2. The benzoyl and *o*-chlorobenzoyl esters and the α-naphthylurethans of the seven phenols were prepared.

3. The structure of each of the seven phenols was established by synthesis.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WORCESTER POLYTECHNIC INSTITUTE]

Quantitative Acetylation of Amines by Means of Acetyl Chloride and Pyridine

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In the case of organic hydroxy compounds, Smith and Bryant[3] recently have developed a rapid and precise method for the quantitative determination of primary and secondary hydroxyl groups. Their method consists essentially in modifying the usual acetic anhydride–pyridine acetylation mixture by the substitution of acetyl chloride for the anhydride, the acetyl chloride being a more reactive acetylating agent.

The above mentioned authors found that primary and secondary amines as well as mercaptans reacted with the acetylating medium to an extent not determined by them and they suggested that these types of compounds might be estimated by their method.

In the present work the applicability of the Smith–Bryant reagent as a quantitative acetylating agent was tested on a wide variety of amines as well as on a limited number of amine derivatives such as hydroxyamines, amine hydrochlorides, amides, anilides, etc., and on thiophenol. It was found that for some compounds practically quantitative results could be obtained, while in the case of other compounds various factors such as insolubility in the acetylating medium, low rate of reactivity due to the presence of certain substituents, decomposition of the amine during acetylation etc., materially decreased the yield of the acetylated compound and indicated the general inapplicability of the Smith–Bryant method.

An increase in the relative amount of pyridine in the acetylating reagent resulted in immaterial changes in the determined acetyl values.

Variation of the acetylating reagent solvent disclosed the fact that substituting di-*n*-butyl ether for toluene and increasing the temperature of the acetylation from 60 to 70° led to materially increased yields for many of the compounds investigated. Only those compounds which were found to be very unreactive using the original Smith–Bryant method or were particularly sensitive to the action of light and heat yielded acetyl values less than 90% of the theoretical.

The results secured using acetyl chloride and pyridine dissolved in di-*n*-butyl ether as an acetylating medium indicate that in addition to serving as a quantitative method for estimating certain amines and amine derivatives, this procedure may serve as a convenient simple method for preparing small amounts of the diacetyl derivatives.

Experimental

Reagents.—The original acetylating mixture was the same as that used by Smith and Bryant. Acetyl chloride (E. K. C. Practical) was dissolved in Mallinckrodt "Analytical Reagent" toluene which previously had been dried over sodium. In the modified reagent, the toluene was substituted by di-*n*-butyl ether (Commercial Solvents Corporation) which had been rendered peroxide free by the method of Brandt.[4] The boiling point of this reagent was 141°. Pyridine used in conjunction with the above reagents was made anhydrous by the method of Zerewitinoff.[5]

Compounds Acetylated.—A few of the compounds investigated were obtained from the Eastman Kodak Co., and the Mallinckrodt Chemical Co. The greater portion were prepared by the authors and were repeatedly recrystallized or distilled until they were at least 99% pure. All materials employed were desiccated for at least twenty-four hours before use.

Analytical Procedure and Apparatus.—The analytical procedure and apparatus, except for the modifications described below, were the same as those used by Smith and Bryant.[3]

In place of the 250-cc. g. s. volumetric flasks, 300-cc. long-necked, round-bottomed Pyrex flasks were used.

As a means of dispensing the acetylating reagent, a 10-cc. calibrated pipet was used. A rubber syringe bulb was attached to the end of this pipet by means of a rubber tube bearing a spring pinchcock.

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[1] Abstracted from a thesis by Verner R. Olson. submitted to the Faculty of Worcester Polytechnic Institute in partial fulfilment of the requirements for the Degree of Master of Science, June, 1937.

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[3] D. M. Smith and W. M. D. Bryant, THIS JOURNAL, **57**, 61 (1935).

[4] Brandt, *Chem.-Ztg.*, **51**, 981 (1927).

[5] Zerewitinoff, *Z. anal. Chem.*, **50**, 683 (1911).

TABLE I

EXPERIMENTAL ACETYL VALUES OF VARIOUS COMPOUNDS

95–100%	80–95%	60–80%	50–60%	Less than 50%
o-Acettoluidide	Acetanilide	Acetamide	Benzylamine	*n*-Butylamine hydrochloride
o-Aminobiphenyl	*m*-Acettoluidide	Aniline hydrochloride	*m*-Nitraniline	2,4-Dinitroaniline
Aniline	*p*-Acettoluidide	*o*-Anisidine	*o*-Nitraniline	*p*-Nitraniline
p-Anisidine	*p*-Aminobiphenyl	*n*-Butylamine	*m*-Nitroacetanilide	*o*-Nitroacetanilide
Diphenylamine	*o*-Aminophenol	*o*-Chloroaniline	*p*-Phenylenediamine	*p*-Nitroacetanilide
Methylaniline	*p*-Aminophenol	*p*-Chloroaniline		2,4,6-Tribromoaniline
α-Naphthylamine	*m*-Chloroaniline	Ethylacetamide		2,4,6-Trinitroaniline
Piperidine	β-Naphthylamine	*n*-Pentylamine		Urea
Thiophenol	*o*-Phenylenediamine	*m*-Phenylenediamine		
o-Toluidine	*m*-Toluidine	*n*-Propylamine		
	p-Toluidine			

Repeated tests of the precision of this pipet in transferring the reagent from the stock solution to the reaction flasks indicated a deviation in the volumes of successive portions of reagent of not more than ±0.04%. In all cases, the sample before acetylation was measured gravimetrically.

Using the above procedure the acetyl value of commercial 95% ethyl alcohol was determined and found to be 94.0 and 94.2% of the theoretical value for absolute alcohol.

Analytical Results and Discussion

In Table I are grouped the experimental results using the Smith–Bryant acetylating reagent, in which toluene was the solvent, and the temperature of acetylation 60°. The results for each compound represent the mean of at least two independent determinations, none of which differed from each other by more than 1.0% and in most cases not more than 0.5%.

Examination of these results shows that simple primary aromatic and secondary amines are acetylated to the extent of from 80 to 100%, while halogen or nitro substituted and aliphatic amines are acetylated to a much smaller extent.

In the case of the aliphatic amines which are acetylated about 60%, the strongly basic properties of these undoubtedly are the cause of this low value. While pyridine has a dissociation constant of 2.3×10^{-9}, the aliphatic amines possess dissociation constants of the order of 10^{-4} so that as acetylation proceeds, the hydrogen chloride formed reacts with the unacetylated aliphatic amine rather than with pyridine. In this way a portion of the aliphatic amine is prevented from being acetylated since the amine hydrochlorides are very unreactive, as is shown by the fact that *n*-butylamine hydrochloride is acetylated about 7% using the Smith–Bryant method. Benzylamine reacts similarly to the aliphatic amines.

Low solubility in the reaction medium is undoubtedly a cause of the low results obtained for many of the other compounds used. This low solubility was observed experimentally in the case of the nitro and halogen derivatives which remained as visible solids during the acetylation period. In case of the trisubstituted derivatives the effect of the nitro and halogen groups in lowering the reactivity of the amino group hydrogens is also an important factor, since it has been found that 2,4,6-trinitroaniline is purified by repeated crystallization from an acetic anhydride medium.[6]

Thiophenol, the only mercaptan available, reacted with the Smith–Bryant reagent to the extent of 100%. Smith and Bryant found that commercial phenol of unknown purity yielded an acetyl value of 95.8% of the theoretical. Since thiophenol and phenol react to about the same extent, one may infer that the other mercaptans would react like the corresponding hydroxyl derivatives.

In an attempt to increase the yields using the Smith–Bryant reagent, the concentration of the

TABLE II

RESULTS OF ACETYLATION USING DI-*n*-BUTYL ETHER AS THE SOLVENT

Substance	Temp., °C.	Detns.	% of theoretical acetyl value
Acetamide	60	2	75.0 ± 0.2
Acetamide	70	4	94.7 ± .3
p-Acettoluidide	70	2	100.9 ± .4
p-Aminophenol	70	2	100.3 ± .3
Aniline	60	1	99.0
Aniline	70	2	84.4 ± .6
p-Chloroaniline	70	2	99.5 ± .5
Diphenylamine	70	2	99.8 ± .1
β-Naphthylamine	70	2	99.3 ± .2
m-Nitraniline	70	2	99.2 ± .4
o-Nitraniline	60	2	67.7 ± .3
o-Nitraniline	70	2	88.3 ± .7
p-Nitroacetanilide	70	2	19.1 ± .5
o-Phenylenediamine	70	2	92.5 ± .4
p-Toluidine	70	2	99.7 ± .3
2,4,6-Tribromoaniline	70	2	13.0 ± .1

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[6] O. N. Witt and E. Witte, *Ber.*, **41**, 3091 (1908).

pyridine was increased 100% (4 cc.). This increased concentration of the pyridine should shift the acetylation reaction equilibrium in a favorable direction by uniting with the hydrochloric acid formed in the reaction. Two compounds, *o*-nitroaniline and acetamide, which were only partially acetylated using the original reagent, were used. Experimentally it was found that no material increase in the amount of acetylation could be secured in this manner.

Since ethers are often used as solvents for various amines, di-*n*-butyl ether was substituted for toluene as the solvent in the acetylating reagent, with the purpose of increasing the acetyl values of compounds through increased solubility. Moreover, due to the fact that di-*n*-butyl ether (b. p. 141°) is less volatile than toluene (b. p. 110°), a higher temperature which caused greater reactivity could be realized. The favorable effect of modification of solvent alone is seen in the results listed for *o*-nitraniline and acetamide in Table II. In both cases the acetyl values were increased materially as compared to the values obtained using the original reagent. Increasing the acetylation temperature from 60 to 70° yielded acetyl values of about 90% or better for these difficultly acetylated compounds. The results of determinations using the modified reagent and a temperature of 70° on the other available compounds are listed in Table II.

In every case when the compounds studied are known to be soluble in ethers, acetyl values of over 90% of the theoretical values were found and in some cases practically the calculated values were obtained. In the case of aniline, decomposition leading to the formation of a tarry substance was observed at the higher temperature with the result that an acetyl value of only 85% was secured. It is only in the case of compounds exceedingly insoluble in the acetylating medium as, for example, tribromoaniline and *p*-nitroacetanilide, that low acetyl values resulted.

The above experimental data indicate that modifying the Smith–Bryant acetylating reagent by introducing di-*n*-butyl ether as the solvent and increasing the temperature from 60 to 70° produces results which are of greater quantitative value in estimating amines and amine derivatives than the original Smith–Bryant reagent.

Summary

1. The method of Smith and Bryant for the determination of alcohols and phenols using acetyl chloride–toluene reagent in the presence of pyridine was found to be inapplicable for the analytical determination of amines. Primary aromatic amines, with the exception of a few compounds, do not react quantitatively but yield widely varying results. Monoacet derivatives of these amines are somewhat less reactive. This may be explained by the low solubility in the reaction medium and by too low a temperature of acetylation in most cases. Secondary aromatic amines react quantitatively in every case. Aliphatic amines yield very low results and these results are explained on the basis of their high basicity. Thiophenol, the only mercaptan studied, reacted quantitatively.

2. Excess pyridine does not increase the acetyl values of amines using the Smith–Bryant reagent.

3. A new acetylating solution of acetyl chloride in di-*n*-butyl ether and a reaction temperature of 70° yields acetyl values greater than 90% of the theoretical in the case of compounds which are soluble in the reagent. Compounds which are known to be insoluble in the solvent do not yield satisfactory results.

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