Natural Coumarins. Part XIV. Synthesis of Some Isoprenyl Ethers of Psoralene Hydroquinone and Related Products

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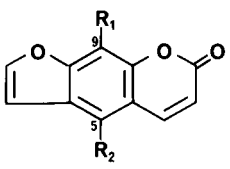
Partial demethylation of isopimpinellin and methylation of psoralene hydroquinone afforded 5-methoxy-9-hydroxypsoralene. The corresponding 5-isoprenyloxy derivative was used in the synthesis of cnidilin and its epoxy and glycol derivatives, which are all biogenetically feasible; the latter two having as yet not been isolated from natural sources.

The known (2) natural isoprenyloxy derivatives of psoralene (7*H*-furo[3,2-*g*][1]benzopyran-7-one) comprise products which carry the C_5 ethereal group on either of the *para* positions of the benzene ring. Imperatorin (I) and its epoxy and glycol variants (heraclenin (II) and heraclenol (III), respectively) have this substituent on C-9, while isoimperatorin (IV) and its epoxy and glycol variants (oxypeucedanin (V) and oxypeucedanin hydrate (VI), respectively) have it on C-5. Phellopterin (VII) is a 5-methoxy-9-isoprenyloxy derivative which also has natural epoxy and glycol counterparts, byakangelicol (VIII) and byakangelicin (IX), respectively. It thus appears reasonable to anticipate that products isomeric with VII-IX carrying the C-5 and C-9 substituents in exchanged positions, being biogenetically feasible, should also be capable of occurrence in plant tissue and their actual isolation may be a future event.

A desirable intermediate for the synthesis of 5-isoprenyloxy-9-methoxypsoralene (X) was 5-hydroxy-9-methoxypsoralene (XI) for which it appears that no convenient synthetic method is available. Attempts to obtain XI by partial demethylation of isopimpinellin (XII) and by partial methylation of psoralene hydroquinone (XIII) failed but afforded useful information. The only product obtained from these reactions, performed under various conditions, was shown to be 5-methoxy-9-hydroxypsoralene (XIV), a compound which itself occurs naturally (3). The latter compound yielded phellopterin (VII) by treatment with γ,γ-dimethylallyl bromide and resulted from VII by acid treatment. These experiments demonstrate the greater stability of the C-5 methoxyl group



(in XII) towards acid treatment and the greater reactivity of the hydroxyl group at the same position (in XIII) towards etherification. Controlled acetylation of XIII, however, affected the C-9 hydroxyl selectively since the product (XV) gave by methylation the same product (XVI) as that obtained from XIV by acetylation.

Based on these studies, it was anticipated that treatment of psoralene hydroquinone (XIII) with γ,γ-dimethylallyl bromide under carefully controlled conditions would give the desirable etherification product, 5-(γ,γ-dimethylallyloxy)-9-hydroxypsoralene (XVII). This was realized, in reasonable yield, by the use of 1 mole of the reagent for 5 minutes reaction time. A byproduct was the diether XVIII which was predominant or the sole product when more of the reagent was used or the reaction allowed longer duration. Cleavage of both ether groups in XVIII with mineral acid was facile giving the hydroquinone (XIII) and subsequently isopimpinellin (XII) by methylation. The desirable phellopterin isomer (X) was finally obtained by methylation of XVII; it had m.p. 117-118° and gave the expected spectral data. These include the characteristic nmr signals of the furocoumarin system with a doublet *gem*-dimethyl group signal arising from the isoprenyl side chain (presumably due to dissimilar magnetic environment) in contrast to phellopterin (VII) which gives a singlet for the same group (4). The mass spectrum was very close to that measured for phellopterin and exhibited the fragmentation pattern described by Lee and Soine (5). A compound, named cnidilin (6), possessing structure X and exhibiting its properties was recently isolated by the latter workers from *Sphenoscidium capitellatum* (A. Gray) and previously by Komissarenko *et al.* (7) from *Cnidium dubium* (Schkuhr) Thell. Mineral acid cleavage of X afforded pure 5-hydroxy-9-methoxypsoralene (XI), m.p. 278-279°, which readily gave isopimpinellin (XII) by methylation

I: $R_1 = OCH_2CH=C(CH_3)_2$, $R_2 = H$.

II: $R_1 = OCH_2CH\text{-}C(CH_3)_2$ (epoxide), $R_2 = H$.

III: $R_1 = OCH_2CH(OH)COH(CH_3)_2$, $R_2 = H$.

IV: $R_1 = H$, $R_2 = OCH_2CH=C(CH_3)_2$.

V: $R_1 = H$, $R_2 = OCH_2CH\text{-}C(CH_3)_2$ (epoxide).

VI: $R_1 = H$, $R_2 = OCH_2CH(OH)COH(CH_3)_2$.

VII: $R_1 = OCH_2CH=C(CH_3)_2$, $R_2 = OCH_3$.

VIII: $R_1 = OCH_2CH\text{-}C(CH_3)_2$ (epoxide), $R_2 = OCH_3$.

IX: $R_1 = OCH_2CH(OH)COH(CH_3)_2$, $R_2 = OCH_3$.

X: $R_1 = OCH_3$, $R_2 = OCH_2CH=C(CH_3)_2$.

XI: $R_1 = OCH_3$, $R_2 = OH$.

XII: $R_1 = R_2 = OCH_3$.

XIII: $R_1 = R_2 = OH$.

XIV: $R_1 = OH$, $R_2 = OCH_3$.

XV: $R_1 = OAc$, $R_2 = OH$.

XVI: $R_1 = OAc$, $R_2 = OCH_3$.

XVII: $R_1 = OH$, $R_2 = OCH_2CH=C(CH_3)_2$.

XVIII: $R_1 = R_2 = OCH_2CH=C(CH_3)_2$.

XIX: $R_1 = OCH_3$, $R_2 = OCH_2CH\text{-}C(CH_3)_2$ (epoxide).

XX: $R_1 = OCH_3$, $R_2 = OCH_2CH(OH)COH(CH_3)_2$.

XXI: $R_1 = OCH_3$, $R_2 = NH_2$.

XXII: $R_1 = OCH_3$, $R_2 = H$.

XXIII: $R_1 = OCH_3$, $R_2 = NH\text{-}CH_2:C(CH_3)_2$.

XXIV: $R_1 = OCH_3$, $R_2 = N[CH_2CH=C(CH_3)_2]_2$.

and cnidilin (X) by treatment with γ,γ-dimethylallyl bromide.

Two other side chain-oxygenated derivatives of cnidilin have been prepared which, likewise, are capable of natural occurrence but do not seem to have as yet been isolated. The first is the epoxide derivative (XIX), m.p. 128-130°, which was obtained from synthetic cnidilin by treatment with monoperphthalic acid and, being the structural isomer of byakangelicol, may be assigned the name "(±)-isobyakangelicol". Treatment of XIX with oxalic acid in aqueous ethanol afforded the second product (XX), m.p. 119-121°, a glycol which may be designated "(±)-isobyakangelicin".

Although it is generally known that coumarins carrying ether groups are by far more common in nature than phenolic products, it seems that the occurrence of compounds XI, XVII, and XVIII in plant tissue is not unlikely.

Attempts to prepare 5-hydroxy-9-methoxypsoralene (XI) from another known 9-methoxylated psoralene derivative, namely 5-aminoxanthotoxin (XXI), have been abortive. A material (m.p. 220-226°) assigned structure XI by Brokke and Christensen (9) and prepared as prescribed by these authors, through reaction of XXI with sodium nitrite and hydrochloric acid in methanol, has been shown to be in fact a mixture comprising predominantly XXI and small amounts of XI and xanthotoxin (XXII), the latter being a product of ambiguous deamination. This fact was realized after treatment of the said material with γ,γ-dimethylallyl bromide when two products were isolated and identified as the *N*-alkyl derivatives XXIII and XXIV, exhibiting the expectable mass spectrometric fragmentations; both compounds also resulted from a pure preparation of XXI by the same treatment.

EXPERIMENTAL

All melting points are uncorrected. The uv spectra were measured in ethanol (unless otherwise stated) using an M4QII Carl Zeiss instrument. The nmr spectra were taken on a 60 Mc Varian instrument in deuteriochloroform with TMS as internal standard. The mass spectra were measured using an Associated Electrical Industries MS9 spectrometer. All thin-layer chromatograms were made on silica gel G using benzene-ethyl acetate (9:1) as solvent system and iodine-potassium iodide solution as spray reagent.

Demethylation of Isopimpinellin (XII).

To a solution of isopimpinellin (1 g.) in acetic acid was added 12 ml. of hydroiodic acid and the mixture was refluxed for 50 hours when the reaction was complete (tlc). After the usual work-up, the reaction product was crystallized from aqueous methanol to give yellowish needles (350 mg.) of 5-methoxy-9-hydroxypsoralene (XIV), m.p. 210-214°, (reported (3) m.p. 221.5-222°). It was identical with the product obtained from phellopterin (VII) by treatment with hot ethanolic hydrochloric acid solution.

A solution of the product (XIV) in acetone containing anhydrous potassium carbonate was treated with γ,γ-dimethylallyl bromide, in the usual procedure, to give a product shown to be identical (tlc and mixed m.p.) with phellopterin (VII). Methylation of the same product (XIV) with methyl iodide in acetone containing potassium carbonate gave isopimpinellin (XII) (tlc and mixed m.p.).

Methylation of Psoralene Hydroquinone (XIII).

A solution of psoralene hydroquinone (300 mg.) in acetone (10 ml.) was treated with methyl iodide (1 mole, 0.09 ml.) in presence of anhydrous potassium carbonate (1 g.) and the reaction allowed to proceed under reflux until the first traces of isopimpinellin started to appear (15 minutes). After the usual work-up, the reaction product was crystallized from methanol to give light greenish needles (50 mg.) of XIV (m.p. and mixed m.p. with the above preparation 208-212°).

5-Methoxy-9-acetoxypsoralene (XVI).

A mixture of psoralene hydroquinone (XIII, 200 mg.) and acetic anhydride (2 ml.) in pyridine (2 ml.) solution was heated at 100° for 2 hours. The product (200 mg.) deposited on cooling as colorless prisms and was recrystallized from chloroform-ethanol to give 5-hydroxy-9-acetoxypsoralene (XV), m.p. 208-210°, R_f 0.30.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.01; H, 3.10. Found: C, 59.60; H, 3.33.

The resulting product was methylated using methyl iodide (in acetone containing potassium carbonate) to give 5-methoxy-9-acetoxypsoralene (XVI) as colorless needles (from aqueous ethanol), m.p. 165-167°, R_f 0.40.

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.31; H, 3.90.

The same compound (XVI) was also obtained by acetylation of 5-methoxy-9-hydroxypsoralene (XIV) in the usual manner; identity established by tlc and mixed m.p.

Treatment of Psoralene Hydroquinone (XIII) with γ,γ-Dimethylallyl Bromide.

A.

A solution of psoralene hydroquinone (1.1 g.) in acetone (20 ml.) containing anhydrous potassium carbonate (4 g.) was treated with γ,γ-dimethylallyl bromide (1 mole, 0.75 ml.) and the mixture refluxed for 5 minutes. After working up and crystallization of the product from ethanol, 5-isoprenyloxy-9-hydroxypsoralene (XVII) was obtained as fine colorless needles (400 mg.), m.p. 142-144°, R_f 0.27. Treatment of the product (XVII, 50 mg.) with concentrated hydrochloric acid (0.1 ml.) in ethanol (2 ml.) under reflux for 1 hour, gave after the usual work-up and crystallization from acetone, 20 mg. of psoralene hydroquinone (XIII) (tlc and mixed m.p.).

B.

When the reaction of XIII with γ,γ-dimethylallyl bromide was repeated (using the same amounts) but extending the reflux period to 15 minutes, three products were detected on the chromatoplates and were isolated by preparative-layer chromatography to give: i) Trace amounts of 5-isoprenylxoy-9-hydroxypsoralene (XVII), ii) 240 mg. of 5,9-diisoprenyloxypsoralene (XVIII, see below), R_f 0.61, and iii) 120 mg. of an unidentified product, m.p. 138-140°, R_f 0.55.

C.

Compound XVIII alone was obtained when the above reaction was conducted (using the same proportions) for a reflux period of 30 minutes, and was isolated as lustrous plates (aqueous ethanol), m.p. 67-68°. The nmr spectrum contained signals arising from the isoprenyl groups at δ 1.74 (CH_3), 4.86 (CH_2) and 5.54 (-CH=), with integrals corresponding to two of each, in addition to signals at δ 6.28 and 8.13 (doublets, for C-3 H and C-4 H, respectively, J_{34} = 10 c/s) and δ 6.95 and 7.64 (doublets, for C-6 H and C-7 H, respectively, J_{67} = 2.5 c/s).

Anal. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.81; H, 6.22.

Treatment of the product (XVIII, 100 mg.) in ethanol (2 ml.) solution containing concentrated hydrochloric acid (3 drops) under reflux for 30 minutes gave, after the usual work-up, 48 mg. of psoralene hydroquinone (XIII) (tlc and mixed m.p.). The latter product was methylated with methyl iodide in the usual manner to give isopimpinellin (XII) (tlc and mixed m.p.).

Synthesis of Cnidilin (X).

A solution of 5-isoprenyloxy-9-hydroxypsoralene (XVII, 500 mg.) in acetone (20 ml.) was refluxed for 1 hour with methyl iodide (2 ml.) in presence of anhydrous potassium carbonate (3 g.). After the usual work-up, the reaction product was crystallized from aqueous ethanol to give colorless flat needles (300 mg.), m.p. 116-118°, R_f 0.52; reported (5) m.p. 115-115.5°. The nmr spectrum contained signals at δ 6.31 and 8.16 (doublets, for the C-3 and C-4 protons, respectively, $J_{3,4}$ = 10 c/s), at δ 6.98 and 7.66 (doublets, for the C-6 and C-7 protons, respectively, $J_{6,7}$ = 2.5 c/s) and at δ 4.22 (methoxyl). The isoprenyl side chain protons gave a doublet at δ 4.82 (2H) and a triplet (1H) at δ 5.57 for the -CH_2-CH= system in addition to a doublet at δ 1.74 due to the *gem*-dimethyl group.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.06; H, 5.47.

Treatment of cnidilin (500 mg.) in ethanol (15 ml.) solution with concentrated hydrochloric acid (0.5 ml.) under reflux for 30 minutes followed by the usual work-up and crystallization of the product from methyl alcohol, gave 230 mg. of 5-hydroxy-9-methoxypsoralene (XI), m.p. 278-279°, R_f 0.17; reported m.p. 260 or 270° (10) and 293-295° (5). The uv spectrum exhibited maxima at 225, 275, and 315 nm (log ε, 4.22, 4.20, and 3.81 respectively) which were shifted to 230, 295, and 328 nm (log ε, 4.20, 4.15, and 3.61, respectively) when the spectrum was measured in ethanolic alkali solution. Treatment of the latter product (XI) with methyl iodide under the usual conditions gave isopimpinellin (XII) identified by direct comparison (tlc and mixed m.p.). Treatment of the same product (XI) with γ,γ-dimethylallyl bromide as described before gave back cnidilin (X) identical (tlc and mixed m.p.) with the preparation described before.

The Epoxide Derivative of Cnidilin: "(±)-Isobyakangelicol" (XIX).

A solution of cnidilin (X, 100 mg.) in ether (10 ml.) was treated at room temperature with a solution of monoperphthalic acid (1.8 g.) in ether (15 ml.) for 72 hours. After working up, the product was crystallized from aqueous ethanol to give creamish needles (14 mg.), m.p. 128-130°, R_f 0.27.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 65.03; H, 5.20.

"(±)-Isobyakangelicin" (XX).

A solution of "(±)-isobyakangelicol" (XIX, 20 mg.) in few drops of ethanol was treated with a solution of oxalic acid (0.2 g.) in water (15 ml.) and the mixture heated at 100° for 15 minutes. After working-up, the isolated product was crystallized from benzene to give colorless needles (7 mg.), m.p. 119-121°.

Anal. Calcd. for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 60.90; H, 5.26.

Treatment of 5-Aminoxanthotoxin (XII) with γ,γ-Dimethylallyl Bromide.

A solution of 5-aminoxanthotoxin (1 g.) in acetone (20 ml.) was treated with γ,γ-dimethylallyl bromide (2 ml.) in presence of anhydrous potassium carbonate under reflux for 15 minutes. The reaction mixture (comprising two products, R_f 0.15 and 0.54) was isolated by the usual work-up and resolved by preparative-layer chromatography into: a) 5-(isoprenylamino)-9-methoxypsoralene (XV), obtained as orange fine needles, m.p. 116-117° (from ethanol), R_f 0.15 (yield 67 mg.). The uv spectrum exhibited maxima at 230, 294, and 327 nm (log ε, 4.39, 4.32, and 4.00, respectively). The mass spectrum exhibited principal

ions at m/e 299 (M^+), 298 (100%, M^+-H), 284 (M^+-CH_3), 283 (298 -CH_3), 242 (298 -2CO), 231 (M^+-C_5H_8), 230 (M^+-C_5H_9), 216 (231 -CH_3), 255 (298 -CH_3, CO), 187 (230 -CH_3, CO), 159 (187 -CO) and 69 (C_5H_9).

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.83; H, 5.62; N, 4.40.

b) 5-(di-isoprenylamino)-9-methoxypsoralene (XVI), obtained as yellow needles, m.p. 69-70° (from ethanol), R_f 0.54 (yield 280 mg.). The uv spectrum exhibited maxima at 226, 273, and 315 nm (log ϵ, 4.39, 4.18, and 3.96, respectively). The mass spectrum, showing no M^+ ion, exhibited principal fragment ions at m/e 296 (M^+-CH_3, 2CO), 230 (M^+-C_5H_8, C_5H_9), 231 (M^+-2 C_5H_8), 216 (231 -CH_3), 202 (230 -CO), 187 (202 -CH_3), 174 (202 -CO), 159 (174 -CH_3), 146 (174 -CO), 131 (159 -CO), 103 (131 -CO) and 69 (100%, C_5H_9).

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.90; H, 7.03; N, 4.22.

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