

bility of false tests, the presence of diethylphthalate in the sample examined should not be considered established unless the red color produced is at least equal in intensity to that produced by 0.5 mg. of diethylphthalate.

*Examination of Commercial Samples.*—Alcohol samples, rubbing alcohols and spirit of camphor may be run directly, using 0.1 to 1 cc. for the test. Beverage liquors, if colored, should be distilled. For example, 25 cc. of an approximately 50 per cent alcoholic preparation is distilled and the first 10 cc. of distillate used for the test. Aromatic spirit of ammonia should be distilled. Tincture of iodine should be reduced with zinc dust and distilled. Vanilla extract should be precipitated with basic lead acetate solution as recommended by Wales<sup>1</sup> and distilled before applying the test. In general, a control should be run on authentic preparations known to be free from diethylphthalate at the same time with the sample in question, to eliminate any possibility of a false test. However, it has been the writers' experience that samples which contained diethylphthalate gave full, clear, red colors, while samples which might be classed as giving false tests produced brown colors, or orange colors rapidly fading to brown.

---

## A REVISION OF THE PENTANOLS.

BY S. M. GORDON.

(Continued from p. 322.)

### THE 3,5-DINITRO-BENZOATES.

3,5-Dinitrobenzoic acid was first prepared by Cahours in 1847 (*Jahresberichte*, 48, 533), its acid chloride by Behrend and Heymann in 1902 (*J. prakt. Chem.*, 65, 291). The first ester to be prepared was the ethyl ester obtained by Voit in 1856 (*Ann.*, 99, 105), by the action of ethyl alcohol on the acid, using sulphuric acid as the condensing agent. It was also obtained by Beilstein and Kurbatow in 1880 (*Ann.*, 202, 223), by acting on ethyl iodide with the silver salt of the acid. The ester in both cases melted at 91° C.

The methyl ester was prepared by Herre in 1895 (*Ber.*, 28, 596) by the action of the acid on methyl alcohol using gaseous hydrogen chloride as the condensing agent. This ester melted at 112° C.

Inasmuch as many of the esters of the alcohols of the methane series are liquid, the crystalline character and the definite melting points of these esters apparently suggested their use for the identification of the so-called fatty alcohols. Thus Mulliken in 1904 ("Identification of Organic Compounds," 1, p. 168), suggests that the alcohols be heated with 3,5-dinitro-benzoyl chloride for ten minutes, and that the reaction product be poured into water and the solid ester be recrystallized from a suitable solvent. He thus prepared the 3,5-dinitrobenzoates up to and including those of the two butyl alcohols.

In 1906 Cohen and Armes (*J. C. S.*, 89, 148), prepared the menthyl ester by heating molecular amounts of menthol with the acid chloride in a boiling water-bath for ten minutes.

In 1922 R. E. Kremers (*Jour. A. Ph. A.*, 12, 626) extended the use of this reagent to the identification of phenols, making use of a modified Schotten-Baumann

---

<sup>1</sup> *J. Assocn. Official Agr. Chem.*, 9, 4, 477 (1926).

reaction. In this way the 3,5-dinitro-benzoates of the following phenols were prepared: phenol, ortho, meta and para cresol, guaiacol, carvacrol and thymol.

The modification of the Schotten-Baumann reaction originally suggested by Einhorn and Hollandt (*Ann.*, 301, 101 (1898)) using pyridine as the base was extended to the preparation of the 3,5-dinitro-benzoates of several of the isomeric pentanols.

As already pointed out, only two of the four isomeric butyl alcohols were included in the study of the 3,5-dinitro-benzoates by Mulliken. A careful search of the literature failed to reveal the preparation of any of the amyl esters. Inasmuch as these promised to be of importance in the identification of such representatives of this isomeric group as are supposed to occur in plants, the esters of six available isomeric pentanols were prepared. The tertiary pentyl alcohol yielded 3,5-dinitro-benzoic acid, when heated with acid chloride, but yielded the corresponding ester by benzylation in pyridine solution.

The ester of isoamyl alcohol prepared by direct interaction of the components and by benzylation in pyridine solution by the method of Einhorn and Hollandt, already mentioned, gave identical products.

#### *Experimental.*

The alcohols, with the exception of active amyl alcohol, were obtained from the Eastman Kodak Company. The active amyl alcohol was a sample from the laboratory stock and after purification by distillation had a specific rotation of  $+ 5.21^\circ$ .

The 3,5-dinitro-benzoyl chloride was prepared according to Berend and Heymann (*J. prakt. Chem.*, 69, 455 (1906)).

The esters were prepared by treating 5 Gm. (1 mol.) of the acid chloride with 2.1 Gm. ( $1\frac{1}{2}$  mols.) of the pentanol, except in the case of the tertiary alcohol, which will be discussed separately. The tube containing the reactants was placed in a bath of boiling water and heated 10-15 minutes, or until no more hydrochloric acid fumes were evolved as shown by a test with filter paper dipped in  $\text{NH}_4\text{OH}$ . The mixture while still liquid was poured into cold water and set aside until solidification took place. When solid, the crude ester was filtered, dried and crystallized from ligroin (to prevent interchange of alkyl groups).

Attempts to prepare the ester of the tertiary alcohol by this method resulted in formation of the corresponding acid. This indicated that dehydration of the alcohol had taken place, which is in agreement with the well-known behavior of tertiary alcohols. However, when esterification was carried out in pyridine solution according to the procedure of Einhorn and Hollandt (*Ann.*, 300, 100 (1898)) slightly modified, the ester was obtained, but in greatly reduced yield.

$$\begin{array}{c} \text{CH}_3 \\ | \\ (\text{CH}_3\text{CH}_2\text{C}-\text{OH}) \\ | \\ \text{CH}_3 \end{array}$$

Five Gm. of tertiary amyl alcohol

cc. of pyridine, cooled in an ice-bath, and 6.5 Gm. of the acid chloride added gradually. As soon as all the acid chloride had gone into solution, the mixture was poured onto ice. If the reaction was allowed to proceed for only an hour before pouring on ice, the acid was completely formed. The solid which separated

was filtered, dried and extracted with ligroin, which serves to dissolve the ester but not the acid simultaneously formed. The ester crystallizes from the ligroin as a mass of colorless, fine needle-like crystals, which melt at  $91^{\circ}$ , yield 0.25 Gm.

The ester of isoamyl alcohol was prepared by this procedure. Instead of pouring on ice immediately after reaction as above, the reaction was allowed to proceed for 24 hours before pouring on ice. The yield was quantitative. M. p.,  $61^{\circ}$  from ligroin.

Alcohol.	M. P. Ester.	Analysis for Nitrogen by Dumas Method.	
		Calc. C <sub>n</sub> H <sub>m</sub> O <sub>2</sub> N.	Found.
1. <i>N</i> -Amyl alcohol	$45^{\circ}$	9.94%	10.5%
2. Propyl methyl carbinol	$60^{\circ}$	....	10.4%
3. Diethyl carbinol	$58^{\circ}$	....	9.3%
4. Isobutyl carbinol	$61^{\circ}$	....	10.4%
5. Active amyl alcohol	$83-84^{\circ}$	....	9.6%
6. Tertiary amyl alcohol	$91^{\circ}$	....	10.1%
Mixtures of 2 and 3 melt at $44^{\circ}$			
2 and 4 melt at $52^{\circ}$			

The melting points of three of the esters listed do not show as large a variation as would be desirable. But it is usually recommended that parallel experiments be made, so that the identity of the esters obtained may be confirmed by the determination of the melting points of mixtures. These derivatives make a distinction between the different isomers possible. The usual method is to identify the alcohol in question by boiling point, oxidation to the acid and analysis of the silver salt. Such a method has the shortcoming that it does not distinguish between the four primary of the eight isomeric pentanols.

#### THE PHENYL URETHANES.

Phenyl isocyanate was first prepared by Hoffmann in 1850 (*Ann.*, 74, 16 (1850)). He also prepared the urethanes of methyl, ethyl and isoamyl alcohols in an impure state. The significance of the reagent, however, for the identification of substances of alcoholic and amine nature was not recognized for over 30 years. Gebhard (*Ber.*, 17, 3033 (1884)) and Kühn (*Ber.*, 17, 2880 (1884)), studied the action of primary and secondary amines on the highly reactive carbanilic acid and thus prepared a number of the urethanes of a basic character. Snape (*Ber.*, 18, 2428 (1885)) and Tessmer (*Ber.* 18, 968 (1885)), prepared the phenyl urethanes of a number of phenols and polyatomic alcohols. Gumpert (*J. prakt. Chem.*, N. F., 31, 278 (1885)) prepared the urethane of isopropyl alcohol by direct interaction of the components.

In spite of the ready reactivity of the body for the identification of alcoholic bodies, it was not until 1904 that the reaction was further applied to mono-atomic aliphatic alcohols. Bloch (*Bull. soc. chim.* (3), 31, 49 (1904)) thus prepared the urethanes of octyl, secondary octyl, undecyl, hexadecyl and myricyl alcohols by direct interactions of the acid and alcohol.

Meanwhile a series of papers dealing with the properties of the methyl,<sup>1</sup>

<sup>1</sup> Hentschell, *Ber.*, 18, 978 (1885); Nolting, *Ber.*, 21, 3155 (1888).

ethyl,<sup>1</sup> propyl<sup>2</sup> and butyl<sup>3</sup> urethanes appeared. The urethanes, however, were prepared by an indirect method.

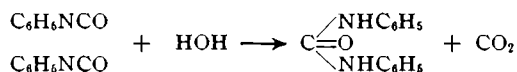
The use up to this time was probably restricted by the difficulty of preparing the reagent.

The first of the phenyl urethanes to be prepared from the isomeric pentanols was the tertiary amyl alcohol derivative by Lambling (*Bull. soc. chim.* (3), 19, 777 (1898)). Marckwald (*Ber.*, 37, 1049 (1904)) prepared the urethanes of isobutyl and secondary isobutyl carbinol and further studied the melting point relations of mixtures of the two isomers. Mannich and Zernik (*Arch. Pharm.*, 246, 178 (1908)) report on the preparation of the urethane of diethyl carbinol as a solid derivative. Repeated attempts according to their procedure and modified procedures did not confirm their preparation of the solid body. A liquid product results, regardless of the mode of preparation. Continued freezing does not cause solidification. Blaise and Picard (*Ann. chim. phys.* (8), 25, 261 (1912)) prepared the urethane of normal amyl alcohol. As part of this investigation, the phenyl urethane of propyl methyl carbinol was prepared.

#### Experimental.

The phenyl isocyanate and alcohols used were from the stocks of the Eastman Kodak Company.

One mol. of phenyl urethane was treated with one mol. of the pentanol and heated just to the boiling point. The heat was then removed and the reaction container set aside until the addition compound crystallized. This usually required about a day. Care was taken to exclude moisture as much as possible to prevent the formation of highly insoluble diphenyl urea



In spite of all precautions to exclude moisture, a small amount of diphenyl urea forms. This was removed by dissolving the urethane in ligroin and filtering. The urethane crystallized on spontaneous evaporation of the ligroin, and was further purified by crystallization from a suitable solvent.

Pentanol.	Solvent.	M. P.	Analysis for N <sub>2</sub>	
			Calc. C <sub>12</sub> H <sub>17</sub> O <sub>2</sub> N.	Found.
1. Normal amyl alcohol	Ethyl alcohol	46°	6.76%	....
2. Secondary carbinol	Methyl alcohol	30°	....	....
3. Isobutyl carbinol	Methyl alcohol	55°	....	....
4. Diethyl carbinol	.....	liquid	....	....
5. Methyl <i>n</i> -propyl carbinol	Ligroin	34°	....	6.70
6. Tertiary butyl carbinol <sup>4</sup>	Methyl alcohol	45°	....	6.65

#### THE $\alpha$ -NAPHTHYL URETHANES.

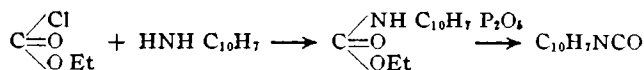
$\alpha$ -Naphthyl isocyanate was first prepared by Hoffmann in 1870 by the interaction of  $\alpha$ -naphthyl amine on ethyl chloro-carbonic acid and subsequent distillation with P<sub>2</sub>O<sub>5</sub> (*Ber.*, 3, 658).

<sup>1</sup> Weddige, *J. prakt. Chem.*, N. F., 10, 1207 (1874).

<sup>2</sup> Roemer, *Ber.*, 6, 1103 (1873).

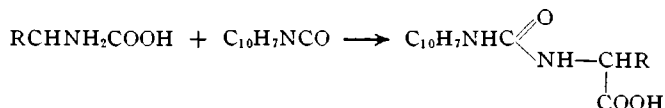
<sup>3</sup> Mylius, *Ber.*, 5, 973 (1873).

<sup>4</sup> Lambling, *loc. cit.*, reports melting point at 42° C.



The yields of the carbamyl acid were low and it was not until 1899 that the process was improved. In that year Vittenet (*Bull. soc. chim.* (3), 21, 957) prepared the reagent by direct interaction of phosgene and  $\alpha$ -naphthyl amine. The ethyl ester obtained by direct interaction of the two components melted at 79°.

Neuberg and Manasse (*Ber.*, 38, 2361, (1905)) showed that the reagent could satisfactorily be used for the identification of  $\alpha$ -amino acids. They react quantitatively to form the corresponding addition products,



which Neuberg and Rosenberg (*Biochem. Z.*, 5, 456 (1907)) further applied the reagent to the identification of  $\alpha$ -amino acids.

Neuberg and Kansky (*Biochem. Z.*, 20, 445 (1909)) were the first to point out the use of the reagent as a general one for the identification of aliphatic alcohols. They prepared and characterized a number of the  $\alpha$ -naphthyl urethanes of the simpler aliphatic alcohols, up to and including *n*-octyl alcohol.

In 1910, Neuberg and Hirschberg (*Biochem. Z.*, 27, 339 (1910)) showed the general application of the reagent to identify bodies of diverse alcoholic character, such as phenols, cinnamic alcohol, terpenic alcohols, furfuryl alcohol and cholesterol.

Walbaum (*J. prakt. Chem.*, N. F., 96, 250 (1917)) prepared the  $\alpha$ -naphthyl-urethane of  $\alpha$ - $\beta$ -hexylenic alcohol by direct interaction of the components.

A recent article by Bickel and French (*J. A. C. S.*, 48, 747 (1926)) repeated some of the preparations of Neuberg and Hirschberg (*loc. cit.*) and extended the use of the reagent for the identification of a variety of other alcohols.

The  $\alpha$ -naphthyl urethanes may conveniently be used for the identification of the isomeric pentanols. Neuberg and Kansky thus prepared the urethanes of the following isomeric pentanols; isobutyl carbinol, secondary butyl carbinol, diethyl carbinol, dimethyl-ethyl-carbinol. The preparation of these compounds was rechecked and in addition the urethanes of the following alcohols not previously described were prepared, normal amyl alcohol and methyl normal propyl carbinol.

#### EXPERIMENTAL.

To one mol. of  $\alpha$ -naphthyl isocyanate an equivalent amount of the pentanol was added and the container tightly stoppered. The container was set aside at room temperature until the odor of the isocyanate disappeared, which usually occurred within 24 hours. Neuberg (*loc. cit.*) and Bickel and French (*loc. cit.*) recommend heating to boiling. The yields were uniformly higher using the procedure followed; because at slightly elevated temperatures the moisture contained in the flask reacts with the reagent to give di- $\alpha$ -naphthyl urea. The small amount of di- $\alpha$ -naphthyl urea which formed was removed by dissolving the mixture in ligroin (60-70°) and filtering. The di- $\alpha$ -naphthyl urea is insoluble and remains on the filter paper. The solvent was allowed to evaporate spontaneously. One

further crystallization gave a pure product. The compounds were dried over  $\text{CaCl}_2$  in a vacuum desiccator for analysis.

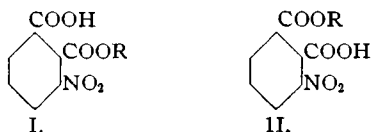
$\alpha$ -Naphthyl Urethane of.	M. P. ° C.	Analysis for Nitrogen by Kjeldahl method.	
		Calc. N, $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}$ .	Found N.
1. Normal amyl alcohol	66-67°	5.45%	5.34
2. Secondary butyl carbinol	76°	.....	.....
3. Isobutyl carbinol	61-62°	.....	.....
4. Diethyl carbinol	68°	.....	.....
5. Methyl propyl carbinol	76°	.....	5.50
6. Tertiary butyl carbinol	71°	.....	.....

### 3-NITRO ACID PHTHALATES.

As already pointed out the reagents most commonly used for the identification of alcohols are phenyl and  $\alpha$ -naphthyl isocyanates and 3,5-dinitro-benzoyl chloride. The use of these reagents is connected with many disadvantages. With the isomeric pentanols, especially, the melting points are quite low and the isomeric compounds melt within a narrow range. The 3-nitro-acid-phthalates, about to be described, readily yield derivatives of the amyl alcohols, and the melting points of the derivatives so prepared lie sufficiently far apart to make them suitable compounds for the isolation and identification of the isomeric pentanols.

Marckwald and McKenzie (*Ber.*, 34, 486 (1901)) used the acid for the separation of active amyl alcohol from the accompanying isomer, secondary butyl carbinol. They esterified the mixture of alcohol with the acid, using sulphuric acid as condensation reagent. Recently (Nicolett and Sacks, *J. A. C. S.*, 47, 234 (1925)), it has been proposed to use the anhydride of this acid for the identification of aliphatic alcohols. The authors repeated the earlier work on the esters of this acid, up to and including the two common primary amyl alcohols, and have further shown that the esters of the aliphatic alcohols may be crystallized from hot water with very slight losses. This has the advantage of preventing interchange of alkyl groups as might take place when an alcohol is used as the crystallizing medium. Further, since the resulting esters contain a free acid group, the molecular weight may be obtained by titration with alkali.

The substances obtained by the interaction of 3-nitro-phthalic acid anhydride on alcohols are 2-mono-alkyl esters of 3-nitro-phthalic acid (I) (Marckwald and McKenzie (*loc. cit.*)).



McKenzie (*J. Chem. Soc.*, 79, 1137 (1901)) has shown that a small amount of an isomeric form (II) results, but if this is so, it is eliminated in the purification process (Nicolett and Sacks, *loc. cit.*).

3-Nitro-phthalic acid, obtained from the Eastman Kodak Company, was readily converted into its anhydride, by heating the acid with acetic anhydride (McKenzie, *loc. cit.*). The yield is quantitative.

The mono-esters of the pentanols were readily prepared by treating molecular parts of the anhydride and pentanols, and heating on the water-bath for ten minutes,

after the mixture became liquid. The products were then dissolved in hot water or 30% alcohol and allowed to crystallize. Constant melting points were obtained after one or two crystallizations, when the primary pentanols were used, but with the secondary pentanols the reaction did not proceed so readily. Regardless of the length of heating, the mixture of anhydride and secondary pentanol did not become thoroughly liquefied. Thus after heating the secondary alcohol mixtures for thirty minutes the liquid portion was decanted and purified. Water could not be used as crystallizing medium because the compound separated as an oil. Dilute alcoholic solutions acted similarly. Hence the esters of the secondary alcohols were purified by dissolving in chloroform and adding two volumes of ligroin. Slow evaporation of the mixed solvent yielded well-defined crystals. A repetition of the process gave products with constant melting points. The molecular weights of the several compounds not previously described were determined by titration with *N*/10 KOH, using phenolphthalein as an indicator. Tertiary amyl alcohol did not react.

2 Mono-ester of.	M. P. ° C.	M. W.	
		Calc. C <sub>17</sub> H <sub>35</sub> O <sub>2</sub> N.	Found.
Pentanol-1	132-133°	281	280
Methyl 4-butanol-1	165-166°	...	...
Methyl 2-butanol-1	157-158°	...	...
Pentanol-2	102-103°	...	279
Pentanol-3	92°	...	276

## SOME APPLICATIONS OF COLLOIDAL CHEMISTRY TO PHARMACY.\*

BY PELL BROADY AND C. B. JORDAN.<sup>1</sup>

Believing that it is possible to make further applications of colloidal principles in the preparation of pharmaceutical products, this work was undertaken with that end in view. We assumed that a number of our official ointments could be improved and that several insoluble medicinals could be suspended in a semi-colloidal condition, thus adding to their therapeutic value, if colloidal suspension methods were applied in their preparation. Our results indicate that the assumption was justified.

We gave attention to the preparation of ointments of mercury, of metallic silver ointment, of metallic silver suspensions, of suspensions of the halides of silver and of the suspension of calomel. We believed that, if the proper degree of fineness of subdivision could be secured coupled with the proper suspending colloid, we would be able to secure satisfactory preparations. The literature on Colloidal Chemistry was rather carefully covered and suggested methods were tried, modified and tried again or new methods were developed. A bibliography of the literature will be found at end of paper.

### A. OINTMENT OF MERCURY.

*Experiment No. I.*—Ten Gm. of mercuric nitrate in 15 cc. of H<sub>2</sub>O were thoroughly mixed with 45 Gm. of cold lanolin, and 3 Gm. of NaOH dissolved in H<sub>2</sub>O

\* Scientific Section, A. P. H. A., Philadelphia meeting, 1927.

<sup>1</sup> Purdue University School of Pharmacy.