The solution was concentrated under vacuum and the remaining oil dissolved in ether. The ether solution was washed free of acid and concentrated to give 600 mg. of a light colored oil.

The hydrolysis product, ethyl N-tosyl-N-(2-hydroxy-2-formylethyl)-*p*-aminobenzoate was dissolved in 20 ml. of methanol and 2 ml. of water containing 300 mg. of cupric acetate. The solution was heated at 60° for 10 minutes and the copper oxide which precipitated was separated. The alcohol was distilled and a viscous yellow oil weighing 600 mg. remained.

Conversion of the cupric acetate oxidation product (IX) to pteroic acid followed essentially the procedure used above in converting ethyl N-tosyl-N-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoate (V), to pteroic acid. The oil was dissolved in 15 ml. of acetic acid and added to a mixture of 150 mg. (0.0007 mole) of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride and 115 mg. (0.0014 mole) of sodium acetate. The mixture was stirred under an atmosphere of nitrogen in the dark for 90 minutes and the solvent distilled under vacuum. The tosyl group was removed by dissolving the residue in 2.5 ml. of a 30% hydrogen bromide in acetic acid solution containing 130 mg. of phenol. The detosylated product was recovered by pouring the mixture into anhydrous ether. After saponification, there was obtained 122 mg. (55.7%) of product which contained 24.8% pteroic acid by chemical analysis.

Pteroylglutamic Acid (XVI).—A sample (6.23 g., 0.01 mole) of diethyl N-[N'-tosyl-N'-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate was dissolved in 25 ml. of methanol and 10 ml. of water containing 1 ml. of concentrated hydrochloric acid. After refluxing for 25 minutes, the methanol was distilled under vacuum, and the residue dissolved in ethyl acetate. The solution was washed free of acid, dried, and concentrated to give 5.2 g. of a light colored viscous oil.

The hydrolysis product (X) was dissolved in 50 ml. of methanol and added to a solution of 1.8 g. of cupric acetate in 50 ml. of methanol and 10 ml. of water. The solution was heated at 60° for 12 minutes, the copper oxide separated, and the methanol distilled under vacuum. The remaining oil was dissolved in ethyl acetate, washed well with water, dried, and concentrated to give 4.6 g. of a yellow viscous sirup.

To a mixture of 150 mg. (0.0007 mole) of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride and 115 mg. (0.0014 mole) of sodium acetate there was added a solution of 380 mg. (0.0007 mole) of diethyl N-[N'-tosyl-N'-(2-keto-2-formylethyl)-*p*-aminobenzoyl]-L-glutamate (X), in 10 ml. of glacial acetic acid. The solution was stirred in the dark under an atmosphere of nitrogen for one hour and the solvent distilled under vacuum to give the crude diethyl N^{10}-tosylpteroylglutamate.

The tosyl group was removed by stirring for ninety minutes with 130 mg. of phenol and 2.5 ml. of 30% hydrogen bromide in acetic acid. The diethyl pteroylglutamate hydrobromide was recovered by precipitation with anhydrous ether, and then saponified. There was obtained 89 mg. (28.8% yield) of product with a chemical assay of 55.8%. The product assayed 48.8% pteroylglutamic acid using *L. casei* and 40.2% using *S. faecalis* R.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

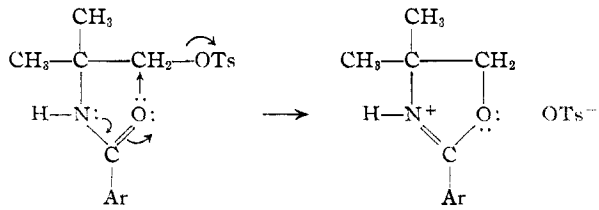
Sulfonic Acid Esters as Alkylating Agents: Formation of 2-Oxazolines[1]

BY ROBERT NEILSON BOYD AND RALPH H. HANSEN[2]

RECEIVED JULY 1, 1952

Attempted tosylation of N-aroyl derivatives of 2-amino-2-methyl-1-propanol gave good yields of the corresponding 4,4-dimethyl-2-aryl-2-oxazolines. The cyclization probably proceeds by way of a sulfonic acid ester, and provides another example of the effective interaction of neighboring groups.

Sulfonic acid esters of 2-nitro-2-methyl-1-propanol have been found to be poor alkylating agents.[3] As a comparative study, it was decided to attempt alkylations with arylsulfonic acid esters of the aminoalcohol, 2-amino-2-methyl-1-propanol, which is closely related to the nitro compound previously studied.[3] Since esters of aminoalcohols rearrange readily to the corresponding amides in the presence of base,[4] the N-acylaminosulfonic esters were used. When N-benzoyl, N-*p*-nitrobenzoyl and N-*p*-ethoxybenzoyl derivatives of 2-amino-2-methyl-1-propanol (Table I) were tosylated, only in the case of the *p*-nitrobenzamide was a sulfur-containing product obtained, and then in poor yield. The main product and, in the case of the other amides, the only product was a 2-substituted 4,4-dimethyl-2-oxazoline (Table II), formed by self-alkylation as



Winstein and Boschan[5] have investigated the neighboring group effect in *cis*- and *trans*-2-amidocyclohexanols, and concluded that the formation of oxazoline salts from O-tosylated compounds proceeds by Walden inversion. The present experiments appear to provide further examples of effective interaction of neighboring groups, the consequent facilitation of a displacement allowing a

TABLE I

AMIDES OF 2-AMINO-2-METHYL-1-PROPANOL

Amide, R =	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
	$(CH_3)_2C(CH_2OH)NHCOC_6H_4R$			
H	74	90.2–91.2	7.25	7.39
p-NO_2	13	118–119	11.76	11.75[a]
p-OEt	62	74.5–75.7	5.91	6.08
	$(CH_3)_2C(CH_2OC_6H_4R)NHCOC_6H_4R$			
H	75	111–112	4.71	4.82[b]
p-NO_2	34	138.5–139.5	10.85	10.87

[a] Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.5; H, 5.9. Found: C, 55.7; H, 5.7. [b] Calcd. for $C_{18}H_{19}O_3N$: C, 72.7; H, 6.4. Found: C, 73.4, 73.5; H, 6.4, 6.3.

(1) Presented at the 122nd Meeting of the American Chemical Society at Atlantic City, N. J., September 19, 1952.

(2) Based on a dissertation presented by R. H. Hansen to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1952.

(3) R. N. Boyd and R. H. Hansen, THIS JOURNAL, **75**, 3737 (1953).

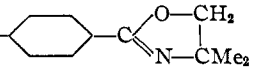
(4) G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950); *Nature*, **164**, 719 (1949).

(5) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).

notably easy ring closure under much milder conditions than are generally required for the production of oxazolines from amidoalcohols.[6]

TABLE II

SUBSTITUTED 2-OXAZOLINES



Oxazoline, R =	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate M.p., °C.	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found
H	74[a]	24[a]	8.0	8.6[b]	131.7–133.0	13.86	14.30
NO_2	50	96.0–97.1	12.72	12.60	195.2–197.5	15.59	14.87
C_6H_5O	71	69.3–70.0	6.39	6.46	137–1.143.7[c]	12.50	12.38

[a] Tryon[7] reported that he was able to synthesize this compound by reducing the benzoate of 2-nitro-2-methyl-1-propanol and then subjecting the reduction mixture to temperatures above 150°, but he did not report yields or physical constants. [b] Calcd.: C, 75.40; H, 7.48. Found: C, 75.85; H, 7.14. [c] The picrate resolidified at 137.7° and began to melt again at 142.4°.

The activity of the amides may appear quite surprising, especially in view of the extreme sluggishness of the sulfonates of the nitroalcohol.[3] Inasmuch as the present reaction is intramolecular in nature, while the previously studied displacement is an intermolecular reaction, little correlation between the series would be expected.

The use of pyridine as a solvent cannot entirely account for the success of the intramolecular alkylations, as against the failure to achieve intermolecular alkylations, for attempts to bring about the latter were as unsuccessful in the presence of pyridine as in its absence.[3]

Further work on the preparation of oxazolines from amidoalcohols by similar procedures is now in progress.

Experimental

Amides of 2-Amino-2-methyl-1-propanol.—A solution of 60 g. (1.5 moles) of sodium hydroxide in 250 ml. of water in a 1-liter beaker was prepared, and to this was added 1.4 moles (125 g.) of technical 2-amino-2-methyl-1-propanol (obtained through the courtesy of Commercial Solvents Corporation). One hundred grams (0.7 mole) of redistilled benzoyl chloride was dropped into the rapidly stirred mixture at a rate that kept the temperature below 50°. When the addition was complete, the mixture was stirred until it had cooled to room temperature. The impure amide, which usually separated as an oil, was washed with water to remove the water-soluble amine and then recrystallized from aqueous methanol to give a yield of 101 g. (74%) of a solid which melted at 90.2–91.2°. The yields of other amides, as well as their melting points and analyses, are recorded in Table I.

(6) R. H. Wiley and L. L. Bennett, Jr., *Chem. Revs.*, **44**, 447 (1949).

(7) P. F. Tryon, U. S. Patent 2,372,409 (March 27, 1945).

In attempts to make the amides by the use of equivalent amounts of aroyl chloride and amine in the presence of large amounts of pyridine, the two diaroylated compounds in Table I were obtained:

One mole (89 g.) of 2-amino-2-methyl-1-propanol was dissolved in about three moles (225 ml.) of anhydrous pyridine, and 1 mole (140 g.) of benzoyl chloride was added at a rate that maintained the temperature between 45 and 50°. The solution was stirred well throughout the addition, and for a period of 2 hours following the last addition of benzoyl chloride. It was then poured into 1 liter of cold water, with stirring. The pasty yellow solid that was obtained was recrystallized from aqueous methanol, and it yielded 112 g. of canary-yellow material, m.p. 111–112°. The yield, based on the acid chloride, was 75% of the theoretical.

A similar reaction with *p*-nitrobenzoyl chloride gave the very pale yellow diaroylated compound in 34% yield (based on the acid chloride).

The melting points and analyses of the diaroylated compounds are listed in Table I.

Conversion of Amides to Oxazolines.—The conversion procedure was essentially that described[5] for the preparation of sulfonic acid esters from alcohols and arylsulfonyl chlorides through the use of pyridine as a catalyst.

A solution of 19.3 g. (0.1 mole) of the benzamide of 2-amino-2-methyl-1-propanol in 45 ml. (0.4 mole) of anhydrous pyridine was prepared in a 250-ml. flask. To this was added 19.1 g. (0.1 mole) of tosyl chloride, in portions. The solution was stirred well and the addition of the tosyl chloride was regulated so that the temperature remained below 20°. The reaction mixture was then allowed to stand for 3 hours at room temperature, after which it was added to a solution of 60 g. of concentrated hydrochloric acid and 200 g. of ice. The solution thus obtained was extracted with benzene in order to remove any unreacted material or tosylated amidoalcohol which might have been formed. Evaporation of the benzene under reduced pressure gave no organic material, so the acidic aqueous solution was made basic by the addition of excess 20% aqueous sodium hydroxide and extracted again with benzene. Removal of the benzene and pyridine left an oil which on distillation gave 13.0 g. (74% yield) of a colorless oil (b.p. 124° at 20 mm., $n^{17}D$ 1.5338) which proved by analysis to be 2-phenyl-4,4-dimethyl-2-oxazoline (Table II).

Similar treatment of the *p*-ethoxy- and *p*-nitrobenzamides gave colorless solid oxazolines which were purified by recrystallization from aqueous methanol rather than by distillation.

In the case of the *p*-nitrobenzamide, a small amount of a white solid was obtained by the evaporation of the benzene extract of the acidic solution. This solid, from its analysis and from its insolubility in acids and bases, was concluded to be the tosylated *p*-nitrobenzamide, *p*-$O_2NC_6H_4CONHC(CH_3)_2CH_2OTs$; yield 19%, m.p. 246–247°. Calcd. for $C_{18}H_{20}O_6N_2S$: N, 7.13. Found: N, 7.22.

Acknowledgment.—The elemental analyses were done by the Micro-Chemical Laboratory at New York University, under the supervision of Professor T. S. Ma. Analyses were carried out by Mr. J. D. McKinley, Jr., Mr. N. R. Watt, and Mr. R. E. Lang.

NEW YORK 3, NEW YORK