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XANTHYDROL AS A REAGENT FOR THE IDENTIFICATION OF SULFONAMIDES

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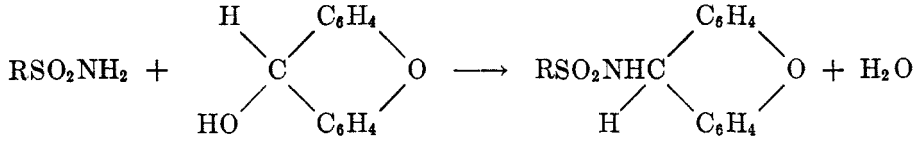
The most general method for the identification of sulfonamides consists of their hydrolysis with acid or alkali (1). This method has the disadvantage of being both laborious and not too satisfactory with respect to the isolation and characterization of the hydrolysis products. Much more desirable would be a non-hydrolytic procedure which operates directly on the sulfonamide group present. Some progress in this direction has been reported by Evans and Dehn (2), who condensed unsubstituted sulfonamides with phthalyl chloride. Work has also been reported on a similar condensation between alkyl halides and sulfonamides (3), although this was directed towards alkyl halide rather than sulfonamide identification.

The use of xanthydrol for the preparation of amide derivatives (4) naturally suggests its possible utility with sulfonamides. Two such derivatives are known. In 1935, Wood (5) reported condensing xanthydrol with *p*-toluenesulfonamide and with sulfanilamide. (He also secured the bis derivative of sulfuryl diamide.) No experimental details were given.

The reaction between sulfonamides and xanthydrol may be expressed by the equation



The condensation requires an acid medium, acetic acid being satisfactory. This is in agreement with the earlier work of Fosse (6) and Adriani (7) on xanthydrol condensations.

The N-xanthylsulfonamides, also in line with their work, form only with unsubstituted amides. The derivatives so prepared are crystalline, easily formed and purified compounds, suitable for use in identification work. A very simple general procedure, requiring only one-quarter gram of sulfonamide, has been developed and applied successfully to twelve benzenoid sulfonamides and one imide. It failed where the alkyl groups on the ring were branched.

In Table I are listed the melting points and analyses of the N-xanthylsulfonamides which have been prepared.

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The following benzenoid sulfonamides failed to give xanthyl derivatives: 2,4,6-triethylbenzenesulfonamide, *p*-t-butyl-, *p*-t-amyl- and the *p*-cymenebenzenesulfonamides, N-ethyl-*p*-toluenesulfonamide. Two compounds, 4-sec-butyl-, and 2-methyl-4-isopropyl-benzenesulfonamides, gave exceedingly poor yields of products. It will be observed that all of these sulfonamides, except the triethyl and the N-ethyl, have branched chain alkyl substituents. It would appear that such groups, even *para* to the sulfonamide group, block the xanthydrol condensation. It was not expected that the N-ethyl compound would condense,

TABLE I

N-XANTHYL-*n*-ALKLYBENZENESULFONAMIDES

-BENENESULFONAMIDE-1	N-XANTHYL DERIVATIVE			
	M.P.°C[a]	% Nitrogen[b]		
		Calc'd	Found	
—	200–200.5	4.16	4.28	4.35
2-Me-	182–183.5	3.99	4.03	4.10
4-Me-	197–197.5[c,d,g]	3.99	4.46	4.47
4-Et-	195.5–197[c,e]	3.84	3.95	4.15
4-*n*-Pr-	199–200.5[d,e]	3.69	3.92	3.95
4-*n*-Bu-	185–186.5	3.56	3.88	3.95
4-*n*-Am-	164.5–165	3.44	3.54	3.64
3,4-di-Me-	189–190[f]	3.84	3.98	3.99
2,4-di-Me-	187–188.5[f]	3.84	3.85	3.94
2,5-di-Me-	175–176	3.84	3.72	3.92
2,4,6-tri-Me-	203–204	3.69	3.85	4.08
4-NH_2-	207–208[h]	5.26 (di)	5.46	5.55
Saccharin[i]	198–199[i]	3.86	4.20	4.33

[a] All melting points are uncorrected and were determined on a copper block with standard 360° melting point thermometer as described in Morton, "Laboratory Technique in Organic Chemistry," 1st Ed., McGraw-Hill, New York, **1933**, pp. 32–33. [b] Nitrogen analyses were semi-micro and were performed by Malcolm L. Brown, whom we wish to thank for his cooperation. [c] Mixed melting point of these derivatives was 185–191°. [d] Mixed melting point of these derivatives was 183–192°. [e] Mixed melting point of these derivatives was 187–189°. [f] Mixed melting point of these derivatives was 163–167°. [g] Melting point reported by Wood (5) was 198°. [h] Melting point reported by Wood (5) was 209°. [i] Melting point reported by Fabre (8) was 199–200°. [j] Saccharin gave lower yields than did the sulfonamides though still enough to work with.

since most of the earlier work has shown that a free amide group is required. However, equally as surprising as the recalcitrance of the branched alkyl compounds was the failure of triethylbenzenesulfonamide to condense. The analogous mesitylene compound worked beautifully, and so did ethylbenzene, but not the triethyl. (Yields on all of the xanthylbenzenesulfonamides except saccharin, which fell to 50% amounted to 80–90%.) Deviations from the standard procedure involving as much as 2 hours heating or 2 weeks standing at room temperature all failed to produce a product.

The failure of 2,4,6-triethylbenzenesulfonamide to condense may be analogous to the like behavior of picramide (7). The failure of N-ethylbenzenesulfonamide to condense offers evidence against the likelihood of C-xanthyl (*i.e.* ring substituted) derivatives, except in cases such as aniline or sulfanilamide, where the ring is activated by the amino group.

The inhibiting effect of the branched alkyl groups is perhaps suggested by the fact that larger *n*-alkyl groups seem to slow down the rate of condensation somewhat, since in a given time, the yields from benzenesulfonamide itself are about 10% greater than those from *p*-*n*-amylbenzenesulfonamide.

EXPERIMENTAL

Xanthydrol. The xanthydrol used was obtained by the sodium-amalgam reduction of xanthone, (9), kindly supplied by the General Chemical Company. Eastman xanthydrol was also used, but was somewhat less satisfactory than the freshly prepared product [*cf.* Phillips and Pitt (4)].

The saccharin, sulfanilamide, and the benzene- and toluene-sulfonamides were Eastman products. All other sulfonamides used were obtained through the courtesy of Professor E. H. Huntress (10) from those prepared by Dr. J. S. Autenrieth as a portion of his doctorate thesis (M.I.T., 1941).

Preparation of N-xanthylalkylbenzenesulfonamides. One-quarter gram of xanthydrol was dissolved in 10 cc. of glacial acetic acid with 0.25 gram of the sulfonamide. This solution was shaken at room temperature for 2–3 minutes and allowed to stand for 90 minutes. The product was filtered and recrystallized from dioxane-water (3:1). One recrystallization was usually sufficient. The products were dried, at room temperature, at the water-pump for about one-half hour.

For recrystallization dioxane-water (3:1) was found to be most generally satisfactory. Cold alcohol does not dissolve the xanthyl derivatives to a very high degree, but dissolves the reactants, so it is useful for washing the products. Dioxane mixed with either acetone (1:1) or alcohol (1:1) is also a useful mixed solvent.

The products were not dried at elevated temperatures since it was found that 80°-drying caused a lowering of the melting points of 2–8°.

The reaction mixture may be heated, but the condensation time saved is not great, and the product becomes more difficult to purify.

3,N¹-Dixanthylsulfanilamide. The analyses in Table I give evidence for a dixanthyl derivative (the mono has a calculated N content of 7.95%). This probably means that a second xanthyl group has gone onto the ring, since aniline is reported to give a C-xanthyl derivative (7). The amino group of the sulfanilamide was shown to be intact by a positive test with nitrous acid.[3] It is believed then, using conventional orientation, that this dixanthyl derivative is probably 3,N¹-dixanthyl sulfanilamide.

SUMMARY

A very simple procedure has been developed for the direct preparation of N-xanthyl derivatives of sulfonamides using xanthydrol as a reagent. No prior hydrolysis is required. Data are given for twelve sulfonamides and saccharin.

[3] That is, diazotization to give nitrogen-test 2.23, Mulliken-Huntress Manual, "Identification of Organic Compounds", 1937, p. 137; Shriner and Fuson, "Systematic Identification of Organic Compounds", 2nd Ed., p. 50.

Seven sulfonamides, five with branched alkyl substituents, failed to condense satisfactorily. The N-xanthyl derivatives are crystalline, easily formed and purified compounds, well suited for the characterization of sulfonamides.

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