2,3-Dimethylbenzyl alcohol (XL) was prepared from 2-methylbenzylmagnesium chloride (obtained from 96.5 g., 0.686 mole of 2-methylbenzyl chloride) and excess trioxymethylene according to the directions of Reichstein and coworkers.[20] This alcohol, b.p. 124–129° at 13 mm. (reported b.p. *ca.* 125° at 12 mm.,[20] 126–133° at 23 mm.[23]), solidified; yield 57%. Two washings with cold petroleum ether gave the pure alcohol, m.p. 63.5–64.5° (reported m.p. 64°,[20] 65–66.5°[23]); yield 50%. Also, there was obtained 3.5 g. (5%) of *o*-xylene, b.p. 40° at 23 mm., 3.8 g. (5%) of the dimer, 2,2′-dimethyldibenzyl, b.p. 190–200° at 16 mm. (reported b.p. 170–180° at 12 mm.),[20] and 11.7 g. of material, b.p. 235–255° at 16 mm. The dimer solidified and, after washing with methanol, melted at 60.5–63° (reported m.p. 65°).[20] Reichstein reported this dimer as the main side reaction product. The 11.7 g. of high boiling material appeared to consist mostly of a single product, possibly the formal derivative of 2,3-dimethylbenzyl alcohol.[23]

2,3-Dimethylbenzoic (hemimellitic) acid, m.p. 142–143° (reported m.p. 144°),[20] was prepared in 71% yield by oxidizing 4 g. of 2,3-dimethylbenzyl alcohol with potassium permanganate.

2,3-Dimethylbenzyl chloride, b.p. 102–103° at 12 mm. (reported b.p. 99° at 12 mm.),[20] was obtained in 89% yield by treating 2,3-dimethylbenzyl alcohol in petroleum ether with hydrogen chloride.

2,3,4-Trimethylbenzyl alcohol (XLI), b.p. 106–110° at 2 mm. (reported b.p. 110–150° at 1 mm.),[20] was obtained from 2,3-dimethylbenzylmagnesium chloride (prepared from 30 g., 0.194 mole, of 2,3-dimethylbenzyl chloride) and excess trioxymethylene as described by Reichstein. Our product (32%) which was obviously purer than that of Reichstein, solidified on cooling to −78° and scratching. Two washings with petroleum ether gave pure 2,3,4-trimethylbenzyl alcohol (XLI), m.p. 49–50° (reported m.p. 49–50°)[20]; yield 20%. Reichstein obtained the pure alcohol in 15% yield by tedious purification through the phthalic acid ester. In agreement with Reichstein, we obtained as side products, hemimellitene (37%) and 2,2′,3,3′-tetramethyldibenzyl (17%).

2,3,4-Trimethylbenzoic (prehnitylic) acid, m.p. 166–167° (reported m.p. 166–168°),[20] was prepared in 73% yield by oxidizing 2.25 g. of 2,3,4-trimethylbenzyl alcohol with potassium permanganate.

DURHAM, N. C. RECEIVED APRIL 11, 1951

[COMMUNICATION NO. 1390 FROM THE KODAK RESEARCH LABORATORIES]

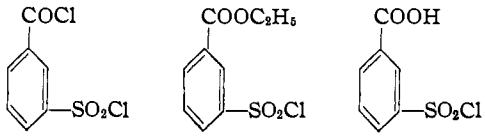
The Reaction of 3-Chlorosulfonylbenzoyl Chloride with Amines

BY C. R. BARR, I. F. SALMINEN AND A. WEISSBERGER

The selective reactivity of 3-chlorosulfonylbenzoyl chloride with amines is demonstrated with the following examples: aniline, *o*- and *p*-aminophenol, 1-aminoanthraquinone, 1-phenyl-3-*m*-aminobenzamido-5-pyrazolone and methylamine. This property is utilized to prepare, (1) mixed amides of the type (R)R′NCO—C_6H_4—$SO_2NR''(R''')$, and (2) pure compounds containing sulfonic acid groups.

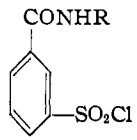
Making use of the well-known difference in reactivity of carboxy acid chlorides and sulfonyl chlorides, *m*-chlorosulfonylbenzoyl chloride (I) can, under suitable conditions, react with two different amines in two stages.[1] The carboxyamide is formed in the first reaction, the sulfonamide in the second. Thus, amines containing active methylene or methine groups have been linked to amines which contain some other function needed in couplers used in color photography. Moreover, the chlorosulfonylcarboxyamides can often be readily purified by recrystallization, and their hydrolysis affords a method for the preparation of pure compounds containing sulfonic acid groups which is sometimes more convenient than the purification of the sulfonic acids or their salts. 3,5-Dichlorosulfonylbenzoyl chloride can be used like I where introduction of *two* sulfonic acid groups is desired.

The marked difference in the reactivity of the functional groups of *m*-chlorosulfobenzoyl chloride is shown by the reactions with alcohol[2] and with water.[3] In the former, ethyl *m*-chlorosulfonylbenzoate (II) and in the latter, *m*-chlorosulfonylbenzoic acid (III) can be obtained in quantitative yields.



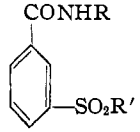
I II III

Suitable conditions for the formation of 3-chlorosulfonylbenzanilide (IVa) are the heating of slightly more than one mole of I with one mole of aniline in toluene, or the reaction at room temperature in toluene of one mole of I with two moles of aniline. Use of dioxane or ethyl acetate instead of toluene gave lower yields. Other conditions lead to the dianilide, Va,[4] for instance, the use of more than one mole of aniline at room temperature in the presence, or of more than two moles of aniline in the absence, of a tertiary amine or inorganic base, or prolonged heating of a reaction mixture containing I and two moles of aniline, or aniline hydrochloride. The m.p. of Va was found to be 13° higher than in the literature. The reaction of IVa with a second



IV

a R = C_6H_5
b R = $C_6H_4OH(2)$
c R = $C_6H_4OH(4)$
d R = anthraquinone(1)



V

a R = C_6H_5; R′ = NHC_6H_5
b R = $C_6H_4OH(2)$; R′ = NHC_6H_5
c R = $C_6H_4OH(2)$; R′ = $N(CH_3)C_6H_5$
d R = $C_6H_4OH(2)$; R′ = $NHC_6H_4OH(2)$
e R = C_6H_5; R′ = OH

(1) A. Weissberger and I. F. Salminen, Eastman Kodak Company, U. S. Patent 2,484,477 (October 11, 1949).

(2) R. Wegscheider and M. Furcht, *Monatsh.*, **23**, 1093 (1902).

(3) S. Smiles and J. Stewart, *J. Chem. Soc.*, **119**, 1792 (1921).

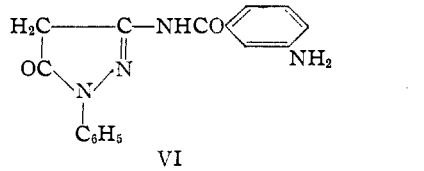
(4) P. Ruggli and F. Grün, *Helv. Chim. Acta*, **24**, 197 (1941).

amine does not require careful control; solution in an excess of the amine at room temperature or a Schotten–Baumann reaction is usually a suitable condition for this reaction.

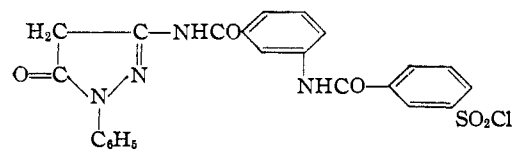
The structure of IVa was proved by hydrolysis with boiling water to the oily 3-phenylcarbamylbenzene sulfonic acid (Ve) and the melting point (249–251°) of its aniline salt.[4]

Reaction of I in dry dioxane for 15 minutes with two moles of *o*-aminophenol gives the 3-chlorosulfonyl-2′-hydroxybenzanilide (IVb) in 64% yield. In the condensation of IVb with aniline or methylaniline, the mixed diamides, Vb and Vc, respectively, are obtained. The diamide, Vd, results from the reaction of four moles of *o*-aminophenol and one of I.

3-Chlorosulfonyl-4′-hydroxybenzanilide (IVc) is obtained in 85% yield by condensation of equal moles of I and *p*-aminophenol in glacial acetic acid and sodium acetate. Boiling water hydrolyzes IVc to the sulfonic acid. Condensation of equal moles of I with 1-phenyl-3-*m*-aminobenzamido-5-pyrazolone (VI) to form VII in a 94% yield in glacial acetic acid in the presence of sodium acetate exemplifies the reaction with a compound containing a methylene group which is activated by an enolizable keto group. Condensation in boiling dioxane or ethyl acetate of equal moles of I and VI is also suitable (yield 93%), but tertiary amines as acid acceptors in dioxane at room temperature yield lower-melting materials, probably because of contamination by *o*-acylated enolized pyrazole.



VI



VII

1-Aminoanthraquinone can be treated with I by boiling equal moles in toluene to yield 71% of IVd. Reaction of IVd with not specially dried pyridine gives the pyridinium salt of 3-(1′-anthraquinolyl)-carbamylbenzene sulfonic acid in quantitative yield, while alcoholic potassium hydroxide hydrolyzes IVd completely to 1-aminoanthraquinone.

Experimental

3-Chlorosulfonylbenzanilide (IVa). Procedure 1.—To a boiling solution of 5.28 g. (0.022 mole) of I in 50 ml. of dry toluene was added, during ten minutes, 1.86 g. (0.02 mole) of aniline in 20 ml. of dry toluene. Refluxing was continued for 30 minutes; the clear solution was cooled at approximately 10° for two hours, a white product crystallizing; yield of IVa was 5.3 g. (90%); m.p. 150–151°. IVa was recrystallized from twenty parts of dry toluene, yielding 5.0 g. (84%) of fine white needles, which melted at 155–156°.

Procedure 2.—To 4.8 g. (0.022 mole) of I in 50 ml. of dry toluene was added dropwise, with stirring, 3.8 g. (0.04 mole) of aniline in 30 ml. of toluene. This mixture was stirred overnight, filtered, and the solid dried. It was stirred into 500 ml. of water to remove aniline hydrochloride. The yield of IVa was 4.5 g. (76.5%); m.p. 142–150°. On recrystallization from toluene, 4.1 g. (70%) was obtained; m.p. 155–156°.

***m*-Sulfobenzoyldianilide (Va). Procedure 1.**—To 4.8 g. (0.02 mole) of I in 50 ml. of dry toluene was added dropwise 3.8 g. (0.04 mole) of aniline in 30 ml. of dry toluene. The mixture was boiled under reflux for 1.5 hours, hydrogen chloride being evolved and a solution resulting. On standing overnight, the product crystallized. The yield was 6 g. (86%); m.p. 163–164°. On recrystallization of Va from toluene followed by alcohol, the melting point was 176–177°, *i.e.*, 13° higher than that given by Ruggli.[4]

Anal. Calcd. for $C_{19}H_{16}N_2O_3S$: C, 64.8; H, 4.6; N, 8.0. Found: C, 64.8; H, 4.6; N, 7.9.

Procedure 2.—The same result was obtained by the use of one mole of IVa and one mole of aniline hydrochloride.

Procedure 3.—To a suspension of 1 g. (0.0034 mole) of IVa in 10 ml. of dry toluene was added, with stirring, 0.63 g. (0.0068 mole) of aniline at room temperature. After a delay of approximately two minutes, the temperature of the mixture rose from 30 to 42°, as a different white solid separated. The reaction was completed by heating to 90° and the mixture recooled to room temperature. Aniline hydrochloride was dissolved by the introduction of 20 ml. of water. The product was filtered, washed on the funnel with 50 ml. of water, and dried. It was crystallized once from toluene and twice from ethanol; m.p. 176–177°.

3-Phenylcarbamylbenzene Sulfonic Acid (Ve).—A suspension of 1 g. of IVa in 100 ml. of distilled water was refluxed for one hour, a clear solution resulting after approximately 30 minutes. The solution was concentrated on a steam-bath to a quantitative yield of the yellow, oily Ve.[4]

Aniline Salt of 3-Phenylcarbamylbenzene Sulfonic Acid.[4]—To the solution of 1 g. of Ve in 10 ml., of 90% ethyl alcohol was added 2 ml. of aniline. A clear solution resulted to which was added 2 ml. of ether, the aniline salt of the Ve crystallizing as white needles; yield 1 g. (70%). The melting point (249–251°) is in agreement with that reported by Ruggli.[4]

3-Chlorosulfonyl-2′-hydroxybenzanilide (IVb).—A solution was prepared of 21.8 g. (0.2 mole) of *o*-aminophenol in 350 ml. of dry dioxane (Eastman white label grade; stored over sodium) by warming to 70° and recooling to 25°. To this pink solution was added, with stirring, 23.9 g. (0.1 mole) of I. A red mixture resulted as the temperature rose from 25 to 40°. After 15 minutes, the mixture was filtered, and the *o*-aminophenol hydrochloride washed on the funnel with 50 ml. of dry dioxane. IVb was crystallized by dilution of the red filtrate with 400 ml. of hexane. The yield was 24 g. (77%); m.p. 177–179° (dec.). Recrystallized from 300 ml. of dry tetrachloroethane, 20 g. (64%) of IVb was obtained in small tan needles which melted at 183° (dec.).

Anal. Calcd. for $C_{13}H_{10}ClNO_4S$: C, 50.01; H, 3.21. Found: C, 49.98; H, 3.15.

3-N-Phenylsulfamyl-2′-hydroxybenzanilide (Vb).—One gram (0.003 mole) of IVb was dissolved, by stirring, into 5 ml. of aniline, the temperature rising from 25 to 50°. The paste was freed from excess aniline with 100 ml. of 10% hydrochloric acid and, after standing overnight, the solid (0.8 g., 68%), m.p. 168–170°, was recrystallized from 100 ml. of toluene, 0.5 g. of fine white needles (42%); m.p. 170°.

Anal. Calcd. for $C_{19}H_{16}N_2O_4S$: C, 61.95; H, 4.32. Found: C, 61.92; H, 4.27.

3-N-Methyl-N-phenylsulfamyl-2′-hydroxybenzanilide (Vc).—This compound was prepared like Vb from 5 g. (0.016 mole) of IVb and 10 g. (0.095 mole) of methylaniline. Before recrystallization the solid was washed with 100 ml. of water, and twice with 50 ml. of ether to remove an oily impurity; 5 g. (82%); m.p. 157–158°, recrystallized from 100 ml. of toluene; 4 g. (66%), m.p. 158°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.82; H, 4.72. Found: C, 63.20; H, 4.81.

3-Chlorosulfonyl-4′-hydroxybenzanilide (IVc).—A suspension of 2.9 g. (0.02 mole) of *p*-aminophenol hydrochloride and 3.28 g. (0.04 mole) of sodium acetate in 50 ml. of glacial acetic acid was heated on the steam-bath for five minutes. To it was added a solution of 4.78 g. (0.02 mole) of I in 50 ml. of glacial acetic acid. After stirring and heating on the steam-bath for one hour and forty-five minutes, the solution was chilled to 0° for 15 minutes, and diluted with 500 ml. of water. The white product was collected, washed with 100

ml. of water and 50 ml. of petroleum ether; 5.24 g. (85%) of 3-chlorosulfonyl-4'-hydroxybenzanilide; m.p. 170°.

1-Phenyl-3-*m*-nitrobenzamido-5-pyrazolone.—Ten grams (0.057 mole) of 1-phenyl-3-amino-5-pyrazolone, prepared by the procedure of Weissberger and Porter,[5] was stirred on the steam-bath with 10.6 g. (0.057 mole) of *m*-nitrobenzoyl chloride and 7 ml. of ethyl oxalate for 20 minutes. The product was broken up by refluxing and stirring with 50 ml. of ethyl alcohol, cooled, collected, and washed on the funnel with 50 ml. of 70% alcohol; 14.5 g. (78%); m.p. 215–220°.

1-Phenyl-3-*m*-aminobenzamido-5-pyrazolone (VI).—Sixteen grams (0.049 mole) of 1-phenyl-3-*m*-nitrobenzamido-5-pyrazolone was added to 145 ml. of glacial acetic acid, 15 ml. of water, and 80 ml. of ethyl alcohol which was refluxed in a 1-l. round-bottomed flask, and followed by 16.0 g. of iron powder, added at once. A vigorous reaction took place, no heating being necessary for about three minutes. The mixture was kept boiling for ten minutes, filtered hot, and the filtrate diluted with 100 ml. of water, cooled without stirring, collected, and washed successively on the funnel with 50 ml. of 50% acetic acid, 150 ml. of water and 50 ml. of alcohol; 11.0 g. (76%) lustrous brown crystals (VI); m.p. 220–222°.

(5) A. Weissberger and H. D. Porter, THIS JOURNAL, **64**, 2133 (1942).

1-Phenyl-3-[3'-(*m*-chlorosulfonyl)-benzamido]-benzamido-5-pyrazolone (VII).—To 2.39 g. (0.01 mole) of I in 25 ml. of glacial acetic acid was added 2.94 g. (0.01 mole) of 1-phenyl-3-*m*-aminobenzamido-5-pyrazolone and 1.64 g. (0.02 mole) of sodium acetate in 55 ml. of warm (50°) glacial acetic acid. The mixture was stirred at room temperature for three hours (a white solid began to separate after approximately one minute), collected, and washed on the funnel with 100 ml. of water, stirred into 300 ml. of water, refiltered, and washed successively with 10 ml. of ethanol and 25 ml. of ether; 5.2 g. (94%) white crystals; m.p. 188–190°. Analysis showed the presence of one mole of acetic acid.

Anal. Calcd. for $C_{25}H_{21}ClN_4O_7S$: C, 54.0; H, 3.8; Cl, 6.4. Found: C, 54.3; H, 4.0; Cl, 6.0.

1-(3'-Chlorosulfonylbenzamido)-anthraquinone (IVd).—To a hot mixture of 4.4 g. (0.02 mole) of 1-aminoanthraquinone in 130 ml. of dry toluene was added, all at once, 6.6 g. (0.028 mole) of I. As the mixture was refluxed for one and one-quarter hours, hydrogen chloride evolved and solution resulted. The solution was cooled to room temperature, and collected in long amber needles; 6.9 g. (81%); m.p. 216–219° (dec.); recrystallized from 180 ml. of toluene; 5.0 g. (59%); m.p. 219–222° (dec.).

Anal. Calcd. for $C_{21}H_{12}ClNO_5S$: Cl, 8.35. Found: Cl, 8.36.

ROCHESTER, N. Y. RECEIVED FEBRUARY 9, 1951

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY AND THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Conversion of Cholic Acid into 3α-Hydroxy-12-keto-Δ$^{9(11)}$-cholenic Acid

BY LOUIS F. FIESER AND SRINIVASA RAJAGOPALAN, EVELYN WILSON AND MAX TISHLER

Methyl 3α,7α-diacetoxy-12-ketocholanate, available in three steps from cholic acid, is convertible with selenium dioxide into the 9,11-unsaturated derivative, which on treatment with alkali affords 3α-hydroxy-12-keto-Δ$^{7,9(11)}$-choladienic acid (IV). Reduction of this dienone with zinc and acetic acid gives a non-conjugated mono-unsaturated ketone capable of being isomerized to 3α-hydroxy-12-keto-Δ$^{9(11)}$-cholenic acid (VI).

3-Hydroxy-12-keto-Δ$^{9(11)}$-cholenic acid (VI), a key intermediate in the Kendall procedure[1] for the production of an 11-oxygenated bile acid derivative from which cortisone can be prepared, hitherto has been available only *via* desoxycholic acid. We have now found a new route to VI that does not involve desoxycholic acid as an intermediate.

A previously reported procedure[2] for the preparation of methyl cholate 3,7-diacetate in 62–70% yield consists in acetylation of the bile acid ester with acetic anhydride and pyridine in benzene solution at room temperature. A still simpler procedure utilizes dioxane as solvent; on addition of a limited amount of water, after a suitable reaction period, the diacetate crystallizes in a state satisfactory for direct use in the next step of oxidation; the mother liquor can be processed for recovery of cholic acid (89% recovery). The ketone I is obtained in nearly quantitative yield by addition of aqueous potassium chromate to an acetic acid solution of the 12-hydroxy compound, and I is dehydrogenated readily to the Δ$^{9(11)}$-12-ketone II by selenium dioxide in acetic acid, as in the standard method for preparation of VI.[3,1] When refluxed with excess aqueous alcoholic alkali, the eneone diacetate II is converted in over 90% yield into the dienone acid IV. The course of the reaction was established by the observation that treatment of II with a limited amount of alkali for a brief period afforded a certain amount of the eneonediol III, which with excess alkali affords the dienone acid IV. The facile elimination of the elements of water from the eneonediol III is attributable to activation of the C_8-hydrogen atom by the 9,11-double bond; the saturated ketone I yields no dehydro product under the conditions used for conversion of II into IV.

Barring an unlikely rearrangement, the newly introduced double bond of the dienone must be at the 7,8-position, as in IV. This structure is consistent with the presence in the spectrum of an intense absorption band at 292.5 mμ, since the maximum calculated[4] for IV from available analogs is 303 mμ. Our dienone corresponds in properties to one obtained by Shimizu, Kazuno and Matsumoto[5] from 3,7-diacetoxy-11-bromo-12-ketocholanic acid; the Japanese investigators, evidently unaware of recent revisions of the literature, erroneously formulated the compound as the Δ$^{8(14),9(11)}$-dien-12-one.[6] On hydrogenation of the dienone, the Japanese chemists obtained a mono-unsaturated ketone that they formulate as having the Δ^8-structure V. We obtained the same compound by re-

(1) B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 271 (1948).

(2) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5534 (1950).

(3) E. Schwenk and E. Stahl, *Arch. Biochem.*, **14**, 125 (1947).

(4) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1949.

(5) T. Shimizu, T. Kazuno and K. Matsumoto, *J. Japan. Biochem. Soc.*, **20**, 164 (1948); *C. A.*, **44**, 164 (1950).

(6) *Chemical Abstracts* (see ref. 5) mistakenly quotes the authors as describing the compound as the Δ$^{7,9(11)}$-diene-12-one.