[Contribution from the School of Chemistry of the University of Minnesota]

Condensation of Salicylaldehyde with Levulinic Acid in Presence of Hydrogen Chloride[1]

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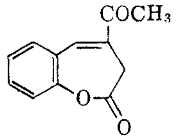
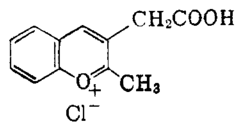
The product obtained from salicylaldehyde, levulinic acid, and hydrogen chloride is a pyrylium salt, and not a lactone containing a 7-membered ring as previously stated. Certain 2-(*o*-hydroxystyryl) benzopyrylium chlorides lose hydrogen chloride when they are boiled with methanol. The organic residues combine to form dimeric products probably containing 12-membered rings.

It has been stated[2] that salicylaldehyde reacts with levulinic acid in presence of hydrogen chloride, forming a lactone containing a 7-membered ring, I. This would be a remarkable reaction, for salicylaldehyde usually condenses with ketonic substances forming benzopyrylium salts like II.[3]

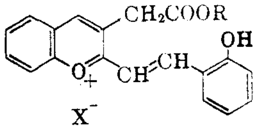


I



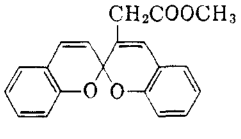
II

Experiments now reported indicate that salicylaldehyde and levulinic acid do yield a benzopyrylium salt. It is not II, however, but a salicylal derivative, III. No substance which might be lactone I could be isolated.



III, $R = H$

IIIa, $R = CH_3$



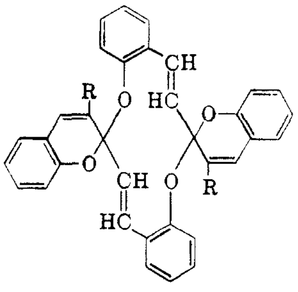
IV

The published description of supposed lactone I, its deep color, high m.p., and solubility characteristics, suggest that the previous investigators were dealing with a crude specimen of salt III. It is likely that analytical figures for the substance and its derivatives resulted from unfortunate coincidences.

Structure III, now assigned to the product, rests on new analytical data and on physical properties of the substance, especially its color. Furthermore methyl levulinate and salicylaldehyde react to form ester IIIa. This ester has the properties of a typical *o*-hydroxystyrylpyrylium salt, and it reacts with weak bases in a normal way[4] to form methyl dibenzospiropyran-3-acetate (IV), a colorless neutral compound. The ultraviolet spectrum of the spiroester is nearly identical with that of dibenzospiropyran and with that of 3-methyldibenzospiropyran.

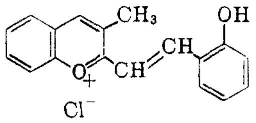
Condensation of levulinic acid and of levulinic ester with 2-hydroxy-1-naphthaldehyde gives benzologs of III and IIIa. Aqueous sodium acetate converts the latter benzolog into methyl dinaphthospiropyran-3-acetate, which like other dinaphthospiropyrans[5] is thermochromic.

A new type of reaction of *o*-hydroxystyrylpyrylium salts was discovered in the present work. When these substances are boiled with methanol they lose acid and form dimers. It is believed that the dimers are represented by structure V, and that their formation involves closure of a 12-membered ring.



V, $R = CH_2COOCH_3$

Va, $R = CH_3$



VI

Usually macro-cyclizations are difficult, but the reaction here may be facilitated by the following factors: (a) C_2 bears a positive charge, and no retreating anion restricts the direction of or otherwise complicates the approach of the reacting nucleophilic group; (b) resonance in the reacting dipoles keeps them flat and rigid, so that probability of proper orientation is good in spite of large ring size (compare[6]); (c) internal hindrance to ring formation through interference of adjacent hydrogen atoms and *trans*-annular crowding are negligible because of the special structure involved. There is room to accommodate the two hydrogens indicated within the ring and in its plane.

Unfortunately only indirect evidence for the structures of the dimers could be obtained. Fusion

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(1) From the Ph.D. Thesis of R. William Cummings, June 1950.

(2) Sen and Roy, *J. Indian Chem. Soc.*, **7**, 401 (1930).

(3) Decker and Fellenberg, *Ann.*, **364**, 1 (1909).

(4) Decker and Felser, *Ber.*, **41**, 2997 (1908); Dilthey and Quint, *J. prakt. Chem.*, **131**, 1 (1931).

(5) Dickinson and Heilbron, *J. Chem. Soc.*, 1699 (1927).

(6) Baker, Gilbert, and Ollis, *J. Chem. Soc.*, 1443 (1952).

with caustic, oxidation with permanganate or chromic acid, ozonolysis, catalytic reduction, zinc dust distillation, etc., gave results of no value, even though the efforts of two years were spent on such experiments. The ester group in V was saponified giving an acid, and re-esterification gave back the original substance. The infrared spectrum of V-a (from VI) indicated that the methyl group was present (peaks at 1370 and 1480 cm^{-1}), and that the compound contained an aromatic ether linkage (peak at 1580 cm^{-1}). Moreover lack of absorption at 3400–3600 cm^{-1} and at 1700 cm^{-1} indicated that hydroxyl and carbonyl groups were absent. The dimers were re-converted to the monomeric benzopyrylium salts from which they were obtained, when treated with acids. They retained solvents tenaciously, a property of many large ring compounds.[6] Analytical and molecular weight data support the structures proposed, and although further support is desirable, no way to obtain it is apparent.

EXPERIMENTAL

2-(o-Hydroxystyryl)benzopyrylium chloride-3-acetic acid (III). A solution of 20 g. of salicylaldehyde (purified through the copper salt), and 19 g. of levulinic acid in 150 ml. of dry ether was cooled in ice and saturated with hydrogen chloride. The mixture was kept at room temperature for three days, and the dark brown crystalline solid then was removed and washed with dry ether; yield 25.8 g., 95%; the mother liquors contained only a purple tar. The compound was recrystallized by adding it to boiling acetic acid, filtering rapidly, and cooling. It formed jet black crystals, m.p. 200–202° with previous sintering.

Anal. Calc'd for $C_{19}H_{15}ClO_4$: C, 66.6; H, 4.4 Found: C, 66.3, 66.4; H, 4.8, 4.8.

The dimeric ester (V) *from* III. A solution of 5 g. of III in 25 ml. of methanol was boiled for two hours, the white crystalline product starting to separate within 20 to 30 minutes. The product was washed with methanol and then was recrystallized from dioxane-methanol giving 2.9 g. m.p. 279–281° (block); further recrystallization gave a product m.p. 281–282° (block preheated to 275°).

Anal. Calc'd for $C_{40}H_{32}O_8$: C, 75.0; H, 5.0; M.W. 640. Found: C, 74.3, 74.5; H, 5.5, 5.9; M.W. (Rast) 637, 726, 723, 689, 826, 736, 726, 712.

Methyl 2-(o-hydroxystyryl)benzopyrylium ferrichloride-3-acetate (III-a). A mixture of 25.4 g. of salicylaldehyde and 13.6 g. of methyl levulinate was added to 200 ml. of dry ether which had been saturated with hydrogen chloride. The mixture was kept for four days and the resulting amorphous brown powder (31.5 g., 85%, m.p. 75–80°) was removed by filtration. This was dissolved in hot acetic acid and mixed with an acetic acid solution of ferric chloride hexahydrate. Cooling gave reddish-purple needles of the ferrichloride; recrystallization from acetic and formic acids and drying over sulfuric acid for 8 hours at room temperature gave a monohydrate, m.p. 183–185°.

Anal. Calc'd for $C_{20}H_{17}Cl_4FeO_4 + H_2O$: C, 44.7; H, 3.6. Found: C, 45.0; H, 3.6.

After the compound had been dried for several weeks at room temperature, it had m.p. 208–211° alone or mixed with the substance obtained by degradation of the dimeric ester (see below).

When 2 g. of III-a suspended in ether was shaken with a little aqueous ammonia for a few minutes, it was decolorized and converted into *methyl dibenzospiropyran-3-acetate.* This substance was isolated by separating and evaporating the ether solution. It was crystallized by allowing a solution in methanol to stand in a desiccator containing water; colorless crystals, m.p. 80–81°.

Anal. Calc'd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0. Found: C, 75.0; H, 5.3.

When 0.5 g. of III-a was boiled in 30 ml. of methanol for five hours, the original red color of the solution faded and there was deposited *ca.* 200 mg. of V, m.p. 283–284° alone or mixed with the dimeric ester obtained from III.

Degradation of the dimeric ester (V) *with hydrogen chloride.* Hydrogen chloride was passed into an ice-cold suspension of 4.5 g. of V in 25 ml. of methanol until a deep red solution was formed. A solution of 1.2 g. of ferric chloride hexahydrate in 20 ml. of methanol then was added, giving 2.3 g. of III-a, purple needles from acetic acid, m.p. 209–210° alone or mixed with the substance obtained from salicylaldehyde and methyl levulinate.

Anal. Calc'd for $C_{20}H_{17}Cl_4FeO_4$: C, 46.3; H, 3.3; Fe, 10.8. Found: C, 46.3; H, 3.6; Fe, 10.5, 10.6.

Saponification of the dimeric ester (V). A mixture of 10 ml. of water, 40 ml. of alcohol, 1.2 g. of sodium hydroxide, and 4.5 g. of V was boiled for three hours. Most of the alcohol then was distilled and replaced with water, and insoluble material was removed by filtration and extraction with ether. Acidification with acetic acid gave a precipitate which was removed by filtration after it had been coagulated at 80° for one hour. Recrystallization from alcohol gave colorless crystals (0.2 g.), which darkened at 200° and melted with decomposition at 210° in a bath pre-heated to 190°.

Anal. Calc'd for $C_{38}H_{28}O_8 + C_2H_6O$: C, 73.0; H, 5.2. Found: C, 72.7, 72.6, 72.9; H, 5.2, 5.1, 5.2.

When the saponification product was treated with excess ethereal diazomethane, nitrogen was evolved immediately. Evaporation of the ether left a solid which was washed with water and dried, giving colorless crystals m.p. 280–281° alone or mixed with the dimeric ester V.

The dimeric ester from methyl 2-(2′-hydroxy-5′-bromostyryl)-6-bromobenzopyrylium chloride-3-acetate. A mixture of 30 g. of 5-bromosalicylaldehyde and 17 g. of levulinic acid in 100 ml. of dry ether was saturated with hydrogen chloride and kept at room temperature for 24 hours. The resulting dark brown amorphous pyrylium salt (19.8 g.) was removed by filtration, but could not be recrystallized. A solution of 10 g. of the salt in 50 ml. of methanol containing 1 ml. of sulfuric acid was boiled for two hours, and the resulting insoluble material was removed and recrystallized from dioxane-methanol. There was obtained 1 g. of faintly yellow prisms, m.p. 280–281°.

Anal. Calc'd for $C_{40}H_{28}Br_4O_8$: C, 50.2; H, 3.0. Found: C, 50.4, 50.4; H, 3.1, 3.3.

Experiments with 2-hydroxy-1-naphthaldehyde. A solution of 5.8 g. of levulinic acid and 8.6 g. of 2-hydroxy-1-naphthaldehyde in 50 ml. of dry ether was cooled, saturated with hydrogen chloride, and kept at room temperature for two weeks. There was obtained 7.7 g. of *2-(2-hydroxy-1-naphthylvinyl)naphthopyrylium chloride-3-acetic acid,* from dil. acetic acid as green plates that contained one molecule of water after drying over sulfuric acid at room temperature; m.p. between 200 and 210° depending on rate of heating.

Anal. Calc'd for $C_{27}H_{19}ClO_4 + H_2O$: C, 70.4; H, 4.6. Found: C, 70.5; H, 5.0.

The *ferrichloride* formed a brown powder from acetic acid.

Anal. Calc'd for $C_{27}H_{19}Cl_4FeO_4$: C, 53.6; H, 3.2. Found: C, 53.1; H, 3.8.

A solution of 6.5 g. of methyl levulinate and 8.6 g. of 2-hydroxynaphthaldehyde in 50 ml. of dry ether that had been saturated with hydrogen chloride deposited 2.2 g. of crystals when it was kept four days. Extraction of the solid with acetic acid left about 0.25 g. of "anhydrobishydroxynaphthaldehyde,"[7] m.p. 241.5° (found: C, 81.1; H, 4.7; $C_{22}H_{14}O_3$ requires: C, 81.0; H, 4.3), identified by conversion into 2-hydroxy-1-naphthaldehyde 2,4-dinitrophenylhydrazone, m.p. 281–282° alone or mixed with an authentic sample (found: C, 57.8; H, 4.0; N, 15.7; $C_{17}H_{12}N_4O_5$ requires: C, 58.0; H, 3.4; N, 15.9). The main product, *methyl 2-(2-hydroxy-1-naphthylvinyl)naphthopyrylium chloride-3-acetate,* formed green crystals, m.p. 203–205°, that were too soluble to be recrystallized. The corresponding *ferrichloride,* green crystals from acetic acid decomposed without melting.

Anal. Calc'd for $C_{28}H_{21}Cl_4FeO_4$: C, 54.3; H, 3.6. Found: C, 54.0; H, 3.6.

When 1 g. of the preceding ester-chloride was suspended in acetone and treated with a few drops of ammonia it was converted into *methyl dinaphthospiro-2,2'-pyran-3-acetate,* colorless crystals from dilute alcohol that melted to a purple liquid at 191–192°. A xylene solution of the substance was colorless when cold and purple when hot.

Anal. Calc'd for $C_{28}H_{20}O_4$: C, 80.0; H, 4.8. Found: C, 80.2; H, 5.1.

When 300 mg. of the ester-chloride was boiled for five hours with 30 ml. of methanol it deposited a yellow solid. Crystallization of this from dioxane-methanol gave *ca.* 50 mg. of the *dimeric ester,* yellow needles, m.p. 251–252°.

Anal. Calc'd for $C_{56}H_{40}O_8$: C, 79.9; H, 4.8 Found: C, 79.5; H, 5.2.

Experiments with 2-(o-hydroxystyryl)-3-methylbenzopyrylium chloride. A solution of 6.1 g. of salicylaldehyde and 3.6 g. of methyl ethyl ketone in 60 ml. of dry ether saturated with hydrogen chloride and kept for 8 hours at room temperature deposited 7.7 g. of the pyrylium chloride, lustrous brown plates. The corresponding ferrichloride, deep red needles from acetic acid, melted in the range 160–170° depending on rate of heating (reported m.p. 172°,[8] 180°.[9]

Anal. Calc'd for $C_{18}H_{15}Cl_4FeO_2$: C, 46.9; H, 3.3. Found: C, 46.9; H, 3.6.

With aqueous ammonia the pyrylium chloride gave 3-methyldibenzospiro-2,2'-pyran which was purified by chromatography on anhydrous magnesium sulfate; m.p. 82–83° (reported m.p. 80°[8,9]).

Anal. Calc'd for $C_{18}H_{14}O_2$: C, 82.4; H, 5.4. Found: C, 82.2; H, 5.8.

A solution of 100 g. of the pyrylium chloride in two liters of methanol was stirred, boiled for three hours, and then was cooled. The resulting white solid was recrystallized from dioxane-methanol (29 g., m.p. 302–304° dec.) and then twice more from the same solvent; m.p 307–308°; (analyses no. 1 and 2). A second preparation was crystallized twice from chloroform-methanol, m.p. 307–308° (analyses no. 3 and 4). A third preparation was made in 95% alcohol instead of methanol, and was crystallized from ethanol-chloroform, giving an identical yield of dimeric condensation product, (V-a), dispiro[3-methylbenzopyran-2,6',2,12'-(1',7'-dioxa-2',3',8',9'-dibenzocyclododeca-2',4',8',10'-tetraene)], m.p. 308–309° (analysis no. 5).

Anal. Calc'd for $C_{36}H_{28}O_4$: C, 82.4; H, 5.4; M.W. 524. Found: C, 81.5, 81.3, 80.5, 80.4, 81.4; H, 5.9, 5.6, 5.8, 5.6, 6.1. M.W. (Rast), 515, 501, 645, 561, 555.

When 1.45 g. of the dimeric product was boiled with 25 ml. of 48% hydrobromic acid, a clear red solution was formed. Steam-distillation and ether extraction gave a few drops of salicylaldehyde which furnished 0.6 g. of the dinitrophenylhydrazone, m.p. 251–252° alone or mixed with a known sample.

When hydrogen chloride was passed in a warm suspension of 3 g. of the dimeric product in 200 ml. of acetic acid, a deep red solution was formed. This was mixed with 20 g. of ferric chloride in 100 ml. of acetic acid, warmed for a few minutes on a steam-bath, and then cooled. Recrystallization of the solid product from acetic acid gave 2 g. of 2-(*o*-hydroxystyryl)-3-methylbenzopyrylium ferrichloride, m.p. 160–170°. Comparison of the powder X-ray diagram with that of a known sample established identity, and analysis was in agreement.

Anal. Calc'd for $C_{18}H_{15}Cl_4FeO_2$: C, 46.9; H, 3.3. Found: C, 46.9; H, 3.6.

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(7) Bradley and Dains, *Am. Chem. J.*, **14,** 293 (1892).

(8) Dilthey, Benes, Hölterhoff, and Wübken, *J. prakt. Chem.*, **114,** 179 (1926).

(9) De, *J. Indian Chem. Soc.*, **4,** 137 (1927).