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Reactions of Hydroxyxanthones. IV.¹ Action of Lithium Aluminum Hydride and of Diazomethane on Hydroxyxanthones

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Treatment of 1-hydroxy-9-xanthones (I and II) and their benzoyl and/or benzenesulfonyl derivatives with lithium aluminum hydride led to the formation of the corresponding xanthene derivatives (IVa and V), respectively. Similar results were obtained with the benzenesulfonyl derivative of 1-hydroxybenzo[b]xanthen-12-one (IIIb), reduction of which yielded 1-hydroxybenzo[b]xanthene (VI).

1-Methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa) now has been obtained by the oxidation of the product which is obtained on treatment of 1-methyl-4-hydroxy- (VIIa), and 1-methyl-4-benzoyloxy-10-thiaxanthenones (VIIb) with lithium aluminum hydride.

Whereas methylation of 4-hydroxy-9-xanthenone could be effected with ethereal diazomethane, methylation of 1-hydroxy-9-xanthenone could only be brought about by the action of ethereal diazomethane in presence of methanol.

It has been found that when certain aromatic ketones containing amino or methoxyl groups ortho or para to the carbonyl group are reduced under forcing conditions with excess of lithium aluminum hydride at elevated temperatures for long periods. hydrogenolysis occurs to a methyl or methylene group.² Recently, similar behavior has been reported in the xanthone series. Thus reduction of xanthones, e.g., 9-xanthenone, 1,2-benzo-, and 3,4benzo-9-xanthenones3 and 10-thiaxanthenone with lithium aluminum hydride proceeds one step further to give the corresponding xanthenes.⁴ Halogensubstituted-9-xanthenones, e.g., 2-chloro-, and 4chloro-9-xanthenones undergo reduction with the same reagent leading to the formation of xanthene in every case with the loss of halogen.⁵ The reaction was carried out in all cases in boiling ether-benzene solution.3,5

The reduction of hydroxy-9-xanthenones and

(3) A. Mustafa and M. K. Hilmy, J. Chem. Soc., 1343 (1952).

(4) Cf. the reduction of decussatin methyl ether (1,2,5,6-tetramethoxy-9-xanthenone) to the xanthene derivative when boiled with excess of lithium aluminum hydride in ether for 12 hr. [R. C. Shah, A. B. Kulkarni, and C. G. Joshi, J. Sci. Ind. Research (India), 13B, 186 (1954)].

(5) A. Mustafa, W. Asker, and M. E. E. Sobhy, J. Am. Chem. Soc., 77, 5121 (1955).

their benzoyl and/or benzenesulfonyl derivatives with lithium aluminum hydride under similar conditions now has been investigated. Thus, when 1-hydroxy-9-xanthenone (Ia) and 1-hydroxy-3-methyl-9-xanthenone (IIa) are allowed to react with the same reagent in boiling ether-benzene solution for three hours and kept aside at room temperature overnight, followed by hydrolysis, the corresponding xanthene derivatives, namely, 1-hydroxy-(IVa) and 1-hydroxy-3-methylxanthene (V), are obtained respectively in an almost quantitative yield. Fractional crystallization of the reaction products does not reveal the presence of the corresponding hydrols.⁶

Reduction of the benzenesulfonyl derivative of 1hydroxy-9-xanthenone (Ic) and of 1-hydroxybenzo-[b]xanthene-12-one (IIIb) with the same reagent, under the same experimental conditions, effects the cleavage of the ester, with the formation of the corresponding hydroxyxanthene derivative (IVa and VI respectively) together with thiophenol. Simi-



(6) Cf. the reduction of xanthone to xanthhydrol with the same reagent [R. Mirza and R. Robinson, Nature, 166, 997 (1950)].

⁽¹⁾ For Part III cf. A. Mustafa and O. H. Hishmat, J. Am. Chem. Soc., 79, 2225 (1957).

⁽²⁾ Cf. the hydrogenolysis of p-aminobenzophenone
[L. H. Conover and D. S. Tarbell, J. Am. Chem. Soc., 72, 3586 (1950)], 2-formyl-, and 2-acetylpyrroles
[A. Treibs and H. Scherer, Ann., 577, 139 (1952); A. Treibs and H. Derra-Scherer, Ann., 589, 188 (1954); W. Herz and C. F. Courtney, J. Am. Chem. Soc., 76, 576 (1954)], 3-formyl-, 3-acetyl, and 3-benzoylpyrroles
[A. Treibs and H. Scherer, loc. cit.; E. D. Rossiter and J. E. Saxton, J. Chem. Soc., 76, 3654 (1953)]; 4-0x0-1,2,3,4-tetrahydroquinoline
[W. S. Johnson and B. G. Buell, J. Am. Chem. Soc., 74, 4517 (1952)], spiro[cyclopentane-1,2'-indolin)-3'-one (B. Witkop, J. Am. Chem. Soc., 72, 614 (1950); W. Witkop and J. B. Patrick, Experientia, 6, 183 (1950)], 2-methyl-2-(2'-methyl-3'-indolyl)indoxyl [B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 73, 713 (1951)], as well as derivatives of acridone [G. M. Badger, J. H. Seidler, and B. Thomson, J. Chem. Soc., 3207 (1951)].

larly, V was produced by the action of lithium aluminum hydride on 1-benzoyloxy-3-methyl-9-xanthenone (IIb).

Whereas the esters of hydroxy-9-xanthenones, e.g. (Ic), are readily cleaved by the action of lithium aluminum hydride, the ether linkage in 1methoxy-9-xanthenone (Ib) is stable toward the same reagent.^{4,7} Thus, 1-methoxyxanthene (IVb) is obtained when (Ib) is allowed to react with the same reagent. IV was proved to be identical with the product, obtained by the action of dimethyl sulfate on an acetone solution of IVa in the presence of anhydrous potassium carbonate.

1-Methyl-4-hydroxy-10-thiaxanthenone (VIIa) undergoes reduction with lithium aluminum hydride to give an oily substance, probably 1-methyl-4-hydroxythiaxanthene, which upon treatment with hydrogen peroxide in glacial acetic acid gives 1-methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa). The same substance was also obtained by the oxidation of the oily substance, obtained by reduction of 1-methyl-4-benzoyloxy-10-thiaxanthenone (VIIb) with the same reagent. Treatment 1-methoxy-4-benzoyloxy-10-thiaxanthenoneof 5,5-dioxide (VIId) with amalgamated zinc dust, acetic and hydrochloric acids under the experimental conditions described by Fehnel⁸ for the preparation of thiaxanthene-5,5-dioxide, led to the formation of a solid substance, which upon hydrolysis with alcoholic sodium hydroxide gave VIIIa.



Whereas VIIa is stable toward the action of hydrogen peroxide in glacial acetic acid, under conditions which bring about the oxidation of 10-thiaxanthenone to 10-thiaxanthenone-5,5-dioxide, 1methyl-4-benzoyloxy-10-thiaxanthenone (VIIb) is readily oxidized with the same reagent to VIId in an almost quantitative yield. The reduction of VIId with lithium aluminum hydride, under conditions similar to those used for VIIb, led to the formation of an oily substance which upon oxidation with hydrogen peroxide in acetic acid gave VIIIa.

Reactions with diazomethane. It has been pointed out that certain o-hydroxy compounds are not methylated by an ethereal solution of diazomethane, e.g., alizarin-2-methyl ether,⁹ 9,10-dihydroxynaphthalene-11,12-quinone,¹⁰ and o-hydroxyketones, e.g., o-hydroxyacetophenone.¹¹ This stability is also shown by o-hydroxybenzophenone, 1-hydroxy-, 1,5-dihydroxy-, and 1,4-dihydroxyanthraquinones, and by the 4-methyl ether of resacetophenone.¹¹



The generally accepted reason¹² for the stability of o-hydroxyketones and related compounds toward diazomethane is the formation of a chelated ring system (*e.g.* IX in the case of o-hydroxyacetophenone).

We now have investigated the behavior of Ia, an o-hydroxyketone,¹³ toward the action of ethereal diazomethane solution. Thus, when Ia is treated with an excess of the same reagent, it is recovered almost completely. But, when methyl alcohol was added to the reaction mixture, Ib was obtained together with unchanged Ia. This reaction finds a parallel in the stability of o-hydroxy compounds, *e.g.*, o-hydroxyacetophenone toward ethereal diazomethane solution, and their ready methylation in presence of methanol.¹¹

Whereas, Ia is stable or almost stable toward the action of ethereal diazomethane solution, 4-hydroxy-9-xanthenone is methylated with an excess of the same reagent to give 4-methoxy-9-xanthenone.

EXPERIMENTAL

Action of lithium aluminum hydride. General procedure. Solvents dried over sodium were used. To 0.7 g. of lithium aluminum hydride (New Metals and Chemicals, Ltd., London) was added 50 ml. of ether. After 15 min. a benzene solution (30 ml.) containing 1 g. of each of Ia-c, IIa-b, and IIIb was added portionwise. The reaction mixture was refluxed for 3 hr. and then kept overnight at room temperature. After treatment with cold aqueous ammonium chloride solution the ethereal solutions were worked up as follows: The solid residues which were obtained after washing with light petroleum (b.p. below 40°; 40 ml.) were crystallized from a suitable solvent to yield the xanthene derivatives listed in Table I.

In the case of Ic and IIIb evaporation of the light petroleum washings gave an oily residue which was identified as thiophenol *via* the preparation of its benzoyl derivative (melting point and mixed melting point with phenylthiobenzoate).

(10) A. Schönberg and R. Moubasher, J. Chem. Soc., 366 (1944).

(11) A. Schönberg and A. Mustafa, J. Chem. Soc., 746 (1946).

⁽⁷⁾ Cf. the stability of anisole toward the action of lithium aluminum hydride [P. Karrer, O. Rüttner, Helv. Chim. Acta, 33, 812 (1950)].

⁽⁸⁾ E. A. Fehnel, J. Am. Chem. Soc., 71, 1063 (1949).

⁽⁹⁾ J. Herzig and K. Klimosch, Monatsh., 30, 535 (1909).

⁽¹²⁾ Cf. H. V. Sidgwick and R. K. Callow, J. Chem. Soc.,
125, 527 (1924); A. G. Perkin and R. C. Storey, J. Chem. Soc., 233 (1928).

⁽¹³⁾ The hydroxyl group in position "1" in hydroxy-9-xanthenone results in the formation of stable chelated compounds, e.g., with nickel acetate and pyroboroacetate (O. Dimroth, Ann., 446, 97 (1926).

TABLE I

XANTHENES OBTAINED BY REDUCTION OF XANTHONES										
				Sol- vent			Analysis, %			
Starting		M.P., ^b	Yield,	for	Color with		Carbon		Hydrogen	
Material	Product ^a	°C.	%	Cryst.	H_2SO_4	Formula	Calcd.	Found	Calcd.	Found
Ia	IVa	144.5	82	A	Yellow-orange turning red	$C_{13}H_{10}O_2$	78.78	78.25	5.05	5.43
Ic	IVa	144.5	80	А	Yellow-orange turning red	$C_{13}H_{10}O_2$	78.78	78.62	5.05	4.98
Ib	\mathbf{IVb}	7071.5	85	В	Orange-red turning violet	$C_{14}H_{12}O_2$	79.24	79.26	5.66	5.46
IIa	v	137 - 138	77	Α	Reddish-orange	$C_{14}H_{12}O_2$	79.24	79.65	5.66	5.97
\mathbf{IIb}	v	137 - 138	72	\mathbf{A}	Reddish-orange					0.01
IIIb	VI	240	86	С	Reddish-brown turning red	$C_{17}H_{12}O_2$	82.26	81.99	4.84	5.38

^a All are soluble in aqueous sodium hydroxide solution except IVb. ^b Melting points are uncorrected. ^c A, petroleum ether (b.p. $80-100^{\circ}$); B, petroleum ether (b.p. $40-60^{\circ}$); C, ethyl alcohol.

Action of lithium aluminum hydride on: (a) 1-Methyl-4. benzoyloxy-10-thiaxanthenone (VIIb). One gram of VIIb¹⁴ was similarly treated with lithium aluminum hydride, followed by decomposition with a cold aqueous ammonium chloride solution containing a few drops of hydrochloric acid. Evaporation of the ethereal extract gave an oily residue; solution of the latter in glacial acetic acid was then treated with hydrogen peroxide (ca. 1 ml.) and was heated for 1 hr. (steam bath). The solid that separated on addition of a few drops of water to the cooled solution, was collected and crystallized from petroleum ether (b.p. 80–100°) as colorless crystals (ca. 0.56 g.), m.p. 141–142°.

Anal. Calcd. for $C_{14}H_{12}O_3S$: C, 64.61; H, 4.61; S, 12.31. Found: C, 64.61; H, 4.69; S, 11.93.

1-Methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa) dissolves readily in aqueous sodium hydroxide solution and develops a brownish red color when treated with concentrated sulfuric acid.

(b) 1-Methyl-4-hydroxy-10-thiaxanthenone (VIIa). Similar treatment of 1.5 g. of VIIa with lithium aluminum hydride under the general conditions led to the formation of an oily product which upon oxidation with hydrogen peroxide as described above gave VIIIa (ca. 0.62 g.); identified by melting point and mixed melting point.

(c) 1-Methyl-4-benzoyloxy-10-thiaxanthenone-5,5-dioxide (VIId). A solution of 2 g. of VIIb in glacial acetic acid (30 ml.) was treated with hydrogen peroxide (5 ml.) under the same experimental conditions described above. The crystals that separated upon cooling the reaction mixture were collected and crystallized from acetic acid as colorless crystals, m.p. 236°. The yield was almost quantitative.

Anal. Caled. for $C_{21}H_{14}O_5S$: C, 66.67; H, 3.70; S, 8.46. Found: C, 66.27; H, 3.82; S, 8.42.

1-Methyl-4-benzoyloxy-10-thiaxanthenone-5,5-dioxide (VIId) is insoluble in cold aqueous sodium hydroxide solution and gives a deep yellow color with concentrated sulfuric acid. When refluxed with alcoholic sodium hydroxide solution (10%) for 15 min., it gave a deep orange solution which upon acidification with dilute hydrochloric acid deposited pale yellow crystals of 1-methyl-4-hydroxy-10thiaxanthenone-5,5-dioxide (VIIc), m.p. 185°. Recrystallization from alcohol did not raise the m.p. Yield is ca. 70%.

Anal. Calcd. for $C_{14}H_{10}O_4S$: C, 61.31; H, 3.65; S, 11.68. Found: C, 61.17; H, 3.62; S, 11.54.

VIIc is soluble in hot aqueous sodium hydroxide solution and gives an orange color changing to red when treated with concentrated sulfuric acid.

Treatment of 1.1 g. of VIId with lithium aluminum

(14) R. N. Sen and S. C. Sen-Gupta, J. Indian Chem. Soc., 6, 267 (1929). hydride by the general experimental procedure gave an oily product which upon oxidation with hydrogen peroxide in acetic acid, as described above, produced VIIIa (m.p. and mixed m.p.). Yield is ca. 82%.

Reduction of VIId with zinc amalgam, acetic acid, and hydrochloric acid mixture. A procedure similar to that described by Fehnel⁸ for the preparation of thiaxanthene-5,5-dioxide was followed. A reaction mixture of 0.5 g. of VIId, 1.23 g. of zinc amalgam, 8 ml. of glacial acetic acid, and 2.5 ml. of hydrochloric acid was refluxed for 3 hr. The solid that separated out during the reaction was separated from the unchanged zinc and was crystallized from acetic acid as colorless crystals, m.p. 252° (ca. 0.3 g.). This was subjected directly to treatment with boiling alcoholic sodium hydroxide (10%; 30 ml.) for 15 min. The resulting orange alkaline solution gave, upon acidification with dilute hydrochloric acid and cooling, colorless solid which was crystallized from petroleum ether (b.p. 80-100°) as colorless crystals, m.p. 140°. It was identified as VIIIa (melting point and mixed melting point). The yield was almost quantitative.

Action of ethereal diazomethane solution on: (a) 1-Hydroxy-9-xanthenone (Ia). An ethereal solution of 0.6 g. of Ia¹⁵ was treated with excess of cold freshly distilled diazomethane solution (prepared from 8 g. of nitrosomethylurethane), and the mixture was left for 48 hr. at 0°. The ether was then evaporated. The product was identified as starting material by melting point and mixed melting point. (Yield was almost quantitative.)

The above experiment was repeated, but one ml. of methyl alcohol was added. The ethereal solution of the reaction mixture was washed with dilute aqueous sodium hydroxide solution (10%) when a canary yellow solid (sodium salt of Ia) separated. The ethereal layer was then washed with water thoroughly, dried, and evaporated. The colorless solid, so obtained, was crystallized from petroleum ether (b.p. 80–100°) as colorless crystals (ca. 0.43 g.), m.p. 136°. Identification as 1-methoxy-9-xanthenone was carried out by melting point and mixed melting point determination.¹⁶

Acidification of a suspension of the canary yellow solid in water gave yellow substance which upon crystallization yielded yellow needles (ca. 0.12 g.) which were identified as Ia (melting point and mixed melting point).

(b) 4-Hydroxy-9-xanthenone. Treatment of a suspension of 0.5 g. of 4-hydroxy-9-xanthenone¹⁷ in 50 ml. of dry ether with ethereal diazomethane solution, prepared as above,

(15) K. S. Pankajamani and T. R. Seshadri, J. Sci. Ind. Research (India), 13B, 396 (1954).

(16) J. Tambor, Ber., 43, 1883 (1910).

(17) F. Ullmann and M. Zlokasoff, Ber., 38, 2118 (1905).

in the absence of methyl alcohol resulted in the partial disappearance of the insoluble solid. The reaction mixture was filtered from the unchanged material and the ethereal solution was washed with cold aqueous sodium hydroxide solution (to remove any unchanged material), then with water, dried, and evaporated. The colorless solid, so obtained, was crystallized from ethyl alcohol as colorless crystals,

ca. 0.15 g., m.p. 169°. It was identified as 4-methoxy-9-xanthenone (melting point and mixed melting point¹⁷).

Acidification of the alkaline washings gave trace of unchanged 4-hydroxy-9-xanthenone.

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Synthesis of *beta*-(3,4-Methylenedioxyphenyl)tropic Acid and Its Derivatives. A Contribution to the Chemistry of the Perkin Reaction

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The belief that the Perkin synthesis involves an intermediate addition compound of the "aldol" type has been accepted since Perkin first described the reaction. Fittig reported the isolation of such an "aldol," but his compound was incapable of losing water, and therefore not a true intermediate. Hauser and Breslow prepared a true "aldol," and with their preparation the "aldol" view of the Perkin synthesis was regarded as established experimentally. Our synthesis of β -(3,4-methylenedioxyphenyl)tropic acid in good yield provides another example of a true "aldol" postulated in the Perkin reaction.

In connection with insecticide studies at Beltsville, Md., β -(3,4-methylenedioxyphenyl)tropic acid (V) and β -(3,4-methylenedioxyphenyl)atropic acid (VII) were synthesized and several of their esters tested as synergists for house flies. The synthesis of V in 65% yield provides another example of an "aldol"¹ intermediate postulated in the Perkin reaction.

Although the history of this interesting reaction dates from Perkin's synthesis of coumarin in the year 1868, uncertainty existed as to the roles of the acid anhydride and the sodium salt in the formation of "aldol" intermediates until just recently. Some textbooks in organic chemistry are still in opposition to Perkin's² original views that this synthesis of cinnamic acid involves the condensation of the aldehyde with the anhydride, the acid salt acting catalytically:

These writings on the subject follow the views of Fittig,³ who by an incorrect interpretation of his data believed that the Perkin synthesis occurs between the aldehyde and the sodium salt of the acid in two stages: first an "aldol" is formed, i.e., condensation took place between the aldehyde and the alpha carbon of the acid and then water was lost by the action of the anhydride.

The results of this investigation and a number of others provide substantial evidence in favor of Perkin's original view. Michael and Hartman⁴ presented strong evidence that reaction was between the aldehyde and the anhydride in the production of intermediate "aldols." Studies by Breslow and Hauser⁵ have led them to conclude that "there no longer need be any doubt that the anhydride condenses in the Perkin synthesis," and not the sodium salt.

Since the "aldol" view of the Perkin reaction has now received considerable support, its further substantiation by the actual isolation of the intermediate "aldols" becomes important. Fittig⁶ reported the preparation of 2,2-dimethyl-3-phenylhydracrylic acid (I).



Muller and co-workers' were unable to repeat this synthesis. Hauser and Breslow¹ were successful and prepared the ethyl ester (II) of I in 30% yield using

⁽¹⁾ H. B. Watson, Ann. Repts. Chem. Soc. (London), 36, 210 (1939), and C. R. Hauser and D. S. Breslow, J. Am. Chem. Soc., 61, 793 (1939), used the term "aldol" to represent beta-hydroxy intermediates.

⁽²⁾ W. H. Perkin, J. Chem. Soc., 388 (1877); 53, 181 (1868).

⁽³⁾ R. Fittig, Ann., 195, 169 (1879); 216, 97 (1883); 227, 48 (1885); Ber., 14, 1824 (1881); 16, 1436 (1883); 27, 2658 (1897).

⁽⁴⁾ A. Michael and R. N. Hartman, Ber., 34, 918 (1901): A. Michael, J. Prakt. Chem., 60, 364 (1899).
(5) D. S. Breslow and C. R. Hauser, J. Am. Chem. Soc.,

^{61, 786 (1939).}

⁽⁶⁾ R. Fittig and H. W. Jayne, Ann., 216, 115 (1883); R. Fittig and P. Ott, Ann., 227, 48, 61 (1885).

⁽⁷⁾ E. Muller, H. Gawlick, and W. Kreutzmann, Ann. 515, 97 (1935); E. Muller, Ann., 491, 251 (1931).