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SELF-CONDENSATION OF 1,3,4,6-TETRAKETONES. THE ELECTROCYCLIC REACTION OF A DIENONE SYSTEM DERIVED FROM THE DIENOLIC FORM.

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Summary: A synthesis of dihydropyrones 4 is described involving the dimerisation of tetraketones 1 and thermal reaction of intermediate dienone 2 derived from a dienolic system.

Recently we reported the first example of the biogenetic-type synthesis of an anthraquinone from the aliphatic polycarbonyl system, octane-2,4,5,7-tetrone[1]. Mechanistic considerations suggested intervention of a ketol 2[2], and now we wish to present a facile synthesis of an equivalent of this intermediate from the analogous 1,6-diarylhexane-1,3,4,6-tetrones 1a-c. The rather unexpected products 4 can be obtained by prolonged heating of a solution of tetraketones 1 in carbon tetrachloride.

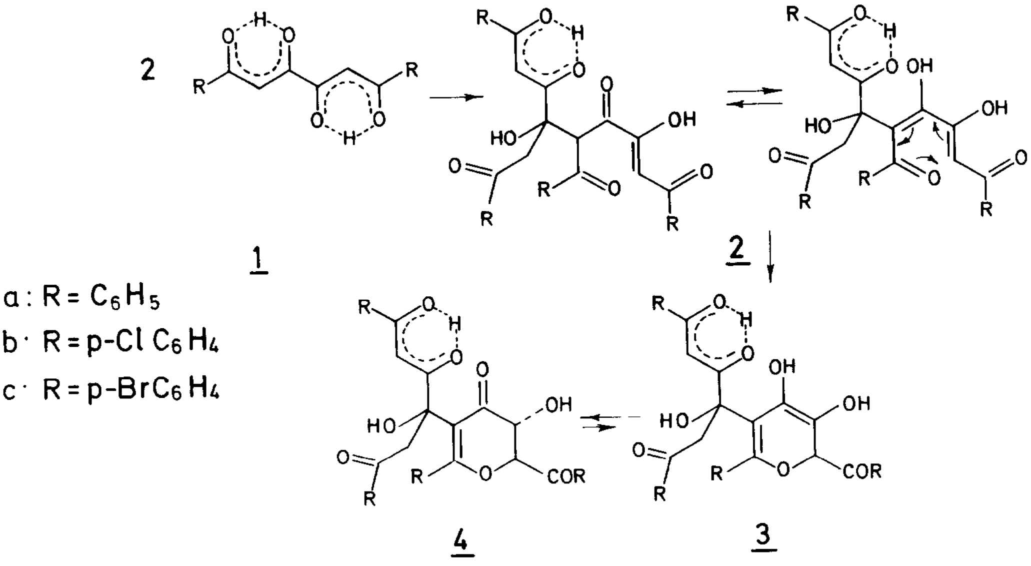


Table: 2-Aroyl-6-aryl-5-(1′,6′-diaryl-4′-hydroxy-1′,3′,6′-trioxo-4′-hexyl)-2,3-dihydro-5-hydroxy-4*H*-pyran-4-ones (4).

Compd[a]	Yield[b]	Recrystn solvent	m.p. (°C)[c]	λ_{max} (nm)[d]	R*f*[e]	Other data
a	41%	carbon tetrachloride	130-1 d.	250,332	0.38	[3]
b	49%	chloroform	176-7 d.	259,333	0.20	[4]
c	49%	chloroform	180-1 d.	263,333	0.23	[5]

a) Satisfactory analytical data (± 0.3% for C,H,Cl,and Br) were obtained for all compounds listed in the Table. *b)* Yields are based on recrystallized products. *c)* M. ps. are uncorrected. *d)* Methanolic solutions. *e)* TLC: Silica gel HF(Merck) chloroform-methanol (9:1); red spots after spraying with 1% methanolic $FeCl_3$.

General procedure : 1,6-Diarylhexane-1,3,4,6-tetrone (1, 0.01 mole), prepared according to original procedure[6], was dissolved in carbon tetrachloride (350 ml) and reflux maintained for ten days (bath temperature 120°). Concentration of orange-red solution yielded a colourless crystalline solid, which was then recrystallized from an appropriate solvent to give the dimer 4 as colourless needles. The results for individual compounds are summarized in the Table. Attempts to prepare carbonyl or hydroxyl derivatives resulted in disruption of 4, giving in most cases complex mixtures of products.

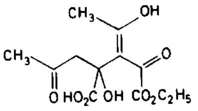
The structures 4 were assigned on the basis of their characteristic spectral properties. In the mass spectrum of 4a a weak molecular ion was observed at m/e 588, and the fragments at m/e 570, 552, and 534 are due to loss of water. The most intense ion of higher masses appears at m/e 406. This corresponds to the loss of two molecules of water and to elimination of the β-dicarbonyl residue from the side-chain. The subsequent loss of benzoyl gave an intense ion at m/e 301. ^1H and ^{13}C NMR spectra exhibited a simple pattern which indicated the presence of only one diastereomeric species. ^1H NMR spectrum of 4a in deuteriochloroform displayed an AB system at δ 3.44 (^2J=17.2) characteristic of diastereotopic phenacyl protons[2]. The two one-proton doublets at δ 6.16 and 5.08, owing to the dihydropyrone hydrogens, permitted the conformational assignment. Compounds 4 most likely exist in either the half-chair or in the boat conformation. Comparison of the two sets of dihedral angles shows that data derived from the vicinal coupling constant (^3J=10.0) favour the half-chair conformation of the dihydropyrone ring with *trans*-diaxial hydrogens. In the ^{13}C NMR the resonance for phenacyl methylene group appeared as triplet at 34.2 ppm, along with two doublets at 46.8 and 57.3 ppm for C(5) and C(6), respectively. The enolic and hydroxylic protons were readily exchanged *in situ*, and on prolonged treatment with an excess of deuterium oxide the exchange took place at the 5-position of the ring indicating a keto-enediol equilibrium $4 \rightleftarrows 3$. Under same conditions both hydrogens of the β-diketone moiety were exchanged, as might be expected for a mobile keto-enol equilibrium. In polar solvents, however, the dimers 4 exhibited very complex NMR patterns, presumably on account of both conformational changes and ring-chain tautomeric equilibria[7]. The infrared spectra showed strong bands at 3390,1680,1665,and 1655 cm^{-1} (not affected by dilution) indicating the intramolecular hydrogen bonding in the dimers 4[8].

The two stages in the conversion 1 → 4 occur with different rates. The self-condensation of tetraketones 1 leading to the intermediate ketol 2 requires refluxing for several days[9]. The final product 4 crystallized on cooling along with the unchanged 1. The fact that no ketol 2 could be isolated from the reaction mixture suggests that subsequent cyclisation occurs fairly rapidly. Among several mechanistic possibilities for the cyclisation step, the thermal reaction of the dienone system appears the most probable under the reaction conditions[10]. This particular reaction indicates that both the *(E,Z)*-geometry and the *s-cis*-conformation of enolic double bonds guide the cyclisation. In line with this view the other polycarbonyl systems, such as the parent tetraketones 1 or their *O*-substituted derivatives, either without access to the favourable geometry or undergoing the facile competitive tautomerism into the cyclic forms[7], exhibited no such thermal reactions. The bulky group introduces a substantial hindrance to coplanarity in the enolized intermediate 2, forcing the dienone into the actual reacting *s-cis-(E,Z)* species 2, and the system assumes a distorted chair arrangement geometrically suitable for a cyclic process. The subsequent ketonization of the cyclic enediol 3 leads to the dihydropyrone 4.

An extension of these observations to related carbonyl systems as well as the synthetic utility of these reactions is currently being investigated[11].

REFERENCES AND NOTES

1. K.Balenović and M.Poje, *Tetrahedron Letters* 1975, 3427.
2. The isolation of an analogous ketol i was reported for a closely related system, ethyl 2,4-dioxovalerate, in reaction of its sodium salt with aqueous acetic acid. The treatment of i with an excess of barium hydroxide afforded 3-hydroxy-5-methyl-benzoic acid: L.Claisen and N.Stylos, *Ber.* 20, 2190 (1887); L.Claisen, *ibid.* 22, 3271 (1889). We prepared i as the model compound: m.p. 90-1° (from water); ^{1}H NMR(DMSO-d_6), δ 6.50(br,3H), 4.18(q,2H,J=7.0), 3.50(d,d,2H,^2J=17.7, $\Delta\nu$=23.3), 2.47(s,3H), 2.13(s,3H), 1.19(t,3H,J=7.0).



i

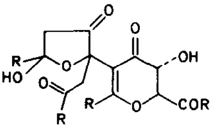
3. Spectral data for 4a: IR(KBr) 3390(br),1769(m),1679(vs),1662(s),1656(s),1598 (vs),1450(s),1230(vs),1221(vs),1095(m),752(s),683(vs)/cm. ^{1}H NMR(CDCl$_3$), δ 15.5 (br,1H), 8.25-7.05 (um,20H), 6.77 (s,1H), 6.24 (s,1H), 6.16 (d,1H,J=10.0), 5.60 (s ,1H), 5.08 (d,1H,J=10.0) , 3.44 (d,d,2H,J=17.2,$\Delta\nu$=32.2). After treatment with D$_2$O for 5 days: δ 8.25-7.05 (um,20H), 6.15 (s,1H), 3.44 (d,d,2H). ^{13}C NMR(CDCl$_3$), 195.4(s),190.9(s),190.7(s),189.7(s),188.9(s),181.4(s),136.7-127.2(m),95.4(d),85.1(s),82.2(s),53.7(d),46.8(d),34.7(t). Mass spectrum, m/e (rel. intensity) 588(0.1),570(0.5),552(0.7),534(0.5),524(0.5),465(0.6),448(1.7), 447(4.1),437(1.4),431(2.2),430(5.4),408(6.0),407(35.0),406(82.3),352(1.3),331 (1.5),307(4.5),306(6.6),302(11.8),301(58.3),273(10.2),223(4.3),196(4.0),147 (4.8),122(7.4),120(9.0),115(5.5),106(28.4),105(100.0),77(50.0),51(21.8).

4. Spectral data for <u>4b</u>: IR(KBr) 3390(br),1769(m),1678(s),1665(s),1655(s),1593 (vs),1488(m),1405(ms),1232(m),1218(ms),1093(vs),1012(m),800(ms) cm^{-1}.

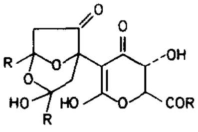
5. Spectral data for <u>4c</u>: IR(KBr) 3390(br),1769(m),1676(s),1665(s),1655(s),1587 (vs),1487(m),1400(ms),1230(ms),1071(vs),1009(ms),1000(ms),797(ms) cm^{-1}.

6. P.F.Schmidt, *Ber.* <u>28</u>, 1206 (1895); D.Keglević, M.Malnar, and T.Tomljenović, *Arhiv Kem.* <u>26</u>, 67 (1954).

7. Ring-chain tautomerism in tetraketone series <u>1</u> was established recently. The cyclic tautomers, 2-hydroxy-3(2*H*)-furanones, were obtained in the pure form: M.Poje and K.Balenović, *J. Heterocyclic Chem.*, in press. It is likely that tautomeric equilibria of <u>4</u> in polar solvents may involve similar cyclic structures <u>ii</u> and/or <u>iii</u>.



II



III

8. Infrared spectra of <u>4</u> exhibited a curious peak of medium intensity at 1769 cm^{-1}. When dissolved in tetrachloroethylene, tetraketone <u>1a</u> as well as several bis(β-diketones) also showed bands at 1779 and 1761 cm^{-1} which were absent from the spectra in bromoform or in the solid phase: D.F.Martin, M.Shamma, and W.C.Fernelius, *J. Am. Chem. Soc.* <u>80</u>, 4891 (1958); the authors proposed the greater tendency for these compounds to exist in keto-form in tetrachloroethylene. However, our ^1H NMR study showed no difference between the spectra of <u>1a</u> in tetrachloroethylene and deuteriochloroform solutions: δ 15.7 (br,2H), 8.03-7.55 (um,10H), 7.13 (s,2H).

9. When kept for several days in contact with an anion exchange resin, biacetyl undergoes a similar self-condensation into a trimeric derivative, 2,5-diacetyl-3a,5,6,6a-tetrahydro-6a-hydroxy-2,3a,5-trimethylfuro[2,3-d]-1,3-dioxole. R.M.Cresswell, W.R.Smyth, and H.C.S.Wood, *J. Chem. Soc.* <u>1961</u>, 4882; the crystalline product is the same as that which separates from some specimens of biacetyl which have been stored for long periods. The structure of the trimer is derived from the dimeric aldol in cyclic form, the third molecule of biacetyl being attached by successive acetal linkages. It is thus realistic to consider the process of formation of the intermediate <u>2</u> as an aldol-type condensation. It appears that an α-dicarbonyl group is necessary for the reaction to take place, and the initial activation probably involves the enolic groupings.

10. A comparable reaction occurs in *cis*-dienones which are valence isomers of 2*H*-pyrans. It seems probable that these thermal transformations might be assisted by a carbonyl group in the δ-position: G.Maier and M.Wiessler, *Tetrahedron Letters* <u>1969</u>, 4987; P.Schiess and H.L.Chia, *Helv. Chim. Acta* <u>53</u>, 485 (1970). It is noteworthy that L.Claisen, *Ann.* <u>291</u>, 126 (1896); W.Dieckmann, *Ber.* <u>53</u>, 1772 (1920); and K.v.Auwers and W.Dieckmann, *ibid.* <u>56</u>, 1527 (1923) reported the thermal isomerisation of mesityloxideoxalic esters into corresponding dihydropyrones. The rearranging dienone system involves an ordinary and an enolic double bond along with the α-dicarbonyl group, being closely related to that in <u>2</u> with two enolic double bonds.

11. We thank Dr. E. Haslinger of the Institute of Organic Chemistry, Vienna, for the ^{13}C NMR spectra. This research was assisted financially by the Croatian Republic Research Fund.

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