm (ε 9000) (no shift in base); δ 0·95, 1·17, 1·28, 1·5, and 1·6 (each s, CH_3), 5·15 (1H, s, 17-H), 5·35 (1H, s, 15-H), and 5·6br (CO_2H, exchangeable with D_2O). With diazomethane it afforded a methyl ester, m.p. 236—240°.

Oxime of 7-Oxokhivorin.—7-Oxokhivorin (5 g) dissolved in pyridine (50 cm³) was treated with hydroxylamine hydrochloride (4 g) in water (4 cm³). After refluxing for 1 h water was added. The chloroform extract gave the *oxime*, which crystallised from methanol (yield 5 g), m.p. 168—170° (Found: C, 64·0; H, 7·4; N, 2·3. $C_{30}H_{39}NO_9$ requires C, 64·6; H, 7·05; N, 2·5%), $\nu_{max.}$ 3200, 3350, and 3500 (OH), and 1640 cm⁻¹ (–C=N–); δ 3·54 p.p.m. (d, *J* 10 Hz, 6α-H).

The oxime (200 mg) in acetyl chloride (10 cm³) was refluxed gently on a steam-bath to give the O-*acetate* (180 mg), m.p. 240—242° (from methanol) (Found: C, 64·0; H, 6·7; N, 2·2. $C_{32}H_{41}NO_{10}$ requires C, 64·1; H, 6·9; N, 2·3%). The i.r. spectrum showed the absence of a hydroxy-group. The same product was obtained on treatment with toluene-*p*-sulphonic acid and acetic anhydride.

The ε-Lactam (VIa).—The foregoing oxime (4 g) in chloroform (50 cm³) was treated with thionyl chloride (5 cm³); after 1 h the excess of thionyl chloride was boiled off on a steam-bath. The rest of the solvent was evaporated off under reduced pressure and the *ε-lactam* (VIa) crystallized from methanol, m.p. 230° (Found: C, 64·1; H, 7·3; N, 2·8. $C_{30}H_{39}NO_9$ requires C, 64·6; H, 7·05; N, 2·5%), $\nu_{max.}$ 3100 (NH) and 1630 cm⁻¹ (C=O), δ 8·28 p.p.m. (CONH).

The Lactone (VIb).—The lactam (VIa) (3 g) in acetic acid (15 cm³) and acetic anhydride (40 cm³) was cooled to 0°. Sodium nitrite (7 g) was added slowly with stirring during 4 h with the temperature maintained at 0°. Cold water was added to dissolve excess of sodium nitrite and the precipitated organic material was extracted with chloroform. The *product* (VIb) (2·5 g) had m.p. 315—318° (from methanol) (Found: C, 64·2; H, 6·9. $C_{30}H_{38}O_{10}$ requires C, 64·5; H, 6·9%). The i.r. spectrum showed no CONH bands at 3300 and 1630 cm⁻¹ but exhibited ε-lactone absorption at 1710 cm⁻¹.

Hydrolytic Cleavage of the Lactone (VIb).—The lactone (VIb) (1·2 g), dissolved in methanolic 5% potassium hydroxide (20 cm³) was left at room temperature for 1 h. Cold dilute hydrochloric acid was added to precipitate the *hydroxy-acid*, m.p. 332° (from methanol), $\nu_{max.}$ 3400 (tertiary OH) and 3200 cm⁻¹ (CO_2H). The acid in methanol (50 cm³) was treated with diazomethane. The *ester* (VII) formed as feathery crystals, m.p. 283—284° (Found: C, 62·8; H, 7·8. $C_{31}H_{42}O_{11}$ requires C, 63·2; H, 7·2%), $\nu_{max.}$ 3400 cm⁻¹ (sharp, tertiary OH).

Dehydration of the Hydroxy-ester (VII).—The ester (0·8 g) in pyridine (15 cm³) was cooled in an ice–salt bath and thionyl chloride (1 cm³) was slowly added. After 0·5 h the material was precipitated with cold water and extracted with chloroform. The *product* (VIIIa) (0·7 g) had m.p. 195—196° (from methanol) (Found: C, 64·5; H, 7·2. $C_{31}H_{40}O_{10}$ requires C, 65·0; H, 7·0%), $\nu_{max.}$ 3050, 1630, and 898 cm⁻¹ (C=CH_2) (no OH absorption); δ 5·08 and 5·38 p.p.m. (C=CH_2).

Hydrolysis of the Ester (VIIIa).—The ester (VIIIa) (0·6 g) was left in methanolic 5% potassium hydroxide (10 cm³) overnight. On addition of dilute hydrochloric acid a precipitate (VIIIb) (500 mg) was obtained which did not crystallise (Found: C, 65·6; H, 7·35. Calc. for $C_{27}H_{36}O_8$: C, 66·4; H, 7·4%), $\nu_{max.}$ 3300 (OH) and 3050, 1635, and 905 cm⁻¹ (C=CH_2).

Oxidation of the Ester (VIIIb).—The ester (VIIIb) (400 mg) in acetone (12 cm³) was cooled in an ice-salt bath and treated with Jones reagent (10 drops). After 0·5 h, methanol (2 cm³) was added and the mixture was shaken. Saturated aqueous sodium chloride was added to precipitate the *ketone* (VIIIc) (350 mg), m.p. 195—196° (from methanol) (Found: C, 67·0; H, 6·8. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7%), $\lambda_{max.}$ 258 nm (ε 15,000) [shifting in alkali to 285 nm (ε 16,000)]. The i.r. spectrum showed no OH peaks.

Reduction of the Ketone (VIIIc).—The diketone (VIIIc) (240 mg) in acetic acid (50 cm³) was reduced overnight with chromium(II) chloride solution (2M; 25 cm³). Saturated aqueous sodium chloride was added to precipitate the organic material, which on extraction with chloroform and crystallisation from methanol gave the *product* (IX) (200 mg), m.p. 230° (Found: C, 68·9; H, 7·4. $C_{27}H_{32}O$ requires C, 69·2; H, 6·9%), $\lambda_{max.}$ 258 nm (ε 14,000 [shifting in alkali to 288 nm (ε 17,000)].

Mexicanolide.—The diketone (IX) (150 mg) in chloroform (4 cm³) was treated with saturated aqueous sodium hydrogen carbonate (1 cm³) and stirred overnight. More chloroform was added; the solution was dried and evaporated and the residue was triturated with methanol to yield mexicanolide (120 mg), m.p. 225°, identical (i.r., t.l.c., mixed m.p., and n.m.r.) with natural mexicanolide.

Oxime of 14,15-Deoxy-7-oxokhivorin.—14,15-Deoxy-7-oxokhivorin (400 mg) and hydroxylamine hydrochloride (300 mg) in water (0·5 cm³) and pyridine (10 cm³) yielded the *oxime*, m.p. 308—310° (from methanol) (Found: C, 66·85; H, 7·6; N, 2·9. $C_{30}H_{39}NO_8$ requires C, 66·5; H, 7·3; N, 2·6%). The oxime (250 mg) in pyridine (5 cm³) was treated with thionyl chloride to yield a lactam, m.p. 298—300° (from methanol), $\nu_{max.}$ 3030, 3350 (NH), and 1635 cm^{-1} (CO). The lactam (200 mg) in acetic acid (5 cm³) and acetic anhydride (7 cm³) was treated at 0° with sodium nitrite (1 g) to give the corresponding lactone, which when passed over silica gel afforded an acid, m.p. 280—285°, $\nu_{max.}$ 3100, 1625, and 895 cm^{-1} (C=CH_2), δ 4·8 and 5·4 p.p.m. (C=CH_2) as well as signals for 4-tertiary Me groups.

Epoxidation of 7-Deacetylisogedunin.—7-Deacetylisogedunin was prepared by partial oxidation of isogedunol [7] with Jones reagent. The compound (2 g) in acetone (100 ml) and 2N-sodium hydroxide (8 cm³) was epoxidised with hydrogen peroxide (30%; 5 cm³). Work-up afforded *7-deacetylepoxyisogedunin*, m.p. 279—280° (Found: C, 68·3; H, 6·7; O, 24·6. $C_{26}H_{32}O_7$ requires C, 68·4; H, 7·1; O, 24·5%).

Treatment of 7-Deacetylepoxyisogedunin with Hydrazine Hydrate.—7-Deacetylepoxyisogedunin (1 g) in t-butyl alcohol (25 cm³) and hydrazine hydrate (8 cm³) was refluxed with acetic acid (0·4 cm³). The product was chromatographed over deactivated alumina to afford gummy material (200 mg) that did not crystallise. This was dissolved in acetone (10 cm³) and treated with Jones reagent (0·4 cm³). Work-up and chromatography over deactivated alumina gave crystals (100 mg); i.r. spectrum identical with that of an authentic sample of 7-deacetoxy-7-oxogedunin; m.p. and mixed m.p. 251—252°.

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