ether solution was decanted and the oil washed several times with 10-ml. portions of absolute ether. The combined ether solutions were made acid to congo red paper with ethereal hydrogen chloride. In many cases, the colorless hydrochlorides were extremely hygroscopic and could only be recrystallized to analytical purity with difficulty. When this was not possible, the base was liberated with sodium carbonate solution, extracted into ether and converted to the methiodide by warming with methyl iodide.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Synthesis of Pteroic and Pteroylglutamic Acids.[1] II.

BY D. I. WEISBLAT, B. J. MAGERLEIN, D. R. MYERS, A. R. HANZE, E. I. FAIRBURN AND S. T. ROLFSON

RECEIVED MARCH 9, 1953

A new synthesis of pteroylglutamic acid is described in which diethyl N-tosyl-*p*-aminobenzoyl-L-glutamate is alkylated with 2,3-oxidopropionaldehyde diethyl acetal, the product oxidized and condensed with 2,4,5-triamino-6-hydroxypyrimidine. Detosylation of this product with hydrogen bromide in acetic acid in the presence of phenol gives the final product in good yield.

In the preceding paper of this series,[2] a synthesis of pteroic acid and pteroylglutamic acid was reported. The general scheme was to alkylate ethyl N-tosyl-*p*-aminobenzoate (I) or diethyl N-[N'-tosyl-*p*-aminobenzoyl]-L-glutamate (II), with a three carbon compound to give a N-substituted sulfonamide. The compound thus formed contained a three-carbon side chain with functional groups either directly or by suitable modifications capable of condensing with 2,4,5-triamino-6-hydroxypyrimidine to form the N^{10}-tosyl-substituted pteroic or pteroylglutamic acids. Although a variety of compounds was prepared and condensed to form pteroic or pteroylglutamic acids, in most cases the yields were low.

In the search for a reactive three-carbon alkylating reagent, the possibility of obtaining a vicinal dicarbonyl or potential vicinal dicarbonyl system was investigated. The oxidation product of ethyl N-tosyl-N-(2-keto-3-hydroxypropyl)-*p*-aminobenzoate[2] with copper acetate in methanol[3] gave an increased yield of pteroic acid over that obtained from the keto-alcohol. This increased yield may be due in part to the fact that in the former case a completely aromatic pteridine nucleus is formed directly whereas in the latter case a dihydropteridine compound is formed which must be oxidized to the completely aromatic compound. This indicated the desirability of using a three carbon alkylating agent which would give directly the desired ethyl N-tosyl-N-(2,3-diketopropyl)-*p*-aminobenzoate. 2,3-Oxidopropionaldehyde diethyl acetal is such an alkylating agent. The use of this compound in the synthesis of pteroic and pteroylglutamic acids is outlined in Fig. 1.

Wohl[4,5] described the preparation of 2,3-oxidopropionaldehyde diethyl acetal by the addition of hypochlorous acid to acrolein diethyl acetal followed by dehydrohalogenation of the halohydrin with solid potassium hydroxide. Acrolein diethyl acetal was prepared[4] by converting acrolein with ethanolic hydrogen chloride to the diethyl acetal of β-chloropropionaldehyde followed by dehydrohalogenation. This is essentially the method later published by Witzemann, *et al.*[6] Acrolein diethyl acetal also has been prepared from acrolein, ethyl orthoformate and ammonium nitrate in boiling ethanol[7] and in a method published by Pingert[8] from acrolein, anhydrous hydrogen chloride, and an excess of ethanol. Since the yields reported by these methods were low or not attainable by us, the following method was developed. In the presence of only 0.002 molar amounts of an acid catalyst, such as *p*-toluenesulfonic acid, acrolein and ethanol were allowed to react to give yields of acrolein diethyl acetal as high as 82%. The water formed by the reaction was removed continuously by codistillation with Skellysolve F. Hypochlorous acid was added to the acrolein acetal by vigorously stirring a solution of the two reagents at low temperature. The 2-chloro-3-hydroxypropionaldehyde diethyl acetal was then extracted and the halohydrin dehydrochlorinated with solid sodium hydroxide to give 2,3-oxidopropionaldehyde diethyl acetal in 60% yield.

The alkylation of ethyl N-tosyl-*p*-aminobenzoate (I)[2] and diethyl N-[N'-tosyl-*p*-aminobenzoyl]-L-glutamate (II)[2] was accomplished by dissolving the solid in 2,3-oxidopropionaldehyde diethyl acetal and stirring the mixture at the desired temperature in the presence of a basic catalyst. Ethyl N-tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate (III) was obtained in crystalline form, but diethyl N-[N'-tosyl-N'-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (IV), could only be obtained as a heavy sirup. Numerous attempts to crystallize the parent substance or to find a crystalline derivative were unsuccessful. The material could, however, be purified by chromatography over alumina.

In the oxidation of these compounds to the corresponding ketones (V and VI) it was found that a heterogeneous oxidation in the cold employing an aqueous acid solution of sodium dichromate was superior to the chromic acid oxidation in glacial acetic acid previously used.[2] Although neither

(1) Presented in part before the Division of Biological Chemistry at the XIIth International Congress of Pure and Applied Chemistry, New York, September 10–13, 1951.

(2) D. I. Weisblat, B. J. Magerlein, A. R. Hanze, D. R. Myers, and S. T. Rolfson, THIS JOURNAL, **75**, 3625 (1953).

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(4) A. Wohl, *Ber.*, **31**, 1796 (1898).

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(6) E. J. Witzemann, W. L. Evans, H. Hass and E. F. Schroeder, "Org. Syn.," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 17.

(7) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

(8) F. P. Pingert, *Org. Syn.*, Vol. 25, p. 1, John Wiley and Sons, Inc., New York, N. Y., 1945.

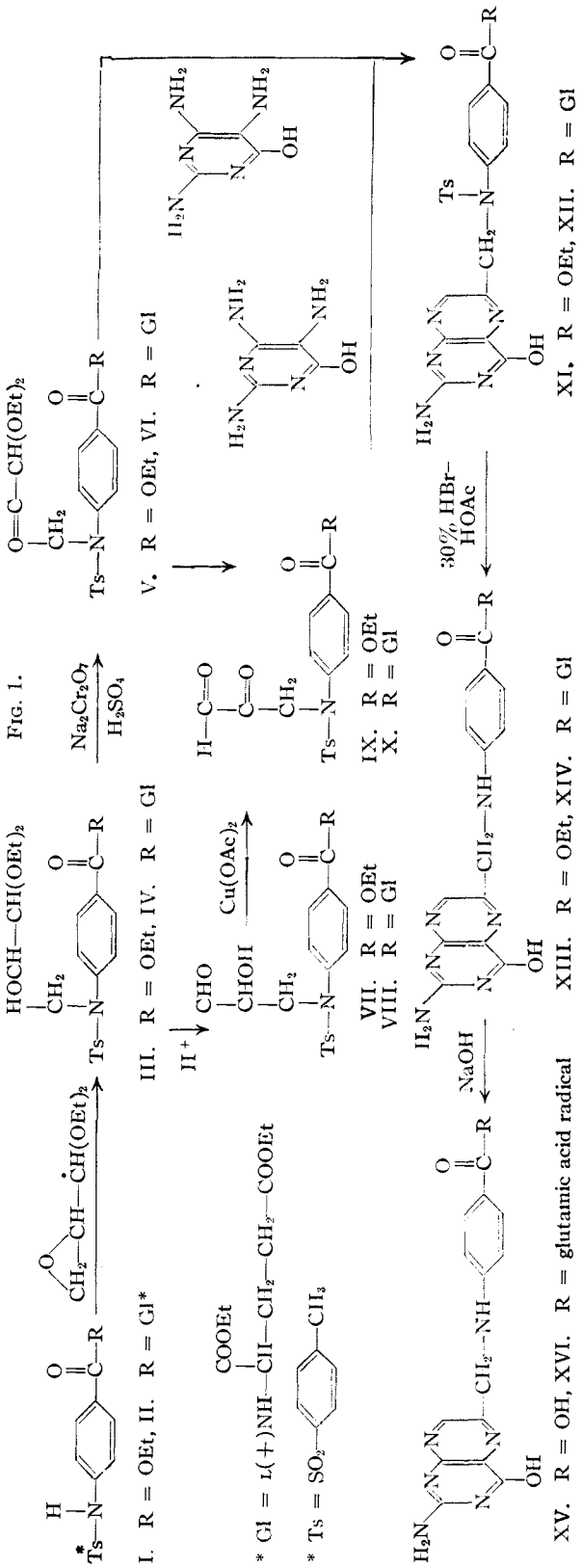

FIG. 1.

I. R = OEt, II. R = Gl*
III. R = OEt, IV. R = Gl
V. R = OEt, VI. R = Gl
VII. R = OEt
VIII. R = Gl
IX. R = OEt
X. R = Gl
XI. R = OEt, XII. R = Gl
XIII. R = OEt, XIV. R = Gl
XV. R = OH, XVI. R = glutamic acid radical

* Gl = L(+)NH—CH(COOEt)—CH$_2$—CH$_2$—COOEt
* Ts = SO$_2$—CH$_3$

ethyl N-tosyl-N-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoate (V) or diethyl N-[N′-tosyl-N′-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (VI) could be obtained crystalline, the latter compound gave a crystalline bis-2,4-dinitrophenylhydrazone. The high yields obtained were particularly surprising in view of the presence of an extremely labile ketal group in the molecule. In addition to the above oxidation products, small amounts of crystalline acidic materials, which proved to be ethyl N-tosyl-N-(carboxymethyl)-*p*-aminobenzoate, and diethyl N-[N′-tosyl-N′-(carboxymethyl)-*p*-aminobenzoyl]-L-glutamate, respectively, were also obtained.

The sirups from the oxidation procedure were condensed directly with 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride in refluxing glacial acetic acid in the presence of sodium acetate. Although N^{10}-*p*-tosylpteroylglutamic acid can be recovered in a pure state at this point, usually no attempt was made to isolate this product, but, after concentration, the crude residue was detosylated with 30% hydrogen bromide in acetic acid in the presence of phenol.[9] It is interesting to note here the remarkable stability of the pteridine molecule in 30% hydrogen bromide in acetic acid in the presence of phenol. If phenol is not present during the detosylation, a brominated pteridine is formed which possesses subtantially no biological activity. The over-all yields (weight yield times assay) of crude pteroic and pteroylglutamic acid obtained, calculated from (I) or (II), ranged from 40–50 per cent. by chemical assay.[10] Hydrolysis of the ketal group before condensation did not improve the yield. Purification of the crude folic acid by dissolving in concentrated acid and precipitating by dilution gave folic acid which was essentially pure by infrared analysis.

An alternate route in the preparation of pteroic (XV) and pteroylglutamic acid (XVI), depending upon the acid hydrolysis of ethyl N-tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate (III), or diethyl N-[N′-tosyl-N′-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoy]-L-glutamate (IV), respectively, was also investigated. The hydrolysis products, ethyl N-tosyl-N-(2-hydroxy-2-formylethyl)-*p*-aminobenzoate (VII), and diethyl N-[N′-tosyl-N′-(2-hydroxy-2-formylethyl)-*p*-aminobenzoyl]-L-glutamate (VIII), were isolated as light colored viscous oils. Oxidation of these compounds with copper acetate gave sirupy ethyl N-tosyl-N-(2-keto-2-formylethyl)-*p*-aminobenzoate (IX), and diethyl N-[N′-tosyl-N′-(2-keto-2-formylethyl)-*p*-aminobenzoyl]-L-glutamate (X). These compounds were then condensed with 2,4,5-triamino-6-hydroxypyrimidine and detosylated in the manner described above to give pteroic and pteroylglutamic acids in yields of 15%.

We wish to express our appreciation to Miss J. I. Mejeur for chemical assays; to H. H. Buskirk and E. M. Stapert for bioassays; to Dr. G. Pish, L. Scholten, and Mrs. J. L. Johnson for spectra analyses and to W. A. Struck and associates for microanalyses.

Experimental[11]

Acrolein Diethyl Acetal.—A solution containing 60.5 g. (1.08 moles) of commercial acrolein, 92.0 g. (2.0 moles) of

(9) D. I. Weisblat, B. J. Magerlein and D. R. Myers, THIS JOURNAL, **75**, 3630 (1953).

(10) B. L. Hutchings, E. L. R. Stokstad, J. H. Boothe, J. H. Mowat, C. W. Waller, R. B. Angier, J. Semb and Y. SubbaRow, *J. Biol. Chem.*, **168**, 705 (1947).

(11) All melting points are uncorrected.

absolute ethanol, 450 ml. of Skellysolve F and 3 mg. of *p*-toluenesulfonic acid monohydrate was refluxed until 26.5 ml. of a lower aqueous layer was collected in a water separator. This required 24 hours. The solution was cooled, 0.5 g. of copper carbonate added, and then vigorously stirred for 15 minutes. The solution was filtered and fractionally distilled at atmospheric pressure. The fraction boiling at 120–124° was collected. There was obtained 81.3 g. or 62.6% of acrolein diethyl acetal of $n^{25}D$ 1.3983.

2,3-Oxidopropionaldehyde Diethyl Acetal.—A solution of hypochlorous acid was prepared by the method of Wohl.[4] The addition of hypochlorous acid to acrolein diethyl acetal was accomplished by adding with vigorous stirring, 740.0 ml. of hypochlorous acid solution (0.034 g./ml., 0.480 mole) in three equal portions to an ice-cooled solution (4–6°) of 60.0 g. (0.461 mole) of acrolein diethyl acetal in 200 ml. of water precooled to 0–2°. The temperature was maintained below 18° with about 5-minute intervals between additions. Cooling and stirring was continued for 25 minutes and the solution was then made basic with 60.0 g. of sodium bicarbonate. The excess hypochlorous acid was destroyed with 3–5 ml. of 1 *M* sodium thiosulfate solution. The basic solution was saturated with sodium chloride and then extracted three times with benzene. The benzene solution was dried with anhydrous sodium sulfate and 36.9 g. (0.918 mole) of powdered sodium hydroxide was added. The mixture was stirred for 30 minutes, heated to reflux, and stirred an additional hour. The sodium chloride and sodium hydroxide were filtered and the benzene removed by distillation at atmospheric pressure. The product was fractionated and the fraction boiling 60–64° at 13 mm. was collected to give 39.9 g. (59.5%) of 2,3-oxidopropionaldehyde diethyl acetal of $n^{25}D$ 1.4128.

Ethyl N-Tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate (III).—A mixture of 127.6 g. (0.4 mole) of 2,3-oxidopropionaldehyde diethyl acetal and 70.0 g. (0.48 mole) of ethyl N-tosyl-*p*-aminobenzoate was heated at 150–155° for 2 hours in the presence of 1 ml. of pyridine. The clear melt was cooled and dissolved in 300 ml. of 2-propanol and 100 ml. of Skellysolve B. After standing, 169 g. (91.0%) of crystals was obtained, m.p. 89–94°. Five recrystallizations from 2-propanol raised the melting point to 92.5–93.5°.

Anal. Calcd. for $C_{23}H_{31}NSO_7$: C, 59.3; H, 6.7; N, 3.0; S, 6.9. Found: C, 59.2, 59.5; H, 7.0, 6.8; N, 3.3, 3.1; S, 7.1, 7.3.

The *p*-nitrobenzoate was prepared, m.p. 155–157°.

Anal. Calcd. for $C_{30}H_{34}NSO_{10}$: C, 58.6; H, 5.5; N, 4.6. Found: C, 58.6, 58.8; H, 5.6, 5.5; N, 4.9, 4.8.

Diethyl N-[N'-Tosyl-N'-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (IV).—To sixty grams (0.125 mole) of diethyl N-[N'-*p*-tosyl-*p*-aminobenzoyl]-L-glutamate fused at 130° there was added 20.18 g. (0.138 mole) of 2,3-oxidopropionaldehyde diethyl acetal and 0.5 ml. of pyridine. At the end of 0.5 hour, another 0.5 ml. of pyridine was put in and the temperature of the mixture gradually brought to 140° and maintained between 140–145° for the remainder of the 2 hour reaction period. The melt was cooled and was usually used without further purification. Repeated attempts to crystallize the product or a derivative were unsuccessful, and a portion was chromatographed on alumina. One fraction, consisting of 40% of the total sample chromatographed, was analyzed.

Anal. Calcd. for $C_{30}H_{42}N_2O_{10}S$: C, 57.8; H, 6.8; N, 4.5. Found: C, 58.2, 58.2; H, 7.1, 6.8; N, 4.4, 4.6.

Ethyl N-Tosyl-N-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoate (V).—Ninety-three grams (0.20 mole) of ethyl N-tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate was dissolved in 760 ml. of chlorobenzene and added slowly to a solution of 105 g. of sodium dichromate in 461 ml. of water and 138 ml. of concentrated sulfuric acid precooled to 0–2°. The addition was made with vigorous stirring and at such a rate as to maintain the temperature below 5°. After stirring an additional two hours at 0–5°, the organic layer was separated, washed with water and sodium bicarbonate solution, dried and concentrated. A clear light yellow gum weighing 78 g. (84% recovery) was obtained. All attempts to crystallize this compound were unsuccessful.

By acidifying the sodium bicarbonate solution with dilute hydrochloric acid, a crystalline acid, ethyl N-tosyl-N-carboxymethyl-*p*-aminobenzoate, was obtained in small amounts, m.p. 166–168°.

Anal. Calcd. for $C_{18}H_{19}NO_6S$: C, 57.3; H, 5.1; N, 3.7. Found: C, 57.5, 57.6; H, 4.9, 5.3; N, 3.8, 3.9.

Pteroic Acid (XV).—To a mixture of 27.6 g. (0.336 mole) of sodium acetate, 3.6 g. of potassium iodide, and 36.0 g. (0.1685 mole) of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride was added 78 g. (0.1685 mole) of ethyl N-tosyl-N-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoate dissolved in 960 ml. of glacial acetic acid. The mixture was stirred under an atmosphere of nitrogen and in the dark for 45 minutes at room temperature and then at the reflux temperature for an additional two hours. The acetic acid was distilled under vacuum.

The tosyl group was cleaved by dissolving the condensation product in 600 ml. of a solution of 30% hydrogen bromide in glacial acetic acid containing 31.3 g. of phenol. The reaction mixture was poured into 5 l. of anhydrous ether after standing at room temperature for 90 minutes. The product was washed with water, dried, and found to contain 39.0 g. (57.0%) of ethyl pteroate with a chemical assay of 60%.[10]

Diethyl N-[N'-tosyl-N'-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (VI).—A solution of 6.23 g. (0.01 mole) of diethyl N-[N'-tosyl-N'-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate in 38 ml. of chlorobenzene was cooled to 0–2° and added with vigorous stirring to a solution of 5.25 g. of sodium dichromate in 23 ml. of water and 6.91 ml. of concentrated sulfuric acid. The mixture was stirred for 3 hours at 0–5°, and then the organic layer was separated. The water layer was now extracted with benzene. The organic layers were combined, washed with water and sodium bicarbonate solution, and dried with anhydrous sodium sulfate. After concentrating the solution, there was obtained 5.84 g. (94.0% recovery) of a yellow gum-like material.

The oxidation product was allowed to react with 2,4-dinitrophenylhydrazine according to the method of Brady[12] and a bis-2,4-dinitrophenylhydrazone was obtained.

Anal. Calcd. for $C_{38}H_{38}N_{10}O_{15}$: C, 50.3; H, 4.2; N, 15.4. Found: C, 50.5, 50.4; H, 4.2, 4.2; N, 15.1, 15.0.

An acid, diethyl N-[N'-tosyl-N'-carboxymethyl-*p*-aminobenzoyl]-L-glutamate, was isolated by acidifying the sodium bicarbonate solution, m.p. 157–159°.

Anal. Calcd. for $C_{25}H_{30}O_9N_2S$: C, 56.2; H, 5.7; N, 5.2. Found: C, 56.4, 56.5; H, 5.4, 5.6; N, 5.3, 5.5.

N^{10}-*p*-Tosylpteroylglutamic Acid.—From the oxidation of (IV) 5.35 g. (0.0086 mole) of diethyl N-[N'-tosyl-N'-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate was dissolved in 49 ml. of glacial acetic acid and added to a mixture of 1.41 g. (0.0172 mole) of sodium acetate and 1.82 g. (0.0086 mole) of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride. The mixture was stirred in the dark and under an atmosphere of nitrogen for 45 minutes at room temperature and for 2 hours at 118–122°. The solvent was removed under vacuum. Purification by solution in concentrated hydrochloric acid, followed by dilution with water gave N^{10}-tosylpteroylglutamic acid of good purity.

Anal. Calcd. for $C_{26}H_{25}N_7O_8S$: C, 52.43; H, 4.23; N, 16.14. Found: C, 52.57, 52.30; H, 4.57, 4.61; N, 14.95, 14.86.

In 0.1 *N* sodium hydroxide solution the compound had $E^{1\%}_{1\,cm.}$ values of 132.9, 589.2 and 448.4 at 365, 256, and 216 mμ, respectively.

Pteroylglutamic Acid (XVI).—The crude solid residue from the condensation of 5.35 g. (0.0086 mole) of diethyl N-[N'-tosyl-N'-(2-keto-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (VI) with 1.86 g. (0.0086 mole) of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride was dissolved in 31 ml. of a solution of 30% hydrogen bromide in glacial acetic acid containing 1.60 g. of phenol. After ninety minutes, the diethyl pteroylglutamate hydrobromide was precipitated by the addition of anhydrous ether and separated. After saponification with 10% sodium hydroxide, there was obtained 2.69 g. (71%) of pteroylglutamic acid with a chemical assay of 73.0%.

Pteroic Acid (XV).—Acetal hydrolysis of ethyl-N-tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate was accomplished by dissolving 600 mg. (1.3 mM.) in 6 ml. of methanol and 2 ml. of water containing six drops of concentrated hydrochloric acid and heating at 60° for 10 minutes.

(12) O. L. Brady, *J. Chem. Soc.*, 756 (1931).

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]

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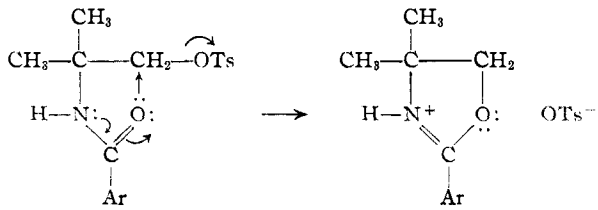
Attempted tosylation of N-aroyl derivatives of 2-amino-2-methyl-1-propanol gave good yields of the corresponding 4,4-dimethyl-2-aryl-2-oxazolines. The cyclization probably proceeds by way of a sulfonic acid ester, and provides another example of the effective interaction of neighboring groups.

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.

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