shown that such hydrolysis is quite liable to remove the acyl group. The production of *o*-acetovanillone therefore appears to be analogous to the formation of isobutyl 3,5-dimethoxy-4-hydroxyphenyl ketone from 3,4,5-trimethoxybenzonitrile and isobutylmagnesium bromide.[6] It differs, however, in the fact that methylmagnesium iodide does not require high temperatures and apparently does not alkylate at the position of attachment of the *o*- or *p*-methoxyl group.

Similar observations have been made on 2-benzyloxy-3-methoxybenzonitrile in which the benzyl ether is split. Since there is no preparative advantage accruing to the use of the benzyl ether rather than the methyl ether, details of these experiments are omitted.

Experimental

An ether solution of 16.3 g. (0.1 mole) of *o*-veratronitrile was added rapidly to an ether solution of Grignard reagent prepared from 28.4 g. (0.2 mole) of methyl iodide and 4.8 g. (0.2 g.-atom) of magnesium. No refluxing was observed and no precipitate formed for about one hour. The solution was therefore refluxed and stirred for eight hours during a total time of about sixty hours. Although a small amount of Grignard reagent was still present the mixture was then worked up in the usual way with water, ammonium chloride solution and finally dilute hydrochloric acid. Phenolic material, removed from the ethereal solution with dilute alkali, proved to be almost pure *o*-acetovanillone and amounted to 12.36 g. (74.5%), m. p. 50–53.1°, mixed with authentic *o*-acetovanillone, m. p. 51.8–53°. The crude neutral material amounted to 3.25 g. (18%), $n^{30.5}D$ 1.5282, observed for authentic *o*-acetoveratrone $n^{26.5}D$ 1.5368. Starting material unaccounted for above was obtained as a water-, ether- and alkali-insoluble resinous gum.

A second run of the same size using a nitrile to Grignard ratio of 1:1.5, refluxing for one hour and standing overnight yielded some tar and 25.6% of *o*-acetovanillone (m. p. 51.8–53°; mixed with authentic, m. p. 51.8–53°) and 32.2% of *o*-acetoveratrone, $n^{26.5}D$ 1.5368. The neutral fraction yielded iodoform (m. p. 121–123°) and an acid, m. p. 118–120.4° (reported for *o*-veratric acid, m. p. 122°).[7] It also formed a 2,4-dinitrophenylhydrazone, m. p. 150–151.8° which did not depress the melting point of an authentic specimen.

(6) Hurd and Winberg, THIS JOURNAL, **64**, 2085 (1942).

(7) Perkin and Robinson, *J. Chem. Soc.*, **105**, 2383 (1914).

DEPT. OF CHEMISTRY
LEHIGH UNIVERSITY
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Purification of Xanthopterin[1]

BY A. G. ANDERSON, JR., AND JERRY A. NELSON

In connection with the studies on the physiological properties of xanthopterin in this Laboratory,[2] xanthopterin free of other pterin impurities was desired. A purification procedure satisfactory as a routine method for this purpose was not found in the literature. In this investigation xanthopterin has been purified *via* a new crystalline derivative, xanthopterin hydrochloride. Crystalline xanthopterin sulfate has also been prepared. The hydrochloride salt affords a simple, effective means for the purification of synthetic xanthopterin as prepared in this Laboratory. Purification was also effected by sublimation *in vacuo*. This procedure gave poor yields and thus was not practical.

(1) This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

(2) Norris and Majnarich, *Amer. J. Physiol.*, **152**, 175, 179, 652 (1948); **153**, 133, 483, 486, 492, 496 (1949); *Science*, **109**, 32, 33 (1949).

Experimental

Xanthopterin.—Leucopterin and, from it, xanthopterin were prepared by the procedures of Purrmann[3] and Totter,[4] respectively, as modified by Dauben and Goheen,[5] the modified procedure being similar to that recently reported by Hitchings and co-workers.[6] The xanthopterin so obtained was used in the experiments described below.

Xanthopterin Hydrochloride.—To 100 mg. of finely powdered xanthopterin was added 20 ml. of concentrated hydrochloric acid and the mixture heated on a steam-bath for ten minutes and filtered by suction while hot. The insoluble material (approximately 20 mg.) was largely xanthopterin hydrochloride and to this was added 5 ml. of hydrochloric acid and the mixture heated and filtered as before. The small quantity (5 mg.) of insoluble material was discarded. The two filtrates were placed in a refrigerator at −5° overnight. The hydrochloride precipitated as tiny, tan hexagonal plates which were separated by filtration, washed with a few ml. of cold alcohol, then with ether and dried. The yield from the first filtrate was 86 mg. (71.5%) and from the second filtrate 10 mg. (8.4%); total yield 96 mg. (79.9%). The salt was recrystallized from hydrochloric acid in corresponding yield. It was soluble in hot water or hot dilute hydrochloric acid but the hydrochloride could not be recovered from these solutions by cooling or concentration. On heating the crystals darkened at 200° and above but no melting point was observed up to 320°.

Anal. Calcd. for $C_6H_6O_2N_5Cl$: N, 32.48. Found: N, 32.41.

Amorphous xanthopterin was recovered quantitatively as a yellow solid on treatment of the hydrochloride with just sufficient 0.1 *N* ammonium hydroxide to effect solution (the xanthopterin began to precipitate a few seconds after the salt had dissolved) and then adjustment of the acidity to *p*H 5–6 by addition of dilute hydrochloric acid. The mixture was cooled, filtered and the collected precipitate washed with a few ml. of cold water, then acetone and dried.

Xanthopterin Sulfate.—Eighty-six mg. of finely powdered xanthopterin was dissolved in 2.3 ml. of sulfuric acid–water (1:1) solution by heating on a steam-bath. As the xanthopterin dissolved the solution became orange in color. On cooling the solution in tap water and scratching the sides of the flask, crystallization occurred and, after standing overnight in a refrigerator, the tiny, tan boat-shaped crystals were separated by filtration, washed with a few ml. of cold alcohol, then with ether and dried; yield 45 mg. (36%). The crystals gradually darkened and decomposed above 200° leaving a black residue at 280°. The sulfate could be recrystallized from the same sulfuric acid solution in corresponding yield. Attempts to obtain a second crop from the filtrate were unsuccessful. Xanthopterin sulfate is quite soluble in dilute or concentrated sulfuric acid and undergoes hydrolysis with water to precipitate amorphous xanthopterin. Recovery of xanthopterin from the sulfate was best effected in the manner described for the hydrochloride.

Anal. Calcd. for $C_6H_7O_6N_5S$: N, 25.27. Found: N, 25.80.

(3) Purrmann, *Ann.*, **544**, 182 (1940).

(4) Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(5) Dauben and Goheen, private communication.

(6) Ellion, Light and Hitchings, THIS JOURNAL, **71**, 741 (1949).

Chromatographic Analysis of Purified Xanthopterin.—Paper chromatographs of the xanthopterin purified *via* the hydrochloride and by sublimation *in vacuo* were obtained by the method of Good and Johnson[7] who employed the *n*-butanol–acetic acid–water mixture of Partridge.[8] Under ultraviolet light the chromatographs showed only one fluorescent spot (Rf = 0.35–0.38) which was in agreement with the value (Rf = 0.38) reported by Good and Johnson.[7] The material was thus free of leucopterin (Rf = 0.12), dihydroxanthopterin (Rf = 0.26) and other fluorescent pterin impurities. It should be noted that some samples of synthetic xanthopterin prepared as indicated did not contain these impurities and thus required no further purification.

Absorption Spectra of Purified Xanthopterin.—Ultraviolet absorption spectra of an aqueous solution (*p*H of 11.25) of the xanthopterin purified by sublimation and *via* the hydrochloride showed absorption maxima at 255 mμ. ($E_m \times 10^{-3} = 18.2$) and 392 mμ; ($E_m \times 10^{-3} = 7.0$) in agreement with other reported spectra.[4,9]

(7) Good and Johnson, *Nature*, **163**, 31 (1949).
(8) Partridge, *Biochem. J.*, **42**, 238 (1948).
(9) Rickes, Chaiet and Keresztesy, THIS JOURNAL, **69**, 2749 (1947).

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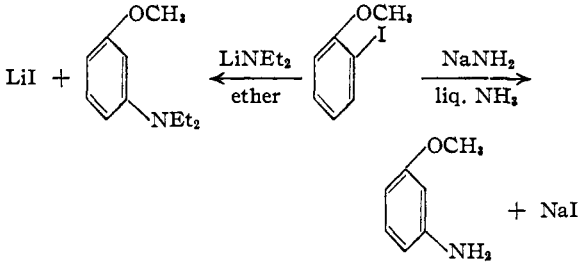
The Reaction of Sodium Amide with *o*- and *m*-Chlorotrifluoromethylbenzene

BY ROBERT A. BENKESER AND ROLAND G. SEVERSON[1]

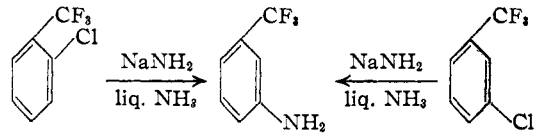
Recently it was reported that certain aryl halides react with a liquid ammonia solution of sodium[2] or potassium amide.[3] It has also been found that ether solutions of aryl halides are attacked by lithium dialkylamides.[4] When the aryl halide has an ether, sulfide or dialkylamino group ortho to the halogen, it was observed that the amino or dialkylamino group does not take up the position which the halogen originally occupied, but rather a meta-substituted product[5,6,7] is formed



The corresponding *p*-haloethers also exhibit this tendency to undergo rearrangement when treated with lithium dialkylamides in ether, but to a somewhat lesser extent.[8]

(1) Research Corporation Fellow.
(2) Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).
(3) Urner and Bergstrom, *ibid.*, **67**, 2108 (1945).
(4) Horning and Bergstrom, *ibid.*, **67**, 2110 (1945).
(5) Gilman and Nobis, *ibid.*, **67**, 1479 (1945).
(6) Gilman, *et al.*, *ibid.*, **67**, 2106 (1945).
(7) Gilman, Kyle and Benkeser, *ibid.*, **68**, 143 (1946).
(8) Gilman and Kyle, *ibid.*, **70**, 3945 (1948).

It has now been observed that the same rearrangement occurs even when the halogen is ortho to a strong meta-directing group. Thus, *o*-chlorotrifluoromethylbenzene upon treatment with sodium amide in liquid ammonia for five hours at −33° gives a 52% yield of pure *m*-aminotrifluoromethylbenzene. Efforts to isolate any of the ortho isomer have been unsuccessful. In contrast, *m*-chlorotrifluoromethylbenzene gives the expected *m*-aminotrifluoromethylbenzene. It is noteworthy that the yield here is only 35%.



Experimental

***m*-Aminotrifluoromethylbenzene.** (a) **From *o*-Chlorotrifluoromethylbenzene.**—Sodium amide[9] was prepared from 16.1 g. (0.7 g. atom) of sodium and 750 ml. of liquid ammonia containing 0.4 g. of hydrated ferric nitrate. To this mixture was added 90.3 g. (0.5 mole) of *o*-chlorotrifluoromethylbenzene[10,11] (b. p. 149–150°) during a period of one hour. After stirring for an additional four hours, ammonium chloride was added and the solvent was allowed to evaporate. The residue was dissolved in ether, filtered and treated with anhydrous hydrogen chloride which precipitated 62 g. of a brown hydrochloride. From the ether filtrate 14.4 g. of *o*-chlorotrifluoromethylbenzene (b. p. 149–150°) was recovered. Crystallization of the crude hydrochloride from an ethanol–ether mixture gave 53 g. of white crystals from which the free base was obtained by adding concentrated ammonium hydroxide. After extracting the basic solution with ether, drying the ether extract over Drierite, removing the solvent, and fractionating the product through a small helices-packed column, there was obtained 35.1 g. (52% yield) of *m*-aminotrifluoromethylbenzene boiling at 86° (20 mm.), $n^{20}D$ 1.4801, $n^{25}D$ 1.4775.

The acetyl derivative[12] melted at 103–104° and the benzoyl derivative[13] at 110–111°. A mixed melting point between this acetyl derivative and that obtained from an authentic sample of *m*-aminotrifluoromethylbenzene[10] showed no depression.[14]

(b) **From *m*-Chlorotrifluoromethylbenzene.**—This procedure was identical with that described above. From 90.3 g. (0.5 mole) of *m*-chlorotrifluoromethylbenzene,[10] 47.8 g. of crude hydrochloride was obtained. This gave 36 g. of pure salt when crystallized from an ethanol–ether mixture and 23.9 g. (35% yield) of the free base boiling at 86° (20 mm.), $n^{20}D$ 1.4800. The acetyl and benzoyl derivatives melted at 103–104° and 110–111°, respectively.

(9) Vaughn, Vogt and Nieuwland, *ibid.*, **47**, 2002 (1925).
(10) Kindly supplied by the Hooker Electrochemical Company, Niagara Falls, N. Y.
(11) For a description of numerous ortho and para derivatives of benzotrifluoride see Jones, THIS JOURNAL, **69**, 2346 (1947).
(12) Swarts, *Bull. acad. roy. Belg.*, 389 (1920); *C. A.*, **16**, 2316 (1922).
(13) *Anal.* Calcd. for $C_{14}H_{10}OF_3N$: N, 5.28. Found: N, 5.35.
(14) The literature[11,12] values for the physical constants of *o*-, *m*- and *p*-aminotrifluoromethylbenzene are

	B. p. °C.	Mm.	n_D	Acetyl deriv.	Benzoyl deriv.
ortho-	72–74	21	1.4785 (25°)	94.5–95°	140–141°
meta-	74–75	10	1.481 (20°)[10]	103°	.....
para-	91	19	1.4815 (25°)	152°	.....