Furanilide from *p*-Toluenesulfonyl-2-benzoylfuranoxime.—A suspension of 10 g. of the oxime in 50 cc. of 95% alcohol was kept at 30° for ten days with occasional shaking. During this time the oxime dissolved gradually. Then the solvent was removed *in vacuo* and the residue dissolved in 25 cc. of ether and 25 cc. of water. The acidic aqueous layer was neutralized with ammonia, and after treatment with charcoal evaporated to dryness. The residue, which could be recrystallized from absolute ethanol, was found to be ammonium *p*-toluenesulfonate. The ether layer was then evaporated and the residue recrystallized from ethanol with charcoal. The substance proved to be furanilide according to its melting point (124°), and mixed melting point with an authentic sample and analysis.

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.57; H, 4.84; N, 7.48. Found: C, 70.82; H, 5.12; N, 7.57.

***p*-Methoxyfuranilide.**—A solution of *p*-toluenesulfonyl-2-*p*-methoxybenzoylfuranoxime in 15 cc. of 95% ethanol was refluxed for five hours. The residue, obtained after evaporation of the reaction mixture, was dissolved in ether and water. After being neutralized with ammonia the aqueous solution yielded ammonium *p*-toluenesulfonate. The ether solution was evaporated and the residue recrystallized from water. The product formed white needles melting at 105–106°; yield, 60%. The substance yielded 2-furoic acid (m. p. 132–133°) and *p*-methoxyaniline (m. p., 54–55°) on hydrolysis with 2 *N* sulfuric acid. This fact established its identity as *p*-methoxyfuranilide. Its structure was confirmed by synthesis. For this purpose a solution of furyl chloride (2.6 g.) in 10 cc. of benzene was added to the solution of *p*-methoxyaniline (5 g.) in 20 cc. of benzene and the mixture was kept at room temperature for one day. The precipitate was collected on a filter, washed with ethanol and water, and recrystallized from water; melting point and mixed melting point with the substance mentioned above, 105–106°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.59; H, 5.17; N, 6.53.

Benzfuranilide from *p*-Toluenesulfonyl-2-benzoylbenzfuranoxime.—A solution of the oxime (5 g.) in 40 cc. of ethanol was refluxed for four hours. After evaporation of the solvent the residue was dissolved in ether and water. The water solution yielded ammonium *p*-toluenesulfonate after neutralization with ammonia, and evaporation. The ethereal solution was evaporated and the residue recrystallized from 40% ethanol; melting point and mixed melting point with benzfuranilide[4] prepared in another way 158°, yield 84%.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 75.95; H, 4.67; N, 5.90. Found: C, 76.25; H, 4.40; N, 6.05.

Summary

The reactions with methanol and ethanol of the *p*-toluenesulfonyl derivatives of several aliphatic and aromatic furyl ketoximes have been studied: 2-propionyl-, 2-hydroxyacetyl-, 2-benzoyl-, 2-(*p*-methoxybenzoyl)-furanoxime and 2-benzoylbenzfuranoxime (III–VIII).

It has been found that the aliphatic *p*-toluenesulfonyl furylketoximes react with alcohols according to scheme 1, illustrated by *p*-toluenesulfonyl-2-acetofuranoxime, and the aromatic ones with a Beckmann rearrangement according to scheme 3.

The experimental results make it seem probable that the mechanism of the reaction represented by scheme 1 consists in the opening of the furan ring with acetal formation and subsequent substitution of the imino group by oxygen according to scheme 2.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Sulfonation of Ketones and Aldehydes

BY WILLIAM E. TRUCE AND C. C. ALFIERI[1]

This paper reports on the reaction of dioxane sulfotrioxide with ketones and aldehydes leading to the formation of ketone-α-sulfonic acids and aldehyde-α-sulfonic acids, respectively. Analogous reactions have been observed in a few isolated cases previously. Acetophenone-ω-sulfonic acid has been obtained by treating a solution of acetophenone in acetic anhydride and ether with 15% oleum at 0°.[2] The action of chlorosulfonic acid on acetophenone has produced the 2,ω-disulfonyl chloride while acetophenone-4-sulfonic acid with chlorosulfonic acid has probably formed the 4,ω-disulfonyl chloride.[3] The sulfonation of acetophenone with 45% oleum at temperatures which do not cause cleavage (to acetic acid and benzenesulfonic acid[4]) has yielded a mixture of ortho and meta acetophenonesulfonic acids.

Acetophenone, 2-acetothienone and acetomesitylene were converted to the corresponding sodium ω-ketonesulfonates in approximately 70% yields (recrystallized) by treatment with dioxane sulfotrioxide followed by neutralization. β-Acetonaphthone yielded a mixture of products. One of these products was shown to be the expected sodium β-acetonaphthone-ω-sulfonate, while another product was a disulfonate. Presumably, the second sulfonic acid group entered the non-substituted ring.

Pinacolone, propiophenone and isobutyrophenone were converted in approximately 70% yields to the corresponding sodium ketonesulfonates, *i.e.*, $(CH_3)_3CCOCH_2SO_3Na$, $C_6H_5COCH(CH_3)SO_3Na$, and $C_6H_5COC(CH_3)_2SO_3Na$, respectively. Similar results were obtained with acetone and cyclohexanone; however, it was more difficult to obtain a pure product in these cases.

The direct sulfonation of an aliphatic aldehyde has not been previously reported. Dioxane sulfotrioxide was found to react with phenylacetaldehyde, heptaldehyde and isobutyraldehyde to form

(1) This paper is taken from the Ph.D. thesis of C. C. Alfieri. A portion of this work was presented before the Division of Organic Chemistry at the 116th Meeting of the American Chemical Society, Atlantic City, September, 1949.

(2) Doering and Beringer, THIS JOURNAL, **71**, 2221 (1949).

(3) Weston and Suter, *ibid.*, **61**, 389 (1938).

(4) Krekeler, *Ber.*, **19**, 676, 2627 (1886).

the corresponding sodium aldehyde-α-sulfonates in fair yields.

The structures of sodium ω-acetophenonesulfonate, sodium 2-acetothienone-ω-sulfonate, sodium ω-acetomesitylenesulfonate, sodium pinacolone-α-sulfonate, sodium propiophenone-α-sulfonate and sodium isobutyrophenone-α-sulfonate were proved by comparing their S-benzylthiuronium salts with those derived from authentic samples prepared by the Strecker synthesis.[5] The structures of sodium ω-acetophenonesulfonate, sodium 2-acetothienone-ω-sulfonate and sodium pinacolone-α-sulfonate were further proved by treatment with alkaline sodium hypoiodite solution. In no case was iodoform obtained; however, benzoic acid, 2-thiophenecarboxylic acid and pivalic acid respectively were recovered from the reaction mixtures.

Sodium hypoiodite solution did not cleave sodium ω-acetomesitylenesulfonate.[6] Boiling sodium ω-acetomesitylenesulfonate for fourteen hours with 20% sodium hydroxide solution produced no cleavage of the compound to the expected sodium mesitoate and sodium methanesulfonate,[7] thus further demonstrating that the carbonyl group in this compound is so sterically hindered as to be practically immune to attack by reagents which must first add to the carbonyl carbon atom.[8,9,10] The best method of preparing sodium ω-acetomesitylenesulfonate, sodium propiophenone-α-sulfonate and sodium isobutyrophenone-α-sulfonate is by the direct sulfonation of the corresponding ketones with dioxane sulfotrioxide as described herein. Displacement of the bromine atom in ω-bromoacetomesitylene by sodium sulfite did not proceed satisfactorily even at reflux temperatures. Although the nucleophilic displacement is taking place on the carbon atom adjacent to the carbonyl group, apparently there is still sufficient steric interference at this position to affect the rate of reaction and reduce the yield. With α-bromopropiophenone and α-bromoisobutyrophenone, the yields obtained by the displacement reaction were poor and the reaction took place very slowly. Sodium propiophenone-α-sulfonate and sodium isobutyrophenone-α-sulfonate were oxidized with alkaline permanganate to benzoic acid, thus further demonstrating that sulfonation had occurred on the side chain.

The structures of sodium acetonesulfonate, sodium phenylacetaldehyde-α-sulfonate and sodium heptaldehyde-α-sulfonate were proved by cleavage with 20% sodium hydroxide solution.[7] The resulting alkanesulfonates were identified through their S-benzylthiuronium salts, the carboxylates through their p-bromophenacyl esters. Sodium phenylacetaldehyde-α-sulfonate was also oxidized with alkaline permanganate to benzoic acid, showing that sulfonation had occurred on the side chain. The sodium aldehyde-α-sulfonates all gave positive Schiff and Tollens tests for the presence of an aldehyde group.

The structures of sodium cyclohexanone-α-sulfonate and sodium isobutyraldehyde-α-sulfonate could not be proved readily. However, on the basis of analogy and analytical results, it is probable that the structures assigned to these two products are correct.

The course of this reaction appears to be similar to the mechanism which has been proposed for the acid-catalyzed bromination of ketones.[11] This would involve an enolate-type structure as an intermediate.

$$ArCOCH_3 + A \longrightarrow Ar\overset{+}{C}(OA^-)-CH_3 \xrightarrow{B} ArC(OA^-)=CH_2 + BH^+$$

$$ArC(OA^-)=CH_2 \xrightarrow{SO_3{}^a} A + ArCOCH_2SO_3^- \xrightarrow{BH^+} ArCOCH_2SO_3H + B$$

[a] Dioxane sulfotrioxide reagent. "A" may be SO_3 or H^+. "B" may be OC_4H_8O, $ArCOCH_3$ or $-SO_3^-$.

Support for this hypothesis is offered by the fact that methyl p-tolyl sulfone is inert toward this reagent. Apparently an analogous enolate-type structure cannot form since it would involve expansion of the sulfur valence shell from eight to ten electrons. Sulfur is reluctant to undergo such a change.[12,13] Furthermore, pivalophenone, which contains no alpha hydrogen atoms and therefore is incapable of forming an enolate-type structure, is also inert toward this reagent.

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Experimental

Preparation of Dioxane Sulfotrioxide Reagent.—Exactly 0.35 mole of dioxane sulfotrioxide reagent was prepared according to directions given in the literature.[14]

Sulfonation of Acetophenone.—The previously-prepared dioxane sulfotrioxide was allowed to reach room temperature and 0.35 mole (42 g.) of acetophenone was added at a rate such that the temperature of the reaction mixture never exceeded 35°. All the acetophenone was added within an hour; the mixture was stirred for two more hours and then hydrolyzed by pouring into 300 ml. of water. The organic layer was separated, washed with water, dried, and the ethylene chloride was evaporated. About 1 g. of a pale yellow solid remained; it was recrystallized from ethylene chloride and melted at 158°.

Anal. Found: C, 63.6; H, 4.60; S, 11.49.

The aqueous layer was neutralized to a pH of 7 with cold sodium hydroxide solution. The aqueous layer was then

(5) Zuffanti, THIS JOURNAL, **62**, 1044 (1940).
(6) Johnson and Fuson, *ibid.*, **57**, 919 (1935).
(7) Suter, Evans and Kiefer, *ibid.*, **60**, 538 (1938).
(8) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932).
(9) Lock and Schreckeneder, *Ber.*, **72B**, 511 (1939).
(10) Kadesch, THIS JOURNAL, **66**, 1207 (1944).
(11) Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, p. 96.
(12) Ziegler and Conner, THIS JOURNAL, **62**, 2596 (1940).
(13) Kohler and Tishler, *ibid.*, **57**, 218 (1935).
(14) Bordwell and Rondestvedt, *ibid.*, **70**, 2429 (1948).

TABLE I

SUMMARY OF RESULTS

Sodium Sulfonate	Formula	Anal., % Calcd.	Found	S-Benzylthiuronium salts M. p., °C.	Formula	N Anal., % Calcd.	Found
ω-Acetophenone-	$C_8H_7O_4SNa$	Na, 10.36	10.57	152	$C_{16}H_{17}O_4S_2N_2$	7.67	7.57
			10.60				7.52
2-Acetothienone-ω-	$C_6H_5O_4S_2Na$	Na, 10.10	10.38	140	$C_{14}H_{16}O_4S_2N_2$	7.53	7.46
			10.38				
ω-Acetomesitylene-	$C_{11}H_{13}O_4SNa$	Na, 8.71	8.70	160	$C_{19}H_{24}O_4S_2N_2$	6.86	6.83
			8.60				
β-Acetonaphthone-ω-	$C_{12}H_9O_4SNa$	Na, 8.45	11.4	206	$C_{28}H_{30}O_7S_4N_4$	8.46	8.41
	$C_{12}H_8O_7S_2Na_2$	Na, 12.30	11.4				
Pinacolone-α-	$C_6H_{11}O_4SNa$	Na, 11.39	11.27	162	$C_{14}H_{22}O_4S_2N_2$	8.09	8.06
Propiophenone-α-	$C_9H_9O_4SNa$	Na, 9.75	9.86	126	$C_{17}H_{20}O_4S_2N_2$	7.37	7.36
Isobutyrophenone α-	$C_{10}H_{11}O_4SNa$	Na, 9.20	9.25	160	$C_{18}H_{22}O_4S_2N_2$	7.11	7.12
Acetonesulfonate	$C_3H_5O_4SNa$	Na, 14.38	13.40				
Cycohexanone-α-	$C_6H_9O_4SNa$	Na, 11.5	10.1	160	$C_{14}H_{20}O_4S_2N_2$	8.14	8.19
Phenylacetaldehyde-α-	$C_8H_7O_4SNa$	Na, 10.36	10.05				
		C, 43.3	44.2				
		H, 3.15	3.29				
Isobutyraldehyde-α-	$C_4H_7O_4SNa$	Na, 13.22	13.16				
		C, 27.6	27.6				
		H, 4.02	4.05				
Heptaldehyde-α-	$C_7H_{12}O_4SNa$	Na, 10.65	10.62				
		C, 38.9	38.7				
		H, 6.02	6.12				

evaporated to dryness by blowing a stream of air over it. The solid mass which remained was extracted with a boiling 60% alcohol–water mixture. Upon cooling the alcohol–water solution, crystals of sodium ω-acetophenonesulfonate separated. The yield was 54 g. or 70%. A similar procedure was used in the sulfonation of 2-acetothienone, acetomesitylene, β-acetonaphthone, pinacolone, propiophenone and isobutyrophenone.

Preparation of S-Benzylthiuronium Salts.—Approximately 0.2 g. of the sodium sulfonate was dissolved in 5 ml. of water. In another test-tube 0.2 g. of S-benzylthiuronium chloride was dissolved in 5 ml. of water. The two solutions were mixed, the precipitate was filtered and recrystallized from 25 ml. of water which contained one drop of 10% hydrochloric acid. In some cases it was necessary to blow a stream of air over the solution in order to induce the salt to precipitate; however, once a few crystals had formed, the remainder of the salt crystallized upon cooling the solution.

Preparation of the Sodium ω-Ketonesulfonates by the Displacement Reaction.—Sodium ω-acetophenonesulfonate was prepared as described in the literature.[15] Sodium 2-ω-acetothienonesulfonate was prepared as follows: To 0.2 mole (41 g.) of 2-ω-bromoacetothienone, there was added a solution of 25 g. of sodium sulfite in 100 ml. of water. The reaction flask was placed on the steam-bath overnight. The next morning the hot solution was filtered and the sodium salt of the acid crystallized from the chilled filtrate. The same procedure was used to prepare sodium ω-acetomesitylenesulfonate, the only difference being that this solution was refluxed. The solution was then evaporated to dryness and the resulting mass was extracted with a boiling 60% alcohol–water mixture. The alcohol–water solution was cooled and a few crystals of sodium ω-acetomesitylenesulfonate precipitated. 2-ω-Bromoacetothienone was prepared by the method of Brunswig[16]; ω-bromoacetomesitylene was prepared in an analogous manner. Sodium pinacolone-α-sulfonate, sodium propiophenone-α-sulfonate and sodium isobutyrophenone-α-sulfonate were prepared by analogous procedures.

(15) Parkes and Tinsley, *J. Chem. Soc.*, 1861 (1934).

(16) Brunswig, *Ber.*, **19**, 2890 (1886).

Modified Procedure for Sulfonation of Acetone.—Exactly 0.225 mole of dioxane sulfotrioxide reagent was prepared.[14] The reagent was allowed to reach room temperature and 10 cc. more of dioxane was added to dissolve all of the reagent. This solution was added dropwise and with stirring to 130.5 g. (2.50 moles) of acetone. The temperature was maintained below 35°. After the last addition of the reagent, the mixture was stirred for three hours and then hydrolyzed by pouring it into 300 cc. of water. The organic layer was separated, washed with water, dried, and the ethylene chloride was distilled off. Ten grams of mesityl oxide (2,4-dinitrophenylhydrazone, m. p. 203°) was obtained from the still pot. The aqueous layer was neutralized to *p*H 7 with a cold sodium hydroxide solution. The neutralized solution was evaporated to dryness by blowing air over it. The residue was extracted with 95% ethanol, leaving 10 g. of sodium sulfate. On concentrating and cooling the ethanol extract a heavy oil separated which solidified in a vacuum desiccator. The yield of this hygroscopic material was 25 g. Attempts to prepare a crystalline S-benzylthiuronium salt failed. The structure of this sulfonate was proved by cleavage with 20% sodium hydroxide, as described in the literature.[7] Sodium cyclohexanone-α-sulfonate was prepared by this same procedure.

Sulfonation of Phenylacetaldehyde.—Exactly 0.363 mole of dioxane sulfotrioxide reagent was prepared.[14] The reagent was allowed to reach room temperature and 43.6 g. (0.363 mole) of phenylacetaldehyde was added at a rate such that the temperature of the reaction mixture did not exceed 40°. The reaction mixture was stirred for one hour after the last addition of aldehyde, and then it was hydrolyzed by pouring it into 300 cc. of water. The organic layer was separated, washed with water, dried and the ethylene chloride was distilled off. Ten grams of tarry material formed the residue. The aqueous layer was neutralized to *p*H 7 with a cold sodium hydroxide solution. Upon neutralization, 5 g. of a pale yellow solid separated; this was filtered off and recrystallized from a mixture of benzene and petroleum ether. This solid melted at 94°. *Anal.* Found: C, 83.4; H, 5.75. This material formed a phenylhydrazone which melted at 120°. *Anal.* Found: N, 9.30. The remainder of the aqueous layer was evaporated to dryness by blowing air over it. The residue was

extracted with 95% ethanol leaving 30 g. of sodium sulfate. The ethanol extract was evaporated to dryness and this residue was washed repeatedly with acetone and ether. This resulted in the isolation of a white crystalline salt, sodium phenylacetaldehyde-α-sulfonate. The yield was 33 g. or 41.3%.

A similar procedure was used for the sulfonation of heptaldehyde and isobutyraldehyde. The aldehydesulfonates failed to form S-benzylthiouronium salts. Attempts to form oximes and phenylhydrazones of the aldehydesulfonates also failed.

Cleavage of Sodium Phenylacetaldehyde-α-sulfonate.—Two grams of sodium phenylacetaldehyde-α-sulfonate was refluxed with 50 cc. of 20% sodium hydroxide for four hours. The alkaline mixture was acidified with sulfuric acid and formic acid was steam distilled from the mixture. Formic acid was identified through its *p*-bromophenacyl ester (m. p. 140°). The acidified mixture was then neutralized with sodium hydroxide solution and evaporated to dryness. The mixture of salts which remained was extracted with 95% ethanol and 1 g. of a sodium sulfonate was obtained by evaporating the ethanol extract to dryness. The S-benzylthiuronium salt of this sulfonate was prepared (m. p. 162°) and it did not depress the melting point of an authentic sample of S-benzylthiuronium ω-toluenesulfonate.

Anal. Calcd. for $C_{15}H_{18}O_3S_2N_2$: N, 8.28. Found: N, 8.12.

Sodium heptaldehyde-α-sulfonate was cleaved in a similar manner to give formic acid and 1 g. of a sodium sulfonate. The S-benzylthiuronium salt of the sodium sulfonate (m. p. 95°) did not depress the melting point of an authentic sample of S-benzylthiuronium 1-hexanesulfonate.

Anal. Calcd. for $C_{14}H_{24}O_3S_2N_2$: N, 8.43. Found: 8.44.

Summary

1. Four ketones, acetophenone, 2-acetothienone, acetomesitylene and β-acetonaphthone, have been sulfonated using dioxane sulfotrioxide. For the first three ketones, the corresponding sodium ω-ketonesulfonates have been isolated as the principal products in approximately 70% yields (recrystallized). β-Acetonaphthone yielded a mixture of sulfonates.

2. Pinacolone, acetone, cyclohexanone, propiophenone, and isobutyrophenone have been sulfonated with dioxane sulfotrioxide to the corresponding sodium ketone-α-sulfonates.

3. Phenylacetaldehyde, isobutyraldehyde, and heptaldehyde have been sulfonated with dioxane sulfotrioxide to the corresponding sodium aldehyde-α-sulfonates.

4. A mechanism has been proposed for the course of this reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE]

Apparent Ionization Exponents of Homologs of Quinacrine; Electrostatic Effects[1]

BY J. LOGAN IRVIN AND ELINOR MOORE IRVIN

Correlation of the pharmacological properties of the 9-aminoacridine series of antimalarials[2] with their physico chemical characteristics is obviously desirable in attempting to determine their mode of action. For this purpose data concerning the ionization exponents are particularly useful inasmuch as the degree of ionization of these compounds at the *p*H values of body fluids is an important factor in the distribution of these drugs in various tissues,[3,4] in their reversible combination with certain proteins,[3,5] and in their excretion in the urine.[4]

Ionization exponents of quinacrine, 2-methoxy-6-chloro-9-(4′-diethylamino-1′-methylbutylamino)-acridine, have been reported by Christophers.[6] In the present paper data are presented for two homologous series of derivatives of quinacrine with side-chains of varying length but possessing a diethylamino group on the terminal carbon atom in each case. The members of one series of compounds differ from the corresponding members of the other series in lacking the 1′-methyl group of the quinacrine side-chain. The data for these compounds have provided the basis for an evaluation of the effect of electrostatic charges upon proton-equilibria involving a resonating compound. The data are compared with those reported by Schwarzenbach for a series of aliphatic diamines.

Formulation of Equilibria.—By potentiometric titration of aqueous solutions of the 9-aminoacridines reported in this paper two ionization exponents, pK_1' and pK_2', were determined in each case. Another exponent, pK_3', was evaluated spectrophotometrically for each compound by a procedure similar to that described in a study of various 4-aminoquinolines.[7] This exponent is defined by the following equation (with the restriction of constant ionic strength)

(1) The work reported in this paper was aided by a grant from the Penrose Fund of the American Philosophical Society.

(2) Data concerning the pharmacological testing of these and many other compounds have been tabulated in a monograph, "A Survey of Antimalarial Drugs, 1941–1945," edited by Wiselogle, Edwards Bros., Ann Arbor, Mich., 1947. At some points in this paper compounds are designated by numbers preceded by the letters SN. These are the code numbers assigned by the Office of the Survey and recorded in the monograph.

(3) Personal communication from Drs. J. Taggart and J. Shannon.

(4) Jailer, Zubrod, Rosenfeld and Shannon, *J. Pharmacol. Exptl. Therap.*, **92**, 345 (1948); Jailer, Rosenfeld and Shannon, *J. Clin. Invest.*, **26**, 1168 (1947).

(5) Irvin and Irvin, *Federation Proc.*, **8**, 209 (1949).

(6) Christophers, *Ann. Trop. Med. Parasitol.*, **31**, 43 (1937).

(7) Irvin and Irvin, THIS JOURNAL, **69**, 1091 (1947).