After evaporation of the ether, the mixture was heated for 3 hours on a steam-bath. After standing overnight at 25° it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution to which 3 ml. of concentrated hydrochloric acid was added, and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The solidified residues, after washing with light petroleum were crystallized from the appropriate solvents.

The Grignard products listed in Table I were prepared similarly. They are all colorless, insoluble in cold aqueous sodium hydroxide (10%), give no color with alcoholic ferric chloride and are generally soluble in hot benzene and/or alcohol but are difficultly soluble in light petroleum.

Action of Aqueous Sodium Hydroxide Solution on IIIa.—Two grams of IIIa and 20 ml. of aqueous sodium hydroxide solution (10%) were heated on a steam-bath for one hour until all the solid was dissolved. The reaction mixture was cooled, poured onto crushed ice and acidified with dilute hydrochloric acid. The solid so obtained was filtered off and crystallized from aqueous ethyl alcohol (50%) as colorless crystals, yield *ca.* 1.2 g., m.p. 146°, identified as VIa (m.p. and mixed m.p.[4]).

Reaction of VIa with (a) Ethyl Iodide.—One gram of VIa was dissolved in 10 ml. of ethyl alcohol, treated with 4 ml. of aqueous sodium hydroxide (10%) and with 3 ml. of freshly distilled ethyl iodide. The reaction mixture was refluxed on a water-bath for 0.5 hour, set aside to cool, and then poured into 100 ml. of cold water. It was filtered off and the filtrate was acidified with cold dilute hydrochloric acid. The solid so obtained was crystallized from petroleum ether as colorless crystals (*ca.* 0.8 g.), m.p. 136°, identified as VIc (m.p. and mixed m.p.[4]).

(b) **Benzoyl Chloride.**—A solution of 1 g. of VIa in 10 ml. of aqueous sodium hydroxide solution was treated gradually with 2 ml. of benzoyl chloride. The reaction mixture was vigorously shaken for 20 minutes, then poured onto 200 ml. of cold water and acidified with dilute hydrochloric acid. The solid so obtained was collected and crystallized from dilute ethyl alcohol as colorless crystals (*ca.* 0.5 g.), m.p. 178°, identified as VIb (m.p. and mixed m.p.[4]).

(c) **Hydrogen Peroxide.**—A mixture of 0.5 g. of VIa and 10 ml. of glacial acetic acid and 2 ml. of hydrogen peroxide was kept aside at room temperature for 2 days. It was poured onto crushed ice, and the solid thus separated was collected and crystallized from dilute acetic acid as colorless crystals (*ca.* 0.20 g.), m.p. 155°, not depressed with an authentic sample of VII.[11]

Action of Potassium Hydroxide Solution on Va.—Treatment of Va with an alcoholic potassium hydroxide solution (10%), as described in the case of IIIa, and extending the heating period for 3 hours gave, after acidification, an impure colorless substance having a wide range of m.p. The reaction was repeated using 0.5 g. of Va and 20 ml. of an alcoholic potassium hydroxide solution (20%) and was refluxed for 10 hours. The solid that separated during refluxing was collected, dissolved in water and acidified with cold dilute hydrochloric acid. The solid that separated was crystallized from aqueous alcohol as colorless crystals (*ca.* 0.25 g.), m.p. 155° (not depressed when mixed with a sample of VII prepared as above).

Action of Potassium Permanganate on VII.—A solution of 0.5 g. of VII in 30 ml. of acetone was treated portionwise with 40 ml. of 5% aqueous potassium permanganate solution. The reaction mixture was refluxed for 2 hours, cooled and poured onto ice-cold water. It was extracted with ether, dried and evaporated. A solution of the oily residue in 4 ml. of absolute alcohol was treated with a concentrated alcoholic solution of 2,4-dinitrophenylhydrazine containing a few drops of concentrated hydrochloric acid. The reaction mixture was refluxed for 10 minutes and the separated crystals, upon cooling, were collected and identified as benzophenone 2,4-dinitrophenylhydrazone (m.p. and mixed m.p.).

Acknowledgment.—The authors are indebted to Professor C. L. Stevens of Wayne State University for the determination of the infrared and ultraviolet absorption spectra.

(11) Prepared after E. P. Kohler and C. Heritage, *Am. Chem. J.*, **33**, 21 (1905); E. P. Kohler and R. M. Johnstin, *ibid.*, **33**, 35 (1905).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY]

Cyclization of Acylaminoalkanols to 2-Oxazolines[1]

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Through the use of *o*-toluenesulfonyl chloride and pyridine it has been found possible to form 2-oxazolines from acylaminoalkanols in which the amido group is attached to primary, secondary or tertiary carbon, and the alcohol is primary or secondary. The yield of oxazoline ranged from 21–85% depending upon the structure of the acylaminoalkanol. Sulfonic acid esters are suggested as intermediates.

In earlier work in this Laboratory[2] it was found that the treatment of various N-aroyl derivatives of 2-methyl-2-amino-1-propanol (I) with *p*-toluenesulfonyl chloride in pyridine gave excellent yields of the corresponding 2-aryl-4,4-dimethyl-2-oxazolines. This work has been extended to other amides of (I), and to the preparation of 2-oxazolines from N-aroyl derivatives of 2-aminoethanol (II), 2-amino-1-butanol (III) and 1-amino-2-propanol (IV). The amides and oxazolines which were prepared are listed in Tables I and II.

(1) Abstracted from a thesis submitted by Robert C. Rittner in partial fulfillment of the requirements for the degree of Doctor of Philosophy, New York University, February, 1954, and presented at the 124th Meeting of the American Chemical Society, Chicago, Ill., September, 1953.

(2) R. N. Boyd and R. H. Hansen, THIS JOURNAL, **75**, 5896 (1953).

The oxazolines from I were prepared in the manner previously outlined,[2] at temperatures below 20° but with the use of *o*-toluenesulfonyl chloride (b.p. 129–131° (14 mm.)). When the same procedure was followed with the *p*-chloro- and *p*-ethoxybenzamides of II, the chief products were the corresponding chloroamides, $ArCONHCH_2CH_2Cl$, rather than the oxazolines. Since it was possible that a chloro compound might have arisen from the action of hydrochloric acid in the course of attempted isolation of an oxazoline (see Experimental section), one isolation sequence was run (with Ar = *p*-chlorophenyl) in the absence of hydrochloric acid, and in another hydrobromic acid was substituted for hydrochloric acid. In both cases, the chloroamide was the product. Thus, it appeared likely that the chloroamide was

TABLE I

ACYLAMINOALKANOLS, ArCONHCRR'CR''R'''OH

Ar	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
	R, R', R'', R''' = H			
C_6H_5[a]	42	62.5–63.5		
p-ClC_6H_4	78	116.5–118	7.0	6.9
o-$EtOC_6H_4$	54	75–77	6.7	6.4
p-$EtOC_6H_4$	69	122–123	6.7	6.8
p-$O_2NC_6H_4$[b]	61	132–133		
	R = C_2H_5; R', R'', R''' = H			
C_6H_5[c]	75	102–103		
p-ClC_6H_4	67	112–114	6.2	5.9
p-$O_2NC_6H_4$	47	113–114	11.8	12.1
	R, R' = CH_3; R'', R''' = H			
o-ClC_6H_4	57	129–131	6.2	6.2
p-ClC_6H_4	62	88–89	6.2	6.5
	R, R', R'' = H; R''' = CH_3			
C_6H_5	23	96.5–97	7.8	8.0
	$ArCONHCH_2CH_2CH_2OH$			
p-ClC_6H_4	72	107–108	6.6	6.6
p-$O_2NC_6H_4$	56	95–96	12.5	12.8
	$ArCONHCH_2CH_2Cl$			
p-ClC_6H_4	23[d] 42[e]	106–108	6.4	6.4
p-$EtOC_6H_4$	26[d]	140–142	6.1	6.0

[a] Ref. 4; m.p. 61–63°. [b] W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 412 (1915); m.p. 132–133°. [c] J. H. Billman and E. E. Parker, THIS JOURNAL, **66**, 538 (1944); m.p. 98–99°. [d] At 20°. [e] At 50–60°.

produced during the treatment with the sulfonyl halide, probably through cleavage of the ring of the hydrochloride of the desired oxazoline, such transformations being known to occur readily,[3,4] although generally at somewhat elevated temperatures.

Accordingly, the cyclizations of the benzamides of 2-aminoethanol were carried out at a temperature of −30° to −40°; fair yields of 2-aryl-2-oxazolines were obtained in 15 minutes, and no chloroamides were detected. As a further check, the reaction with one amide was run at a higher temperature (50–60°); the expected chloroamide was obtained in much higher yield than at 20°, and no trace of a 2-oxazoline was detected. When the low temperature modification was applied to the previously reported[2] synthesis of 2-phenyl-4,4-dimethyl-2-oxazoline, the yield was raised to 84%.

The low temperature procedure was not successful, however, for the preparation of oxazolines from amides of III; instead it was found necessary to carry out the cyclizations for two hours at reflux temperatures (approximately 125°); the yields were good.

The cyclizations so far discussed were applied only to primary alcohols, although the amido group was found attached to primary (II), secondary (III) or tertiary carbon (I). When the low temperature procedure was applied to the N-benzoyl derivative of a secondary alcohol, 1-amino-2-propanol (IV), a 43% yield of the corresponding oxazoline was obtained.

Several attempts were similarly made to bring about the cyclization of the benzamide of 3-amino-1-propanol to the six-membered ring structure of a dihydroöxazine, but no material having the properties expected of such a compound could be isolated.

Pyridine (or some similar base) appears to be essential for cyclization to oxazolines, since runs with dioxane as solvent were unsuccessful. A sulfonyl halide appears necessary, too, since runs with pyridine and dry hydrogen chloride gave no cyclization. Both points support the suggestion[2] that the cyclization proceeds *via* an intermediate sulfonic acid ester as has been postulated[5] for certain reactions of derivatives of 2-amino-1-cyclohexanol, the oxygen of the amido group serving as the basic group which displaces the sulfonate anion. However, sulfur-containing compounds, isolated (in poor yield) only from runs involving the *p*-nitrobenzamides of I and III, could not be transformed into oxazolines, although they gave back the original amidoalcohol when treated with alkali.

A so-called "difference effect"[6] appears in the relationship between ease of cyclization and the number of alkyl substituents beta to the hydroxyl group of the amidoalcohol. The presence of a single alkyl substituent (as in the amides of III) results in a difficult cyclization (125°, 2 hours); the presence of two alkyl substituents (as in the amides of I) results in a cyclization that is as easily carried out (−30°, 15 minutes) as it is with amides of unalkylated 2-aminoethanol (II).

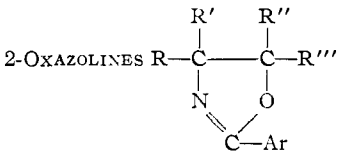
As to the stability of the various oxazolines toward cleavage of the ring to yield chloroamides, the critical step would appear to be the bimolecular attack on the ring by chloride ion.[3] The presence of alkyl substituents would interfere with this; hence the 4-substituted and 4,4-disubstituted oxazolines are more resistant to cleavage than the unsubstituted oxazolines from 2-aminoethanol, which are easily transformed into the corresponding chloroamides. Ingold[7] and, earlier, Baeyer and Villiger[8] observed an unusually high stability for heterocyclic rings carrying *gem*-dimethyl substituents; the resistance to cleavage on the part of the 4,4-dimethyl-2-aryl-2-oxazolines is further evidence of this sort.

In the course of the present work it was found that what had previously been reported[9] as 2-phenyl-4,4-dimethyl-2-oxazoline, m.p. 87°, appears to have been an impure sample of the benzamide of I, m.p. 91.5–93°; while the substance, m.p. 223–224°, claimed[10] to be the hydrochloride of the same oxazoline, was actually the corresponding aminoester hydrochloride,[11] m.p. 223–224°. The present work showed that the oxazoline hydrochloride had a melting point of 149.5–150°.

(3) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).
(4) E. E. van Tamelen, THIS JOURNAL, **74**, 2074 (1952).
(5) S. Weinstein and R. Boschan, *ibid.*, **72**, 4669 (1950).
(6) C. W. L. Bevan, E. D. Hughes and C. K. Ingold, *Nature*, **171**, 301 (1953).
(7) C. K. Ingold, *J. Chem. Soc.*, **119**, 305 (1921).
(8) A. von Baeyer and V. Villiger, *Ber.*, **30**, 1954 (1897).
(9) R. Lusskin and J. J. Ritter, THIS JOURNAL, **72**, 5577 (1950).
(10) S. Weinstein, Ph.D. Dissertation, New York University, 1951.
(11) G. E. Ullyot, U. S. Patent, 2,463,831 (March 8, 1949).

TABLE II

2-OXAZOLINES



Ar	Yield, %	M.p. or b.p., °C. (mm.)	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate M.p., °C.	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found
			R, R', R'', R''' = H				
C_6H_5[a]	23	99–100 (2)			179–180		
p-ClC_6H_4	47	87–88	7.7	8.1	180–182	13.6	13.9
p-$EtOC_6H_4$	55	106–107.5	7.3	7.5	194.5–195	13.3	13.3
p-$O_2NC_6H_4$[b]	21	180–182			175–176	16.6	16.6
			R = C_2H_5; R', R'', R''' = H				
C_6H_5	60	112–113 (7)	8.0	8.2	136–137	13.9	14.0
p-ClC_6H_4	58	25	6.7	6.8	156–157	12.8	12.9
p-$O_2NC_6H_4$	33	76–77	12.7	12.4	161–163	15.6	16.0
			R, R' = CH_3; R'', R''' = H				
C_6H_5[c]	84	23–24			133–135		
C_6H_5 as HCl	90	149.5–150	6.6	6.6	.....	..	..
p-ClC_6H_4	71	33–34	6.7	6.8	152–154	12.8	13.3
o-ClC_6H_4	20	140–142 (20)	6.7	6.8	115–116.5	12.8	12.8
			R, R', R'' = H; R''' = CH_3				
C_6H_5[d]	43	120–121 (16)			172–173	14.4	14.7

[a] H. Wenker, THIS JOURNAL, **57**, 1079 (1935); b.p. 243–244°; picrate, m.p. 177°. [b] M. T. Leffler and R. Adams, *ibid.*, **59**, 2252 (1937); m.p. 178–178.5°. [c] Ref. 2; m.p. 24°; picrate, m.p. 131.7–133°. [d] S. Gabriel and T. Heymann, *Ber.*, **23**, 2493 (1890); b.p. 243–244°.

Experimental Section

The various amides were prepared by standard procedures, care being taken to ensure an excess of aminoalcohol over aroyl chloride in order to prevent the formation of diaroylated products.

The method for the preparation of oxazolines from the amides was essentially that described[12] for the preparation of sulfonic acid esters from alcohols and arylsulfonyl chlorides through the use of anhydrous pyridine as a catalyst. The temperatures employed were −30° to −40° for amides of I, II and IV; for amides of III, mixing of reagents was allowed to take place at 50–60°, and then cyclization was accomplished during a 2-hour reflux at 125°. Isolation of an oxazoline was accomplished by neutralization with aqueous 20% sodium hydroxide followed by extraction with chloroform. After the extract was dried over potassium carbonate, the chloroform was evaporated, the pyridine was stripped off by distillation under reduced pressure and the remaining oxazoline, if a liquid, was distilled. If the residue was a solid, it was extracted with 10% hydrochloric acid, and the oxazoline was precipitated from the acidic extract by 20% sodium hydroxide and recrystallized from aqueous ethanol. The initial neutralization, after a low temperature cyclization, was made at −30°, and the basic mixture was allowed to warm to room temperature before the subsequent operations were carried out. After a high temperature cyclization, the mixture was cooled to room temperature before the neutralization.

Picrates of the oxazolines were prepared by standard methods.

Chloroamides, $ArCONHCH_2CH_2Cl$, were formed by heating the corresponding alcohols, $ArCONHCH_2CH_2OH$, with *o*-toluenesulfonyl chloride and anhydrous pyridine, for 0.5 hour at 50–60°. They were isolated as solids by pouring the mixtures into water, and they were recrystallized from aqueous ethanol. They were transformed into oxazolines by a previously reported procedure.[4]

A possible sulfonic acid ester was isolated in one case. *o*-Toluenesulfonyl chloride (0.1 mole) was added to a rapidly stirred solution of 0.1 mole of the *p*-nitrobenzamide of 2-amino-1-butanol in 0.4 mole of pyridine. The addition was carried out at such a rate that the reaction temperature remained below 20°. The reaction mixture was allowed to stand overnight and then was poured over 200 g. of ice. A white solid was collected and recrystallized from water. Ten grams of product (31% yield, m p. 166–167°), believed to be the hydrate of 2-(*p*-nitrobenzamido)-1-butyl *o*-toluenesulfonate, was isolated. Calcd. for $C_{18}H_{22}N_2O_7S$: C, 52.7; H, 5.4; N, 6.8; S, 7.8. Found: C, 52.9; H, 5.4; N, 7.1; S, 7.0. It could not, however, be cyclized to an oxazoline by the usual procedures.

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(12) *Org. Syntheses*, **20**, 50 (1940).