

By products from the Preparation of Dehydrobenzoylacetic acid-Substituted-2H, 5H-pyrano [4, 3-b] pyran-2, 5-diones and their synthesis

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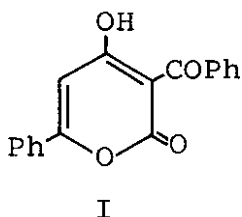
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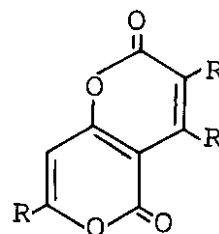
Summary: Substituted-2H, 5H-pyrano (4,3-b) pyran-2, 5-diones (IIa) and (IIb) have been isolated as by products in the preparation of dehydrobenzoylacetic acid (1) from the self condensation of ethylbenzoylacetate. A facile method of general applicability for the synthesis of substituted-2H, 5H-pyrano-pyran-2, 5-diones (IIb-g, V) from β -ketoesters and 4-hydroxy-pyran-2-ones (III, IV) using sodium bicarbonate as condensing agent has been described. For spectral comparison a number of substituted-4H, 5H-pyrano-pyran-4, 5-diones (VI, VII) have also been synthesised.

Starting point for the present investigation was the isolation of two by products in the preparation of dehydrobenzoylacetic acid (1) by the self condensation of ethylbenzoylacetate in the presence of sodium bicarbonate. A yellow solid (A), $C_{27}H_{16}O_5$, m.p. $315^\circ C$ was obtained during the recrystallisation of (I) from ethanol while a faint yellow solid (B), $C_{20}H_{12}O_4$, m.p. $241-243^\circ C$ was isolated from the residual liquid portion of the reaction mixture after the removal of (1).



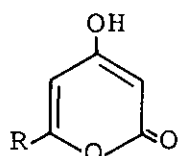
The yellow solid (A) was assigned structure (IIa) on the basis of mass spectrum m/e (M^+ 420); nmr spectrum which showed signals at 7.4-7.9 ppm (m, 15H, Aromatic) and at 7.2 ppm (s, 1H, C-8); ultraviolet absorption maxime at 385 nm exhibited the extended region of conjugation in the molecule and infrared absorptions at $1750, 1720\text{ cm}^{-1}$ and at 1675 cm^{-1} were appropriately placed for the carbonyl of 2-pyrone rings² and carbonyl of the aromatic ketone³ respectively. Additional evidence in support of structure (IIa) was obtained by debenzoylation with sulphuric acid which gave the dilactones (IIb) identical with second by product (B). The infrared absorptions at $1725, 1715\text{ cm}^{-1}$ (CO of 2-pyrone rings) and nmr signals at 6.18 ppm (s, 1H, C-8), 6.8 ppm (s, 1H, C-3) and 7.45-7.8 ppm (m, 10H, Aromatic) were strongly indicative of a dilactone structure

(IIb) for the second by product (B) but for firm structural assignment its synthesis was required.



	R	R'	R''
a	Ph	Ph	PhCO
b	Ph	Ph	H
c	Ph	Me	H
d	Ph	Me	Me
e	Me	Ph	H
f	Me	Me	Me
g	Me	Me	H

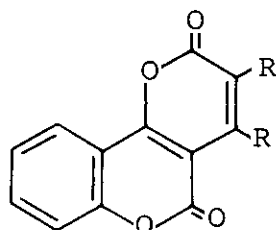
Analogous to the Pechmann's method⁴ the condensation of ethylacetoacetate with 4-hydroxy-6-methyl-pyran-2-one (IIIa) and 4-hydroxy-coumarin in (IV) in the presence of concentrated sulphuric acid or trifluoroacetic acid has been reported⁵ to yield 2H, 5H-pyrano-pyran-2, 5-diones (IIg) and (Va) respectively. On the contrary Woods⁶ have claimed the formation of 4-H, 5H-pyrano-pyran 4, 5-diones (VIa) from ethylacetoacetate and 4-hydroxy-coumarin in the presence of trifluoroacetic acid. In spite of all these claims our attempts to synthesise (IIb) from ethylbenzoylacetate and 4-hydroxy-6-phenyl-pyran-2-one (IIIb) using these acids as condensing agents were unsuccessful.



III

a R=Me

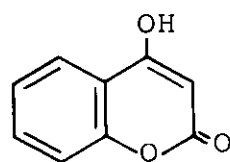
b R=Ph



V

R'

R''



IV

a
b
c
d
eMe
Me
Ph
Me
MeH
Me
H
CH₂Ph
Cl

A convenient solution to the problem was found by adding catalytic amount of sodium bicarbonate to the mixture of (IIIb) and ethylbenzoylacetate which on refluxing gave the anticipated dilactone (IIb) in appreciable yield.

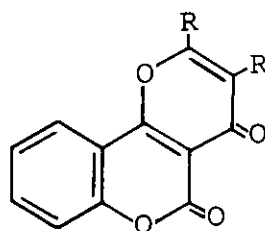
In view of the failure of Pechmann's method in the condensation of ethylbenzoylacetate with 4-hydroxy-pyran-2-one (IIIb), low yields (10-19 %) and time consuming (15 hrs.) method reported^{5c} for the preparation of (V), the general applicability of the use of sodium bicarbonate for the synthesis of pyranopyran-2, 5-diones was further investigated. A number of substituted-pyranopyran-2, 5-diones (IIb-g,V) have been prepared from 4-hydroxy-pyran-2-ones (III,IV) and β -ketoesters using sodium bicarbonate as condensing agent. All compounds were obtained in fairly good yields and in a short periods of reaction time (0.25-5 hrs.) (Table-II). The method provides not only an efficient substitute for Pechmann's method but also a convenient route for the synthesis of polypyrones which are being investigated to study the biogenetic-type⁷ synthesis of pehnolic compounds.

The dilactone structure of all these products is supported by the consistent appearance of two carbonyl absorptions in the region 1700-1750 cm^{-1} (Table-I). The compounds (IIb-e) having phenyl group as the substituent in the pyrone ring show carbonyl stretching frequency at 1720.1725 cm^{-1} , a lower frequency than alkyl substituted pyrone rings, this is attributable to the conjugative effect⁸ of the phenyl groups. In conformity with their 2-pyrone structures all compounds show principal absorption maxima above 300nm (Table-I). A bathochromic shift is obser-

vable in those compounds where phenyl groups are present as additional chromophores.

All these findings are in agreement with the views of other workers^{5,9} about the structure of the condensation products from β -ketoesters and 4-hydroxy-pyran-2-ones but contradict those of L.L. Woods who have claimed the formation of 4H, 5H-pyranopyran-4,5-dione (VI a) in the reaction of ethylacetoacetate with 4-hydroxy-coumarin. Re-investigation of the reaction gave in our hand a product unlike (VI a) but identical with 2H, 5H-pyranopyran-2, 5-dione (Va). The identity of the two was established by m.p., mixed m.p. and comparison of spectral data.

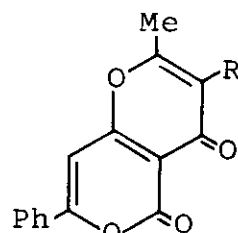
Further substantiation for the 2H, 5H-pyranopyran-2, 5-dione structure of our products (II,V) was obtained by the comparison of their infrared spectra with those of 4-H, 5H-pyranopyran-4, 5-dione (VI, VII) which were obtained by the concomitant acylation and cyclisation⁹ of the appropriate 3-acyl-4-hydroxy-pyran-2-one using acetic anhydride and perchloric acid. All these compounds (VI, VII) showed infrared absorption bands at 1642-1668 cm^{-1} and at 1750-1758 cm^{-1} which were appropriately placed for the carbonyl stretching frequencies of γ -pyrone and α -pyrone rings respectively. On the contrary all of our products (II,V) obtained by the condensation of ketoesters with 4-hydroxy-pyrones (III, V) were devoid of carbonyl absorption in the region 1642-1668 cm^{-1} expected of γ -pyrone ring but exhibited two carbonyl absorptions above 1700 cm^{-1} of two α -pyrone rings. These results conclusively prove that the condensation products from β -ketoesters and 4-hydroxy-pyran-2-one (III, IV) are invariably the 2H, 5H-pyranopyran-2, 5-diones (II, V) rather than the 4H, 5H-pyranopyran-4, 5-diones of type of (VI, VII) as claimed by L.L. Woods.



VI

R'

R''

a
b
c
dH
Me
Et
MeMe
Me
Me
Et

VII

a R=H
b R=Me

Table-I

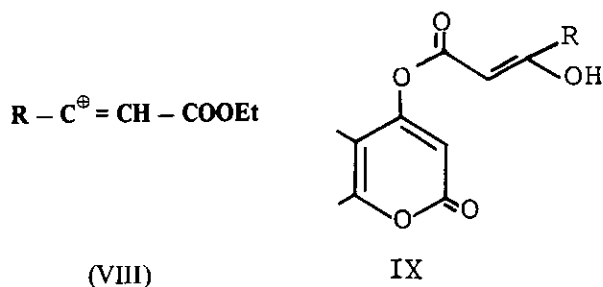
Light Absorption data of the compounds (IIb-g), (V), (VI) and (VII).

Compound.	ν_{\max} . Cm^{-1}	CO α -pyrones	λ_{\max} . nm (ϵ log.)
IIb	1725,	1715	375, 296 (4.12, 3.72)
c	1740,	1720	364, 286 (4.25, 3.88)
d	1740,	1715	365, 288 (4.10, 3.85)
e	1750,	1725	345, 228 (4.01, 4.16)
f	1755,	1740	340, 280 (4.05, 4.03)
g	1760,	1740	339, 275 (4.01, 4.00)
Va	1710,	1740	355, 350 (3.46, 3.88)
b	1720,	1735	350, 340 (3.05, 4.00)
c	1720,	1740	355, 346 (3.75, 3.95)
d	1715,	1735	350, 345 (3.07, 3.09)
e	1715,	1730	355, 340 (3.65, 3.08)

CO α -pyrone, CO γ -pyrone

VIIa	1758	1668	334, 260 (4.0, 3.08)
b	1753	1655	331, 258 (3.9, 3.09)
VIa	1750	1662	310, 265 (4.1, 3.08)
b	1739	1640	308, 259 (4.5, 3.09)
c	1748	1648	309, 260 (4.1, 3.08)
d	1750	1648	307, 258 (4.0, 3.09)

The limited applicability of the strong acids as condensing agent (Pechmann's method) in the condensation of β -ketoesters with 4-hydroxy-pyran-2-one is explicable in terms of the steric hindrance. In an acidic medium the carbonium ion (VIII) is formed the approach of which to attack the 3-position of the 4-hydroxy-pyrone (III, IV) is hindered due to presence of R = Me group and the effect becomes more enhanced when R = Ph. on the other hand in the presence of a base the anion derived from 4-hydroxy-pyran-2-one (III, IV) would preferably form the enolester (IX) with subsequent cyclisation to pyranopyran-2, 5-diones (IIb-g, V). Formation of enolester in basic medium and carbonium ion in the acidic medium has also been reported¹⁰ as the favoured mode of condensation reaction between the phenols and β -ketoesters.



Experimental

Ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer in ethanol, infrared spectra on Unicam SP 200 for mulls in Nujol and nuclear magnetic resonance spectra were measured with Perkin-Elmer R10 (60 MHz) spectrometer, with deuterochloroform as solvent, tetramethyl silane is internal

reference and are quoted in ppm. unless otherwise states. All melting points are uncorrected.

Triacetic acid lactone (III a) was obtained by deacetylating the dehydroacetic acid as described by Collie¹¹. m.p. 189°C.

4-Hydroxy-6-phenyl-pyran-2-one (III b) was prepared by the method of Butt and Elvidge^{2b}, m.p. 245°C.

4-Hydroxycoumarin (IV) used was from Koch Light m.p. 212°C.

Dehydrobenzoylactic acid. (1):- Ethylbenzoylacetate (25.0ml) was heated rapidly at 160-65°C for 15-20 minutes in the presence of three drops of sodium methoxide (0.3g. of sodium in 10 ml of methanol) as catalyst. After cooling the reaction mixture was poured into methylated spirit (100ml). An oily mass was obtained which eventually turned into solid mass. Solid product was filtered and filtrate was preserved. The solid product was crystallised from absolute ethanol. The insoluble yellow material (A) was filtered off and the filtrate on cooling gave yellow solid (1) m.p. 171-172°C (Lit¹ m.p. 171-172°C).

The ethanol insoluble yellow material (A) on recrystallisation from chloroform-ethanol mixture (5:1) gave yellow solid (II a) m.p. 315°C. ν_{\max} . 1750, 1720 cm^{-1} ; λ_{\max} , 385, 298 nm (log ϵ 4.21, 3.68); nmr (TFA) 7.2 (s, 1H, C-8), 7.4-7.9 (m, 15H aromatic); (Found: C, 76.76, H, 4.11 $\text{C}_{27}\text{H}_{16}\text{O}_5$ requires C, 77.14; H, 3.81 %); m/e (M^+ , 420).

The preserved filtrate was evaporated under reduced pressure and the resulting syrupy mass was chromatographed using silica gel (40 g.) column and benzene-petroleum ether (60.80°C) mixture (4:1) as eluent. Evaporation of the solvent gave light yellow oil which on cooling and trituration with ether gave light yellow solid (B) m.p. 241-243°C ν_{\max} . 1725, 1715 cm^{-1} ; λ_{\max} . 375 nm 296 nm (log ϵ 4.12, 3.72); nmr (CDCl_3) 6.18 (1H), 6.85 (1H), 7.4-7.8 (10H aromatic); (Found: C, 76.0; H, 3.65 $\text{C}_{20}\text{H}_{12}\text{O}_4$ requires C, 75.94; H, 3.79 %).

Debenzoylation of (II a): Compound (II a) (2 g.) in 90 % sulphuric acid (8ml) was heated rapidly to 140-145°C in an oil bath. After cooling the reaction mixture was poured into ice-water mixture. The solid product was filtered and dried which on recrystallization from benzene-ethanol mixture gave light yellow solid m.p. 241-243°C. The compound was found to be identical with second by product (B) The identity of two was established by m.p. mixed m.p. and comparison of

spectral data.

General method for the preparation of 2H, 5H-pyranopyran-2, 5-diones (IIb-g), (V); 4-Hydroxypyron (III) or (IV) (2.0 g.) and appropriate β -ketoester (8ml) in the presence of catalytic amount of sodium bicarbonate was refluxed for various periods of time. After cooling the solid product was filtered out, washed with ether and recrystallised from ethanol-benzene (II b), and benzene (II c-g), Reaction conditions and analytical data for individual compounds are given in the Table-II.

General method for the preparation of 4H, 5H-pyran (4, 3-b) pyran-4, 5-diones (VI a-d):-

3-Acyl-4-hydroxycoumarin was suspended or dissolved in acetic anhydride. The reaction mixture was cooled to 0°C and perchloric acid (72 %) was added dropwise with constant shaking. During the addition of perchloric acid the temperature of reaction mixture rose sharply which was maintained in the range of 40-50°C in order to obtain a clear solution of the reaction mixture. After 24 hours at room temperature the solid product was filtered off and crystallised from ethanol-water mixture. The reaction conditions for the individual compounds are given in table-III.

2-Methyl-7-phenyl-4H, 5H-pyran (4, 3-b) pyran-4, 5-diones (VII a):- A mixture of 3-acetyl-4-hydroxy-6-phenyl-pyran-2-one (2.0 g.) in acetic anhydride was cooled to below 0°C. Perchloric acid (72 %) (1.5ml) was added dropwise to the reaction mixture with continuous shaking keeping the temperature below 10°C. The resulting dark brown solution was kept at room temperature for 4 days. The dark brown solid was filtered out. Which on crystallisation from ethanol-water (1:3) mixture gave light yellow solid m.p. 225°C. ν_{\max} . 1753, 1668 cm^{-1} ; λ_{\max} . 334, 260; nmr (CDCl_3) 2.43 (s, 3H, 2), 6.20 (s, 1H, 8), 6.75 (s, 1H, 3), 5.6 (m, 5H Aromatic, 7); (Found:- C, 70, 55; H, 3.93; $\text{C}_{15}\text{H}_{10}\text{O}_4$ requires C, 70.89, h, 3.9 %).

2,3-Dimethyl-7-phenyl-4H, 5H-pyran (4, 3-b) pyran-4, 5-dione (VII b):- A mixture of 4-hydroxy-3-propionyl-6-phenyl-pyran-2-one (2 g.) and acetic anhydride (40ml) was cooled to below 0°C in ice-salt freezing mixture. Perchloric acid (72 %) (4ml) was added dropwise with vigorous shaking temperature rose sharply during the addition of perchloric acid and was controlled at 30-35°C to obtain the clear solution of the reaction mixture which was left at ambient temperature for 2 hours. The solid product was filtered which on crystallisation from water-ethanol. mixture gave white

Table-II.
Reaction conditions for the preparation of (IIb-g), (VI) and analytical data (IIb-g)

Products	4-Hydroxy-pyrone(III)	keto esters (R' COCHR'' COOEt.	Reflux time (Hrs.)	m.p. °C	Yield %
IIb	b	R'=Ph R''=H	5	241-243	35
c	b	R'=Me R''=H	1	233	50
d	b	R'=Me R''=Me	1	215	40
e	a	R'=Ph R''=H	3	208	35
f	a	R'=Me R''=Me	1	210	50
g	a	R'=Me R''=H	0.5	217 (Lit. ^{5a} 215)	60
V a	4-Hydroxy coumarin (IV)	R'=Me R''=H	0.25	244-245 (Lit. ^{5d} 243)	60
b	"	R'=Me R''=Me	1	216 (Lit. ^{5c} 216-217.5)	50
c	"	R'=Ph R''=H	3	204-205 (Lit. ^{5c} 204-205)	60
d	"	R'=Me R''=PhCH ₂	1	185 (Lit. ^{5c} 181.5-184)	50
e	"	R'=Me R''=Cl	1	(Lit. ^{5c} 265-265.7)	

Analytical data (IIb-g)

Products.	Formula	Found		Calculated	
		C	H	C	H
IIb	C ₂₀ H ₁₂ O ₄	76.0	3.65	75.94	3.79
c	C ₁₅ H ₁₀ O ₄	70.65	3.09	70.79	3.94
d	C ₁₆ H ₁₂ O ₄	71.65	4.53	71.64	4.48
e	C ₁₅ H ₁₀ O ₄	70.86	4.09	70.89	3.94
f	C ₁₁ H ₁₀ O ₄	64.06	5.03	64.08	4.86
g	C ₁₀ H ₈ O ₄	62.32	4.12	62.05	4.16

Table III. Reaction conditions for the preparation of 4H, 5H-pyrano [4,3-b] pyran-4,5-diones (VI).

Products. (VI).	3-Acyl-4-hydroxy coumarin (g)	Acid anhydride (ml).	HClO ₄ (ml).	Yield (%)	M.P. °C
a	COCH ₃ (3)	Ac ₂ O (40)	1	60	246-248 (Lit. ^{5d} 245°C)
b	COCH ₂ CH ₃ (30)	Ac ₂ O (50)	1.5	65	226-227 (Lit. ^{5c} 227-228°C)
c	COCH ₂ CH ₂ CH ₃ (3)	Ac ₂ O (40)	2	60	235-236 (Lit. ^{5c} 237°C).
d*	COCH ₂ CH ₃ (2)	(EtCO) ₂ O (30)	1.5	10	235-236 (Lit. ^{5c} 237°C).

*Reaction mixture was left at room temperature for one week. Solid was filtered out and the dark brown filtrate was poured into ether which gave additional quantity of the solid product,

needle m.p. 239-241°C. ν_{\max} . 1753, 1655; λ_{\max} . 331, 254; nmr (CDCl₃) 1.97 (s, 3H, 2), 2.34 (s, 3H, 3), 6.65 (s, 1H, 8), 7.4-7.9 (m, 5H aromatic, 7), (Found: C, 71.78; H, 4.75; C₁₆H₁₂O₄ requires C, 71.64; H, 4.4 %).

References.

1. F. Arndt, B. Eistort, H. Scholz and E. Aron., *Ber.* **69**, 2373, (1936).
2. (a) J.D. Bu' Lock and H.G. Smith. *J. Chem. Soc.*, **103**, 502 (1960). (b) M.A. Butt and J.A. Elvidge, *J. Chem. Soc.* 4483 (1963). (c) D. Herbst, W.B. Mors, O.R. Gottlieb and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959).
3. L. J. Bellamy, 'The Infrared spectra of complex molecules' Methuen. London 1964 p-137.
4. (a) H.V. Pechmann and C. Duisberg, *Ber.*, **16** 2199, (1883). (b) H. V. Pechmann and J.B. Cohen, *Ber.*, **17** 2829, (1884).
5. (a) Fleischmann, *J. Chem. Soc.*, **81**, 250 (1907). (b) F.C. Cheng and S.F. Ton, *J. Chem. Soc.* 543 (1969). (c) D. Cook and J.S. McIntyre *J. Org. Chem.*, **33**, 1748, (8968). (d) H. Mustafa, O.H Hismat, M. A.D. Zayed and A.H. Nawar *Tetrahedron*, **19**, 1831 (1963).
6. L.L. Woods, *J. Org. Chem.* **27**, 696 (1962).
7. (a) T. Money, *Chem. Review*, **70**, 553 (1970). (b) T.M. Harris, C.M. Harris and K.B. Hindley, *Fortschr. Chem. Org. Naturstoffe*, **31**, 217 (1974).
8. (a) I.El. Sayed El. Kholy, Fathi Kamel Rafla and M.M. Mishriky, *J. Chem. Soc. (C)*, 19579 (1970). (b) I.E.S.El. Kholy, F.K. Rafla and G. Soliman, *J. Chem. Soc.* 4490, (1961).
9. P.F.G. Prail and Whitear, *Proc. Chem. Soc.*, 122, (1961).
10. R.N. Lacey. *J. Chem. Soc.*, 854, (1954).
11. J.N. Collie *J. Chem. Soc.*, **59**, 607 (1891).