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The Use of Xanthydrol as a Reagent for the Characterization of Primary Amides

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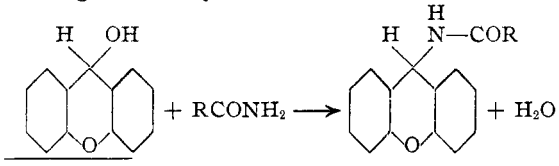
The standard procedures used for the preparation of derivatives of amides require their hydrolysis and the subsequent isolation and characterization of the acid and amine residues.[4,5] Much less laborious and therefore preferable would be a one-step procedure which will yield derivatives directly, without the preceding hydrolytic step. Some progress in this direction has been previously reported (1) by Evans and Dehn,[6] who condensed amides with phthalyl chloride; (2) by MacKenzie and Rawles,[7] who formed the oxalate salts of certain primary aliphatic amides; and (3) most recently by Williams, Rainey and Leopold,[8] who have formed the mercury derivatives of some fifteen amides. The present paper reports further progress through the preparation of xanthyl derivatives of 22 amides.

The use of xanthydrol as a reagent for amides is suggested by its well-known use in characterizing urea as dixanthyl urea.[9] Fosse[10] has summarized earlier work with xanthydrol up to 1927, giving many results, but very little experimental detail. Using his and Adriani's[11] work as a basis, this paper reports the extension in a systematic manner of the xanthydrol condensation with amides to 22 mono-amides and 2 imides.

The formation of xanthyl amides proceeds according to the equation



in the presence of acetic acid.

Two general methods have been developed for the preparation of N-xanthyl amides, one using a solution of xanthydrol in acetic acid and the other a saturated solution of xanthydrol in a mixture of acetic acid, alcohol and water. Stock reagent solutions of xanthydrol can be made up for either procedure. These will keep for at least four months without undergoing serious decomposition[12,13] and are advantageous, both from the viewpoint of convenience and that of increased stability of the reagent.

By means of either procedure it is possible to carry a derivative preparation through the amide to the pure dry crystalline derivative in as short a time as one-half hour. In Table I are listed the melting points and analyses of the various xanthylamides which were prepared.

The melting points of the N-xanthyl amides may be plotted to form a smooth curve. Not all of the N-xanthylamides have been prepared, but by means of such a curve, it is possible at least to approximate the melting points of the missing members.

The following compounds failed to give satisfactory xanthyl derivatives: di- and trichloroacetamides, salicylamide, oxamide, guanidine and cyanoguanidine (dicyandiamide), picramide and acetanilide. The behavior of the polychloroacetamides is adumbrated by the slower reaction noted for chloroacetamide. Presumably this decreasing reactivity with increased chlorine content is due to the increased acidity of the $-NH_2$ hydrogens. Salicylamide did not give a reproducible product, probably because of ring reactivity (analogous to aniline which gives a C-xanthylaniline). Oxamide was found to be too insoluble to work with. The unreactivity of the remaining compounds confirms earlier observations of Fosse and Adriani. The case of acetanilide points to the fact that the xanthydrolamide condensation occurs only with amides having a free $-CONH_2$ group, not with N-substituted amides.

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(4) Mulliken, "Identification of Pure Organic Compounds," Vol. II, p. 36; Mulliken–Huntress, "Manual for the Systematic Identification of Organic Compounds," Test 2.34, p. 166.

(5) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., p. 143.

(6) Evans and Dehn, THIS JOURNAL, **51**, 3651–3652 (1929).

(7) MacKenzie and Rawles, *Ind. Eng. Chem., Anal. Ed.*, **12**, 737–738 (1940).

(8) Williams, Rainey and Leopold, THIS JOURNAL, **64**, 1738–1739 (1942).

(9) Clarke, "Handbook of Organic Analysis," 4th ed., pp. 30, 212.

(10) Fosse, "L'Uree et les Fonctions Dinaphthopyranol, Xanthylet Sel de Pyrrole," Presses Universitaires de France, Paris, 1927.

(11) Adriani, *Rec. trav. chim.*, **35**, 180–210 (1915).

(12) Xanthydrol tends to dissociate on standing into xanthone and xanthene; Kny-Jones and Ward, *Analyst*, **54**, 574–575 (1929).

(13) Fosse, *Compt. rend.*, **145**, 813–815 (1907); *Ann. chim.*, (9) **6**, 35–42 (1916).

TABLE I

DATA ON N-XANTHYL AMIDE DERIVATIVES

Amide	M. p., °C. obsd. of derivative (uncor.)[a]	Analyses,[b] % Nitrogen Calcd.	Found	
Acetamide	238–240[c]	5.85	5.76	5.78
Propionamide	210–211[d]	5.53	5.74	5.84
n-Butyramide	185–187[e]	5.24	5.07	5.05
n-Valeramide	166–167	4.98	5.17	5.38
n-Caproamide	159–160	4.75	5.01	5.12
n-Heptamide	154–155[f,g]	4.53	4.77	4.77
Pelargonamide	147.5–148.5[h]	4.16	4.25	4.35
Palmitamide	140–142[i]	3.22	3.38	3.42
Stearamide	139–141[i]	3.02	3.25	3.30
Isobutyramide	210–211	5.24	5.20	5.28
Isovaleramide	182–183[j]	4.98	4.93	5.23
Isocaproamide	159–160	4.75	5.04	5.11
Phenylacetamide	194–195[k]	4.44	4.47	4.50
β-Phenylpropionamide	188–189	4.26	4.66	4.72
α-Phenylbutyramide[l]	157–158	4.08	4.28	4.42
Chloroacetamide[m]	208–209	5.12	5.56	5.63
Cyanoacetamide	222–223	10.6	10.6	10.7
Benzamide[n]	222.5–223.5	4.65	..	..
o-Toluamide[o]	199–200.5	4.44	4.46	4.54
p-Toluamide[o,p]	224–225	4.44	4.38	4.52
p-Nitrobenzamide[o,p]	231–233	8.10	8.03	8.05
Furoamide[l]	209–211	4.80	4.80	4.93
Succinimide	245–247	5.02	4.93	5.14
Phthalimide[o,q]	176–177	4.27	4.48	4.57

[a] All melting points are uncorrected. They 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 Book Co., New York, N. Y., 1938, pp. 32–33. [b] Analyses were semi-micro and were done by Malcolm L. Brown, whose cooperation we wish to acknowledge. They are given for all derivatives, whether new or not, because with the exception of N-xanthyl benzamide, no earlier analyses have been published on these compounds. [c] Fosse[13] reported 238–244°. [d] Fosse reported 211–214°.[13] [e] Fosse reported 186–187°.[13] Melting point tabulated is for product using Procedure 1. Procedure 2 gave a derivative of m. p. 153–154°. [f] Mixed melting point of heptamide and pelargonamide derivatives 134–136°. [h] Melting point tabulated from procedure 1. Procedure 2 gave a derivative melting 147–148°. [i] Mixed melting point of palmitamide and stearamide derivatives 133–135°. [j] Fosse reported 182–184°.[13] [k] Fosse reported 196–197°.[13] [l] Procedure 1 works best for this amide. The product appears as an oil, but readily crystallizes. [m] Xanthyl chloroacetamide forms more slowly than the other aliphatic amides, but nevertheless crystallizes overnight. [n] The formation of xanthyl benzamide by either of the two procedures in about ten minutes serves to illustrate the marked improvement offered by these procedures, since Adriani[11] reported a required time of several weeks before crystal formation began. He reported a melting point of 218°, and gave the only analysis on these compounds in the literature—4.66% N (theoretical 4.65). [o] Either procedure works, but the second one requires heating to effect solution. [p] With Procedure 1, the supernatant solution was decanted from the insoluble amide. [q] This is the only xanthyl amide prepared melting lower than the original amide (m. p. 220°).

Some work was done with formamide and a product of m. p. 184° (% N calcd. 6.22; found 6.37) obtained, but it was difficultly reproducible and due to its increased solubility, not preparable by the two standard procedures, so it is not considered to be a satisfactory or a finished derivative as yet.

Experimental

The amides used were mostly Eastman Kodak Co. products, checked for their melting points. A few were Kahlbaum materials.

The xanthydrol was prepared by the reduction of xanthone, kindly provided by the General Chemical Company. Some Eastman xanthydrol also was used.

The xanthone was reduced to xanthydrol with sodium amalgam, following the method of "Organic Syntheses."[14] A pure white product of m. p. 119–121° was obtained in 90% yields. This gave better results than did the commercially available yellow Eastman Kodak Co. product, although the latter can be (and was) used.

Two general procedures were developed, which for the most part can be used at will.

Procedure I.—One-half gram of xanthydrol is dissolved in a mixture of 5 cc. of ethyl alcohol, 2 cc. of glacial acetic acid and 3 cc. of water. If an oil separates (presumably consisting of the disproportionation products—and it often does appear if the yellow commercial xanthydrol is used), it is allowed to settle, possibly overnight, and the supernatant solution decanted. A half gram of amide is added to this solution, which is then heated on the water-bath at about 85° in a loosely corked test-tube, either until product appears, or, if none does, for not longer than forty minutes. If no product appears in the hot solution, it will crystallize out on cooling.

Procedure II.—For this method a half gram of xanthydrol is dissolved in 7 cc. of glacial acetic acid. As above, if an oil separates, the clear solution is decanted. One-half gram of amide is added and the solution allowed to stand. The product may appear in anywhere from ten minutes to a few hours, depending on the amide. If more rapid condensation is desired, heating for not more than forty minutes on the water-bath may be resorted to.

Longer heating is unnecessary and is undesirable with either procedure since the product becomes contaminated through disproportionation of the xanthydrol. Either of the two procedures can be used cold or hot; where room temperature is used, in most cases, the product appears overnight. Because of the easier manipulation and because the derivative formed is usually purer, the acetic acid technique is recommended. Where, because of the insolubility of the amide, it appears to be inadequate, then the first procedure is preferable.

The best general solvent for recrystallizing the products was found to be 65% dioxane and water. Where necessary a higher percentage of dioxane takes care of the more insoluble derivatives. Two other pairs—pyridine and water and acetic acid and water—may also be used in a similar manner, although the dioxane was preferred. The products were most often dried in an 80° oven for about fifteen minutes.

(14) Holleman, "Org. Syn.," Coll. Vol. I, pp. 544–555.

The amount of product obtained in both procedures is about the same—yields amount to about 55% of theoretical. However, the derivative prepared in acetic acid (Procedure II) usually required less recrystallization and consequently gave higher yields. This may be attributed to the fact that in heating the reaction mixture, some disproportionation products must be removed by recrystallization.

In general it was found that the aliphatic amides gave purer initial products than the aromatic amides, possibly due to their greater solubility in the condensing medium and consequent decreased contamination of the derivative with amide.

Summary

The N-xanthyl derivatives of 22 amides have been prepared by one or both of two standard, very simple procedures. These procedures eliminate the necessity for hydrolysis of the amides in the process of their identification. The N-xanthyl derivatives are crystalline, easily purified compounds, well adapted to identification purposes.

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Alkoxyl Interchange by γ-Alkoxyquinoline Derivatives in Alcoholic Alkali

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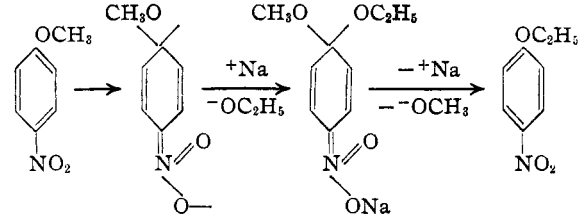
In a preliminary study of the alkaloids of *Fagara coco*, skimmianine (β-fagarine) and γ-fagarine whose structures were then unknown, De Langhe found that they were altered by the action of alcoholic alkali. The demonstration that β-fagarine is identical with skimmianine and that γ-fagarine is a methoxy-dictamine[1] has prompted us to make a more detailed study of the reaction involved.

We have demonstrated that under the influence of alcoholic alkali, there is produced an interchange of the methoxyl group at the γ position of the pyridine ring and the alkoxyl group of the particular alcohol used. In this manner skimmianine has been transformed into the corresponding ethoxy and propoxy derivatives and γ-fagarine into an ethoxy analog. The new alkoxy derivatives so obtained may be reconverted into the original alkaloids by the action of alkali in methanol.

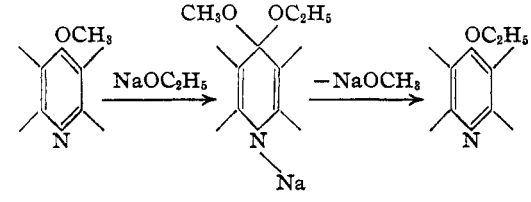
That the interchange alters no other portion of the molecule is also demonstrated by the observation that oxidative degradation of the new derivatives yields the same dihydroxyquinoline as the original compounds.[1,2] The ethoxy analog of skimmianine, moreover, when treated with methyl iodide, eliminates the ethoxyl group and is converted into the known compound isoskimmianine[2] in which the γ-position is occupied by a carbonyl group.

Interchange of alkoxy groups in alkaline media apparently has not been studied among alkoxypyridines or -quinolines. Similar reactions have been described, however, among other compounds. Fox and Bogert[3] recently described analogous reactions of 6-methoxy-7-nitrobenzothiazole, and Hodgson and Habeshaw[4] have made similar observations upon ethers of 4-nitrophenol.

We believe that many of these cases are similar in nature and may be given a common explanation. According to classical theory, nitro derivatives give rise to quinonoid structures, permitting the addition of the reagent with a subsequent reversion to the benzoid form by loss of sodium alkoxide.



Similar transformations also may be postulated for the alkoxyquinolines



Hodgson and Habeshaw explain this inter-

(1) Deulofeu, Labriola and De Langhe, THIS JOURNAL, **64**, 2326 (1942).

(2) Asahina and Inubuse, *Ber.*, **63**, 2052 (1930).

(3) Fox and Bogert, THIS JOURNAL, **63**, 2996 (1941).

(4) Hodgson and Habeshaw, *J. Chem. Soc.*, 45 (1942).