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A Convenient Synthesis of Psoralen Derivatives: Psoralen, 4-Methyl-psoralen and 4-Phenyl-psoralen

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A convenient synthesis of psoralen derivatives, viz., 7*H*-furo [3.2—g] [1] benzopyran-7-one (psoralen), 5-methyl-7*H*-furo [3.2—g] [1] benzopyran-7-one(4-methyl-psoralen) and 5-phenyl-7 *H*-furo [3.2—g] [1] benzopyran-7-one-(4-phenyl-psoralen) by blocking the 8-position of the starting compounds with iodine, subsequent *Claisen* migration followed by cyclisation is described

(Keywords: Claisen migration; Coumarins; Psoralen derivatives)

Ein einfacher Syntheseweg zu Psoralen-Derivaten: Psoralen, 4-Methyl-psoralen und 4-Phenyl-psoralen

Zur Synthese der Titelverbindungen wird die 8-Position des als Ausgangsmaterial dienenden 7-Hydroxy-benzopyranons mit Jod blockiert, dann erfolgt Allylierung und nach einer *Claisen*-Wanderung die Cyclisierung.

The occurrence of psoralen derivatives and their physiological activity[1,2] prompted us to device a convenient method for their synthesis. A few syntheses[3–11] of these coumarins are known but these involve a number of steps and the overall yield is poor.

It has been long known[12] that 7-allyl ether of 2 *H*-1-benzopyran-2-ones on *Claisen* migration gives exclusively 8-allyl isomers. But if the 8-position is substituted[13], the corresponding 6-allyl isomers are obtained, which on oxidation with OsO_4—KIO_4 followed by cyclisation afford 8-substituted psoralens. This method could not be used for the synthesis of psoralens having the 8-position unsubstituted. However these psoralens have been synthesised by very tedious method[3–11]. A convenient method has now been developed for the synthesis of such psoralen derivatives by blocking the 8-position of 2 *H*-1-benzopyran-2-ones with an easily introducable and removable group like iodine. The

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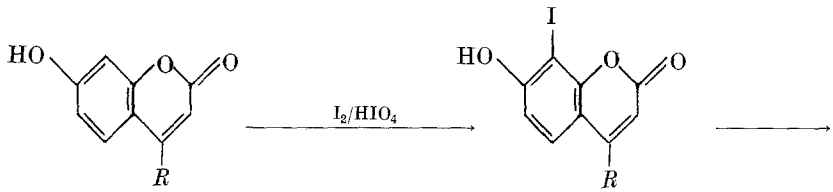
required intermediate, viz., 7-allyloxy-8-iodo-2 *H*-1-benzopyran-2-one derivatives were prepared by selective iodination of 7-hydroxy-2 *H*-1-benzopyran-2-ones by iodine-periodic acid followed by allylation. Using this method we report the synthesis of 7 *H*-furo [3.2—g] [1] benzopyran-7-one (**1**), 5-methyl-7 *H*-furo [3.2—g] [1] benzopyran-7-one (**2**) and 5-phenyl-7 *H*-furo [3.2—g] [1] benzopyran-7-one (**3**).

Psoralen has been synthesised as follows: Iodination of 7-hydroxy-2 *H*-1-benzopyran-2-one[14] with iodine-periodic acid gave 7-hydroxy-8-iodo-2 *H*-1-benzopyran-2-one (**4**), which on allylation afforded the required intermediate 7-allyloxy-8-iodo-2 *H*-1-benzopyran-2-one (**5**). **5** on *Claisen* migration by refluxing in *N*,*N*-dimethyl-aniline gave an alkali soluble product without iodine, indicating that iodine was removed in the above reaction; the structure assigned was 6-allyl-7-hydroxy-2 *H*-1-benzopyran-2-one (**6**). Absence of iodine and allyl group in the 6-position is proved by ^{1}H NMR spectroscopy, which showed two singlets for *p*-coupled H-5 and H-8 protons. **6** on oxidation with OsO_4—KIO_4 followed by cyclisation of the intermediate phenyl acetaldehyde with polyphosphoric acid afforded **1**.



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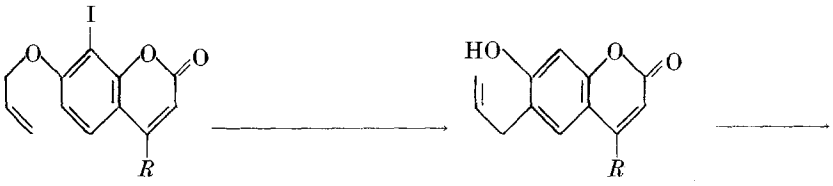
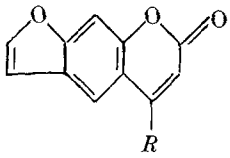


5, 8, 10 **6, 9, 12**



1—3

1, 4—6, R=H
2, 7—9, R=CH_3
3, 10—12, R=C_6H_5

Similarly, 4-methyl-psoralen (**2**) has been synthesised starting from 7-hydroxy-8-iodo-4-methyl-2*H*-1-benzopyran-2-one (**7**), which was obtained by the iodination of 7-hydroxy-4-methyl-2*H*-1-benzopyran-2-one[15]. Its allylation, followed by *Claisen* migration of the formed 7-allyloxy-4-methyl-2*H*-1-benzopyran-2-one (**8**) gave 6-allyl-7-hydroxy-2*H*-1-benzopyran-2-one (**9**), the structure of which was in agreement with its NMR spectra. Its oxidation with OsO_4—KIO_4 followed by cyclisation with polyphosphoric acid afforded **2**.

Using this procedure 4-phenyl-psoralen (**3**) has also been synthesised starting from 7-allyloxy-8-iodo-4-phenyl-2*H*-1-benzopyran-2-one (**10**), obtained by iodination of 7-hydroxy-4-phenyl-2*H*-1-benzopyran-2-one[16] followed by allylation of the formed 7-hydroxy-8-iodo-4-phenyl-2*H*-1-benzopyran-2-one (**11**). Its *Claisen* migration in *N*,*N*,-dimethyl-aniline, gave 6-allyl-7-hydroxy-2*H*-1-benzopyran-2-ones (**12**), which on oxidation with OsO_4—KIO_4 and cyclisation yielded **3**.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. The NMR spectra were measured on a Varian A-60 and R-32 spectrometers with $SiMe_4$ as internal reference.

7H-furo [3.2—g] [1] benzopyran-7-one (Psoralen) (**1**)

(a) *7-Hydroxy-8-iodo-2H-1-benzopyran-2-one* (**4**)

7-Hydroxy-2*H*-1-benzopyran-2-one[14] (2 g) was dissolved in the minimum amount of alcohol and to this solution iodine (1.32 g) and periodic acid (0.56 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give the coumarin **4** (2.2 g, 62%). It crystallized from alcohol as yellow needles, m.p. 210–212° (Found: C 37.4; H 1.8%. $C_9H_5O_3I$ requires C 37.5; H 1.8%).

Its acetate (prepared by acetic anhydride—pyridine) melted at 182–183°. NMR ($CDCl_3$): δ 2.45, s, 3 H, 7-O*Ac*; 6.42, d, 1 H, $J_0 = 9.5$ Hz, H-3; 7.14, d, 1 H, $J_0 = 10$ Hz, H-6; 7.68, d, 1 H, $J_0 = 10$ Hz, H-5; 8.10, d, 1 H, $J_0 = 9.5$ Hz, H-4.

(b) *7-Allyloxy-8-iodo-2H-1-benzopyran-2-one* (**5**)

A solution of **4** (1.0 g) in dry acetone (75 ml) was refluxed for 6 h with allyl bromide (0.42 ml) in presence of anhydrous potassium carbonate (2.0 g). The solution was filtered. The solvent was distilled off and treated with ice to give **5**, which crystallised from methanol as colourless prisms (0.9 g, 78%), m.p. 157–158° (Found: C 43.7; H 2.7%. $C_{12}H_9O_3I$ requires C 43.8; H 2.7%). NMR ($CDCl_3$): δ 4.78, d, 2 H, $J = 5.5$ Hz, $OC\mathbf{H}_2$—$CH=CH_2$, 5.64, m, 2 H, OCH_2—$CH=C\mathbf{H}_2$; 6.02, m, 1 H, OCH_2—$C\mathbf{H}=CH_2$; 6.24, d, 1 H, $J_0 = 9.5$ Hz, H-3; 6.91, d, 1 H, $J_0 = 10$ Hz, H-6; 7.65, d, 1 H, $J_0 = 10$ Hz, H-5 and 8.06, d, 1 H, $J_0 = 9.5$ Hz, H-4.

(c) *6-Allyl-7-hydroxy-2H-1-benzopyran-2-one* (**6**)

The coumarin **5** (0.5 g) was refluxed with N,N-dimethyl-aniline (5 ml) for 6 h. The reaction mixture was cooled and poured over ice cold hydrochloric acid. The separated solid was filtered, washed with water and crystallised from methanol as yellow crystals: **6** (0.25 g, 82%), m.p. 168–170°. Found: C 71.1; H 4.9%. $C_{12}H_{10}O_3$ requires: C 71.2; H 5.0%. NMR (CD_3COCD_3): δ 3.35, d, 2 H,

$J = 7$ Hz, —C**H**$_2$—CH=CH$_2$; 5.10, m, 2 H, —CH$_2$—CH=C**H**$_2$; 5.95, m, 1 H, CH$_2$—C**H**=CH$_2$; 6.22, d, 1 H, $J_0 = 9.5$ Hz, H-3; 7.02, s, 1 H, H-8; 7.52, s, 1 H, H-5; 8.02, d, 1 H, $J_0 = 9.5$ Hz, H-4.

(d) *7-H-furo [3.2—g] [1] benzopyran-7-one (Psoralen)* (**1**)

The above coumarin **6** (250 g) in ethyl acetate (80 ml) containing an equal volume of water was stirred with osmium tetraoxide (60 mg). The mixture was shaken for 1.5 h and during this period potassium periodate (2 g) added in small lots. The reaction mixture was stirred for 2 h more, the ethyl acetate layer separated and the aqueous solution extracted with more ethyl acetate. The combined ethyl acetate was washed well with water, dried (Na_2SO_4) and distilled. The residue consisting of the intermediate phenyl acetaldehyde was heated on a boiling water bath with polyphosphoric acid (10 ml) for 20 min. and then poured over crushed ice. The separated solid was taken up in ether, extracted, washed successively with aqueous sodium carbonate (5%), water, dried (Na_2SO_4) and then distilled. The residue crystallised from benzene-petroleum ether to give **1** (125 mg, 54%) as yellow needles, m.p. 161-162°. (Found: C 70.5; H 3.3%. $C_{11}H_6O_3$ requires C 70.4; H 3.2%). NMR ($CDCl_3$): δ 6.18, d, 1 H, $J_0 = 9.5$ Hz, H-6; 6.72, dd, 1 H, $J_{\beta,\alpha} = 2.5$ Hz, $J_{\beta,9} = 1$ Hz, H-β; 7.25, d, 1 H, $J_{9,\beta} = 1$ Hz, H-9; 7.62, d, 1 H, $J_{\alpha,\beta} = 2.5$ Hz, H-α; 7.72, s, 1 H, H-4; 8.06, d, 1 H, $J_0 = 9.5$ Hz, H-5.

5-Methyl-7 H-furo [3.2—g] [1] benzopyran-7-one (4-Methyl-psoralen) (**2**)

(a) *7-Hydroxy-8-iodo-4-methyl-2 H-1-benzopyran-2-one* (**7**)

7-Hydroxy-4-methyl-2 *H*-1-benzopyran-2-one[15] (2 g) was dissolved in a minimum amount of alcohol and to this solution, iodine (1.24 g) and periodic acid (0.52 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give **7** (2.5 g, 72%). It crystallized from alcohol as light yellow needles, m.p. 219-220° (Found: C 39.6; H 2.3%. $C_{10}H_7O_3I$ requires C 39.7; H 2.3%). Its acetate (prepared by acetic anhydride—pyridine) melted at 180-181°. NMR ($CDCl_3$): δ 2.5, bs, 6 H, 4-CH$_3$ and 7-O*Ac*; 6.48, s, 1 H, H-3; 7.34, d, 1 H, $J_0 = 9.5$ Hz, H-6 and 7.85, d, 1 H, $J_0 = 9.5$ Hz, H-5.

(b) *7-Allyloxy-8-iodo-4-methyl-2 H-1-benzopyran-2-one* (**8**)

A solution of the coumarin **7** (1.0 g) in dry acetone (75 ml) was refluxed with allyl bromide (0.32 ml) in presence of anhydrous potassium carbonate (2.0 g) for 6 h. Working up of the reaction mixture gave a solid, which crystallized from ethanol as colourless prisms, (0.8 g, 70%), m.p. 164-165°. (Found: C 45.7; H 3.3%, $C_{13}H_{11}O_3I$ requires C 45.6; H 3.2%). NMR ($CDCl_3$): δ 2.42, s, 3 H, 4-CH$_3$; 4.76, d, 2 H, $J = 5$ Hz, OC**H**$_2$CH=CH$_2$; 5.6, m, 2 H, OCH$_2$CH=C**H**$_2$; 6.0, m, 1 H, OCH$_2$C**H**=CH$_2$; 6.19, s, 1 H, H-3; 6.85, d, 1 H, $J_0 = 9.5$ Hz, H-6; 7.61, d, 1 H, $J_0 = 9.5$ Hz, H-5.

(c) *6-Allyl-7-hydroxy-4-methyl-2 H-1-benzopyran-2-one* (**9**)

The above coumarin **8** (0.5 g) was refluxed with *N*,*N*-dimethyl-aniline (5 ml) for 6 h. The reaction mixture was cooled and poured over ice cold hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from benzene—petroleum ether as greenish yellow needles (240 mg, 76%), m.p. 155-156° (Found: C 72.1; H 5.4%; $C_{13}H_{12}O_3$ requires C 72.2; H 5.6%). Its acetate

(prepared by acetic anhydride—pyridine) melted at 133-134°. NMR ($CDCl_3$): δ 2.35, s, 3 H, 7-O*Ac*, 2.44, s, 3 H, 4-CH_3; 3.34, d, 2 H, J = 7 Hz, $CH_2CH=CH_2$; 5.06, m, 2 H, $CH_2CH=CH_2$; 5.85, m, 1 H, $CH_2CH=CH_2$; 6.25, s, 1 H, H-3; 7.08, s, 1 H, H-8; 7.45, s, 1 H, H-5.

(d) *5-Methyl-7 H-furo [3.2—g] [1] benzopyran-7-one (4-Methyl-psoralen)* (**2**)

The above coumarin **9** (250 mg) in ethyl acetate (80 ml) containing an equal volume of water was stirred with osmium tetraoxide (60 mg). The mixture was shaken for 1.5 h and during this period potassium periodate (2 g) added in small lots. The reaction mixture was stirred for 2 h more. Working up the reaction as for **1** gave the intermediate phenylacetaldehyde, which cyclised with *PPA* (10 ml) to yield **2** (100 mg, 43%). It crystallized from benzene—petroleum ether as colourless prisms, m.p.178-179° (Found: C 72.1; H 4.1%). $C_{12}H_8O_3$ requires C 72.0; H. 4.0%. NMR ($CDCl_3$): δ 2.48, s, 3 H, 5-CH_3; 6.25, s, 1 H, H-6; 6.75, dd, 1 H, $J_{\beta,\alpha}$ = 2.5 Hz, $J_{\beta,9}$ = 1 Hz, H-β; 7.35, d, 1 H, $J_{9,\beta}$ = 1 Hz, H-9; 7.68, d, 1 H, $J_{\alpha,\beta}$ = 2.5 Hz, H-α; 7.8, s, 1 H, H-4; Infrared ν_{max} (KBr): 1,715 (C=O), 1,625 (C=C), 1,080 and 765 cm^{-1} (furan ring).

5-Phenyl-7 H-furo [3.2—g] [1] benzopyran-7-one (4-phenyl-psoralen (**3**)

(a) *7-Hydroxy-8-iodo-4-phenyl-2 H-1-benzopyran-2-one* (**11**)

7-Hydroxy-4-phenyl-2 *H*-1-benzopyran-2-one[16] (2 g) was dissolved in minimum amount of alcohol and to this solution iodine (0.91 g) and periodic acid (0.39 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give coumarin **11** (2.5 g, 81%). It crystallized from alcohol as light yellowish needles m.p. 263-264° (Found: C 49.3; H 2.4%. $C_{15}H_9O_3I$ requires C 49.4; H 2.5%). Its acetate (prepared by acetic anhydride—pyridine) melted at 178-179°. NMR ($CDCl_3$): δ 2.44, s, 3 H, 7-O*Ac*; 6.38, s, 1 H, H-3; 7.05, d, 1 H, J_0 = 9.5 Hz, H-6; 7.32, d, 1 H, J_0 = 9.5 Hz, H-5; 7.4, bs, 5 H, 4-*Ph*.

(b) *7-Allyloxy-8-iodo-4-phenyl-2 H-1-benzopyran-2-one* (**10**)

A solution of above coumarin **11** (1.0 g) in dry acetone (75 ml) was refluxed with allyl bromide (0.28 ml) in the presence of anhydrous potassium carbonate (2.0 g) for 6 h. Working up the reaction mixture gave a solid, which crystallized from methanol as colourless prisms (0.8 g, 72%), m.p. 148-149° (Found: C 53.3%; H 3.2%. $C_{18}H_{13}O_3I$, requires C 53.4; H 3.2%). NMR ($CDCl_3$): δ 4.85, d, 2 H, J = 5 Hz, $OCH_2CH=CH_2$; 5.58, m, 2 H, $OCH_2CH=CH_2$; 6.11, m, 1 H, $OCH_2CH=CH_2$; 6.4, s, 1 H, H-3; 6.92, d, 1 H, J_0 = 9.5 Hz, H-6; 7.54, d, 1 H, J_0 = 9.5 Hz, H-5; 7.7, s, 5 H, 4-*Ph*.

(c) *6-Allyl-7-hydroxy-4-phenyl-2 H-1-benzopyran-2-one* (**12**)

The coumarin **10** (0.5 g) was refluxed with *N*,*N*-dimethyl-aniline (5 ml) for 6 h. The reaction mixture was cooled and poured over ice cold hydrochloric acid. The separated solid was filtered, washed with water and crystallized from methanol to give greenish yellow crystals of **12** (250 mg, 72%), m.p. 223-224° (Found: C 77.5; H 5.0%. $C_{18}H_{14}O_3$ requires C 77.6; H 5.0%). Its acetate (prepared by acetic anhydride—pyridine) melted at 85-86°. NMR ($CDCl_3$): δ 2.36, s, 3 H, 7-O*Ac*; 3.29, d, 2 H, J = 7 Hz, CH_2—$CH=CH_2$; 4.9, m, 2 H, $CH_2CH=CH_2$; 5.5, m, 1 H, $CH_2CH=CH_2$; 6.34, s, 1 H, H-3; 7.18, s, 1 H, H-8; 7.35, s, 1 H, H-5; 7.5, s, 5 H, 4-*Ph*.

(d) *5-Phenyl-7-H-furo [3.2—g] [1] benzopyran-7-one (4-Phenyl-psoralen)* (**3**)

The above coumarin **12** (250 mg) in ethyl acetate (80 ml) containing an equal volume of water was stirred with osmium tetraoxide (60 mg). The mixture was shaken for 1.5 h and during this period sodium periodate (2 g) added in small lots. Work up as for **1** yielded the intermediate phenylacetaldehyde, which cyclised with *PPA* (10 ml) to give **3** (125 mg, 53%). It crystallized from benzene—petroleum ether as light yellow needles, m.p. 181–182° (Found: C 77.7; H 3.8%. $C_{17}H_{10}O_3$ requires C 77.8; H 3.8%). NMR ($CDCl_3$): δ 6.2, s, 1 H, H-6; 6.62, dd, 1 H, $J_{\beta,\alpha} = 2.5$ Hz, $J_{\beta,9} = 1$ Hz, H-β; 7.2, d, 1 H, $J_{9,\beta} = 1$ Hz, H-9; 7.36, s, 5 H, 5-*Ph*; 7.51, d, 1 H, $J_{\alpha,\beta} = 2.5$ Hz, H-α; 7.56, s, 1 H, H-4. Infrared ν_{max} (KBr): 1,715 (C=O), 1,625 (C=C), 1,082 and 765 cm^{-1} (furan ring).

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