

The Relative Ease of Esterification of Amino Alcohols

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Whenever in an organic compound two functional groups are present on nearby carbon atoms, each group modifies the properties of the other. For example, the *beta*-phenoxyethyl halides are relatively inert to meta-thetical reactions (1) which the simple ethyl halides undergo readily, and the hydroxyl groups of ethylene glycol react with hydrogen bromide much more slowly than does the hydroxyl group of methanol (2).

Although many hundred amino alcohols have been made for pharmacological testing, not much attention has been paid to the influence of the amino and hydroxyl groups on the chemical properties of each other. Glasstone and Schram (3) have shown that the hydroxyl group lowers the basicity of the amino group in a series of *beta*-amino-alcohols such as aminoethanol, 2-amino-1-propanol, etc. This is the result which would be predicted from the electron-attracting inductive effect of the hydroxyl group. Glasstone and Schram did not extend their work to amino alcohols wherein the amino and hydroxyl groups are separated by more than two carbon atoms.

Some years ago we became interested in studying the effect of the amino group on the properties of the alcoholic hydroxyl group. The reactions of alcohols are of two general types; those, such as dehydration and replacement by halogen, in which the entire OH group is lost; and those, such as esterification, in which only the hydrogen of the hydroxyl group is replaced. Tertiary alcohols, in which the electron pair of the C-O link is greatly displaced toward the oxygen atom, readily undergo the first type of reaction, while primary alcohols, in which the C-O link is relatively strong, are also stronger acids, and undergo the second type of reaction more readily. The amino group, which is relatively electron-attracting (-I effect) should tend to strengthen the C-O bond, and it would be predicted, therefore, that tertiary amino alcohols of the general type I would be more easily esterified and more difficult to dehydrate than the corresponding tertiary alcohols (II) without the amino group.

This prediction was verified, as far as dehydration is concerned, in earlier work from this Laboratory (4). Amino alcohols of type I, where R, R' and R'' are methyl groups, are extremely resistant to dehydration until there are at least five carbon atoms ($n=4$) between the amino and hydroxyl groups. Whereas simple tertiary alcohols can be dehydrated by heating with iodine or copper sulfate, the amino alcohols studied in this work could not be dehydrated by such mild reagents, and it was necessary to use concentrated sulfuric acid or to pyrolyze the Grignard complex in order to obtain olefinic amines.

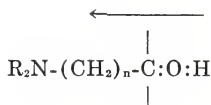
Other work (4, 5) on the preparation of amino alcohol esters with such reagents as benzoyl chloride indicated that the tertiary hydroxyl group is much more easily esterified than is the case with simple tertiary alcohols, but no quantitative data were reported. In the present work we investigated the esterification of a series of dialkylamino alcohols with acetic anhydride. The reactants were used in equimolar quantities, and the reactions were carried out at 100° for one-half hour. At the end of this time an aliquot portion of the reaction mixture was analyzed for acetic acid, and the remainder was hydrolyzed and the ester isolated. Duplicate runs were made in all cases; usually the results agreed within one or two percent. The results are recorded in Table I. Some alcohols not containing amino groups were esterified for comparison purposes; these results are also included in Table I.

TABLE I. Esterification of Amino Alcohols with Acetic Anhydride in Benzene Solution.

Alcohol Used	100°C. 30 minutes. 0.2106 moles of each reactant	
	Percent of Ester Formed, Dctd. By analysis	By distillation
Me ₂ N-CH ₂ CH ₂ OH	55	54
Et ₂ N-CH ₂ CH ₂ OH	83	83
Me ₂ N-CH ₂ CH ₂ CH ₂ OH	65	65
Et ₂ N-CH ₂ CH ₂ CH ₂ OH	76	—
Me ₂ N-CH ₂ CHOH-CH ₃	81	78
Me ₂ N-CH ₂ C(CH ₃) ₂ OH	69	70
Me ₂ N-CH ₂ CH ₂ C(CH ₃) ₂ OH	86	84
Me ₂ N-CH ₂ CH ₂ CH ₂ C(CH ₃) ₂ OH	53	54
CH ₃ CH ₂ OH	74	
CH ₃ CH ₂ CH ₂ OH	77	
CH ₃ CHOH-CH ₃	46	
(CH ₃) ₃ C-OH	11	

Certain conclusions may be drawn from the data in Table I. Secondary and tertiary alcohols containing an amino group in the molecule esterify much more completely than do alcohols of the same type without the amino group. A similar effect was not observed in the case of the primary alcohols, but this may not be significant, since primary alcohols without an amino group are easily esterified under the conditions used. In the case of tertiary alcohols the effect is still marked when the amino and hydroxyl groups are separated by four carbon atoms. The diethylamino alcohols apparently esterify more readily than do the dimethylamino analogs.

It seems to us that the effect of the dialkylamino group on the ease of esterification of an alcoholic hydroxyl group is due to two factors. The first factor undoubtedly is an electron-attracting inductive effect of the amino group operating, with diminished intensity, through the carbon chain:



As a result of this electron-displacement toward the nitrogen atom, the oxygen atom of the hydroxyl group has less share than usual in the electron-pair binding it to the carbon atom, consequently, the hydrogen atom of the hydroxyl group is held more loosely. The concept of simple inductive effect, however, does not explain the great ease of esterification of 4-dimethylamino-2-methyl-2-butanol, since the inductive effect of an electron-attracting group operating through a saturated chain does not usually continue through more than three carbon atoms. The acid strengths of the propionic acids may be cited as an example of this: propionic acid has $K_a=1.4 \times 10^{-5}$; alpha-chloro-propionic acid is much stronger, with $K_a=1.47 \times 10^{-3}$ but beta-chloropropionic acid is not much stronger as an acid than the unsubstituted compound; K_a in this case is 8.6×10^{-5} .

A second factor which appears to be important in explaining the effect of the amino group on the ease of esterification of amino alcohols is chelation. If the molecule of the amino alcohol "curls up," as in all probability it does, then the amino and hydroxyl groups approach very close in space, and a hydrogen bond can be formed.

Molecular models indicate that this type of hydrogen bonding can occur readily until six carbon atoms separate the two groups. When such a chelate ring takes part in a chemical reaction the proton can remain attached to either the nitrogen or the oxygen atom. This explains the reduced basicity of the amino group and the increased ease of esterification of the hydroxyl group. The difference in effect between the dimethylamino and diethylamino groups is probably one of basic strength—diethylamine is considerably stronger as a base ($K_b=1.26 \times 10^{-3}$) than is dimethylamine ($K_b=7.4 \times 10^{-4}$) (6) and hence would have a greater attraction for the proton.

It might seem that the greatly increased ease of esterification of the tertiary amino alcohols could be due to simple catalysis by the tertiary amino group, since tertiary bases such as pyridine are known to catalyze some alcohol-anhydride reactions. While catalysis may play some part, we do not believe that this is a complete explanation for the results obtained in the present work, as in general the reaction of tertiary alcohols with acetic anhydride is not markedly influenced by the presence of a tertiary base. For example, Mitchell, Hawkins and Smith (7) found that at 60° tertiary butyl alcohol and acetic anhydride gave only a 6% yield of ester, even though a large quantity of pyridine was present.

Experimental

Preparation of Amino Alcohols.—These were prepared as described previously (4,8) from the chlorohydrin or, in some cases, the olefin oxide and secondary amine. The amino alcohols were purified by distillation

through a Whitmore-Fenske column packed with single turn glass helices, and only those fractions of constant boiling point and constant index of refraction were used. The physical constants of the fractions employed are shown in Table II.

TABLE II. Data on Amino Alcohols.

ALCOHOL	B.pt./Press.	n_D^{20}
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{OH}$	133-134/740	1.4292
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{CH}_2\text{OH}$	159-161/740	1.4360
$\text{Me}_2\text{N-CH}_2\text{CHOH-CH}_3$	124/740	1.4192
$\text{Me}_2\text{N-CM}_2\text{C(CH}_3)_2\text{OH}$	128/740	1.4212
$\text{Me}_2\text{NCH}_2\text{CH}_2\text{C(Me)}_2\text{OH}$	79-80/50	1.4289
$\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{C(Me)}_2\text{OH}$	96-97/27	1.4393

Esterification of Amino Alcohols.—An accurately weighed sample (0.2106 mole) of the amino alcohol in 156 g. of reagent grade anhydrous benzene was placed in a 300 ml. glass ampoule, and 0.2106 mole (20 ml.) of reagent grade acetic anhydride was added from a calibrated pipet. The ampoule was quickly sealed, shaken and immersed in a thermostat at 100° , where it was kept for thirty minutes. It was then removed, cooled in an ice bath and opened. The contents were shaken with 100 ml. of distilled water to hydrolyze unreacted acetic anhydride, and the water layer was made basic with 6 N sodium hydroxide. The organic layer was separated, dried over anhydrous potassium carbonate, filtered, and placed in a 250 ml. volumetric flask, which was then filled to the mark with dry benzene. A 10 ml. portion of this solution was removed for analysis, and the remainder was distilled through a column packed with a tantalum spiral, and the yield calculated from the weight of ester isolated. The physical constants of the aminoalkyl acetates obtained are given in Table III.

TABLE III. Data on Aminoalkyl Acetates.

Aminoalkyl Group	B.p./ Press.	n_D^{20}	d_4^{20}	MR_D Calc.	obs.	M.p. of HCl Salt
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{-}$	150/740	1.4161	0.9290	35.6	36.2	130-131
$\text{Et}_2\text{N-CH}_2\text{CH}_2\text{-}$	112/80	1.4238	0.9124	44.7	44.5	113-114
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{CH}_2\text{-}$	114/120	1.4207	0.9178	40.1	40.1	118-119
$\text{Me}_2\text{N-CH}_2\text{CH(CH}_3\text{)-}$	151/740	1.4133	0.9058	40.0	40.1	125-126
$\text{Me}_2\text{N-CH}_2\text{C(CH}_3)_2\text{-}$	159/740	1.4179	0.8955	44.7	44.8	143
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{C(CH}_3)_2\text{-}$	120/100	1.4257	0.8995	49.4	49.3	180-181
$\text{Me}_2\text{N-CH}_2\text{CH}_2\text{CH}_2\text{C(CH}_3)_2\text{-}$	119/50	1.4287	0.8902	54.0	54.2	133-134

Analytical Method.—The usual procedure for determining acetyl groups had to be modified because of the presence of the amino group, and the following technique was devised. The 10 ml. aliquot of the

benzene solution was refluxed for one hour with methyl alcoholic sodium prepared by dissolving 0.5 g. of clean sodium in 14 ml. of reagent methanol, and adding 2 ml. of boiled distilled water. The solution was then distilled to dryness under reduced pressure in a small Kjeldahl apparatus. The residue was taken up in 10 ml. of distilled water and 5 g. of reagent sodium dihydrogen phosphate and 10 ml. of reagent 90% phosphoric acid were added. The mixture was distilled almost to dryness at 60 mm. pressure from an oil bath kept at 100°; the distillate was collected in a known volume of standardized barium hydroxide solution. Three 10 ml. portions of distilled water were added to the residue, the mixture being evaporated almost to dryness each time. The excess barium hydroxide was titrated to the phenolphthalein end point with 0.1 N hydrochloric acid. The whole operation, except the titration, was carried out in the same apparatus, which was protected from carbon dioxide by means of potassium hydroxide towers. Control experiments showed that the amount of acetic acid liberated could be determined with an accuracy of 1%.

Summary

1. The ease of esterification of certain amino alcohols by acetic anhydride has been determined under constant conditions. It has been shown that secondary and tertiary alcohols containing an amino group esterify much more readily than do the analogs without an amino group.
2. An explanation has been developed for these observations.

References

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