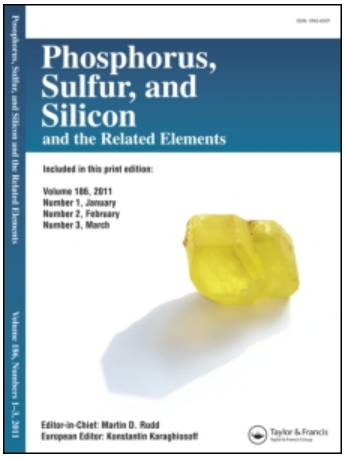

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ORGANOPHOSPHORUS CHEMISTRY 25.[1] THE UTILIZATION OF WITTIG REAGENTS IN LACTONE RING FORMATION. APPLICATION TO THE SYNTHESIS OF LINEAR FUROCOUMARINS AND PYRANOCOUMARINS

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ORGANOPHOSPHORUS CHEMISTRY 25.[1] THE UTILIZATION OF WITTIG REAGENTS IN LACTONE RING FORMATION. APPLICATION TO THE SYNTHESIS OF LINEAR FUROCOUMARINS AND PYRANOCOUMARINS†

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A new and improved method for the preparation of linear furocoumarins (7a,b) and pyranocoumarins (10a,b) in high yields, is described. It depends upon reacting ylid-phosphoranes (5) with suitably substituted benzofuran-, (3) or the benzo-γ-pyrone-(4) moiety. Formation of the target compounds (7 and 10) is assumed to proceed via lactonization of *cis* alkyl α-hydroxycinnamate intermediates of types 6 and 9, respectively. The *trans* analogues 8 do not lactonize to 10 even upon heating in boiling toluene. The new compounds have been characterized by their spectroscopic data (IR, PMR, ^{13}C NMR) and elementary analyses.

Key words: Wittig-reaction; lactonization; preparation of linear furocoumarins, pyranocoumarins.

INTRODUCTION

Our interest was directed toward the use of furocoumarins (furobenzopyrans, cf. 1) as photo-chemotherapeutic agents in the systemic treatment of psoriasis[2–4] and as effective photo-reactive cross linkage reagents for nucleic acids.[5] Besides, many of them are known to evoke significant tuberculostatic[6] and molluscicidal[7] activities. The attention paid to pyranocoumarins (benzodipyrans) was attributed to otherwise similar reasons.[8]

Despite the presence of many approaches for the synthesis of furocoumarins and pyranocoumarins, most of these methods are of limited scope, require many steps for precursor synthesis and/or proceed in low yields.[2,8] As part of a running study on structure-activity relationships, we sought convenient and general method for synthesis of furocoumarins and pyranocoumarins. Both as a model and because of its intrinsic importance, we focused our research on an improved approach for building a lactone ring on a suitably substituted benzofuran ring (3) and/or benzopyran moiety (4) by making use of the stabilized ylid-phosphoranes (Wittig-reagents, 5). The requisite starting materials (3a,b) are readily accessible through alkali hydrolysis of the appropriate naturally occurring furochromones (visnagin, 2a or khellin, 2b).[9] Meanwhile, compounds 4a,b are essentially produced by the furan ring rupture of compounds 2a,b under the influence of oxidizing agents.[10,11]

†Dedicated to Professor M. Sidky on the occasion of his 63rd birthday.
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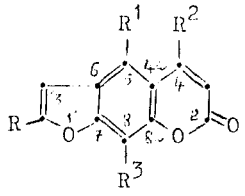
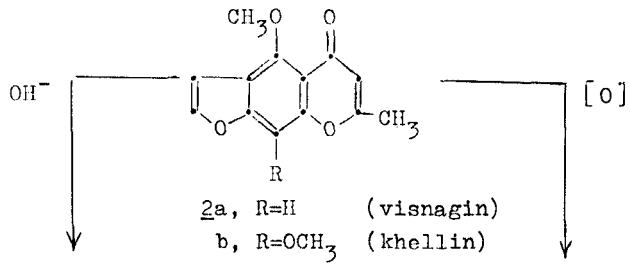
RESULTS AND DISCUSSION

We have found that the reaction of visnaginone (3a) with carbmethoxymethyl-enetriphenylphosphorane (5a) proceeds in boiling toluene to give 4-methoxy-5-methyl-7H-furo(3,2-g)-1-benzopyran-7-one (7a) (5-methyl-bergapten) as colorless crystalline needles in 95% yield. Triphenylphosphine oxide (TPPO) was also isolated and identified[12] in this reaction. Compound 7a and TPPO were similarly produced upon reacting 3a with 5b under the same conditions. In the same sense, 4,9-dimethoxy-5-methyl-7H-furo(3,2-g)-1-benzopyran-7-one (5-methyl-isopimpi-



1a, $R=R^1=R^2=R^3=H$ (psoralene)
b, $R=R^1=R^2=H$; $R^3=OCH_3$ (xanthotoxin)
c, $R=R^2=R^3=H$; $R^1=OCH_3$ (bergapten)
d, $R=R^2=H$; $R^1=R^3=OCH_3$ (isopimpinellin)
e, $R=R^2=R^3=CH_3$; $R^1=H$



2a, R=H (visnagin)
b, $R=OCH_3$ (khellin)

3a, R=H (visnaginone)
b, $R=OCH_3$ (khellinone)

4a, R=H
b, $R=OCH_3$

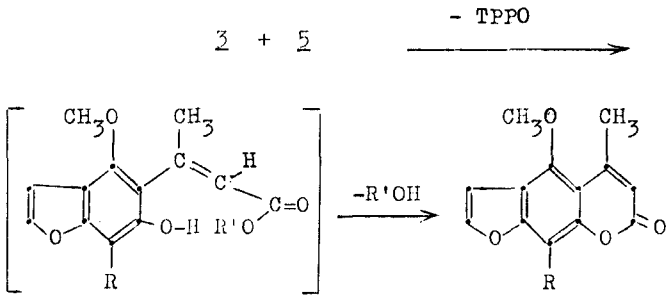
5a, $R=COOCH_3$
b, $R=COOC_2H_5$

SCHEME 1

nellin, 7b) was produced in 95% yield by reacting khellinone (3b) with 5a and/or 5b. Structural support for compounds 7a,b were based upon the following evidence: (a) correct elementary analyses and molecular weight determination (MS) were recorded for both compounds. (b) they are insoluble in dilute aqueous alkali and exhibit no color reaction with alcoholic ferric chloride solution. (c) The IR spectrum of 7b, taken as an example (in KBr, cm^{-1}) showed on OH bands in the 3500–3200 region. The spectrum however showed strong absorption bands at 1700 (lactone-carbonyl), 1610, 1591 (C=C) and 1350 (C—O, stretching). (d) the ^1H NMR spectrum of 7b (in $CDCl_3$, δ ppm scale) showed protons of the CH_3 group as a doublet (J_{HH} = 2.5 Hz) at 2.35 due to allylic coupling[13,14] with the vinyl proton on C-6 which appeared as an ill-defined quartet at 6.05. The furan ring protons gave two doublets (each with J_{HH} = 2.5 Hz) at 7.60 (HC-2) and at 6.85 (HC-3). The signals present at 4.05 (3H) and at 4.15 (3H) were attributable to protons of the OCH_3 groups. The distinguishing features of the ^{13}C NMR spectrum of 7b were presence of signals at 162.3 (C=0), 147.1 (—C—CH_3), 25.7 (—C—CH_3) and 63.2, 63.4 for the carbon atoms of both OCH_3 groups (cf. experimental). (e) the UV-spectrum of 7b (in absolute ethanol) showed absorption maxima which are similar to those recorded for naturally occurring furocoumarins.[8,15] It showed bands at 195 nm (benzene), 250 nm (coumarin) and 340 nm (α-pyrone), respectively.

It is evident that formation of compounds 7 involves the intermediary of an unstable α-hydroxycinnamic acid ester species of type 6 (essentially in the *cis* form) which spontaneously lactonizes to 7 via displacement of an alcohol (R'OH) molecule.

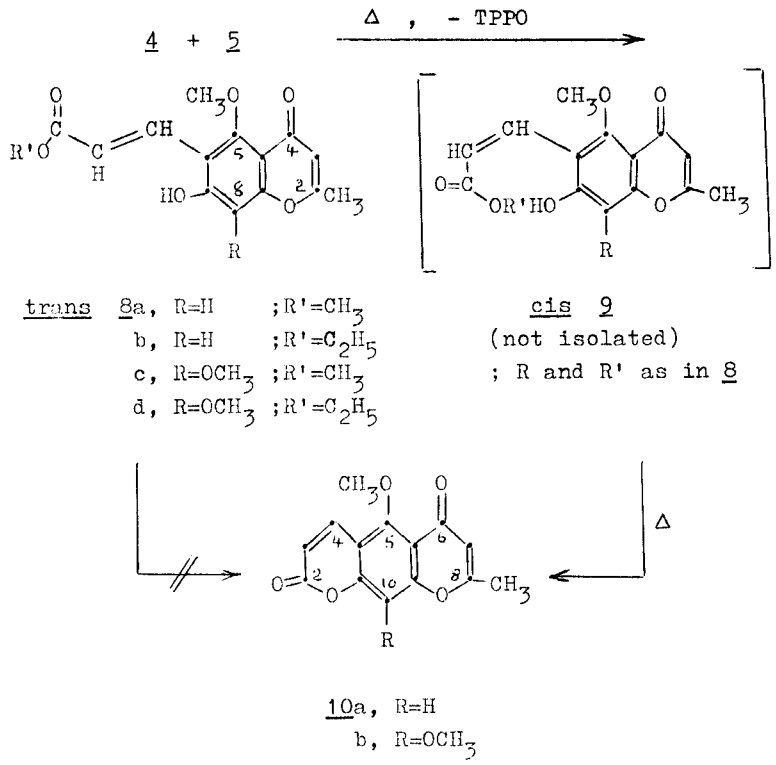
6-Formyl-7-hydroxy-5-methoxy-2-methylchromone (4a) was found to react with the ylid-phosphorane 5a in boiling toluene, to give TPPO along with a mixture of two main products (A + B), which could be resolved by column chromatography. The first product (A) was formulated as 5-methoxy-8-methyl-2,6-dioxo-2H,6H-benzo 1,2-b:5,4-b'-dipyran (10a) for the following reasons: (a) its elemental analyses and molecular weight determination (MS) corresponded to $C_{14}H_{10}O_5$, (b) it is insoluble in dilute aqueous alkali and gives no color reaction with alcoholic ferric



cis 6, R=H or OCH_3
R'=CH_3 or C_2H_5
(not isolated)

7a, R=H
b, R=OCH_3

SCHEME 2



SCHEME 3

chloride solution, (c) its IR spectrum (in KBr, cm^{-1}) showed two strong absorption bands at 1745 and 1655 which coincide with lactone-carbonyl and γ-pyrone-carbonyl group absorptions, respectively, (d) the ^1H NMR spectrum of 10a showed protons of the CH_3 group on the γ-pyrone nucleus as a doublet (J_{HH} = 2.5 Hz) at δ 2.24 due to allylic coupling with the vinyl proton which appeared as a diffused quartet at 5.95 ppm. Protons of the α-pyrone ring (2H) appeared as two doublets (each with J_{HH} = 8 Hz) at 7.75 and 6.80 ppm. The aromatic proton appeared as a singlet at δ 6.64 while the singlet due to protons of the OCH_3 group was shown at δ 3.70 ppm.

The second product (*B*) was formulated as 7-hydroxy-5-methoxy-2-methylchromone-6-acrylic acid methyl ester (8a, *trans* form). Its elemental analyses and molecular weight determination (MS) agreed with the molecular formula, $C_{15}H_{14}O_6$. Its IR spectrum (in KBr, cm^{-1}) showed strong absorption bands at 3270 (OH, free), 1710 (C=O, ester), 1645 (C=O, γ-pyrone), 1550 (C=C) and at 1270 (C—O, stretching). Its ^1H NMR spectrum was also compatible with the proposed structure. Its characteristic features were appearance of protons of the exocyclic ethylenic linkage as a pair of doublets (each with J_{HH} = 8 Hz) at δ 8.08 and 6.64 ppm while protons of the $COOCH_3$ group gave a singlet at δ 3.95 and the OH proton was shown as a broad singlet (exchangeable with D_2O) at δ 10.20 ppm. Compounds 10a and 8b were similarly obtained by reacting 4a with 5b.

It is worthy to report that the reaction of reagents 5a,b with benzofurans 3a,b

to give 7a,b or with benzopyrones 4a,b to give 8a–d (and/or 10a,b) is temperature-dependent. Thus, while it proceeds in toluene at the reflux temperature to give the final products, no reaction was observed when the reactants were allowed to stand in the same solvent at ambient temperature even for 12 hr.

Apparently, formation of compounds 10a,b involves the intermediate formation of an alkyl-α-hydroxycinnamate product of type 9 (essentially in the *cis* form) which readily lactonizes to give 10 upon displacement of an R'OH molecule. Concurrent with formation of compounds 9, their *trans* analogues 8 are also produced which do not lactonize to give 10. Since stereochemical factors are essential requisites for the ring closure of heterocyclic precursors,[16] it appears that conversion of 9 to 10 is a stereoselective process. In favour of this idea is the finding that 8a (which is assumed to be the *trans* analogue of 9a) is recovered practically unchanged upon heating alone in boiling toluene even for 12 hr.

CONCLUSIONS

The reaction of stabilized ylid-phosphoranes 5a,b with 3a,b and/or with 4a,b represents a novel approach for lactonization of benzofurans and benzo-γ-pyrones to produce linear furocoumarins (7a,b) and/or pyranocoumarins (10a,b), respectively in high yields. This new trend supplements the wide utilization of Wittig-reagents like 5 in preparative work.[17,18] Lactonization of the presumably formed alkyl α-hydroxycinnamate intermediates (6 and/or 9) to the final products seems to be a stereospecific process and simulates the biosynthetic approach for the elaboration of many naturally occurring coumarins and furocoumarins (cf. 1).[2] Thus, the findings of the present investigation might foreshadow the existence of furocoumarins 7a,b in higher plants (e.g. umbelliferae, rutaceae and leguminosae families) and the probability of their isolation from these plants, in future. Moreover, the present study introduces a new and simple approach for the interconversion of naturally occurring furochromones (2) to furocoumarins (7) and/or pyranocoumarins (10).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were run at a Perkin Elmer Infracord Spectrometer Model 197 (Grating) in KBr. The ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker Spectrometer Model WH-90 and the chemical shifts are recorded in δ ppm scale. The mass spectra were done at 70 eV with MS-50 Kratos (A.E.I.) Spectrometer provided with data system. The ylid-phosphoranes (5a)[19] and (5b)[20] were prepared according to known procedures. Column chromatography was performed using silica gel G. (E. Merck).

Preparation of 4-methoxy-5-methyl-7H-furo(3,2-g)-1-benzopyran-7-one (7a). A mixture of visnaginone 3a (0.62 g; 0.003 mol) and 5a (1.00 g; 0.003 mol) in dry toluene (50 ml) was refluxed for 3 hr. After cooling, the precipitated material was filtered off (filtrate A), dried and recrystallized from toluene to give 7a as colorless needles, m.p. 170°C (yield: 0.65 g; 95%).

The solvent was evaporated from filtrate A, in *a vacuo*, till dryness. The residue (0.8 g; 95%) was recrystallized from ligroin to give colorless needles proved to be triphenylphosphine oxide (TPPO) (m.p., mixed m.p. and comparative IR spectra).

Compound 7a (ca. 95%) and TPPO (95%) were also obtained and identified upon reacting 3a (0.003 mol) with 5b (0.003 mol) in refluxing toluene (50 ml) for 3 hr.

In a similar manner, 4,9-dimethoxy-5-methyl-7H-furo-(3,2-g)-1-benzopyran-7-one (7b) was obtained in ca. 95% yield along with TPPO (ca. 95% yield) upon refluxing khellinone 3b (0.003 mol) and 5a

TABLE I

Physical and analytical data of compounds 7a,b, 8a–d and 10a,b

Compound	Yield in %	m.p. °C	Mol. Form (M. Wt.)	Anal. Found/Calcd. % C%	Anal. Found/Calcd. % H%	M^+ (m/z%)
7a	95	170[a]	$C_{13}H_{10}O_4$ (230.2)	67.63 67.82	4.23 4.37	230 (100)
7b	95	209[b]	$C_{14}H_{12}O_5$ (260.2)	64.47 64.61	4.52 4.64	260 (100)
8a	95[c]	250[b]	$C_{15}H_{14}O_6$ (290.2)	61.73 62.06	4.52 4.86	290 (20)
8b	95[c]	248[b]	$C_{16}H_{16}O_6$ (304.3)	62.85 63.15	5.01 5.29	304 (52)
8c	90[d]	225[b]	$C_{16}H_{16}O_7$ (320.3)	59.63 59.99	4.87 5.03	320 (25)
8d	90[d]	220[b]	$C_{17}H_{18}O_7$ (334.3)	60.78 61.07	5.68 5.42	334 (55)
10a	95[c]	230[a]	$C_{14}H_{10}O_5$ (258.2)	65.03 65.11	3.77 3.90	258 (100)
10b	90[d]	260[a]	$C_{15}H_{12}O_6$ (288.2)	62.25 62.50	3.88 4.19	288 (100)

[a] Crystallized from toluene.
[b] Crystallized from ethanol.
[c] Based on 4a.
[d] Based on 4b.

TABLE II

IR and ^1H NMR spectral data of compounds 7a,b, 8a–d and 10a,b

Compound	IR (cm^{-1}) $\bar{\nu}$ OH	$\bar{\nu}C=O$ ester	$\bar{\nu}C=O$ α-pyrone	$\bar{\nu}C=O$ γ-pyrone	^1H NMR (in $CDCl_3$) (δ-ppm)
7a	—	—	1740	—	
7b	—	—	1700	—	
8a	3270	1710	—	1645	
8b	3290	1745	—	1645	1.02 (3H, ethoxy-CH_3, t), 2.30 (3H, CH_3, d, J_{HH} = 2.5 Hz), 3.72 (3H, OCH_3, s), 4.10 (2H, ethoxy-CH_2, q), 5.96 (1H, HC-3, diffused q), 6.68 (1H, HC-8, s), 6.88, 7.84 (2H, CH=CH, 2d, J_{HH} = 8 Hz)
8c	3220	1745	—	1665	2.32 (3H, CH_3, d, J_{HH} = 2.5 Hz), 3.68 (3H, OCH_3, s), 3.76 (3H, OCH_3, s), 3.92 (3H, $COOCH_3$, s), 5.92 (1H, HC-3, diffused q), 6.88, 7.80 (2H, CH = CH, 2d, J_{HH} = 8 Hz), 8.16 (OH, bs)
8d	3300	1750	—	1660	
10a	—	—	1745	1665	2.24 (3H, CH_3, d, J_{HH} = 2.5 Hz), 5.95 (1H, HC-7, diffused q), 7.75 (1H, HC-3, d, J_{HH} = 8 Hz), 6.80 (1H, HC-4, d, J_{HH} = 8 Hz), 6.64 (HC-10, s), 3.70 (3H, OCH_3, s)
10b	—	—	1765	1670	

(or 5b) (0.003 mol) in dry toluene (50 ml) for 3 hr. For analytical, physical and spectroscopic data of compounds 7a and 7b, cf. Tables I and II.

Compound 7a. UV.-(in absolute ethanol): λ max 330 nm; log ε = 4.15; λ max 255 nm; log ε = 3.94; and λ max 195 nm; log ε = 3.68.

^{13}C NMR (in $CDCl_3$, δ ppm); for better comparison, numbering of the carbon atoms is given according to that of isopimpinellin (1d)[21]: The data recorded for compound 7b are: 162.3 (C-2), 107.0 (C-3), 147.1 (C-4), 107.7 (C-4a), 148.3 (C-5), 111.5 (C-6), 156.2 (C-7), 115.7) (C-8), 147.5 (C-8a), 151.0 (C-2'), 105 (C-3'), 63.2 ($O\underline{C}H_3$ at C-5), 63.4 ($O\underline{C}H_3$ at C-8), 25.7 ($\underline{C}H_3$ at C-4).

Compound 7b. UV.-(in absolute ethanol): λ max 340 nm; log ε = 4.20 ; λ max 250 nm; log ε = 4.00; and λ max 195 nm; log ε = 3.75.

Preparation of 5,8-dimethoxy-6-formyl-7-hydroxy-2-methylchromone (4b). The method described[11] for production of 4b in 40.6% yield was improved as follows: Ozone was bubbled steadily at a moderate rate into a solution of khellin (2b, 2.6 g) in methylene chloride (150 ml) containing 1 ml of dimethylsulfide at −30°C (dry ice-acetone) for 2 hr (hood). Excess of ozone was expelled from the mixture under a stream of dry N_2 and the volatile materials were evaporated in *a vacuo*. The residual material was recrystallized from ethanol (charcoal) to give 4b (2.3 g; 90%) as colorless needles, m.p. 200–202°C; reported in Reference 11: m.p. 200–202°C.

The Reaction of ylid-phosphoranes 5a,b with 4a,b. A mixture of 4a (0.45 g; 0.002 mol) and 5a (0.66 g; 0.002 mol) in dry toluene (50 ml) was refluxed for 6 hr. The solvent was evaporated to dryness in the presence of silica gel (5 g) then introduced into a column charged with silica gel (Kieselgel 60, particle size 0.2–0.5 mm; E. Merck) and packed with light petroleum (b.r. 40–60°C). After elution with toluene (200 ml), the eluent was evaporated in *a vacuo*. The residual substance (0.25 g; 24%) was recrystallized from toluene-hexane (1:2 v/v) to give 10a as colorless needles, m.p. 230°C.

Elution with toluene-chloroform (6:4, v/v) gave a fraction from which 7-hydroxy-5-methoxy-2-methyl-6-acrylic acid methyl ester (8a) was obtained (0.27 g; 26% yield), m.p. 250–252°C.

Elution with chloroform alone afforded a fraction from which triphenylphosphine oxide (TPPO) was obtained (0.52 g; 50% yield) and identified (m.p. and mixed m.p.).

Compounds 10a (ca. 25%), 8b (ca. 25%) and TPPO (ca. 50%) were likewise produced and identified upon reacting 4a (0.45 g; 0.002 g; 0.002 mol) with 5b (0.7 g; 0.002 mol) in refluxing toluene (50 ml) for 6 hr. In a similar manner, compounds 10b, 8c (and/or 8d) were obtained and characterized upon reacting 4b with 5a (and/or 5b) in boiling toluene for 6 hr. For analytical, physical and spectral data of compounds 8a–d and 10a,b, cf. Tables I and II.

Action of heat on compounds 8a–d. Compound 8a, taken as a representative example, (0.5 g) was refluxed in dry toluene (50 ml) for 12 hr. After evaporation of the solvent to dryness in *a vacuo*, the residual substance was recrystallized from ethanol to give colorless needles (ca. 0.45 g; 95%) and proved to be unchanged 8a (m.p., mixed m.p. and comparative IR-spectra).

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