Studies of the Syntheses of Heterocyclic Compounds containing Benzopyrone. Part 2.[1] Syntheses of Khellin Analogues

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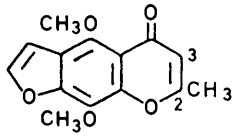
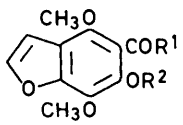
6-Acetoxy-4,7-dimethoxybenzofuran-5-carbonyl chloride (4), prepared from khellin (1) by three steps, was condensed with enamines or lithium enolates. Further treatment with acid afforded the khellin analogues (10). Better yields were obtained with lithium enolates than with enamines.

KHELLIN (1),[2] obtained from the fruits and seeds of *Ammi visnaga* L., has antispasmodic activity and is a coronary vasodilator; the importance of a methyl or methylene group in the 2-position of norkhellin for its physiological activity has been stressed.[3] We are interested in the structure–activity relationship and have tried to synthesize khellin analogues by ring closure at the 2- and 3-positions of khellin (1). There have been



(1)



(2) R^1 = OH, R^2 = H
(3) R^1 = OH, R^2 = Ac
(4) R^1 = Cl, R^2 = Ac
(5) R^1 = OCO_2Et, R^2 = Ac

many reports on syntheses of chromones [4] from which we note the lithium enolate [5] and enamine methods.[4d-g]

6-Acetoxy-4,7-dimethoxybenzofuran-5-carbonyl chloride (4), to which these methods can be applied, is easily obtained from khellin (1) in three steps as follows. Khellin (1) was oxidized with hydrogen peroxide to afford 4,7-dimethoxy-6-hydroxybenzofuran-5-carboxylic acid (2).[6] Acetylation of the acid (2) with acetic anhydride and pyridine gave 6-acetoxy-4,7-dimethoxybenzofuran-5-carboxylic acid (3) which was quantitatively converted to the acid chloride (4) by treatment with oxalyl chloride.

There are few reports on the acylation of silyl enolates [7] compared with those for alkylation, and acylation of oxygen as well as carbon can occur in some cases.[8] When cyclohexanone trimethylsilyl enol ether, prepared by House's method,[9] was treated with benzoyl chloride a trace of 2-benzoylcyclohexanone was obtained. However the lithium enolate of cyclohexanone,[10] obtained by treatment of trimethylsilyl enolate with methyl-lithium, when treated with benzoyl chloride afforded 2-benzoylcyclohexanone in 80% yield. This silyl enolate was also treated with *o*-acetoxybenzoyl chloride (6) to yield a diketone which, without further purification, was converted into the tetrahydroxanthone (8d) by heating with acid in 72% yield.

As shown previously,[5] an alternative method of lithiation with phenyl-lithium increased the amount of acylation products. 2-Benzoylcyclohexanone was obtained in 95% yield from lithium enolate and benzoyl chloride by this method. The lithium enolate of ketones (Scheme 1) was treated with (6) in dimethoxyethane at −70 °C. Ammonium chloride solution was then added and the resulting diketone (7) was extracted with benzene. The diketone (7), without further purification, was treated with hydrochloric acid–acetic acid to furnish chromones (8) in high yield except for (8c). Chromones obtained by this method are shown in the Table. As the modest yield of (8c) might be due to the unfavourable enol form of cyclopentanone,[11] we examined the con-

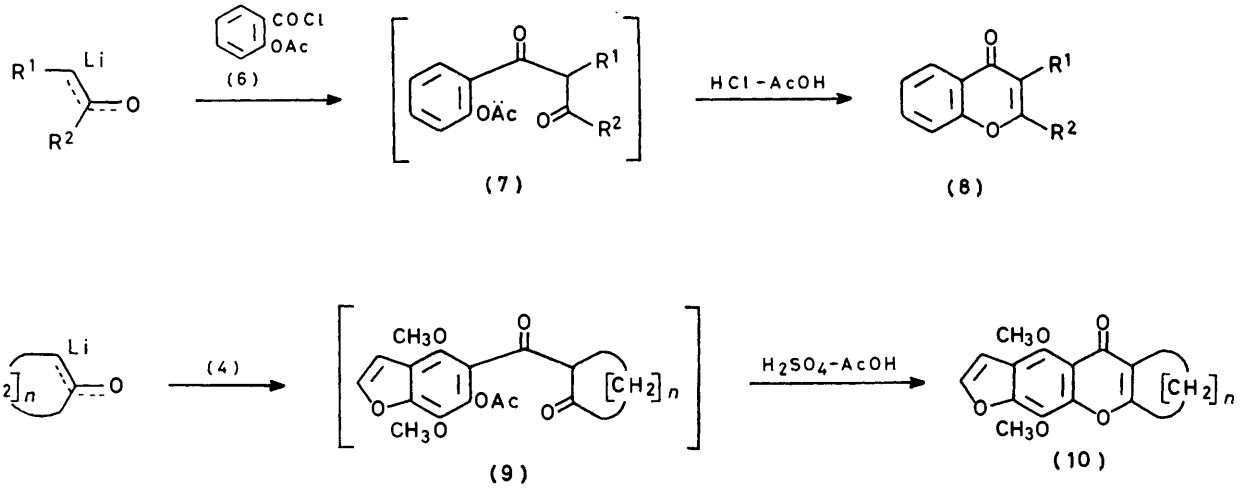
Chromones (8)

Compound	R^1	R^2	Yield (%) [a]	M.p. (°C)
(8a)	H	Me	87	71—72 [b]
(8b)	Me	M	80	94—94.5 [c]
(8c)	$[CH_2]_3$		30	118.5—120.5 [d]
(8d)	$[CH_2]_4$		90	91—92 [e]
(8e)	$[CH_2]_5$		80	84—85 [f]

[a] From silyl enol ether. [b] M. Bloch and S. von Kostanechi, *Ber.*, 1900, **33**, 1799, give m.p. 72—73°. [c] S. Lehmann, *Ber.*, 1914, **47**, 698, gives m.p. 97°. [d] H. I. Hall and S. G. P. Plant, *J. Chem. Soc.*, 1933, 232, give m.p. 121—122° and ref. 4*g* gives 122—123°. [e] This exists in two crystalline modifications, m.p.s 93—94 (M. Miyano, *J. Amer. Chem. Soc.*, 1965, **87**, 3958) and 104° (H. I. Hall and S. G. P. Plant, *J. Chem. Soc.*, 1933, 232). The lower melting form changes into the other over two years.[4g] [f] Lit.,[4g] 86—87°

[1] Part 1, T. Watanabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2778.
[2] H. Schmid, in 'Progress in the Chemistry of Organic Natural Products,' ed. L. Zechmeister, Springer Verlag, Vienna, 1954, vol. XL, p. 125.
[3] A. Schoenberg and A. Sina, *J. Amer. Chem. Soc.*, 1950, **72**, 1611.
[4] (*a*) E. Petschek and H. Simonis, *Ber.*, 1913, **46**, 2014; (*b*) T. A. Geissman, *J. Amer. Chem. Soc.*, 1951, **73**, 3514; (*c*) D. T. Witiak, W. P. Heilman, S. K. Sankarappa, R. C. Cavestri, and H. A. I. Newman, *J. Medicin. Chem.*, 1975, **18**, 934; (*d*) L. A. Paquette, *Tetrahedron Letters*, 1965, 1291; (*e*) L. A. Paquette and H. Stucki, *J. Org. Chem.*, 1966, **31**, 1232; (*f*) M. Uchiyama, M. Ohhashi, and M. Matsui, *Agric. Biol. Chem.*, 1966, **30**, 1145; (*g*) G. V. Boyd, D. Hewson, and R. A. Newberry, *J. Chem. Soc. (C)*, 1969, 935.
[5] T. Watanabe, Y. Nakashita S. Katayama, and M. Yamauchi, *J.C.S. Chem. Comm.*, 1977, 493.
[6] A. Schoenberg, N. Badran, and N. A. Starkowsky, *J. Amer. Chem. Soc.*, 1953, **75**, 4992.
[7] J. K. Rasmussen, *Synthesis*, 1977, 91.
[8] J. F. Klebe *Adv. Org. Chem.*, 1972, **8**, 130.
[9] H. O. House, L. J. Czuba, M. Gall, and H. D. Ohmstead, *J. Org. Chem.*, 1969, **34**, 2324.
[10] G. Stork and P. F. Hudrlick, *J. Amer. Chem. Soc.*, 1968, **90**, 4462, 4464.
[11] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, London, 1969, 2nd edn., p. 818.

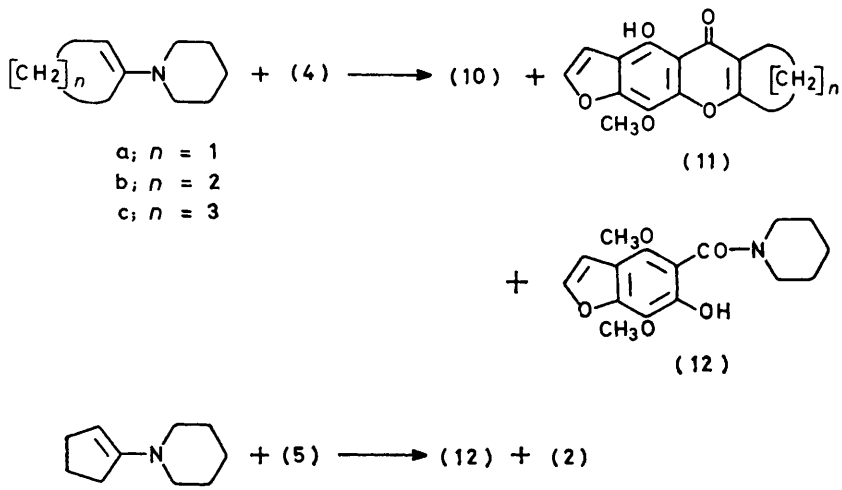
densation of the acid chloride (4) with the lithium enolate from cyclohexanone or cycloheptanone and treated the resulting diketone (9) with sulphuric acid–acetic acid in order to avoid demethylation (see later). The yields of khellin analogues [30% for (10b), 50% for (10c)] were lower than for the corresponding chromones. This was treated with dilute hydrochloric acid demethylation took place at the methoxy-group *peri* to carbonyl. In fact, the reaction of (4) with the piperidine enamine of cycloalkanone followed by treatment with hydrochloric acid gave a small amount of the demethylkhellin analogue in addition to (10) and (12). Compound (11)



SCHEME 1

might be due to the fact that the steric hindrance of the *o*-methoxy-group overcomes the resonance effect facilitating the departure of chloride ion in (4).

The acid chloride (4) was refluxed with piperidine showed an n.m.r. signal for phenol OH at δ *ca.* 13.2 instead of that (δ 4.2) for the methoxy-group *peri* to carbonyl in (10). Other pyrrolidine or morpholine enamines also decreased the amount of (10). The best



SCHEME 2

enamines of cycloalkanones and followed by acid hydrolysis to afford the khellin derivatives (10) along with the amide (12). The amount of (10) was increased by treatment with sulphuric acid rather than hydrochloric acid. This may be due to the fact that the methoxy-group *peri* to carbonyl is hydrolysed by hydrochloric acid. Schoenberg *et al.*[12] reported that when visnagin yields of (10) from the acetoxy-acid (3) were 29% ($n = 1$), 10% ($n = 2$), and 12% ($n = 3$), lower than those obtained by the lithium enolate method. In general, acylation of enamines can take place on carbon or on nitrogen and acylation at nitrogen is kinetically controlled but reversible so that a high yield of *C*-acylated product is normally obtained.[13] However, the *N*-acylated

[12] A. Schoenberg and N. Badran, *J. Amer. Chem. Soc.*, 1951, **73**, 2690.

[13] A. G. Cook, 'Enamines,' Marcel Dekker, New York and London, 1969, p. 135.

product (amide) is formed under conditions such that heterolysis of the enamine carbon–nitrogen bond takes place, particularly at high temperatures.[14] When the acid chloride (4) was treated with piperidine enamines at room temperature no reaction took place. Thus it seems likely that the considerable yield of amide (12) is due to the high temperature (refluxing solvent).

The reaction of the mixed anhydride (5), easily obtained by treatment of (3) with ethyl chloroformate, with the piperidine enamine of cyclopentanone furnished the piperidine amide (12) and the starting hydroxy-acid (2).

EXPERIMENTAL

M.p.s were determined with a Mitamura micro m.p. apparatus. I.r. spectra were recorded on a Hitachi model 215 spectrophotometer. U.v. spectra were recorded with a Hitachi model 200-10 spectrophotometer. Mass spectra were recorded with Shimazu LKB-9000 and Hitachi RMU-7M mass spectrometers, and n.m.r. spectra for $CDCl_3$ solutions with a JEOL C-60HL spectrometer with tetramethylsilane as internal reference. Column chromatography was carried out on silica gel (Mallinckrodt) using chloroform–methanol as eluant.

6-*Acetoxy*-4,7-*dimethoxybenzofuran*-5-*carboxylic Acid*. (3).—A mixture of the hydroxy-acid (2) (1.19 g), pyridine (4 ml), and acetic anhydride (0.7 ml) was kept overnight at room temperature. The mixture was poured into ice–water and extracted with chloroform. The chloroform layer was washed with dilute HCl and water and dried ($MgSO_4$). Evaporation of the solvent gave 6-*acetoxy*-4,7-*dimethoxybenzofuran*-5-*carboxylic acid* (1.02 g, 73%), m.p. 119—121 °C (from benzene) (Found: C, 55.55; H, 4.4. $C_{13}H_{12}O_7$ requires C, 55.7; H, 4.3%), $\nu_{max.}$ (KBr) 3 200—2 400 (COOH), 1 775 ($OCOCH_3$), and 1 683 cm^{-1} (COOH), δ 2.40 (3 H, s, $OCOCH_3$), 4.15 (3 H, s, OCH_3), 4.18 (3 H, s, OCH_3), 7.05 (1 H, d, *J* 2 Hz, 3-H), 7.75 (1 H, d, *J* 2 Hz, 2-H), and 10.62 (1 H, s, COOH).

6-*Acetoxy*-4,7-*dimethoxybenzofuran*-5-*carbonyl Chloride* (4).—Oxalyl chloride (3 ml) was slowly added to a solution of the acetoxy-acid (3) (560 mg) in dry benzene (15 ml) at room temperature. After the addition of the chloride the mixture was heated at 50 °C for 1 h. Evaporation of the solvent and excess of oxalyl chloride gave the acid chloride (4), which was so unstable that it reverted to the starting acid (3) on contact with atmospheric moisture, and it was employed in the following reactions without further purification.

6-*Acetoxy*-4,7-*dimethoxybenzofuran*-5-*carboxylic Propionic Anhydride*. (5).—Triethylamine (61 mg) was slowly added to a solution of the acetoxy-acid (3) (148 mg) in chloroform (3 ml) below 5 °C. The resulting solution was cooled to −10 °C and ethyl chloroformate (69 mg) was added at such a rate to keep the temperature below −5 °C. Five hours after stirring at −10 to 0 °C, the mixture was washed with cold water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give the mixed anhydride (5) in quantitative yield, $\nu_{max.}$ (film) 1 800 and 1 770 cm^{-1} (C=O), δ 1.42 (3 H, t, *J* 10 Hz, $COOCH_2CH_3$), 2.35 (3 H, s, $COCH_3$), 4.05 (3 H, s, OCH_3), 4.08 (3 H, s, OCH_3), 4.39 (2 H, q, *J* 10 Hz, $COOCH_2CH_3$), 6.93 (1 H, d, *J* 2 Hz, 3-H), and 7.64 (1 H, d, *J* 2 Hz, 2-H).

Chromones from Lithium Enolate and o-*Acetoxybenzoyl Chloride*.—The silyl enol ether of the appropriate ketone in dry ether (1 ml $mmol^{-1}$) was cooled to −70 °C and phenyllithium (1.2 equiv.) in dry ether was added dropwise with stirring and the resulting solution was left at room temperature for 1 h. The solution changed from colourless to brown during addition. Ether was then evaporated under reduced pressure at room temperature. To the residue dry glyme (3 ml $mmol^{-1}$) was added and cooled to −70 °C. *o*-Acetoxybenzoyl chloride in glyme (1 ml $mmol^{-1}$) was added dropwise and stirred for 5 h at the same temperature and stirring was continued at room temperature for a further 5 h. Saturated ammonium chloride solution was added and extracted with benzene. The combined benzene solutions were washed with saturated NaCl, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was treated with concentrated HCl–AcOH (1 : 20) (3 ml $mmol^{-1}$) at 60 °C for 1 h. The mixture was poured into ice–water and extracted with benzene. The combined benzene solution was washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to chromatography to yield chromones as the first fraction. 2-*Methylchromone* (8a) had m.p. 71—72 °C (from ether–light petroleum) (Found: C, 75.15; H, 5.25. $C_{10}H_8O_2$ requires C, 75.0; H, 5.6%), $\nu_{max.}$ (KBr) 1 640 cm^{-1} (C=O), δ 2.35 (3 H, s, 2-CH_3), 6.00 (1 H, s, 3-H), 7.10—7.70 (3 H, m, 6-, 7-, and 8-H), and 7.95—8.20 (1 H, m, 5-H). 2,3-*Dimethylchromone* (8b) had m.p. 94—94.5 °C (from ether–light petroleum) (Found: C, 75.7; H, 5.75. $C_{11}H_{10}O_2$ requires C, 75.85; H, 5.8%), *m/e* 174 (M^+), $\nu_{max.}$ (KBr) 1 625 cm^{-1} (C=O), δ 2.09 (3 H, s, 3-CH_3), 2.44 (3 H, s, 2-CH_3), 7.20—7.90 (3 H, m, 6-, 7-, and 8-H), and 8.20—8.40 (1 H, m, 5-H). Physical and spectral data for the other cycloalkenochromones were given previously.[1]

Reaction of (4) *with Lithium Enolate of Cycloalkanone*.—The lithium enolate of cycloalkanone and the acid chloride (4) was treated as above, and acid treatment was carried out with 20% sulphuric acid–acetic acid (1 : 2). Cyclohexanone gave 4,11-*dimethoxy*-6,7,8,9-*tetrahydro*-5H-*furo*[1,3-d]-*xanthen*-5-*one* (10b; *n* = 2) (30%), m.p. 115—117 °C (from light petroleum) (Found: C, 68.1; H, 5.35. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.35%), *m/e* 300 (M^+), $\nu_{max.}$ (KBr) 1 620 cm^{-1} (C=O), $\lambda_{max.}$ (ethanol) 248 (ε 45 000), 282 (3 900), and 332 nm (4 200), δ 1.83 (4 H, m, 7- and 8-CH_2), 2.67 (4 H, m, 6- and 9-CH_2), 4.08 (3 H, s, 11-OCH_3), 4.20 (3 H, s, 4-OCH_3), 7.05 (1 H, d, *J* 2 Hz, 3-H), and 7.65 (1 H, d, *J* 2 Hz, 2-H). Cyclopentanane gave 4,12-*dimethoxy*-5H-*cyclopentano*[b]*furo*[3,2-g][1]*benzopyran*-5-*one* (10c; *n* = 3) (50%), m.p. 112.5—113.5 °C (from benzene–n-hexane) (Found: C, 68.6; H, 6.2. $C_{18}H_{18}O_5$ requires C, 68.8; H, 6.2%), $\nu_{max.}$ (KBr) 1 630 cm^{-1} (C=O), $\lambda_{max.}$ (ethanol) 248 (ε 50 000), 282 (3 100), and 331 nm (4 200), δ 1.77 (6 H, m, 7-, 8-, and 9-CH_2), 2.93 (4 H, m, 6- and 10-CH_2), 4.12 (3 H, s, 12-OCH_3), 4.23 (3 H, s, 4-OCH_3), 7.08 (1 H, d, *J* 2 Hz, 3-H), and 7.68 (1 H, d, *J* 2 Hz, 2-H).

Reaction of the Acid Chloride (4) *with* 1-*Piperidinocycloalkenes*.—*Method A*. To a solution of 1-piperidinocycloalkene (20 mmol) and triethylamine (10 mmol) in chloroform (20 ml) was added a solution of the acid chloride (4), prepared from (3) (10 mmol), in chloroform (40 ml) for 4 h. Concentrated HCl (80 ml) was added, and further refluxing was continued for 1 h. The mixture was cooled and the organic layer was separated, washed successively with water, saturated Na_2CO_3, water, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the

[14] P. W. Hickmott, *Chem. and Ind.*, 1974, 731.

residue was subjected to chromatography, and eluted the following products. From 1-piperidinocyclopentene 4-*hydroxy*-10-*methoxy*-5H-*cyclopenta*[b]*furo*[3,2-g][1]*benzopyran*-5-*one* (11a; $n = 1$) (1%), m.p. 162—163 °C, *m/e* 272 (M^+), $\nu_{max.}$ (KBr) 1 630 cm^{-1} (C=O), δ 2.30 (2 H, m, 7-CH_2), 2.90 (4 H, m, 6- and 8-CH_2), 4.10 (3 H, s, 10-OCH_3), 6.95 (1 H, d, *J* 2 Hz, 3-H), 7.55 (1 H, d, *J* 2 Hz, 2-H), and 13.20 (1 H, s, phenolic OH), 4.10-*dimethoxy*-5H-*cyclopenta*[b]-*furo*[3,2-g]*benzopyran*-5-*one* (10a; $n = 1$) (19%), m.p. 137—138.5 °C (from light petroleum) (Found: C, 67.1; H, 4.85. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.95%), *m/e* 286 (M^+), $\nu_{max.}$ (KBr) 1 635 cm^{-1} (C=O), $\lambda_{max.}$ (ethanol) 249 (ε 45 000), 282 (4 100), and 330 nm (4 000), δ 2.20 (2 H, m, 7-CH_2), 3.00 (4 H, m, 6- and 8-CH_2), 4.10 (3 H, s, 10-OCH_3), 4.25 (3 H, s, 4-OCH_3), 7.10 (1 H, d, *J* 2 Hz, 3-H), and 7.73 (1 H, d, *J* 2 Hz, 2-H), and 4,7-*dimethoxy*-6-*hydroxy*-5-*piperidinocarbonylbenzofuran* (12) (9%), m.p. 162—164 °C (from benzene–ethanol) (Found: C, 62.75; H, 6.25; N, 4.55. $C_{16}H_{19}O_5N$ requires C, 62.95; H, 6.25; N, 4.6%), *m/e* 305 (M^+), $\nu_{max.}$ (KBr) 3 200 (OH) and 1 620 cm^{-1} (C=O), δ 1.67 (6 H, m, 3′-, 4′-, and 5′-CH_2), 3.57 (4 H, m, 2′- and 6′-CH_2), 4.03 (3 H, s, OCH_3), 4.12 (3 H, s, OCH_3), 6.90 (1 H, d, *J* 2 Hz, 3-H), and 7.57 (1 H, d, *J* 2 Hz, 2-H) were obtained. From 1-piperidinocyclohexene 4-*hydroxy*-11-*methoxy*-6,7,8,9-*tetrahydro*-5H-*furo*[2,3-d]*xanthen*-5-*one* (11b; $n = 2$) (trace), m.p. 113—115 °C, $\nu_{max.}$ (KBr) 1 650 cm^{-1} (C=O), δ 1.83 (4 H, m, 7- and 8-CH_2), 2.67 (4 H, m, 6- and 9-CH_2), 4.08 (3 H, s, 11-OCH_3), 7.00 (1 H, d, *J* 2 Hz, 3-H), 7.58 (1 H, d, *J* 2 Hz, 2-H), and 13.27 (1 H, s, phenolic OH), and 4,7-*dimethoxy*-6,7,8,9-*tetrahydro*-5H-*furo*[2,3-d]*xanthen*-5-*one* (10b; $n = 2$) (8%), and the amide (12) (7%) were obtained. From 1-piperidinocycloheptene 4-*hydroxy*-12-*methoxy*-5H-*cyclohepta*[b]*furo*[3,2-g][1]*benzopyran*-5-*one* (11c; $n = 3$) (trace), m.p. 145—147 °C, $\nu_{max.}$ (KBr) 1 610 cm^{-1} (C=O), δ 1.83 (6 H, m, 7-, 8-, and 9-CH_2), 2.88 (4 H, m, 6- and 10-CH_2), 4.17 (3 H, s, 12-OCH_3), 7.07 (1 H, d, *J* 2 Hz, 3-H), 7.67 (1 H, d, *J* 2 Hz, 2-H), and 13.47 (1 H, s, phenolic OH), and 4.12-*dimethoxy*-5H-*cyclohepta*[b]*furo*[3,2-g]*benzopyran*-5-*one* (10c; $n = 3$) (11%), and the amide (12) (9%) were obtained.

Method B. To a solution of 1-piperidinocycloalkene (20 mmol) and triethylamine (10 mmol) in n-hexene (15 ml) was added over 5 min a solution of the acid chloride (4), prepared from (3) (10 mmol) in ether (10 ml). After the mixture was refluxed for 4 h, the resulting salt was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in acetic acid (20 ml)–20% sulphuric acid (10 ml) and refluxed for 1 h. The mixture was poured onto crushed ice and extracted with chloroform. The extract was washed with 5% $NaHCO_3$, water, dried ($MgSO_4$), and distilled, and the residue was subjected to chromatography. From 1-piperidinocyclopentene 4,10-*dimethoxy*-5H-*cyclopenta*[b]*furo*[3,2-g][1]*benzopyran*-5-*one* (10a; $n = 1$) (29%) and the amide (12) (trace) were obtained. From 1-piperidinocyclohexene 4,11-*dimethoxy*-6,7,8,9-*tetrahydro*-5H-*furo*[2,3-d]*xanthen*-5-*one* (10b; $n = 2$) (10%) and the amide (12) (8%) were obtained. From 1-piperidinocycloheptene 4,12-*dimethoxy*-5H-*cyclohepta*[b]-*furo*[3,2-g][1]*benzopyran*-5-*one* (10c; $n = 3$) (12%) and the amide (12) (11%) were obtained.

Reaction of the Mixed Anhydride (5) *with* 1-*Piperidinocyclopentene.*—1-Piperidinocyclopentene (170 mg) was added dropwise to a stirred solution of the mixed anhydride (5) (115 mg) and triethylamine (64 mg) in chloroform (15 ml) in an ice-bath. The cooling bath was removed and the stirring was continued for 13 h. Concentrated HCl (1 ml) was added and the mixture was heated under reflux with stirring for 4 h. The mixture was cooled and the organic layer was separated and washed successively with water, saturated Na_2CO_3, and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. Chromatography of the residue gave 4,7-dimethoxy-6-hydroxy-5-piperidinocarbonylbenzofuran (12) (37 mg, 23%) and starting hydroxy-acid (2) (18 mg, 14%).

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