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## PHENYL AND NAPHTHYL URETHANES AND THE CORRESPONDING DI-SUBSTITUTED UREAS.\*

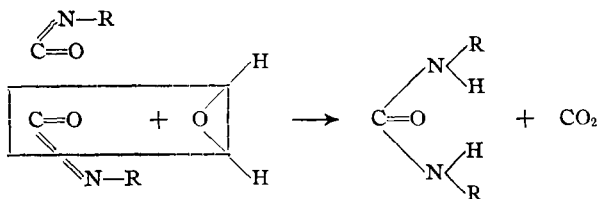
BY PAUL JANNKE.<sup>1</sup>

In a report on the study of *Gnaphalium obtusifolium* L., (1) it was stated that a phenyl urethane was prepared from a comparatively crude mixture of phenols. Though this derivative was easily prepared and readily separable from the reaction mixture, the naphthyl urethane of supposedly the same phenol was difficult to isolate from the unreacted substances and from di- $\alpha$ -naphthyl urea, a side reaction product.

Since the yield of di- $\alpha$ -naphthyl urea was so great when attempting to prepare the urethane of the unknown phenol, these questions arose:

(a) What precautions may be taken to prevent the formation of the di-substituted urea, and to assist the desired reaction? (b) What is the per cent of di-substituted urea contamination in the crystalline reaction product? (c) How might the urethane be separated from the di-substituted urea when the formation of the latter cannot be prevented?

It is a generally accepted fact that when an iso-cyanate comes into contact with moisture, the di-substituted urea is formed, and carbon dioxide is eliminated.



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It is for this reason that great care is taken to dry thoroughly the sample as well as the solvent (usually high boiling hydrocarbon). The hydrocarbon is used as a solvent with the assumption that the reaction product, the urethane, is poorly soluble in the hot hydrocarbon while the unreacted iso-cyanate and the side reaction product, the di-substituted urea, remain in solution. Numerous workers, however, have experienced the fact that  $\alpha$ - $\beta$ -diphenyl urea is but appreciably soluble in boiling kerosene and much less so in the cold solvent. Naturally, the di- $\alpha$ -naphthyl urea is far less soluble in both hot and cold kerosene.

Kamm (2) suggests the addition of an ethereal solution of trimethyl amine to catalyze the reaction, while other investigators have used aluminum chloride for the same purpose.

In his work on the phenyl and naphthyl urethanes of thymol, carvacrol and hydrothymoquinone, D. C. L. Sherk (3) does not report difficulty in obtaining pure products. He prepared these urethanes on a quantitative basis and reported the crystalline yields as being 100 per cent urethane. For example, the 71 per cent yield of thymol phenyl urethane was, according to its recorded melting point and nitrogen content, practically 100 per cent urethane, with little or no di-substituted urea present. As a further illustration, Sherk subjected 14 Gm. of crude hydrothymoquinone di-phenyl di-urethane to purification by extracting it once with boiling benzene, seven times with alcohol, three times with ethyl acetate and twice with acetone. None of these fractions does he regard as containing  $\alpha$ - $\beta$ -diphenyl urea, even though the melting point of the latter is but 4° higher than that of the di-urethane.

The urethanes of the three phenols, thymol, carvacrol and hydrothymoquinone, were prepared with strict adherence to the directions of Sherk, and with special attention given to the concentrated hydrocarbon mother liquors.

Urethane.	Percentage Yield.		Melting Point.		Mother Liquor Residue.
	Sherk.	Jannke.	Sherk.	Jannke.	
Thymol phenyl	71.0	70.3	106-7°	106-7°	Brown, sticky
Carvacrol phenyl	86.0	91.6	138°	136-7°	Brown, sticky
Hydrothymoquinone di-phenyl	83.2	60.0	229-30°	230-31°	Yellow, glass-like
Thymol $\alpha$ -naphthyl	43.0	76.4	156-7°	163-4°	Reddish brown, sticky
Carvacrol $\alpha$ -naphthyl	35.9	71.9	114°	104°	Reddish brown, sticky
Hydrothymoquinone di- $\alpha$ -naphthyl	67.8	..	...	135°	Brown
	93.8	..	135°	235°	Glass-like

Thus it becomes apparent that the crystals which Sherk separated from his various reaction mixtures were practically 100 per cent urethane, except in the case of the di- $\alpha$ -naphthyl urethane of hydrothymoquinone. In this he showed that a quantity of the mono-urethane was present along with some of the urea. For this same reason, the writer has not reported a figure for the percentage yield of that reaction, since the reaction product was definitely shown to be a mixture of 3 compounds whose identity was not established.

The observations made during the preparation of the phenyl urethanes of thymol and carvacrol were in agreement with those of Sherk. The hydrothymoquinone derivative, however, did not crystallize out of the cold hydrocarbon as Sherk reported, but instead, it separated as an insoluble body whose consistency depended upon the temperature; when warm, it was semi-solid, but when cold, it was brittle. When it was dissolved in boiling alcohol and the hot solution cooled, snow white, soft crystals of hydrothymoquinone di-phenyl di-urethane separated. The difference of 17 per cent in the total yield may be in part explained by the unusual way in which the derivative separated from the solution.

Sherk reported difficulty in causing the thymol  $\alpha$ -naphthyl urethane to separate from its mother liquor. This, however, was contrary to the experience of the writer, in which case the entire reaction mixture set to a stiff mush as soon as it cooled a bit. So heavy was the deposit of urethane that no trace of solvent was visible until it was drawn off with suction. The mother liquid yielded no more crystals. The yield of the derivative was correspondingly higher than that reported by Sherk.

The observations on the carvacrol  $\alpha$ -naphthyl urethane were not much different from those on the thymol derivative, except that it took about 10 hours for the reaction mixture to set to a mush. The dried crystals melted at 107°. When dissolved in alcohol and allowed to cool, a crop of crystals separated which melted at 288°, indicating that they were the di-substituted urea

When the mother liquor from them was concentrated and cooled, a large amount of crystals was obtained which melted at 104°. Recrystallization did not change the melting point. Evidently, the impurity raised the melting point of the urethane. In his experiments, Sherk did not observe di- $\alpha$ -naphthyl urea as an impurity in his carvacrol  $\alpha$ -naphthyl urethane, and incidentally, the melting point of his pure urethane was 119°. Albers (4) recorded the melting point of this substance as 107°. Apparently, the  $\alpha$ -naphthyl urethane is not a choice derivative for the identification of the phenol, for as Albers points out, only 3 of the 40 or more well-known workers on thymol and carvacrol problems have anything to say regarding the melting point of carvacrol  $\alpha$ -naphthyl urethane. Even of these 3, one was shown to be working with the di-substituted urea instead of the urethane.

Identical with the case of the di-phenyl di-urethane of hydrothymoquinone and again opposite to Sherk's report, was the separation of the di-naphthyl di-urethane of hydrothymoquinone. Again, the derivative separated from the cooled hydrocarbon solution in the form of an insoluble liquid which solidified at a lower temperature. When recrystallized from alcohol, it melted at 232° with decomposition. Further recrystallization raised the melting point to 235° with but a trace of decomposition. This was insoluble in 1 per cent sodium hydroxide. The mother liquor (alcoholic) from these crystals yielded a second crop which, however, melted at 135°, and which dissolved in alkali with the production of a yellow color. A third crop of crystals was obtained, but this melted at 288°. In line with Sherk's reasoning, the compound melting at 135° may have been the mono- $\alpha$ -naphthyl urethane of hydrothymoquinone, as its solubility in alkali indicates the presence of a free hydroxyl group. The fact that the next compound is insoluble in alkali and melts at a higher temperature may show it to be the di- $\alpha$ -naphthyl urethane. The melting point of the third substance is indicative of its being di- $\alpha$ -naphthyl urea. If any analogy can be drawn from Kamm's (5) statement,<sup>1</sup> it is quite indefinite as to whether or not the di-urethane was present in the reaction product which seems to be a mixture of at least three substances.

On two occasions, Sherk mentions the melting point of di- $\alpha$ -naphthyl urea as 266–270°. This is not unusual, for an investigation on the literature showed that at least 5 different melting points are given for the same substance.

1879 Schiff (6), 270°; 1889 Vittenet (7), 314–315°; 1897 Pagliani (8), 270°, 1897 Clark and Young (9), 284–286°; 1920 Sherk (10), 266–270°; 1928 Clark (11), 314°; 1929 Beilstein (12), 289°.

The difference between melting points is caused not only by the methods of determining them, but also by the origin of the di-substituted urea. Thus, Schiff (13) points out that the ureas must not be heated long in determining their melting points, or, as in the case of the hydrazones and osazones, decomposition results. For this reason, when determining the melting point of the urea, the tubes with the samples were plunged into a bath previously heated to within a few degrees of the supposed melting point. It was repeatedly noted that when the temperature of the oil-bath was raised slowly, the sample of di- $\alpha$ -naphthyl urea melted enough to assume a wet appearance at 210°. At 260°, the sample became distinctly brown, and at 274–276°, it fused into a black liquid. However, when the test sample was plunged into a preheated oil-bath, it melted sharply at 289° with but a trace of decomposition.

Clark's reference for the high melting point of 314° is undoubtedly Vittenet who determined it by throwing the crystals onto a mercury-bath heated to that temperature.

When a few drops of  $\alpha$ -naphthyl iso-cyanate were dissolved in boiling acetone, and water was added dropwise to produce cloudiness, the cooled reaction mixture yielded the di-substituted urea which melted at 288°. Recrystallization from benzene and from amyl acetate failed to change the melting point, but when some of the substance was sublimed under reduced pressure, the sublimate melted at 289°.

The melting point reported by Sherk for the di-substituted urea which he filtered from the iso-cyanate reagent was shown to be that of an impure compound. A quantity of it was dried during 2 weeks on a porous plate, in contact with air. Even at the end of this time, it smelled strongly of isocyanate, and appeared to be wet. That the urea was impure was shown by attempts to obtain duplicate melting points:

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<sup>1</sup> Kamm lists hydroquinone among the di-atomic phenols which do not react with  $\alpha$ -naphthyl iso-cyanate.

264–265° with decomposition  
 249° with decomposition after softening at 230°  
 268° after softening at 230°  
 270° with decomposition.

When this substance was recrystallized from boiling amyl acetate, it melted at 288°. Recrystallization raised its melting point to 288.5°.

As was previously pointed out, the phenyl urethane was prepared of a crude, green mixture of phenols. Albers (14) was successful in preparing the phenyl urethanes of crude mixtures of thymol and of carvacrol obtained from various species of *Monarda*, when he utilized this reaction to conserve all of the small amounts of crude material. Thus, the urethanes may be used not only for identification purposes, but also for isolating phenolic substances, with a bit of consideration as to the nature of the crude material.

When applying the urethane reaction to a comparatively crude plant extract containing phenols, the temperature attained may often cause the liberation of moisture from some of the less stable compounds, in spite of the fact that the sample may have been thoroughly dried, with the subsequent formation of large amounts of di-substituted urea, thus contaminating the reaction product sometimes in excess of 50 per cent.

In preparing the  $\alpha$ -naphthyl urethane of carvacrol, it was observed that the di-substituted urea crystallized out before any of the urethane did. In other cases, the urethane and the urea crystallized simultaneously. Hence the assumption that the urethanes are less soluble in high boiling hydrocarbons than the ureas are, and therefore crystallize out of the solution on cooling while the ureas remain dissolved, does not always hold true. Ethyl alcohol is an excellent solvent and crystallizing medium for the urethanes, but it is undesirable for separating mixtures of ureas and urethanes because with the excess of iso-cyanate present, some ethyl-alkyl urethane may form and add to the contamination.

As an unreacting solvent, ethylene dichloride was found highly desirable. The phenyl urethane of the unknown phenol from *G. obtusifolium* L., was exceedingly soluble in cold ethylene dichloride, while the  $\alpha$ - $\beta$ -di-phenyl urea was difficultly soluble even in the boiling solvent. Thus, an efficient separation of a mixture of these two substances was readily effected. In order to eliminate specificity and to allow for generalization, the solubility of the urethanes previously prepared was determined and is herewith compared. The solubility of each substance was determined at 22.5°, and is reported as the number of parts of solvent required to dissolve 1 part of substance.

Substance.	Solubility in:	
	Alcohol.	Ethylene Dichloride.
Thymol phenyl urethane	4.96	2.40
Thymol $\alpha$ -naphthyl urethane	165.30	26.40
Carvacrol phenyl urethane	10.82	3.59
Carvacrol $\alpha$ -naphthyl urethane	18.70	9.20
Hydrothymoquinone di-phenyl di-urethane	405.70	512.00
Hydrothymoquinone di- $\alpha$ -naphthyl di-urethane	.....	.....
$\alpha$ - $\beta$ -Di-phenyl urea	135.30	681.60
Di- $\alpha$ -naphthyl urea	4516.00	2611.00

A study of the above table illustrates the practicability of ethylene dichloride treatment in separating the reaction mixture. For example, thymol phenyl urethane is approximately 300 times as soluble in ethylene dichloride (22.5° C.) as is  $\alpha$ - $\beta$ -di-phenyl urea, whereas in the case of alcohol being the solvent, the thymol phenyl urethane is only a bit more than 30 times as soluble as is the  $\alpha$ - $\beta$ -di-phenyl urea. It is true that di- $\alpha$ -naphthyl urea is about 1.7 times as soluble in ethylene dichloride as it is in alcohol, yet thymol  $\alpha$ -naphthyl urethane is 100 times as soluble in ethylene dichloride as is di- $\alpha$ -naphthyl urea, while in alcoholic solution thymol  $\alpha$ -naphthyl urethane is only 30 times as soluble as the di-substituted urea is. Ob-

viously, even in this extreme case the urethane can readily be separated from the di-substituted urea, using cold ethylene dichloride as the solvent.

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THE PREPARATION OF THE MANNONIC LACTONES FROM THE SEEDS OF THE DATE PALM (PHŒNIX DACTYLIFERA) AND A STUDY OF THEIR ACTION AND THAT OF NEW DERIVATIVES UPON GASTRIC MUCIN SMEARS.\*,\*\*

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The sugar lactones have been known for many years (1, 2), but it is only within comparatively recent times that they have assumed scientific and industrial importance.

From the viewpoint of theoretical organic chemistry, these compounds have been of great importance, since it was through them that the structure of the monosaccharides was proved. Also, the mechanism of the oxidation of the monosaccharides was not clearly understood until the properties of the lactones themselves had been determined.

The pharmaceutical uses of the sugar lactones include the substitution of gluconic acid for part of the citric acid in the preparation of Solution of Magnesium Citrate (3). It is said to produce a stable solution without the disagreeable sour taste of the pharmacopœial solution.

The calcium salts of the aldonic acids are used in calcium therapy and have been shown to be readily absorbed when administered orally (4). Calcium gluconate, included in the U. S. P. XI, has the advantage of being practically tasteless; non-irritant by hypodermic or intramuscular injection; and its intravenous toxicity is about a fourth that of calcium chloride (5).

In an investigation having for its purpose the determination of the relative merits of various dentifrices, Nichols, Hatton and Doherty (6) studied the effect of

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