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THE CONDENSATION OF p-TROPOQUINONES WITH 5-HYDROXYTROPOLONE: A "PHENOL OXIDATION REACTION" IN THE TROPONOID SYSTEM

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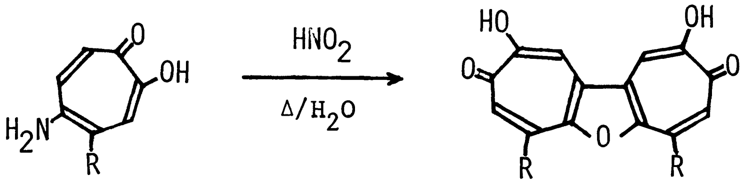
Condensation of *p*-tropoquinones and 5-hydroxytropolones, preferably by acid, yielded dicycloheptafurandione derivatives, which have the same carbon framework with utahin, a naturally-occurring dimeric tropolone. Partial oxidation of 5-hydroxytropolones and partial reduction of *p*-tropoquinones respectively yielded the condensates. This should exemplify the "phenol oxidation" in troponoids.

The phenol oxidation is an important reaction in the biogenesis of naturally occurring phenolic compounds,1) and many of the complicated natural products have been totally synthesized by this method.2) Tropolones, having a sort of phenolic hydroxyl, are also capable of this reaction as utilized in the Scott's total synthesis of colchicine.3) Interestingly, utahin (**A**), a metabolite from *Juniperus utahensis Lemm.*,4) was suggested to be identical5) with the product obtained by an oxidative dimerization of 5-aminohinokitiol (**B**) with nitrous acid in hot water;6) the biogenesis of **A** is therefore likely to involve the phenol oxidation. For the same type of a dimeric condensate from 5-amino-4-methyltropolone (**C**), the structure (**D**), 2,10-dihydroxy-5,7-dimethyl-3,9(2H)-dicycloheptafuran-3,9-dione, has been assigned by Haworth *et al.*7) This paper will describe the dicycloheptafurandione formations based on the phenol oxidation of the 5-hydroxytropolones, together with a reductive condensation of *p*-tropoquinones.



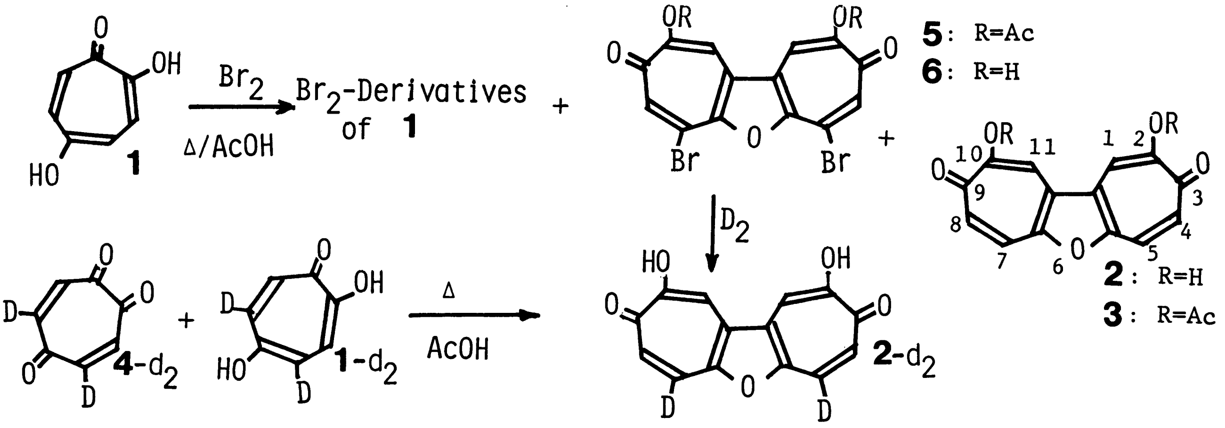
B: R=CHMe$_2$
C: R=Me

A: R=CHMe$_2$
D: R=Me

During the study of the bromination of 5-hydroxytropolone (**1**),8,9) we have noticed a formation of sparingly soluble by-products, which seemed to be a mixture of the dimeric condensates of the troponoid. By inspections of the mass spectrum, this dark-colored material was shown to be a mixture of bromine-free (**2**, $C_{14}H_8O_5$) and its monobromo, dibromo, and tribromo derivatives.

The catalytic hydrogenation of this mixture gave dark-green plates (**2**), mp >300°C, which can be characterized as a diacetate (**3**), mp 219-220°C [δ:10) 2.35 (6H, s), 7.20(2H, d, J=12 Hz), 7.57(2H, d, J=12 Hz), and 7.64(2H, s). δ(C): 20.6, 118.7, 122.6, 125.3, 136.8, 154.1, 154.3, 168.3, and 178.2(all for 2C)]. The IR spectrum of 2 [ν: 1620, 1545 cm^{-1}] still showed the characteristic peaks due to the troponoid ring, and the NMR spectrum of 2 [δ^{TFA}: 8.20(2H, d, J=12 Hz), 8.54 (2H, d, J=12 Hz), and 8.68(2H, s)], indicated its structure to be symmetrical. The UV spectrum of 2 [$\lambda_{max}^{CHCl_3}$: 272 nm(ε=76800), 385(30300), 403(63300), 413(50500)] was similar to that of D.

The condensation of 1-4,6-d_2 and 4,6-dideuterio-*p*-tropoquinone (4-4,6-d_2) in refluxing acetic acid formed 2-d_2 [Found: *m/e*, 258.0486 (M^+). Calcd for $C_{14}H_6D_2O_5$: 258.0473. δ^{TFA}: 8.23(2H, s) and 8.70(2H, s)]. Therefore, the C-C bond formation occurred at the 4-position of the troponoids, and the structure of 2 must be expressed as 2,10-dihydroxy-3,9(2H)-dicycloheptafuran-3,9-dione. The formation of bromine-free condensate, 2, during the bromination and an independent derivation of 2 from 1 and 4 in acid suggested that the bromination of 1[9] may proceed not in a fashion of simple electrophilic substitution but in a two-step reaction involving an oxidation to 4 and subsequent conjugate addition of hydrobromic acid.[11]



Although, the least soluble component, 2, could be isolated by fractional recrystallizations, the further fractionations of the mixture were carried out by an intensive column and high-pressure liquid chromatography on their acetate mixture, and from a fraction containing dibromo derivatives, a diacetate (5), mp 241-242°C, of the major compound (6), mp>300°C, was isolated. The NMR spectrum of 5 [δ: 2.36(6H, s), 7.50(2H, s), and 7.78(2H, s). δ(C): 20.6, 117.6, 121.7, 124.1, 140.3, 151.2, 153.9, 168.0, and 175.3(all for 2C)], clarified it to be symmetrical.[12] The positions of bromine atoms were elucidated by the NMR comparison after reduction with deuterium gas to the d_2-derivative of 2; since the reduction product of 6 was identical with the d_2-condensate, 2-5,7-d_2, derived from 1-4,6-d_2 and 4-4,6-d_2, 6 must be the 5,7-dibromo derivative.

Furthermore, 2 was obtained also in the silver-salt-mediated oxidation of 1 to 4,[9] if the oxidizing agent were less than the stoichiometric quantity. This could be the "phenol oxidation reaction" taken place in the troponoid series.

Interestingly, when 4 was irradiated in methanol by means of a high-pressure mercury lamp, 2 was isolated as a by-product of methyl (2,5-dioxo-3-cyclopentenyl)-acetate,[13] and this formation of 2 does not contradict to the previously-noticed photochemical reduction of 4 to 1.[14]

The formation of 2 under various conditions was compiled in Table 1.

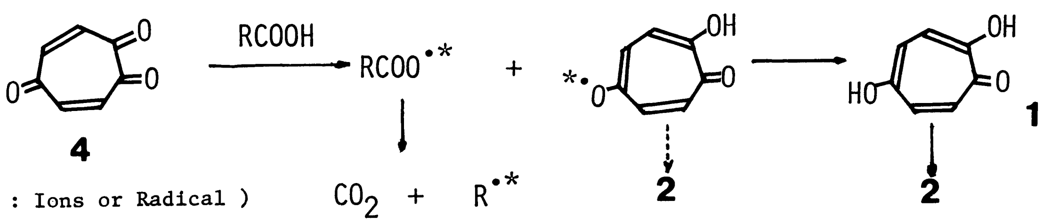
Table 1. The Formation of 2, a Dicycloheptafurandione.

Runs	Quantities/mmol (1)	(4)	(Additives)	Conditions	Yields/% of **2**
1	0.3	0.3		117°C, 2 h, A[a]	41
2	0.5	0.5	BP=0.05	117°C, 4 h, A	22
3	0.7	0.7	BP=0.35	117°C, 1.5 h, A	28.
4	0.7	—	BP=0.7	117°C, 2 h, A	6
5	0.5	0.5		80°C, 2 h, D[a]	trace
6	0.75	0.75		80°C, 2 h, B[a]	12
7	—	0.9		117°C, 2.5 h, A	49
8	—	15		117°C, 2 h, A	67
9	—	1.0		141°C, 0.5 h, P[a]	52
10	—	0.5		$h\nu$,[b] 15°C, 5 min, M[a]	12
11	1.5	—	AgOAc=1.5	117°C, 1 h, A	11

a) A=acetic acid, D=dimethylformamide, B=benzene, P=propionic acid, and M=methanol. b) Irradiations were performed by means of a high-pressure mercury lamp.

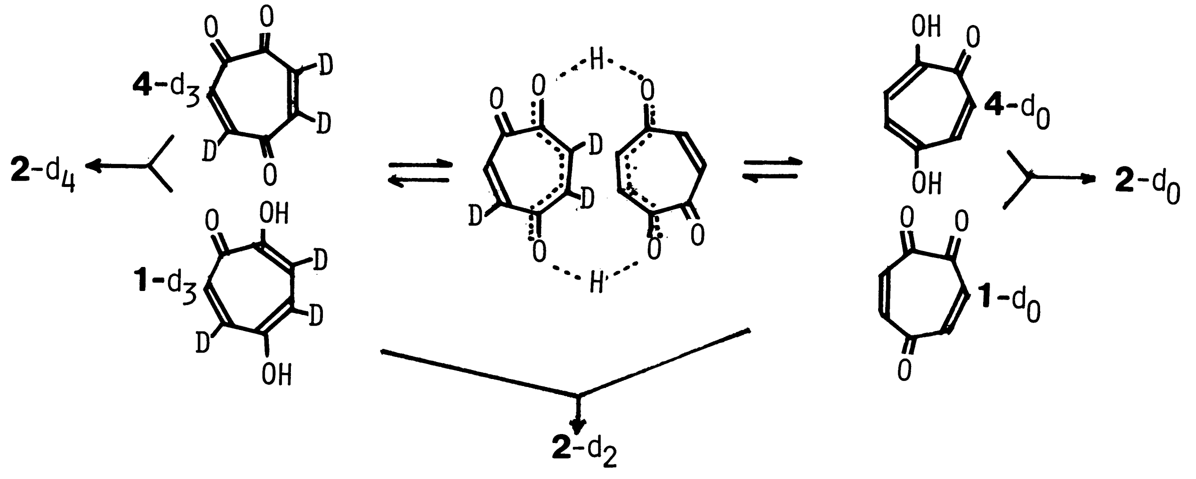
As shown in Table 1, an attempted generation of a radical species from 1, 5-hydroxytroponyloxy radical, through the hydrogen-abstraction process by benzoyl peroxide (BP) led to a formation of a small amount of 2, but this method was inferior in a practical stand point; probably, 4 suffered a further decomposition by the action of BP.

On the contrary, reductive condensation of 4, in the absence of oxidizing agent, gave better results than the above oxidative condensation of 1; when an acetic acid solution of 4 was refluxed for 2.5 h, 2 was formed in a considerably good yield, 67%, as the only identifiable condensate. Rather surprising feature in this case was the occurrence of chemical reduction of 4 to 1 by acetic acid, and recovered troponoid in the reaction of a 1:1-mixture of the two was only 1, 28%. This chemical reduction of 4 to 1 was also effective in propionic acid. By titration, the liberated carbon dioxide, trapped as barium carbonate, was determined to be 67%; from 1.0 mmol of 4 in the acid, 0.2 mmol of 2 and 0.4 mmol of 1 were formed with an evolution of 0.4 mmol CO_2 (Calcd: 0.6 mmol). Thus, it is certain that an oxidative decarboxylation of the carboxylic acid is accompanied by a reduction of 4 to 1, however, a fate of the decarboxylated off-spring is unknown.



(•* : Ions or Radical)

Another characteristic feature on the mechanism of formation is that the condensate, 2-*d*, from either 1-3,4,6-d_3 and 4 or 1 and 4-3,4,6-d_3 in refluxing acetic acid for 2 h is shown to contain not only 2-d_2, but also 2-d_0 and 2-d_4. Thus, a rapid redox equilibrium between 1 and 4 must occur in this system, and may be playing an important role in the condensation;[15)] several attempts for obtaining the cross-condensates from 4 and phenols or tropolone (E) in the acid failed, *e.g.*, 4 and E merely gave 2 (51%) and the unreacted E (98%).



Further fractionations of the bromination mixture of 1 and related experiments to prepare derivatives of 2 will be reported in a full paper.

References

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8) The early paper[6)] has in fact recorded a formation of pale green needles, mp 188-189°C, in small amounts by bromination of 1.

9) H. Takeshita, T. Kusaba, and A. Mori, *Bull. Chem. Soc. Jpn.*, 55, in press (1982).

10) The NMR spectra were measured in either CF_3COOD (TFA) or $CDCl_3$ solutions, and the chemical shifts were expressed in the δ unit from the internal Me_4Si.

11) S. Itô and M. Hirama (*Tetrahedron Lett.*, 1976, 2339) have observed a formation of 4-chloro-5-hydroxytropolone from 4 and hydrochloric acid.

12) The NMR spectral measurement of 6 was difficult due to its insufficient solubility and quantity in hands.

13) A. Mori and H. Takeshita, *Kyushu Daigaku Sogo Rikogaku Kenkyuka Hokoku*, 3, 125 (1981).

14) Y. Shoji and S. Itô, Abstract Papers of 6th Symposium of the Chemistry of Non-Benzenoid Aromatic Compounds (Fukuoka, Oct. 1973), p 132.

15) This may be a good indication for the quinhydrone formation, but at this stage, the intermediacy of such species in the condensation remains as a matter of an independent study.

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