Natural Coumarins. XV. Some Reactions of Dihydrobergapten and Dihyrdoisopimpinellin

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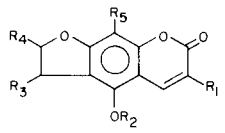
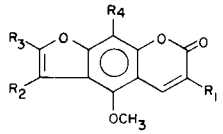
Current literature (1) bears evidence to the effect that substitution in the linearly disposed furocoumarin nucleus with methyl groups enhances the activity of these compounds as skin photosensitizing agents. In a study of the general substitution behavior of certain methoxylated (naturally occurring and readily accessible) furocoumarin models, we sought to explore the effects of saturation of the 3,4- and 6,7-double bonds (numbering starts from the hetero atom in the pyrone system). We now report some of the results obtained with the latter type of compounds, using 6,7-dihydrobergapten (I) and isopimpinellin (II).

Treatment of I (obtained in good yield by hydrogenation of bergapten, III) with one mole of bromine afforded the 3-bromo derivative (IV) in which the location of the halogen atom was proven through treatment (2) with hot alkali leading to contraction of the pyrone system to give 2′,3′-dihydro-5,6-furo-4-methoxycoumarilic acid (V). Reaction of I with two moles of bromine gave a mixture which was resolved into IV and a dibromo derivative, formulated as VI. The latter compound also resulted by further bromination of IV and was the sole resultant from reaction of I with ten moles of bromine. The presence of one halogen atom at C-3 in VI was evident from the origin of the compound and was also demonstrated by its reaction with alkali whereupon the corresponding coumarilic acid (VII, from which a methyl ester was obtained) resulted. The placement of the second bromine atom on the benzene ring (in VI and VII) is conjectured from the the analogous behavior of 6,7-dihydroxanthotoxin (3). The halogen content of both bromo derivatives IV and VI could be removed with facility using activated zinc dust in boiling ethanol to give dihydrobergapten (I).

In contrast (4) to xanthotoxin (the C-9 methoxy counterpart of III), bergapten failed to respond to treatment with one mole of bromine or to *N*-bromosuccinimide, but gave a tribromo derivative when reacted with ten moles of bromine. The product, assigned structure VIII, may be visualized as resulting from an addition of bromine to the furan double bond, to give IX, followed by dehydrobromination, to give X, and further bromination. This sequence finds parallel in the reported (5)





I, R_1 = R_3 = R_4 = R_5 = H, R_2 = CH_3

II, R_1 = R_3 = R_4 = H, R_2 = CH_3, R_5 = OCH_3

IV, R_1 = Br, R_2 = CH_3, R_3 = R_4 = R_5 = H

VI, R_1 = R_5 = Br, R_2 = CH_3, R_3 = R_4 = H

IX, R_1 = H, R_2 = CH_3, R_3 = R_4 = R_5 = Br

XI, R_1 = NO_2, R_2 = CH_3, R_3 = R_4 = R_5 = H

XIII, R_1 = Br, R_2 = CH_3, R_3 = R_4 = H, R_5 = OCH_3

XIX, R_1 = R_2 = R_3 = R_4 = H, R_5 = OH

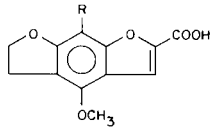
III, R_1 = R_2 = R_3 = R_4 = H

VIII, R_1 = H, R_2 = R_3 = R_4 = Br

X, R_1 = R_2 = H, R_3 = R_4 = Br

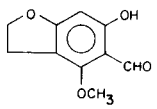
XV, R_1 = R_2 = R_3 = H, R_4 = OCH

XVI, R_1 = Br, R_2 = R_3 = H, R_4 = OCH_3

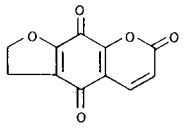


V, R = H; VII, R = Br; XIV, R = OCH_3

XVII, R = OCH_3, 5,6-unsaturated



XII



XVIII

behavior of benzofuran where the corresponding intermediates were actually isolated. The presence of an intact furan double bond in VIII was also evidenced by a strong ultraviolet absorption in the 240-270 nm region; in dihydrofurocoumarins absorption in this region would be considerably less intense (2).

Nitration of 6,7-dihydrobergapten (I) expectedly led to substitution at C-3 since the resulting product (XI) was found susceptible (6) to the action of alkali to give an *o*-salicylaldehyde constituted as XII.

Expectedly, the bromination of dihydroisopimpinellin (II) with one mole or excess of bromine gave one monobrominated product, formulated as XIII, in which the location of the halogen on C-3 was demonstrated by reac-

tion with alkali to give the dihydrofurocoumarilic acid XIV. Removal of the halogen atom from XIII was readily accomplished by treatment with activated zinc dust in ethanol. Bromination of isopimpinellin (XV) was found to give an intractable mixture of 3 products of which one was isolated and is believed to be the 3-bromo derivative (XVI) since it was affected by alkali treatment to give the corresponding furanocoumarilic acid (XVII). The action of nitric acid on dihydroisopimpinellin was found to give no nitration product; instead a quinone, formulated as XVIII, was obtained. The latter compound was reduced by treatment with stannous chloride-hydrochloric acid to the hydroquinone (XIX) which, upon methylation, afforded dihydroisopimpinellin (II).

EXPERIMENTAL

Melting points are uncorrected. Uv spectra were measured in ethanol using an M4QII Carl Zeiss instrument.

6,7-Dihydrobergapten (I).

A solution of bergapten (III, 1 g.) in ethanol (100 ml.) was shaken with 10% palladized charcoal (0.5 g.) under atmospheric pressure for 2 hours. Work-up in the usual manner gave needles (720 mg.) from aqueous methanol, m.p. 156-158° (reported (7) m.p. 160-161.5°).

3-Bromo-6,7-dihydrobergapten (IV).

A solution of 6,7-dihydrobergapten (I, 250 mg.) in chloroform (4 ml.) was treated with a bromine (0.055 ml., 1 mole) solution in chloroform (2 ml.). After 5 minutes, the reaction mixture was evaporated to a small volume with addition of 15 ml. of ethanol. The precipitated product (250 mg.) was crystallized from ethanol to give fine needles, m.p. 235-238°.

Anal. Calcd. for $C_{12}H_9BrO_4$: C, 48.48; H, 3.03. Found: C, 48.27; H, 3.10.

3,9-Dibromo-6,7-dihydrobergapten (VI).

A.

A solution of compound I (300 mg.) in chloroform (5 ml.) was allowed to stand for 5 minutes in admixture with bromine (10 moles). After the usual work-up, the product was obtained as colorless needles (270 mg., ethanol), m.p. 290-291° dec.

Anal. Calcd. for $C_{12}H_8Br_2O_4$: C, 38.32; H, 2.15. Found: C, 38.52; H, 2.21.

B.

Reaction of compound I (300 mg.) with bromine (2 moles) in chloroform solution in the manner described above afforded a crude yellowish mixture (350 mg.) shown by tlc to comprise two products (IV and VI). These were resolved by preparative-layer chromatography to give pure samples of both compounds identified by direct comparison.

C.

Treatment of 100 mg. of compound IV with 2 moles of bromine in chloroform solution afforded pure VI (120 mg.), m.p. and mixed m.p. 290-293°.

2′,3′-Dihydro-5,6-furo-4-methoxycoumarilic Acid (V).

3-Bromo-6,7-dihydrobergapten (IV, 200 mg.) was refluxed in 6*N* potassium hydroxide solution (14 ml.) for 0.5 hour. After acidification and extraction with chloroform, the extract was processed in the usual manner to give light greyish needles (ethanol), m.p. 205-208°.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.31; H, 3.79.

2′,3′-Dihydro-5,6-furo-4-methoxy-7-bromocoumarilic Acid (VII).

The 3,9-dibromo derivative (VI, 200 mg.) was treated in the same manner as above with 6*N* alkali. After the usual work-up, the crude product was crystallized from ethanol to give VII as colorless needles, m.p. 275-278°.

Anal. Calcd. for $C_{12}H_9BrO_5$: C, 46.06; H, 2.88. Found: C, 45.90; H, 2.50.

Debromination of Compound IV.

A solution of compound IV (100 mg.) in ethanol (15 ml.) was refluxed with activated zinc dust (1 g.) for 10 hours. After filtration, the alcoholic solution was concentrated to give 40 mg. of 6,7-dihydrobergapten (I), m.p. and mixed m.p. 161-162°.

A similar treatment of compound VI (the reflux period being extended to 16 hours) gave 6,7-dihydrobergapten (I) identified by direct comparison.

Bromination of Bergapten (III).

A solution of bergapten (III, 200 mg.) in chloroform (2 ml.) was treated with 10 moles of bromine and processed in the usual manner. After crystallization from ethanol, the product (VIII) was obtained as needles, m.p. 183-185°.

Anal. Calcd. for $C_{12}H_8Br_3O_4$: C, 31.58; H, 1.76. Found: C, 31.11; H, 2.11.

3-Nitro-6,7-dihydrobergapten (XI).

6,7-Dihydrobergapten (I, 1 g.) dissolved in glacial acetic acid (10 ml.) was treated with nitric acid (sp. gr. 1.41, 8 ml.) by dropwise addition while maintaining the reaction temperature at 20° with stirring. After 15 minutes, the mixture was poured onto ice-water and the product collected (1.1 g.) and then crystallized from ethanol to give compound XI (800 mg.) as yellow needles, m.p. 216-218°.

Anal. Calcd. for $C_{12}H_9NO_6$: C, 54.76; H, 3.45. Found: C, 55.55; H, 3.21.

4-Methoxy-5-formyl-6-hydroxy-2,3-dihydrobenzofuran (XII).

A solution of the previous compound (XI, 100 mg.) in 5% potassium hydroxide aqueous solution was allowed to stand at room temperature for 5 hours after which time the mixture was acidified with dilute hydrochloric acid. The greyish product which deposited was crystallized from ethanol to give pale yellowish plates, m.p. 120-121°.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.34; H, 5.46.

The 2,4-dinitrophenylhydrazone derivative was prepared, m.p. 275-280°.

3-Bromo-6,7-dihydroisopimpinellin (XIII).

6,7-Dihydroisopimpinellin (II, m.p. 156-157°, prepared as described in the literature (7) (250 mg.) was treated with 1 mole of bromine under the usual conditions. After work-up, the bromo derivative (XIII) was obtained as colorless needles (methanol), m.p. 232-235°.

Anal. Calcd. for $C_{13}H_{11}BrO_5$: C, 47.72; H, 3.33. Found: C, 47.37; H, 3.50.

2′,3′-Dihydro-5,6-furo-4,7-dimethoxycoumarilic Acid (XIV).

The bromo compound described above (XIII, 200 mg.) was

refluxed with 6*N* potassium hydroxide (14 ml.) for 0.5 hour. After acidification with dilute sulfuric acid and work-up in the usual manner, the product was crystallized from ethanol to give colorless needles, m.p. 275-279°.

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.23; H, 4.76.

Debromination of the above compound (XIII, 100 mg.) was performed by treatment with activated zinc dust in ethanol as described before to give 6,7-dihydroisopimpinellin (II, 40 mg.), m.p. and mixed m.p. 156-157°.

3-Bromoisopimpinellin (XVI).

Isopimpinellin (XV, 250 mg.) solution in chloroform (5 ml.) was treated with bromine (10 moles) in the manner described before. After the usual work-up, the crude reaction product (shown by tlc to comprise 3 products) was subjected to preparative-layer chromatography whereupon one component was isolated (110 mg.) and obtained as colorless needles, m.p. 208-211°.

Anal. Calcd. for $C_{13}H_9BrO_5$: C, 48.00; H, 2.77. Found: C, 48.61; H, 2.97.

6,7-Dihydropsoralenequinone (XVIII).

6,7-Dihydroisopimpinellin (II, 500 mg.) dissolved in acetic acid (5 ml.) was treated with nitric acid (sp. gr. 1.41, 4 ml.) added dropwise while stirring and maintaining the temperature at 20° during 15 minutes. After pouring the reaction mixture on ice-water, the deposited product (200 mg.) was collected and crystallized from acetic acid to give orange plates, m.p. 217-220°.

Anal. Calcd. for $C_{11}H_6O_5$: C, 60.56; H, 2.77. Found: C, 60.43; H, 3.01.

6,7-Dihydropsoralenehydroquinone (XIX).

The quinone (above, 250 mg.) was finely ground into a paste with 2 ml. of ethanol. This was treated with a solution of stannous chloride (2 g.) in a mixture of concentrated hydrochloric acid (3 ml.) and alcohol (3 ml.) which was added gradually with stirring. The product (200 mg.) which deposited crystallized from ethanol as needles, m.p. 270-275°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.60; H, 3.74.

The latter compound was methylated in the usual manner (methyl iodide-potassium carbonate-acetone) to give 6,7-dihydroisopimpinellin (II), m.p. and mixed m.p. 156-157°.

REFERENCES

(1) M. A. Pathak, J. H. Fellman and K. D. Kaufman, *J. Invest. Dermat.*, **35**, 165 (1960).

(2) E. A. Abu-Mustafa and M. B. E. Fayez, *J. Org. Chem.*, **26**, 161 (1961).

(3) E. A. Abu-Mustafa and M. B. E. Fayez, *J. Chem. UAR*, **8**, 41 (1965).

(4) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1858).

(5) R. Stroemer and B. Kahlert, *Ber.*, **35**, 1633 (1902).

(6) S. M. Sethna and N. M. Shah, *Chem. Revs.*, **36**, 27 (1945); A. Clayton, *J. Chem. Soc.*, 1937 (1910).

(7) J. Trojanek, J. Hodkova and Z. Cekan, *Planta Medica*, **9**, 200 (1961).