4-Hydroxy-6-methyl-2-pyrone (Triacetic Acid Lactone) and Its 3-Phenylthiomethyl Derivative Towards Aldehydes in the Presence of Piperidine

M. Moreno-Mañas (a),* E. Papell (a), R. Pleixats (b), J. Ribas (a) and A. Virgili (a)

(a) Departamento de Química Orgánica, Facultad de Ciencias,
(b) Departamento de Química, Facultad de Veterinaria,
Universidad Autónoma de Barcelona, Bellaterra, Barcelona, Spain

Recieved July 8, 1985

Aldehydes react with triacetic acid lactone, **1**, in the presence of piperidine to afford the pyrones **3a-d** and **5**. The intermediacy of quinone-methides of type **2a-e** has been postulated, and experimental evidence for their existence has been achieved by generation by thiophenol elimination from **7** and subsequent trapping in Diels-Alder reactions. Two examples are given in reactivity of **7** at the sluggish C-5 position.

J. Heterocyclic Chem., **23**, 413 (1986).

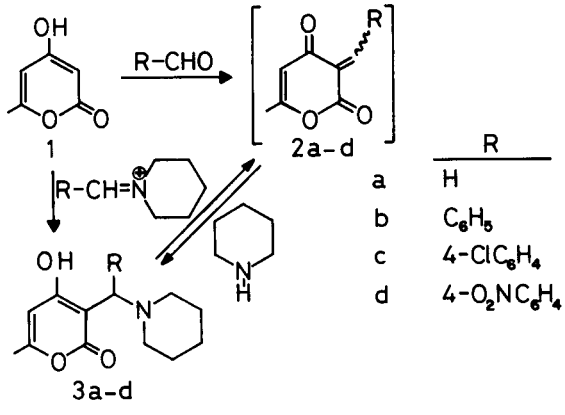
Introduction.

4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone), **1**, is an industrially available material having the basic structure of a 6-substituted-4-hydroxy-2-pyrone, which can be found in many poliketides. Indeed, **1** is itself a natural product [1]. Since many of the natural poliketides bear substituents at C-3 and C-5, we have studied in this laboratory the reactivity at these positions. Thus, a method to alkylate the C-3 [2], and studies on the reactivity of C-3 towards aldehydes and ketones [3,4,5,6] have been published. Rearrangements involving transfer of functionality from the methyl group at C-6 have afforded partial solutions for alkylation at C-5 [7,8]. Finally, methods to prepare brominated derivatives at C-3, C-5 and the methyl group at C-6 are now available [9].

Results.

When **1** is treated with formaldehyde or aromatic aldehydes and piperidine, the aminopyrones **3** are formed in good yields (Scheme 1). Product **3a** is, at least partially, a betaine in solid phase as indicated by infrared absorptions between 2800 and 2500 cm^{-1} (potassium bromide). This is not the case for the other products **3** prepared.

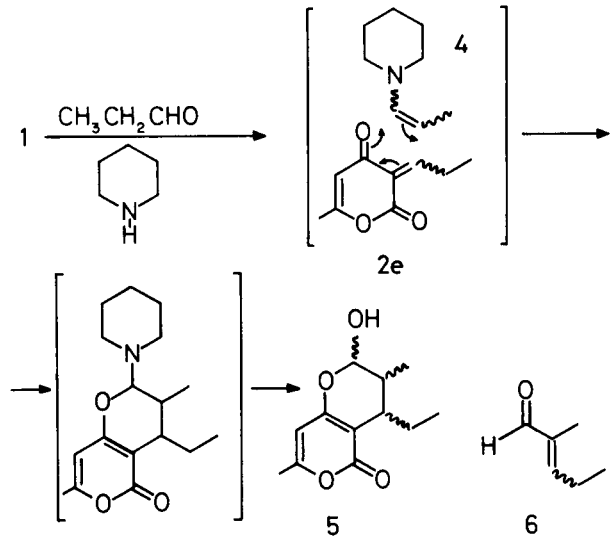
Scheme 1



Products **3a-d** can arise from Michael addition of piperidine to the electrophilic quinone-methide type intermediates **2** or, alternatively, from reaction of **1** with the iminium cations derived from piperidine and the corresponding aldehydes. Quinone-methide intermediates similar to **2** have been postulated in 4-hydroxycoumarin [10] and 4-hydroxyquinolone [11] chemistry. Moreover, addition of amines to quinone-methides can be reverted to recover the Michael acceptors [11].

When **1** is allowed to react with two equivalents of propanal and piperidine, 4-ethyl-2-hydroxy-3,7-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one, **5**, (Scheme 2) is

Scheme 2



formed in good yield after a working up which involved passing through a column of silica gel. The aminoether precursor of **5** was probably hydrolyzed to **5** during the working up procedure. The sharp melting point of **5** suggests it to be a single stereoisomer in solid phase. However, its nmr spectrum in deuteriochloroform showed two broad singlets at δ 5.26 and 5.38 corresponding to the hydrogen atoms at C-2 for two different stereoisomers.

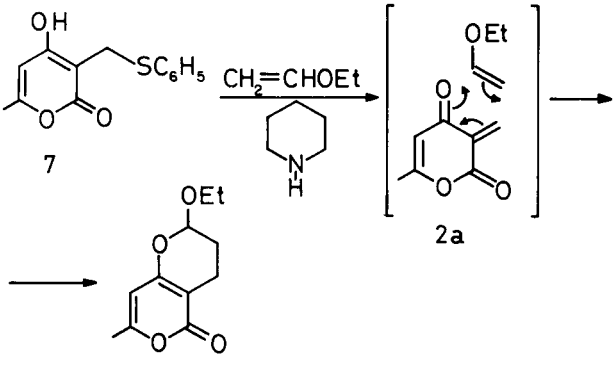
Most probably, the quinone-methide **2e**, formed by any of the mechanisms of the Scheme 1, reacts with the ena-

mine **4** in a Diels-Alder fashion to afford the aminoether which in turn is hydrolyzed to the hemiacetal **5** (Scheme 2).

Products structurally analogue of **5** were isolated as by-products in the reactions of **1** with aliphatic aldehydes and thiophenol in the presence of piperidine and acetic acid [5]. Note that product **5** can be considered as arising formally from the reaction of **1** with 2-methyl-2-pentenal, **6**, aldehyde accessible by aldol condensation of propanal. Also, the byproducts mentioned in reference [5] can be considered to arise from the α,β-unsaturated aldehydes derived from aldol condensations of *n*-butanal and of *n*-decanal.

To get further evidence for the *in situ* generation of intermediates **2**, the pyrone **7** [2] was treated wtih piperidine in refluxing ethyl vinyl ether. Under these conditions, 2-ethoxy-7-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one, **8**, could be isolated in 47% yield. The pyrone **8**

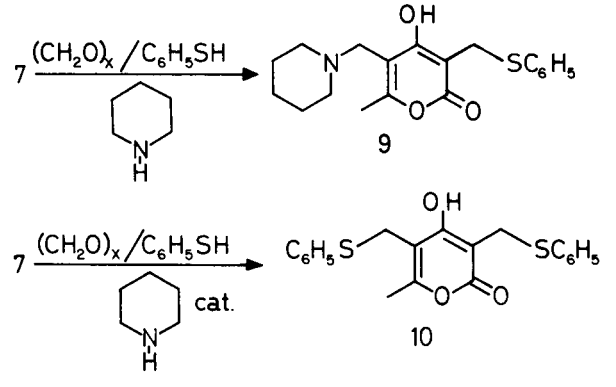
Scheme 3



must have been formed by Diels-Alder reaction between ethyl vinyl ether and **2a** (Scheme 3). It must be pointed out that elimination of methanethiol to afford a quinone-methide has been postulated in 4-hydroxycoumarin chemistry [11].

Very few cases have been reported of direct substitution at C-5 in 4-hydroxy-(or alkoxy)-2-pyrones. Thus, 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) reacts at C-5 with benzhydrol under cobalt(II) catalysis [12], and can also be brominated at C-5 under specific conditions [13]. We have found that **7** can be a reasonable candidate for reactions at C-5. Thus, when **7** is made to react with paraformaldehyde, thiophenol and piperidine in anhydrous dimethoxyethane, 4-hydroxy-6-methyl-3-phenylthiomethyl-5-piperidinomethyl-2-pyrone, **9**, precipitated out and was isolated in 37% yield (Scheme 4). The thiophenol was added to the reaction mixture to avoid formation of **2a**.

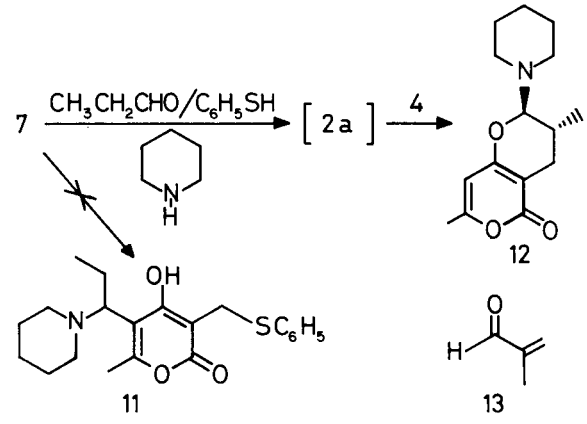
Scheme 4



A similar reaction in which piperidine was added only in catalytic amounts, afforded 31% yield of 4-hydroxy-6-methyl-3,5-bis(phenylthiomethyl)-2-pyrone, **10**.

Next, we tried to prepare product **11** (Scheme 5), which is structurally analogue to **9**. For this purpose, the pyrone

Scheme 5



7 was made to react with propanal, piperidine and thiophenol, the last being incorporated again to the reaction mixture to prevent formation of **2a**. However, in this case 3,7-dimethyl-2-piperidino-3,4-dihydro-2*H*,5*H*-pyrano-[3,2-*c*]pyran-5-one, **12**, was isolated in 75% yield. The aminoether **12** formally derives from 2-methylpropenal, **13**, the α,β-unsaturated aldehyde related to formaldehyde and propanal through a crossed aldol condensation. Even in the presence of thiophenol, product **11** did not precipitate out, and the concentration of **2a** present in the reaction mixture was significant enough to react with the enamine **4** to afford the product **12**. This was separated without column chromatography thus avoiding hydrolysis. The proton at C-2 appeared in pmr as a doublet (J = 8.6 Hz) at δ 4.3, the coupling constant indicating a *trans* relationship with the vicinal proton at C-3.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The pmr and cmr spectra were recorded on a Brucker WP80SY spectrometer. The ms were run on a Hewlett-Packard 5985-B spectrometer; only peaks with intensity higher than 20% are reported unless they belong to molecular ions.

4-Hydroxy-6-methyl-3-(α-piperidinobenzyl)-2-pyrone (**2b**).

A mixture of the pyrone **1** (1.008 g, 8 mmoles), benzaldehyde (0.830 g, 8 mmoles), piperidine (0.671 g, 8 mmoles), a drop of acetic acid, and dimethoxyethane (10 ml) was stirred at room temperature for 2 hours. The formed precipitate was filtered, washed with dimethoxyethane and dried to give 1.94 g of a white solid which upon recrystallization from acetone/hexane afforded **2b** (1.55 g, 65%), mp 140-142°; ir (potassium bromide): 1680 cm^{-1}; pmr (deuteriochloroform): δ 1.3-2.0 (broad absorption, 6H), 2.10 (s, 3H), 2.2-3.9 (broad absorption, 4H), 4.85 (s, 1H), 5.73 (s, 1H), 7.2-7.6 (m, 5H); cmr (deuteriochloroform): δ 19.5, 22.7, 24.4, 52.1, 70.6, 94.9, 128.51, 128.68, 128.73, 136.7, 160.7, 164.7, 176.1; ms: 299 (M^+, 1), 214 (32), 213 (69), 115 (21), 102 (96), 69 (38), 43 (100).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.47; H, 6.95; N, 4.57.

4-Hydroxy-6-methyl-3-piperidinomethyl-2-pyrone (**2a**).

Paraformaldehyde was used to prepare this compound which had mp 147-148° (from chloroform/hexane); ir (potassium bromide): 2850, 2720, 2580, 1665 cm^{-1}; pmr (deuteriochloroform): δ 1.5-2.0 (broad absorption, 6H), 2.10 (s, 3H), 2.3-3.6 (broad absorption, 4H), 3.92 (s, 2H), 5.63 (s, 1H), 6.0-6.6 (broad s, 1H); ms: 223 (M^+, 20), 180 (20), 138 (50), 110 (40), 98 (35), 85 (80), 84 (100), 69 (45), 54 (50), 43 (95).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 63.84; H, 7.71; N, 6.04. No good carbon elemental analysis could be achieved.

3-(4-Chloro-α-piperidinobenzyl)-4-hydroxy-6-methyl-2-pyrone (**2c**).

This compound had mp 102.5-105° (from acetone/hexane); ir (potassium bromide): 1670 cm^{-1}; pmr (deuteriochloroform): δ 1.30-2.0 (broad absorption, 6H), 2.10 (d, J = 1 Hz, 3H), 2.3-3.85 (broad absorption, 4H), 4.79 (s, 1H), 5.71 (q, J = 1 Hz, 1H), 7.23, 7.33, 7.41 and 7.51 (AA'BB' system, 4H); cmr (deuteriochloroform): δ 19.5, 22.7, 24.6 (two carbons), 52.1, 69.8, 95.2, 104.7, 128.9, 130.1, 134.5, 135.5, 161.1, 164.6, 175.6; ms: 333 (M^+, 0.6), 248 (29), 247 (33), 213 (73), 164 (35), 136 (100), 101 (41), 85 (37), 84 (81), 69 (52), 57 (32), 56 (47), 43 (80).

Anal. Calcd. for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.63; H, 6.08; N, 4.28.

4-Hydroxy-6-methyl-3-(4-nitro-α-piperidinobenzyl)-2-pyrone (**2d**).

This compound had mp 145-147° (from dimethoxyethane/hexane); ir (potassium bromide): 1670, 1520, 1345 cm^{-1}; pmr (deuteriochloroform): δ 1.38-2.00 (broad absorption, 6H), 2.15 (s, 3H), 2.27-3.40 (broad absorption, 4H), 4.88 (s, 1H), 5.76 (s, 1H), 7.64, 7.74, 8.12 and 8.22 (AA'BB' system, 4H); cmr (deuteriochloroform): δ 19.6, 22.9, 24.7, 52.4, 69.4, 95.6, 104.0, 123.9, 129.5, 144.6, 147.8, 161.7, 163.3, 174.5; ms: 216 (21), 85 (43), 84 (31), 56 (86), 43 (100).

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.41; H, 5.84; N, 8.16.

4-Ethyl-2-hydroxy-3,7-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (**5**).

A mixture of the pyrone **1** (1.008 g, 8 mmoles), propanal (0.920 g, 16 mmoles), piperidine (0.671 g, 8 mmoles), a drop of acetic acid and dimethoxyethane (10 ml) was stirred at room temperature for 70 hours, after which it was evaporated to give 2.53 g of an oil which was partitioned between chloroform and water. The organic layer was dried and evaporated to give 1.93 g of an oil which was passed through a silica gel column. Upon elution with chloroform/ethyl acetate, product **5** (1.11 g, 62%) was isolated. It has mp 141-143° (from acetone/pentane); ir (potassium bromide): 3600-3000 (broad), 1680 cm^{-1}; pmr (deuteriochloroform): δ 0.85-1.1 (m, 6H), 1.1-2.8 (m, 4H), 2.20 (s, 3H), 3.30 (broad s, 1H), 5.26 and 5.38 (two singlets corresponding to two diastereoisomers), 5.73 (s, 1H); ms: 224 (M^+, 20), 195 (55), 167 (55), 153 (90), 139 (20), 111 (25), 85 (30), 69 (20), 55 (22), 43 (100).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.48; H, 7.09.

2-Ethoxy-7-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (**8**).

A mixture of the pyrone **7** [2] (0.20 g, 0.81 mmoles), piperidine (0.43 g, 5 mmoles) and ethyl vinyl ether (30 ml) was refluxed for 4 days, after which it was evaporated to afford an oil which upon chromatography on silica gel gave diphenyl disulphide and the pyrone **8** (80 mg, 47%) (elution with hexane/chloroform). It had bp 80-85° (oven temperature)/0.05 torr, and crystallized spontaneously upon distillation to exhibit mp 50-53°; ir (film): 1705 cm^{-1}; pmr (deuteriochloroform): δ 1.22 (t, J = 7 Hz, 3H), 1.5-2.5 (m, 4H), 2.10 (s, 3H), 3.5-4.1 (m, 2H), 5.15 (dd, J = 2.4 and 3.6 Hz, 1H), 5.72 (s, 1H); cmr (deuteriochloroform): δ 15.3, 15.5, 20.1, 26.4, 65.1, 99.1, 99.5, 100.7, 160.6, 162.9, 165.1; ms: 210 (M^+, 51), 181 (33), 139 (100), 43 (34).

Anal. Calcd. for $C_{11}H_{14}O$: C, 62.85; H, 6.71. Found: C, 62.55; H, 7.00.

4-Hydroxy-6-methyl-3-phenylthiomethyl-5-piperidinomethyl-2-pyrone (**9**).

A mixture of the lactone **7** (1.00 g, 4 mmoles), thiophenol (1.32 g, 12 mmoles), paraformaldehyde (0.36 g, 12 mmoles), piperidine (1.02 g, 12 mmoles) and anhydrous dimethoxyethane (25 ml) was heated at 60-70° in a closed reactor under argon atmosphere. The initial precipitate dissolved spontaneously, and a second precipitate was formed. After 2 days the reaction was stopped, the precipitate was filtered and washed with dimethoxyethane to afford **9** (0.52 g, 37%) which had mp 185-187° (from chloroform/dimethoxyethane); ir (potassium bromide): 1660 cm^{-1}; pmr (deuteriochloroform): δ 1.6 (broad absorption, 6H), 2.05 (s, 3H), 2.6 (broad absorption, 4H), 3.55 (s, 2H), 4.00 (s, 2H), 7.0-7.5 (m, 5H), 8.7 (broad s, 1H); ms: 236 (85), 164 (20), 151 (53), 110 (100), 109 (76), 98 (81), 97 (33), 84 (76), 69 (40), 66 (30), 65 (40), 55 (48), 43 (65).

Anal. Calcd. for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.06. Found: C, 66.35; H, 6.63; N, 4.25.

4-Hydroxy-6-methyl-bis(3,5-phenylthiomethyl)-2-pyrone (**10**).

A mixture of the lactone **7** (2.0 g, 8 mmoles), paraformaldehyde (0.48 g, 16 mmoles), thiophenol (2.01 g, 18 mmoles), piperidine (0.17 g), acetic acid (0.21 g) and dimethoxyethane (25 ml) was heated at 60° in a closed reactor for 6 days. The mixture was evaporated and the residue was partitioned between chloroform and water. The organic layer was washed, dried and evaporated to give an oil which was chromatographed through a silica gel column. Upon elution with hexane/ethyl acetate, the pyrone **10** (0.91 g, 31%) was isolated as an oil which crystallized upon standing for months to show mp 100-110° dec. Product **10** had ir (film): 1670 cm^{-1}; pmr (deuteriochloroform): δ 1.69 (s, 3H), 3.68 (s, 2H), 4.04 (s, 2H), 7.18 (m, 10H); cmr (deuteriochloroform): δ 15.9, 27.6, 29.1, 97.2, 107.3, 126.3, 126.9, 128.1, 129.5, 131.8, 132.4, 133.4, 158.8, 162.8, 165.0; ms: 151 (50), 110 (100), 109 (42), 97 (39), 66 (30), 65 (22), 55 (27), 43 (27).

Anal. Calcd. for $C_{20}H_{18}O_3S_2$: C, 64.84; H, 4.90. Found: C, 64.58; H, 4.93.

3,7-Dimethyl-2-piperidino-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (**12**).

A mixture of the pyrone **7** (0.50 g, 2 mmoles), thiophenol (0.642 g, 6 mmoles), propanol (0.348 g, 6 mmoles), piperidine (0.516 g, 6 mmoles) and dimethoxyethane (25 ml) was stirred at 60-70° for 70 hours and then evaporated to afford a precipitate which was filtered and washed with hexane. Upon recrystallization with ethanol, **12** was obtained in pure condition (0.389 g, 75%). It had mp 168-170°; ir (potassium bromide): 1680 cm^{-1}; pmr (deuteriochloroform): δ 1.00 (d, J = 6.5 Hz, 3H), 1.6 (broad absorption, 6H), 2.10 (s, 3H), 2.0-3.0 (m, 7H), 4.3 (d, J = 8.6 Hz, 1H), 5.70 (s, 1H); ms: 263 (M^+, 4), 125 (100), 110 (80), 43 (46).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.73; H, 8.20; N, 5.50.

Acknowledgements.

Financial support from the "Comisión Asesora de Investigación Científica y Técnica" (Project 2014/83), a grant (to R. P.) from INAPE (Ministerio de Educación y Ciencia) and a generous gift of dehydroacetic acid from LONZA A. G. (Basel) are gratefully acknowledged.

REFERENCES AND NOTES

[1] R. Bentley and P. M. Zwitkowits, *J. Am. Chem. Soc.*, **89**, 676 and 681 (1967).

[2] M. Moreno-Mañas and R. Pleixats, *Synthesis*, 430 (1984).

[3] P. de March, M. Moreno-Mañas, R. Pi and A. Trius, *J. Heterocyclic Chem.*, **19**, 335 (1982).

[4] P. de March, M. Moreno-Mañas, and J. L. Roca, *ibid.*, **21**, 1371 (1984).

[5] P. de March, M. Moreno-Mañas, J. Casado, R. Pleixats, J. L. Roca and A. Trius, *ibid.*, **21**, 85 (1984).

[6] P. de March, M. Moreno-Mañas, R. Pleixats and J. L. Roca, *ibid.*, **21**, 1369 (1984).

[7] R. Bacardit, M. Moreno-Mañas and R. Pleixats, *ibid.*, **19**, 157 (1982).

[8] P. de March, M. Moreno-Mañas and I. Ripoll, *Synth. Commun.*, **14**, 521 (1984).

[9] P. de March, M. Moreno-Mañas, R. Pi, I. Ripoll and F. Sánchez-Ferrando, *J. Heterocyclic Chem.*, **22**, 1537 (1985).

[10] K-Z. Khan, N. Minhaj, K. Tasneen, A. Zaman, D. Shiengthong, F. M. Dean and M. Varma, *J. Chem. Soc., Perkin Trans. I*, 841 (1983).

[11] J. L. Asherson and D. W. Young, *ibid.*, 512 (1980).

[12] J. Marquet and M. Moreno-Mañas, *Chem. Letters*, 173 (1981).

[13] T. M. Harris, C. M. Harris, and C. K. Brush, *J. Org. Chem.*, **35**, 1329 (1970).