tilling water from a mixture of diisopropanolamine and aniline which had been made slightly acidic with concentrated hydrochloric acid. The crude piperazine derivative boiling at 120–125° (1.0 mm.) was used in the next step without further purification.

A suspension consisting of 9.0 g. (0.047 mole) of 2,6-dimethyl-1-phenyl-piperazine, 8.7 g. (0.047 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 10.9 g. (0.13 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 12 hr. The basic derivative was isolated following the procedure used in synthesizing the compounds reported in Table II. This substance boiled at 215–220° (0.4 mm.); 3.9 g. (25%).

Anal. Calcd. for $C_{22}H_{31}N_3$: C, 78.4; H, 9.2; N, 12.5. Found: C, 78.1; H, 9.4; N, 12.2.

The base was not characterized as a hydrochloride because of the hygroscopicity of the salt.

2-Hydroxymethyl-piperazine Dihydrobromide.—This intermediate was prepared by the interaction of 2,3-dibromopropanol-1 and the disodio derivative of N,N'-di-*p*-tosylethylenediamine in refluxing ethanol following the procedure previously described by Bach, Kushner and Williams,[1] m.p. 254–260° dec.

Anal. Calcd. for $C_5H_{14}Br_2N_2O$: C, 21.6; H, 5.0; Br, 57.6; N, 10.1. Found: C, 22.1; H, 5.3; Br, 58.0; N, 9.8.

1,4-Di-[β-(N-Ethyl-N-phenylamino)-ethyl]-2-hydroxymethylpiperazine.—A suspension consisting of 11.8 g. (0.0425 mole) of 2-hydroxymethylpiperazine dihydrobromide, 15.7 g. (0.085 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 42.0 g. (0.50 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 15 hr. After this period of time the reaction mixture was concentrated to a semi-crystalline residue and the desired product was obtained following the procedure outlined for the isolation of compounds described in Table II. This derivative was an oil distilling at 245–250° (1.5 mm.); 4.5 g. (25%).

Anal. Calcd. for $C_{25}H_{38}N_4O$: N, 13.7. Found: N, 13.6.

The dihydrochloride of this material was extremely hygroscopic.

(15) F. L. Bach, Jr., S. Kushner and J. H. Williams, THIS JOURNAL, **77**, 6049 (1955).

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Reactions with Substituted Xanthones. III. Reactions with Hydroxy-9-xanthenones

BY AHMED MUSTAFA AND ORKEDE HASSAN HISHMAT[1]

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1-Hydroxy-9-xanthenone (Ia) condenses with the acyl and arylsulfonyl chlorides in the presence of aluminum chloride to give 2-acylated-1-hydroxy-9-xanthenones (Table II). The acyl, aroyl and benzenesulfonyl derivatives of Ia and of 1-hydroxy-3-methyl-9-xanthenone (Ii) undergo Fries migration of the acyl group under the influence of aluminum chloride to give the corresponding 2-acyl derivatives (Table II). 1-(β-Naphthoyloxy)-4-benzoyloxy-9-xanthenone and 4-benzoyloxy-1-methyl-10-thiaxanthenone undergo elimination reaction when treated with aluminum chloride under the Fries reaction conditions, yielding the corresponding hydroxy-9-xanthenone and hydroxy-10-thiaxanthenone derivatives, respectively, together with, *e.g.*, β-naphthoic in the case of the naphthoyl ester. Benzoyl esters of 2-hydroxy-3-methyl- and of 2-hydroxy-4-methyl-10-thiaxanthenones proved to be stable toward the action of aluminum chloride under similar conditions. Nencki's reaction offers a convenient method for the preparation of the new 1-hydroxybenzo[b]xanthene-12-one (IIIa), using resorcinol and 2-hydroxy-3-naphthoic acid. The same reaction, using salicylic acid and resacetophenone and/or 2,4-dihydroxybenzophenone, resulted in the formation of Ia in each case together with the removal of the acetyl- and/or the benzoyl group.

Previous work[2] on the study of reactions of substituted xanthenones now has been continued. Hydroxyxanthones, *e.g.*, 1-hydroxy-9-xanthenone (Ia), show the typical reactions of phenols[3] and it should be expected that they undergo the Friedel–Crafts as well as the Fries rearrangement, resulting in the formation of acylated derivatives of hydroxy-9-xanthenones which so far as we are aware[4] have not been synthesized and, meanwhile, constitute important intermediates for the syntheses of naturally occurring substances. Thus, when Ia is treated with acetyl chloride in the presence of aluminum chloride (2.5 moles), using anhydrous nitrobenzene as a solvent, on a steam-bath for three hours and kept aside at room temperature overnight, 2-acetyl-1-hydroxy-9-xanthenone (IIa) is obtained in *ca.* 50% yield. IIa forms a benzoyl derivative with benzoyl chloride in pyridine.

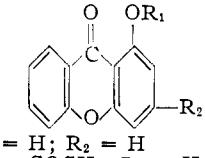
(1) Abstracted from a portion of the dissertation to be submitted by Orkede H. Hishmat in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) A. Mustafa, W. Asker and M. E. E. Sobhy, THIS JOURNAL, **77**, 5121 (1955).

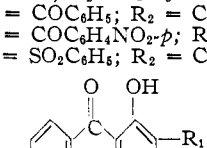
(3) *Cf.* R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 439.

(4) A perusal of the literature revealed that hardly any work has been done on the migration of esters of condensed heterocyclic ring system phenols, though migration has been reported recently in the case of 1-acetoxy-9-xanthenone (*cf.* ref. 8).

Although substitution may occur in more than one way, we have only been able to isolate one



Ia, R_1 = H; R_2 = H
b, R_1 = $COCH_3$; R_2 = H
c, R_1 = COC_6H_5; R_2 = H
d, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
e, R_1 = $SO_2C_6H_5$; R_2 = H
f, R_1 = $COC_{10}H_7(\beta)$; R_2 = H
g, R_1 = CH_3; R_2 = H
h, R_1 = $CH_2{\cdot}CH{:}CH_2$; R_2 = H
i, R_1 = H; R_2 = CH_3
j, R_1 = COC_6H_5; R_2 = CH_3
k, R_1 = $COC_6H_4NO_2$-*p*; R_2 = CH_3
l, R_1 = $SO_2C_6H_5$; R_2 = CH_3



IIa, R_1 = $COCH_3$; R_2 = H
b, R_1 = COC_6H_5; R_2 = H
c, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
d, R_1 = $SO_2C_6H_5$; R_2 = H
e, R_1 = COC_6H_5; R_2 = CH_3
f, R_1 = $SO_2C_6H_5$; R_2 = CH_3

product (IIa) in a pure form for analytical purposes. The Friedel–Crafts reaction seems to be of preparative nature for the *o*-isomer as we have not been able to demonstrate the presence of the *p*-isomer, since fractional crystallization of the mother liquors leads to difficultly separable mixtures of the probable isomers.

The ready acylation of Ia with acyl chloride and aluminum chloride and the stability of 9-xanthenone toward the same reagent may be attributed to the activating effect of the hydroxyl group.[5] Moreover, it seems very probable that the inhibiting action of the ketone group in xanthone toward Friedel–Crafts acylation nullifies the activating effect of the heterocyclic oxygen atom; a fact which is favored by the observation that xanthene condenses with benzoyl chloride in the presence of aluminum chloride to give 2-benzoylxanthene[6] and the ready acylation of dibenzofuran upon treatment with acetyl chloride and aluminum chloride to give 4-acetyldibenzofuran.[7]

Similar results have now been obtained by Fries rearrangement of 1-acetoxy-9-xanthenone (Ib) with aluminum chloride in hot nitrobenzene (at 130–140° for one hour, then at room temperature overnight). IIa is obtained in *ca.* 55% yield.

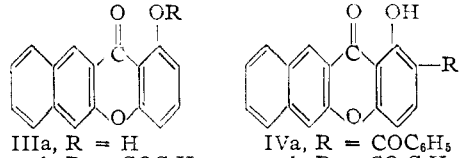
While our investigations were in progress, a publication by Davies and co-workers[8] appeared describing the preparation of IIa, by similar procedure, as an intermediate compound for the preparation of analogs of biologically active chromones, such as khellin. Though the compound IIa reported by them proved to be identical with that prepared by us, there were some points of difference,[9] however, and new material which may be of interest in view of the paucity of information pertaining to this system. IIa was synthesized according to the Friedel–Crafts procedure after Davies and co-workers[8] and we were unable to obtain the unidentified isomeric ketone (m.p. 200°), reported to be obtained in small amount and to depress the m.p. of IIa. The highest m.p. of a substance that was obtained by fractional crystallization of the product contained in the ether extract[10] was 197–198° and it does not depress the m.p. of IIa.

When 1-benzoyloxy-9-xanthenone (Ic) is allowed to undergo the Friedel–Crafts acylation reaction with acetic anhydride, the benzoyl group is eliminated and 2-acetyl-1-hydroxy-9-xanthenone (IIa) is obtained in 71% yield. It appears that the main product is the only one present in appreciable amount. The production of IIa, not contaminated with the 2-benzoyl derivatives[11] (IIb), by treatment with aluminum chloride at 130–140° is unusual in that Ic is isomerized into IIb by treatment with aluminum chloride (see below).

The Friedel–Crafts acylation reaction with Ia now has been extended, using benzoyl and benzenesulfonyl chlorides as acylating agents, under the same experimental conditions described for the acylation of Ia in the presence of aluminum chloride and the corresponding acylated products, believed by analogy to be 2-benzoyl- (IIb) and 2-benzenesulfonyl-1-hydroxy-9-xanthenone (IId), respectively, have been obtained. IIb and IId are obtained in 52 and 58% yield, respectively, and no other isomer was isolated in analytically pure form.

Fries rearrangement of benzoyl (Ic), *p*-nitrobenzoyl (Id) and benzenesulfonyl (Ie) derivatives of Ia, and benzoyl and benzenesulfonyl derivatives (Ij, II, respectively) of 1-hydroxy-3-methyl-9-xanthenone (Ii), under the same experimental conditions described for the rearrangement of Ib, gave, by analogy, the corresponding 2-aroyl and 2-benzenesulfonyl derivatives (IIb-d and IIe-f, respectively). The *p*-nitrobenzoyl rearranged product IIc is obtained in 17% yield, whereas IIb is obtained in 50% yield. The marked *ortho* shift in the rearrangement of Id may agree with the observation of Baltzly and co-workers,[12] that the *para* shift is discouraged by electron-attracting substitution in the acyl portion. IIb forms a benzoyl derivative with benzoyl chloride in pyridine and a monohydrazone derivative with hydrazine hydrate.

Similarly, rearrangement of benzoyl and benzenesulfonyl derivatives of 1-hydroxybenzo[b]xanthene-12-one (IIIa) yielded 2-benzoyl- (IVa) and 2-benzenesulfonyl-1-hydroxybenzo[b]xanthene-12-one (IVb), respectively. In all these cases, fractional crystallization of the crude reaction product failed to reveal the isolation of any other isomer.



IIIa, R = H
b, R = COC_6H_5
c, R = $SO_2C_6H_5$

IVa, R = COC_6H_5
b, R = $SO_2C_6H_5$

When 1-(β-naphthoyloxy)-9-xanthenone (If) is allowed to undergo Fries rearrangement under similar conditions, the β-naphthoyl group is eliminated and Ia is obtained almost quantitatively.[13] A similar elimination reaction also has been ob-

(5) *Cf.* C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 360.

(6) J. Heller and St. v. Kostanecki, *Ber.*, **41**, 1324 (1908).

(7) von P. Galewsky, *Ann.*, **264**, 187 (1891).

(8) J. S. H. Davies, F. Scheinmann and H. Susceshitzky, *J. Chem. Soc.*, 2140 (1956).

(9) Davies and co-workers (ref. 8) reported 14% yield of 2-acetyl-1-hydroxy-9-xanthenone by Fries rearrangement of 1-acetoxy-9-xanthenone with aluminum chloride at room temperature for 60 hours and 24% yield at 80° for three hours. The Friedel–Crafts acylation with acetic anhydride in *sym*-tetrachloroethane on the steam-bath for three hours gave 41% yield, whereas 36% yield was reported when acetyl chloride in nitrobenzene at room temperature for 5 days was used.

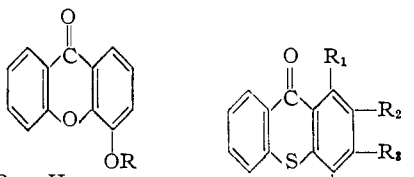
(10) *Cf.* ref. 8, p. 2142. The m.p. of the crude product after evaporation of the ether was 160–165°.

(11) *Cf.* the same observation in the case of N-phenylsulfonyl-1,8-naphthosultam which undergoes the Friedel–Crafts acetylation reaction to give the 4-acetyl derivative, not contaminated with the 4-benzenesulfonyl derivative (A. Mustafa and M. I. Ali, THIS JOURNAL, **77**, 4593 (1955)).

(12) R. Baltzly, W. S. Ide and A. P. Phillips, *ibid.*, **77**, 2522 (1955).

(13) The elimination of the naphthoyl group and the inhibition of the Fries rearrangement may be attributed to the increase in the size of the acyl group (*cf.* A. H. Blatt, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342); *cf.* also the formation of free acid and not a ketone on treatment of *o*-cresyl-1-naphthoate with aluminum chloride at 160° (G. S. Saharia, *J. Sci. Industr. Res.*, **13B**, 544 (1954)).

served when 4-benzoyloxy-9-xanthenone (Vb) is subjected to rearrangement with aluminum chloride, under the given conditions, yielding 4-hydroxy-9-xanthenone (Va). We now have found that, whereas elimination reaction takes place when 1-methyl-4-benzoyloxy-10-thiaxanthenone (VIb) is treated with aluminum chloride yielding 1-methyl-4-hydroxy-10-thiaxanthenone (VIa), 3-methyl-2-benzoyloxy-(VId) and 4-methyl-2-benzoyloxy-10-thiaxanthenone (VIf) are recovered almost quantitatively when treated with aluminum chloride under similar conditions. It seems very probable that the benzoyl esters of methyl substituted 2-hydroxy-10-thiaxanthenones (VId, VIf) are comparatively more stable than the benzoyl esters of VIa, Ia, and of Va toward the action of aluminum chloride under the same experimental conditions.



Va, R = H
b, R = COC_6H_5

VIa, $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = OH$
b, $R_1 = CH_3$; $R_3 = R_2 = H$; $R_4 = OCOC_6H_5$
c, $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = CH_3$
d, $R_1 = R_4 = H$; $R_2 = OCOC_6H_5$; $R_3 = CH_3$
e, $R_1 = R_3 = H$; $R_2 = OH$; $R_4 = CH_3$
f, $R_1 = R_3 = H$; $R_2 = OCOC_6H_5$; $R_4 = CH_3$

The observation that as the temperature of the reaction rises the *ortho* shift increases,[14] may agree with the general observation that high temperatures favor the *ortho* shift using nitrobenzene as solvent.[15] Moreover, that the *ortho* shift is favored at high temperatures, leading to an increase in the yield of IIa, may be attributed to the steric factors which do favor an *ortho* shift.[12] The formation of IIa at room temperature in nitrobenzene solution—under which conditions[15] the formation of the *p*-isomer is usually favored—may be paralleled to the known observation that aliphatic esters of *m*-cresol afford *o*-hydroxyketones at room temperature.[16]

Methods of Preparation.—The utilization of the Nencki reaction for the preparation of hydroxy-9-xanthenones after the procedure described by Pankajamani and Seshadri[17] now has been followed for the preparation of the new substituted xanthenone derivative IIIa.[18] Using freshly fused zinc chloride, the reaction has been effected at 230° for five minutes and at 200° for four hours. Making use of the separation of the 3-hydroxy isomer by its ready solubility in sodium carbonate,[17] does not reveal the presence of the other isomer. IIIa is insoluble in aqueous sodium carbonate, but gives an insoluble yellowish orange sodium salt when treated with cold aqueous sodium hydroxide solution, and is slightly soluble on warming. Acidification of its alkaline solution regenerates IIIa almost quantitatively. It gives a brownish color with alcoholic ferric chloride solution and forms with benzoyl or benzenesulfonyl chlorides in pyridine the corresponding derivatives.

Aroylation of the hydroxyl group in the hydroxy-9-xanthenones, used in this investigation, has been accomplished by means of the corresponding aroyl chloride in pyridine. For the acetylation reaction acetic anhydride in the presence of fused sodium acetate is used. VIb is prepared by the action of benzoyl chloride and alkali on VIa.

VIc and VIe were prepared according to the method of Sen and Sen-Gupta[19] and were reported to have m.p. 210–212° for VIc and 190° for VIe. However, the samples of VIc and VIe in our hands have m.p. 321–322° and 273–274°, respectively, and give the correct analytical values. They are partially soluble in hot aqueous sodium hydroxide solution and form readily the corresponding benzoyl derivatives VId and VIf.

Attempts to prepare acylated derivatives of Ia by condensing salicylic acid with resacetophenone, under the same conditions described for the condensation of salicyclic acid with resorcinol, resulted in elimination of the acetyl group and the formation of Ia. The same result has been obtained when 2,4-dihydroxybenzophenone was used for resacetophenone. The elimination reaction, observed in the case of resacetophenone and 2,4-dihydroxybenzophenone, has been observed when they were treated, independently, with fused zinc chloride under the same experimental conditions described for the preparation of Ia; resorcinol was isolated in every case (identified as the monobenzoyl derivative), together with marked smell of acetic acid in the case of resacetophenone and the isolation of benzoic acid in the case of 2,4-dihydroxybenzophenone.

Ia now has been further identified by preparing the corresponding methyl ether Ig by the action of dimethyl sulfate in the presence of anhydrous potassium carbonate on an acetone solution of Ia.[20] Similarly, the allyl ether of 1-hydroxy-9-xanthenone (Ih) has been obtained by the action of allyl bromide on an acetone solution of Ia in the presence of anhydrous potassium carbonate. The rearrangement of Ih is now under investigation.

Experimental

Preparation of 1-Hydroxybenzo[b]xanthene-12-one (IIIa).—A mixture of 6.8 g. of 3-hydroxy-2-naphthoic acid, 5 g. of resorcinol and 10 g. of freshly fused zinc chloride was heated at 230° (metal-bath temperature) and maintained at that temperature for five minutes to bring it to a molten

(14) *Cf.* the rise in the yield of IIa from 14% at room temperature to 55% at 130–140°.

(15) *Cf.* K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928); A. H. Blatt, *Chem. Revs.*, **27**, 429 (1940); "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342; M. R. Bhatt and N. M. Shah, *J. Indian Chem. Soc.*, **33**, 318 (1956).

(16) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930); R. Baltzly and A. Bass, THIS JOURNAL, **55**, 4292 (1933).

(17) K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res.*, **13B**, 396 (1954).

(18) For the structure of IIIa, *cf.* the formation of benzo[b]xanthene-12-one by the condensation of 2-iodo-3-naphthoic acid with sodium phenate, followed by ring closure (von W. Dilthey and F. Quint, *J. prakt. Chem.*, **141**, 306 (1934)); *cf.* also E. Strohbach, *Ber.*, **34**, 4136 (1901), for the preparation of the 2-methyl substituted derivative.

(19) R. N. Sen and S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **6**, 267 (1929).

(20) The same procedure has been followed by K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **26A**, 288 (1947); *C. A.*, **42**, 3393 (1948), for the preparation of the methyl ether of euxanthone.

TABLE I

ESTERS OF HYDROXYXANTHENONES

Ester	M.p.,[a] °C.	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Id	231	87	Yellow	$C_{20}H_{11}O_6N$	66.48	66.39	3.04	3.14	..	..	3.88	3.92
Ie	148	81	Yellow[b]	$C_{19}H_{12}O_5S$	64.77	64.88	3.41	3.56	9.09	8.30	..	..
If	212–213	72	Canary-yellow	$C_{24}H_{14}O_4$	78.68	78.21	3.82	3.59	..	..	..	..
Ij	187–188	90	Yellow	$C_{21}H_{14}O_4$	76.36	75.87	4.24	4.11	..	..	..	..
Ik	236	85	Yellow	$C_{21}H_{13}O_6N$	67.20	67.09	3.46	3.91	..	..	3.73	4.04
Il	201	88	Yellow	$C_{20}H_{14}O_5S$	65.57	65.74	3.82	3.82	8.75	8.86	..	..
IIIb	203	78	Blood-red	$C_{24}H_{14}O_4$	78.68	78.62	3.82	3.75	..	..	..	..
IIIc	192	75	Red-violet	$C_{23}H_{14}O_5S$	68.65	67.77	3.48	3.61	7.95	7.97	..	..
VId	182	77	Orange-yellow[b]	$C_{21}H_{14}O_3S$	72.83	71.89	4.05	3.98	9.25	8.34	..	..
VIf	179–180	80	Orange[b]	$C_{21}H_{14}O_3S$	72.83	72.77	4.05	4.32	9.25	9.23	..	..

[a] Melting points are uncorrected. [b] The color is accompanied with green fluorescence.

TABLE II

2-ACYLATED-9-XANTHENONES

Xanthenone deriv.	Reaction product	Method of prepn.	M.p.,[a] °C.	Yield, %	Solvent for crystn.	Color with H_2SO_4	Color with $FeCl_3$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	IIa	A	202–203	50	1	Olive green	Red-brown	$C_{15}H_{10}O_4$	70.87	70.89	3.94	4.17
Ib[b]		B	202–203	55	1							
Ia	IIb	A	178	52	1	Green	Red-brown	$C_{20}H_{12}O_4$	75.95	75.57	3.79	3.86
Ic[c]		B	178	50	1							
Ia	IId	A	239	58	1	Yellow, green fluor.	Red-brown	$C_{19}H_{12}O_5S$	64.77	65.05	3.41	3.67
											9.09[e]	8.61[e]
Ie		B	239	56	1							
Id	IIc	B	263–264	71	2	Yellow	Brown	$C_{20}H_{11}O_6N$[d]	66.48	66.18	3.05	2.88
Ij	IIe	B	175–176	58	3	Brown-yellow	Olive green	$C_{21}H_{14}O_4$	76.36	75.80	4.24	4.18
Il	IIf	B	208–209	60	1	Green	Olive green	$C_{20}H_{14}O_5S$	65.57	65.59	3.83	3.67
											8.74[e]	8.26[e]
IIIb	IVa	B	261–262	54	1	Orange-red	Pale brown	$C_{24}H_{14}O_4$	78.69	78.62	3.83	3.89
IIIc	IVb	B	278	56	2	Blood-red	Pale brown	$C_{23}H_{14}O_5S$	68.66	68.12	3.48	3.45
											7.96[e]	7.98[e]

[a] Melting points are uncorrected. [b] Michael (*Amer. Chem. J.*, **5**, 94 (1883)). [c] *Cf.* ref. 21. [d] Calcd.: N, 3.88. Found: N, 3.71. [e] Sulfur, %. [f] 1, benzene; 2, acetic acid; 3, ethyl alcohol.

state. Then the temperature was brought down to 200° and maintained for four hours. The product was repeatedly washed with hot water and the residue was ground up with a solution of sodium carbonate. The insoluble residue was treated with aqueous sodium hydroxide solution (10%) and the sodium salt of IIIa separated out. It was filtered off, suspended in water containing concentrated hydrochloric acid enough for acidification and the reaction mixture was boiled for 10 minutes. IIIa separated out as a dirty-yellow mass. It crystallized from acetone in the form of yellow needles, m.p. 307°, yield *ca.* 27%.

Anal. Calcd. for $C_{17}H_{10}O_3$: C, 77.86; H, 3.81. Found: C, 77.56; H, 3.68.

An acetone solution of IIIa gave a brownish color with alcoholic ferric chloride solution. IIIa is soluble in acetone and hot chloroform, but difficultly soluble in most of the common organic solvents; it gives deep reddish orange color with concentrated sulfuric acid, and is insoluble in hot aqueous sodium carbonate solution.

Acidification of the sodium carbonate extract resulted in the separation of a small amount of an unidentified substance.

Preparation of VIc and VIe.—Crude VIc, obtained after pouring the reaction[19] mixture into ice-cold water, was washed with 40 ml. of 10% aqueous sodium hydroxide and was then suspended in dilute hydrochloric acid. The resulting yellow solid, which was thoroughly washed with water and dried, was crystallized from acetic acid; yield 31% of yellow crystals, m.p. 321–322°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.42; H, 4.13; S, 13.22. Found: C, 69.02; H, 3.98; S, 13.65.

VIe, obtained in 37% yield, melted at 273–274°. *Anal.* Calcd. for $C_{14}H_{10}O_2S$: C, 69.42; H, 4.13; S, 13.22. Found: C, 69.17; H, 4.11; S, 13.26.

They were soluble in hot chloroform, hot acetic acid, but sparingly in cold alcohol. They were insoluble in aqueous sodium carbonate, but were partially soluble in hot aqueous sodium hydroxide. They gave with concentrated sulfuric acid a deep orange color.

Preparation of Esters of Hydroxyxanthenones and Hydroxy-10-thiaxanthenones.—A solution of 0.005 mole of the hydroxy-9-xanthenone in 30 ml. of freshly distilled pyridine was treated with 0.006 mole of the acyl chloride: namely, benzoyl, *p*-nitrobenzoyl, β-naphthoyl and benzenesulfonyl chlorides, respectively. The reaction mixture was heated for one hour (steam-bath), cooled, and the crystals that separated were filtered off and washed with cold alcohol.

The aroyl derivatives of hydroxy-10-thiaxanthenones were prepared by treating a solution of 0.003 mole of the thiaxanthenone derivative in aqueous sodium hydroxide (10%) with 0.006 mole of benzoyl chloride (Schotten–Baumann). The reaction mixture was shaken vigorously at room temperature for 20 minutes, cooled and the separated solid was collected by filtration.

The properties of the above new aroyl and benzene-sulfonyl derivatives are recorded in Table I. They were generally soluble in hot common solvents, formed colorless crystals and were crystallized readily from a mixture of ethyl alcohol and chloroform.

2-Acylated-9-xanthenones. Method A. General Friedel–Crafts Procedure.—In all experiments described in Table II, 0.01 mole of 1-hydroxy-9-xanthenone[17] (Ia) and 0.025 mole of aluminum chloride were used. A solution of Ia in 25 ml. of freshly distilled nitrobenzene and 0.02 mole of the acyl chloride was treated with aluminum chloride in portions as rapidly as it dissolved. The reaction mixture was heated for three hours (steam-bath) and kept aside at room temperature overnight. It was poured into 150 ml. of ice-water containing 25 ml. of concentrated hydrochloric acid, and steam distilled. The solid residue was then extracted with hot petroleum ether (b.p. 100–120°). Concentration

of the petroleum ether extract, by slow evaporation, gave the 2-acyl derivative of Ia which was crystallized from the solvent specified in Table II.

In the case of 2-acetyl-1-hydroxy-9-xanthenone (IIa) the crude product, after evaporation of the petroleum ether, melted at 180–185°. Fractional crystallization of the 2-substituted acyl derivatives (*cf.* Table II) did not raise the m.p.

IIa-d, when treated with cold aqueous sodium hydroxide solution, formed the corresponding deep yellow sodium salt. They formed yellow crystals which were soluble in hot benzene, but sparingly in alcohol, ether and light petroleum (b.p. 40–60°).

Identification of IIa was carried out by m.p. and mixed m.p. determinations with authentic specimens of IIa and of its 2,4-dinitrophenylhydrazone derivative.[8]

Benzoylation of 0.2 g. of IIa with 0.4 g. of benzoyl chloride and 10 ml. of freshly distilled pyridine, as described above, gave a colorless solid on cooling. It was crystallized from alcohol, m.p. 168°, in almost quantitative yield. 2-Acetyl-1-benzoyloxy-9-xanthenone gave no color with alcoholic ferric chloride and developed a yellow color with slight green fluorescence with concentrated sulfuric acid.

Anal. Calcd. for $C_{22}H_{14}O_5$: C, 73.74; H, 3.91. Found: C, 73.57; H, 3.88.

2-Benzoyl-1-benzoyloxy-9-xanthenone, obtained similarly from 0.65 g. of IIb, 0.85 g. of benzoyl chloride and 25 ml. of pyridine, separated from a mixture of ethanol and chloroform in nearly colorless crystals, m.p. 212–213°, yield 86%. It gave a yellow color with concentrated sulfuric acid and was soluble in hot chloroform and benzene, but sparingly in alcohol.

Anal. Calcd. for $C_{27}H_{16}O_5$: C, 77.14: H, 3.81. Found: C, 76.73; H, 3.72.

A solution of 0.5 g. of IIb in 30 ml. of ethyl alcohol was treated with 4 ml. of hydrazine hydrate. The reaction mixture was refluxed on the steam-bath for 6 hours. The solid, obtained on cooling, was collected and crystallized from ethyl alcohol in canary yellow crystals, m.p. 160–161°. The yield was almost quantitative.

Anal. Calcd. for $C_{20}H_{14}O_3N_2$: C, 72.72; H, 4.24; N, 8.48. Found: C, 72.46; H, 4.50; N, 8.80.

The monohydrazone derivative of IIb was soluble in hot ethyl alcohol, and benzene, but slightly in light petroleum. It gave reddish brown color with alcoholic ferric chloride and yellowish orange color with concentrated sulfuric acid, and formed a canary yellow insoluble sodium salt when treated with hot aqueous sodium hydroxide.

2-Acylated-9-xanthenones. Method B. Fries Rearrangement with Aluminum Chloride of Acyl, Aroyl and Benzenesulfonyl Derivatives of Hydroxy-9-xanthenones.—The rearrangement of Ib-e, Ij, Il and IIIb-c was carried out by heating a solution of 0.01 mole of each in 25 ml. of nitrobenzene and 0.025 mole of aluminum chloride in an oil-bath maintained at 130–140° (bath-temp.) for one hour. The reaction mixture was kept aside at room temperature overnight. The dark colored reaction mixture was cooled, decomposed with 100 ml. of cold dilute hydrochloric acid, and steam distilled. The solid residue so obtained was worked out as described above in the Friedel–Crafts procedure. The properties of the reaction products (IIa–d, IIe–f and IVa–b) are recorded in Table II. When treated with cold aqueous sodium hydroxide (10%) they gave the corresponding yellow colored sodium salt.

When 0.5 g. of IIe, obtained by method B, was treated with benzoyl chloride in pyridine in the usual procedure, 3-methyl-1-benzoyloxy-2-benzoyl-9-xanthenone was obtained in 74% yield as colorless crystals from ethyl alcohol–chloroform mixture, m.p. 214–215°.

Anal. Calcd. for $C_{28}H_{18}O_5$: C, 77.41; H, 4.14. Found: C, 77.06; H, 4.23.

3-Methyl-1-benzoyloxy-2-benzenesulfonyl-9-xanthenone was similarly obtained by the action of benzoyl chloride on 0.5 g. of IIf in pyridine. The benzoyl derivative formed colorless crystals from ethyl alcohol–chloroform mixture, m.p. 239–240°.

Anal. Calcd. for $C_{27}H_{18}O_6S$: C, 68.94; H, 3.83; S, 6.81. Found: C, 68.21; H, 3.93; S, 7.39.

When 1 g. of each of If, Vb[21] and VIb,[19] was treated with aluminum chloride at 130–140°, under the same experimental conditions described above for the Fries rearrangement, followed by working out the reaction products in a similar manner, Ia, Va and VIa were obtained in 82, 87 and 79% yield, respectively. β-Naphthoic acid was isolated in appreciable amounts (m.p. and mixed m.p. determination) in the case of If.

VId and VIf were recovered almost quantitatively when 1 g. of each was treated with aluminum chloride under the same experimental conditions.

Action of Acetic Anhydride on Ic in Presence of Aluminum Chloride.—A mixture of 1.1 g. of Ic, 25 ml. of nitrobenzene and 1.1 g. of freshly distilled acetic anhydride was treated portionwise with 1.2 g. of aluminum chloride. The reaction mixture temperature was maintained at 80° during the addition of aluminum chloride. It was raised slowly to 130–140° (bath-temp.) and the reaction mixture was kept at that temperature for one hour. It was kept aside at room temperature overnight, and was then worked out as described above in the general Friedel–Crafts procedure. IIa was obtained in 71% yield, and was identified by m.p. and mixed m.p. determination with an authentic specimen of IIa,[8] and of 2-acetyl-1-benzoyloxy-9-xanthenone.

Fractional crystallization of the crude product obtained by evaporation of the mother liquors did not reveal the presence of any other isomer. Melting point of the crude product, obtained after evaporation of the petroleum ether, was 193°.

Action of Zinc Chloride on: (a) A Mixture of Salicylic Acid and Resacetophenone.—A mixture of 5 g. of resacetophenone, 5 g. of salicylic acid and 10 g. of freshly fused zinc chloride was heated to 200° and maintained at that temperature for 5 minutes. Then the temperature was brought down to 180° and maintained for four hours. On working up the reaction product as described for the preparation of IIIa, yellow crystals of Ia were obtained in 22% yield. Identification was carried out by m.p. and mixed m.p. determination.

Ia was further identified by preparation of its methyl ether (Ig): To a solution of 1.5 g. of Ia in 50 ml. of dry acetone was added 2 ml. of dimethyl sulfate and 5 g. of anhydrous potassium carbonate. The reaction mixture was refluxed on a steam-bath for six hours and cooled. It was poured into ice-cold water and the solid so obtained was collected by filtration, washed thoroughly with cold water, and crystallized from petroleum ether (b.p. 100–120°). It formed colorless crystals, m.p. 136°, identified by m.p. and mixed m.p. determination with an authentic specimen of Ig.[22]

Five grams of resacetophenone was heated with 10 g. of fused zinc chloride at 130–140° under the same experimental conditions described above. The alkaline extract of the reaction mixture was treated with excess of benzoyl chloride (Schotten–Baumann) and the colorless solid so obtained was crystallized from ethyl alcohol; identified as benzoyl resorcinol (m.p. and mixed m.p. with an authentic sample). A marked smell of acetic acid was noticed on decomposition of the reaction mixture.

(b) **A Mixture of Salicylic Acid and 2,4-Dihydroxybenzophenone.**—Similarly, a mixture of 5 g. of 2,4-dihydroxybenzophenone, 5 g. of salicylic acid and 10 g. of fused zinc chloride was heated as described in the case of resacetophenone. On working up the reaction mixture, Ia was obtained in *ca.* 23% yield.

A solution of 1.6 g. of Ia (obtained after the above procedure) in 50 ml. of dry acetone, was treated with 2.2 g. of allyl bromide and 5 g. of anhydrous potassium carbonate. The reaction mixture was refluxed for eight hours and cooled. It was poured into ice-cold water, extracted with ether, dried and evaporated. The solid residue (1.1 g.) so obtained was crystallized from petroleum ether (b.p. 80–100°) in colorless crystals, m.p. 86–87°. 1-Allyloxy-9-xanthenone (Ih) was easily soluble in benzene, but sparingly in light petroleum. It gives yellow-brown color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 76.08; H, 4.98.

2,4-Dihydroxybenzophenone (5 g.) was treated with 10 g. of fused zinc chloride as described in the case of resacetophenone. The cold reaction mixture was poured into ice-

(21) E. König and St. v. Kostanecki, *Ber.*, **27**, 1996 (1894).

(22) J. Tambor, *ibid.*, **43**, 1883 (1910).

cold dilute hydrochloric acid and the solid so obtained was extracted with cold aqueous sodium carbonate solution. The insoluble portion was benzoylated with benzoyl chloride in the presence of sodium hydroxide solution and benzoylresorcinol was obtained (1.1 g.).

Acidification of the carbonate solution followed by crystallization of the separated product gave colorless crystals (0.9 g.), identified as benzoic acid.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Researches on Pyrimidines. Certain Derivatives of 2-Propylpyrimidine[1]

BY HENRY R. HENZE AND STANLEY O. WINTHROP[2]

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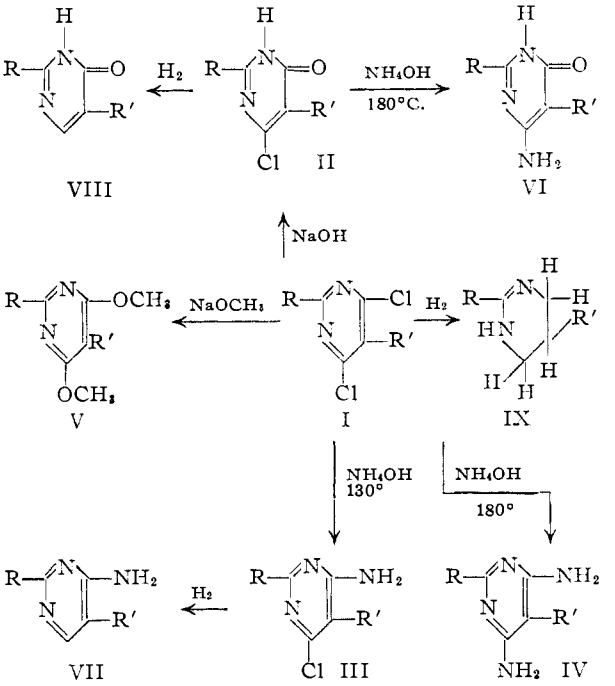
Series of 2-propyl-4,6(1,5)-tetrahydropyrimidinediones and 2-propyl-4,6-dichloropyrimidines have been synthesized. The dichloropyrimidines are useful starting materials for the synthesis of various pyrimidine derivatives, some of which are described.

In continuation of our investigation of the synthesis of pyrimidine derivatives through condensation of amidines with malonic esters,[3,4] we have now studied the interaction of butamidine with ethyl malonate and five ethyl alkylmalonates. The 2-propyl-4,6(1,5)-tetrahydropyrimidinediones thus obtained were converted into 4,6-dichloro derivatives by treatment with phosphorus oxychloride. With the appropriate reagents and reaction conditions, as shown below, the 4,6-dichloropyrimidines (I) yielded the corresponding 6-chloro-4(3)-dihydropyrimidones(II), 4-amino-6-chloropyrimidines (III), 4,6-diaminopyrimidines (IV) and 4,6-dimethoxypyrimidines (V). These derivatives in their turn gave 6-amino-4(3)-dihydropyrimidones (VI), 4-aminopyrimidines (VII) and 4(3)-dihydropyrimidones (VIII).

Catalytic hydrogenolysis of the monochloropyrimidines took place with ease. It was noted, however, that in each case there was an amino or keto substituent present which could have the effect of stabilizing the ring against reduction. Catalytic hydrogenolysis of the dichloropyrimidines did not stop at dechlorination but proceeded with the reduction of the pyrimidine ring. Instead of the anticipated 2-propylpyrimidine, the catalytic hydrogenolysis of 2-propyl-4,6-dichloropyrimidine, in the presence of barium oxide,[5] gave a product which analyzed for a 2-propyltetrahydropyrimidine[6] hydrochloride (IX). A search of the literature reveals little on the chemistry of partially reduced pyrimidines and usually the latter have been prepared directly through condensation reactions, rather than as a direct result of hydrogenation of pyrimidines. Thus, Aspinall[7] has reported the preparation of 2-methyl-1,4,5,6-tetrahydropyrimidine by the interaction of trimethylenediamine and ethylacetate. Naff and Christensen[8] have described a dihydrobenzopyrimidine and its conversion by catalytic dehydrogenation to the more stable benzopyrimidine. Attempts to convert our tetrahydropyrimidine to 2-propylpyrimidine by a similar catalytic dehydrogenation were not successful.



Experimental

Butamidine Hydrochloride.—The procedure utilized followed that of Derby's modification[9] of the method of Pinner[10] for the preparation of amidines. A solution was prepared containing 345 g. (5 moles) of butyronitrile, 230 g. (5 moles) of absolute ethanol, 600 ml. of dry ether and 182.5 g. (5 moles) of dry hydrogen chloride. It was stirred for four days at 0°. After standing for two weeks in the cold the imido ester hydrochloride separated and was removed by filtration. The filtrate, on standing in the cold an additional week, produced a second crop of crystals. The initial crop of imido ester was dissolved in 300 ml. of absolute ethanol, 1000 ml. of 10% alcoholic ammonia was

(1) From the Ph.D. dissertation of Stanley O. Winthrop, University of Texas, 1952.

(2) Humble Oil and Refining Co. Fellow in Chemistry, 1951–1952.

(3) H. R. Henze, W. J. Clegg and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).

(4) H. R. Henze and J. L. McPherson, *ibid.*, **18**, 653 (1953).

(5) After this work had been completed, a paper by N. Whittaker (*J. Chem. Soc.*, 1565 (1950)) came to our attention. This investigator showed that catalytic hydrogenolysis of 2,4,6-trichloropyrimidine in the presence of sodium acetate took place with the uptake of five equivalents of hydrogen indicating the formation of a tetrahydropyrimidine, while in the presence of magnesium oxide, only three equivalents of hydrogen were taken up, and pyrimidine was isolated as a mercuric chloride addition complex.

(6) The position of the remaining double bond has not been proven. The compound is most likely a 1,4,5,6-tetrahydropyrimidine.

(7) (a) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940); (b) G. S. Skinner and P. R. Wunz, *ibid.*, **73**, 3814 (1951).

(8) M. B. Naff and B. E. Christensen, *ibid.*, **73**, 1372 (1951).

(9) I. H. Derby, *Am. Chem. J.*, **39**, 437 (1908).

(10) A. Pinner and F. Klein, *Ber.*, **11**, 1484 (1878).