[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

1-*p*-Toluenesulfonyl-L-pyroglutamyl Chloride and 1-*p*-Toluenesulfonyl-L-glutamyl Dichloride in the Preparation of Glutamic Acid Derivatives[1]

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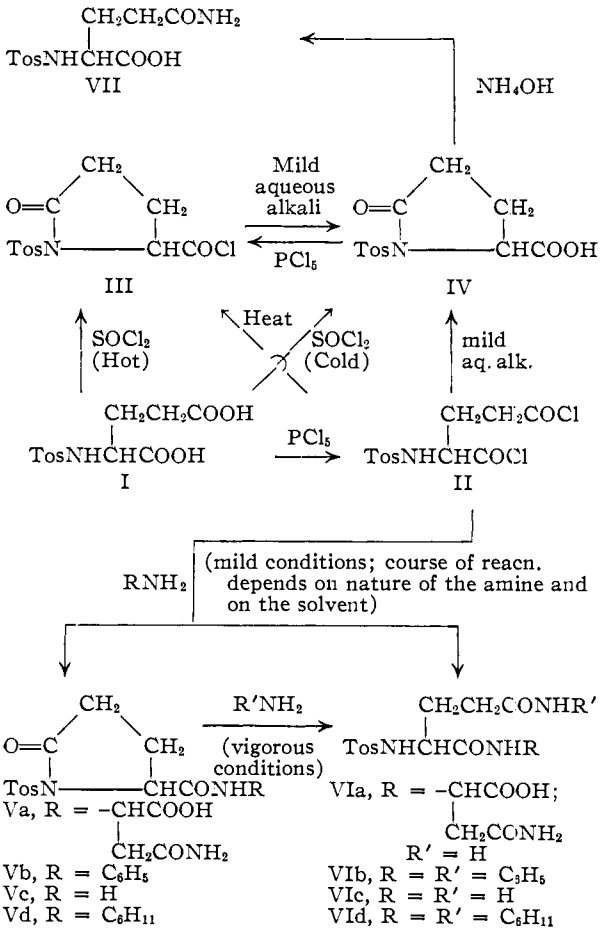
The intermediate in the synthesis of tosyl-L-glutaminyl-L-asparagine[2] (VIa) has now been shown to be tosyl-L-glutamyl dichloride (II), rather than tosyl-L-pyroglutamyl chloride (III) as originally supposed. The dichloride is cyclized readily to the pyroglutamyl chloride and is interchangeable with it in many reactions.

Tosyl-L-pyroglutamic acid[3] and its derivatives have been used for the unambiguous synthesis of peptides and other compounds in which the α- and γ-carboxylic acid groups of glutamic acid are differently combined. Thus, Swan and du Vigneaud[2] have described the preparation of L-glutaminyl-L-asparagine; tosyl-L-pyroglutamyl-L-asparagine (Va) was prepared by the acid chloride method and treated with aqueous ammonia to open the pyrrolidone ring and give tosyl-L-glutaminyl-L-asparagine (VIa), which was reduced to the free dipeptide. L-Glutaminylglycine was prepared in the same way[4] and Rudinger[5] and Clayton, Kenner and Sheppard[6] have prepared α- and γ-derivatives of tosyl-L-glutamic acid by an essentially similar procedure. The intermediate in these syntheses, tosyl-L-pyroglutamyl chloride (III), has been described as the product of the action of phosphorus pentachloride on tosyl-L-pyroglutamic acid (IV)[7] or on tosyl-L-glutamic acid (I)[2] or of hot thionyl chloride on tosyl-L-glutamic acid.[8] No analytical data have been given for the compounds from the two phosphorus pentachloride preparations, but the material prepared by the thionyl chloride reaction has been characterized in two crystalline forms, melting at 83–85°[8] and 105–106°.[9] Although tosyl-L-pyroglutamyl chloride, with m.p. 106.5–107°, has now been obtained by treating tosyl-L-pyroglutamic acid with phosphorus pentachloride, the product of reported m.p. 71–74° dec. from the reaction between tosyl-L-glutamic acid and phosphorus pentachloride[2] has been shown to be the unstable tosyl-L-glutamyl dichloride (II). This compound loses hydrogen chloride, on fusion or prolonged drying, to give the pyroglutamyl chloride (III); on the preparative scale, the cyclization may be carried out in boiling benzene. In contrast to the formation of the dichloride in the present case is the production of tosyl-L-pyroglutamic acid by the action of cold thionyl chloride on tosyl-L-glutamic acid,[8] with cyclization to the pyrrolidone system taking place under conditions where there is no attack on the α-carboxylic acid group. The product from the treatment of tosyl-L-glutamic acid with phosphorus pentachloride is formulated as the dichloride II, rather than as a complex between the pyroglutamyl chloride (III) and hydrogen chloride, on the basis of its reactions with ethanol and with aniline.



Treatment with ethanol yielded diethyl tosyl-L-glutamate, which is unlikely to have arisen from opening of the pyrrolidone ring, since ethyl tosyl-L-pyroglutamate was stable under the conditions of the esterification. The dichloride reacted with aniline in chloroform or aqueous tetrahydrofuran to give the dianilide of tosyl-L-glutamic acid (VIb); III under the same conditions gave tosyl-L-pyroglutamic acid anilide (Vb).

The reaction of II with more strongly basic amino compounds was accompanied by partial or complete ring closure to the pyrrolidone compound V, the extent of the cyclization depending on the

(1) This work was supported by a grant from the National Heart Institute, Public Health Service, Grant H-1675.

(2) J. M. Swan and V. du Vigneaud, THIS JOURNAL, **76**, 3110 (1954).

(3) Tosyl is used to designate the *p*-toluenesulfonyl group and in structural formulas is abbreviated to Tos. Tosylpyroglutamic acid refers to 1-tosyl-5-oxo-2-pyrrolidinecarboxylic acid.

(4) J. M. Swan, *Proceedings of the International Wool Textile Research Conference*, Australia, 1955, page C-175.

(5) J. Rudinger, *Coll. Czech. Chem. Commun.*, **19**, 375 (1954).

(6) D. W. Clayton, G. W. Kenner and R. C. Sheppard, *J. Chem. Soc.*, 371 (1956).

(7) C. R. Harington and R. C. G. Moggridge, *ibid.*, 706 (1940).

(8) J. Rudinger, *Coll. Czech. Chem. Commun.*, **19**, 365 (1954).

(9) Z. Pravda and J. Rudinger, *ibid.*, **20**, 1 (1955).

nature of the solvent. Both II and III reacted with ammonia in chloroform to give tosyl-L-pyroglutamamide (Vc), which has already been described.[2,7] A great excess of concentrated aqueous ammonia gave tosyl-L-glutamide (VIc) with either II[2] or III. The reaction of II with cyclohexylamine was selected for a more detailed study, as the two products, tosyl-L-glutamic acid dicyclohexylamide (VId) and tosyl-L-pyroglutamic acid cyclohexylamide (Vd), were easily separable through their different solubilities in acetonitrile. It was thus possible to isolate both products from the reaction, whereas with ammonia and aniline, only the major component was detected. When the dichloride II was added to an excess of cyclohexylamine in chloroform, the main product was Vd, only 7% of VId being isolated; small quantities of this substance could have arisen from opening of the pyrrolidone ring, as the pyroglutamyl chloride III gave a little of the dicyclohexylamide VId under identical conditions. However, if the reaction was performed in benzene, II gave 18% of the dicyclohexylamide, while III gave only 5%. In aqueous tetrahydrofuran, both acid chlorides gave exclusively the cyclic product Vd, since milder conditions were used to prevent ring opening. For preparative purposes, the dicyclohexylamide VId was made by heating Vd with excess cyclohexylamine. It is plausible that the cyclization of II involves, as a first step, the loss of a proton from the tosylated nitrogen atom and that this takes place most readily in a polar medium and is facilitated by the presence of a strongly basic amine. However, more vigorous conditions, for example, treatment with excess aqueous ammonia or hot cyclohexylamine, cause re-opening of the pyrrolidone ring. Tosyl-L-isoglutamine azide[4] behaves similarly in that it reacts with methanol to give the γ-methyl ester but cyclizes to the pyroglutamamide Vc when treated with amino acids or their esters. In a parallel case, it has been reported that carbobenzoxy-L-glutamic acid α-benzyl ester γ-chloride on treatment with ammonia may give either the γ-amide[10] or benzyl carbobenzoxy-L-pyroglutamate.[11]

Hydrolysis of the dichloride II with aqueous magnesium oxide[2] gave tosyl-L-pyroglutamic acid (IV), which was not isolated, but treated directly with aqueous ammonia to form tosyl-L-glutamine (VII). Some of the diamide VIc also was produced, presumably by the action of ammonia on unchanged starting material or on the symmetrical anhydride[2] of IV, which may be formed during hydrolysis of II. For the preparation of VII from either II or III, it is preferable to carry out the initial hydrolysis in aqueous acetone, buffered with potassium carbonate and bicarbonate. The ready cyclization of II accounts for its successful use in the preparation of tosyl-L-pyroglutamyl-L-asparagine (Va).[2] Although II can thus be used to prepare glutaminyl peptides, better yields of VIa were obtained by the use of the pyroglutamyl chloride III, in a procedure similar to that of Swan and du Vigneaud.[2] The product was indistinguishable from the material obtained by Swan and du Vigneaud.[2] Rudinger, *et al.*,[12] have recently described the preparation of this protected dipeptide from III.

(10) M. Bergmann, L. Zervas and L. Salzmann, *Ber.*, **66**, 1288 (1933).

(11) M. Berenbom and J. White, THIS JOURNAL, **71**, 2246 (1949).

Experimental[13]

Tosyl-L-glutamyl dichloride (II) was prepared by the method described in the literature[2] for tosyl-L-pyroglutamyl chloride, through the action of phosphorus pentachloride on an ether solution of tosyl-L-glutamic acid,[14] prepared as described by Harington and Moggridge.[7] The product was crystallized by the addition of hexane, dried for 30 minutes *in vacuo* over solid sodium hydroxide and used immediately. It was obtained as long plates, m.p. 74–75° dec., lowered by prolonged drying; lit.[2] m.p. 71–74° dec.

Anal. Calcd. for $C_{12}H_{13}O_4NSCl_2$: C, 42.6; H, 3.87; N, 4.14; Cl, 21.0. Found: C, 42.6; H, 4.01; N, 4.13; Cl (by hydrolysis), 20.9. Prolonged drying lowered the chlorine content.

Diethyl Tosyl-L-glutamate.—The dichloride (1.69 g.) was added portionwise to ice-cold absolute ethanol (25 ml.), and the solution was stored at 0° for 48 hr. The ethanol was evaporated under reduced pressure without heating, and the oily residue was taken up in ether (30 ml.). The addition of hexane (30 ml.) caused the deposition of the diester as matted needles; yield 1.44 g. (81%), m.p. 76–76.5°, not changed by recrystallization; lit.[15] m.p. 76–78°.

Anal. Calcd. for $C_{16}H_{23}O_6NS$: N, 3.92. Found, in material dried at 50°: N, 4.01.

Tosyl-L-glutamic Acid Dianilide (VIb).—Tosyl-L-glutamyl dichloride (1.00 g.) was added portionwise to a swirled ice-cooled solution of aniline (3 ml.) in chloroform (20 ml.). A white solid was immediately precipitated and, when the mixture had stood for 40 minutes at room temperature, was collected and washed first with chloroform and then ice-cold 95% ethanol. The yield of crude product was 1.27 g. (95%), m.p. 238.5–240.5°. Recrystallization from 90% acetic acid gave the dianilide (0.96 g.) as long prisms, m.p. 243.5–244.5°, possibly a dimorphic form of the compound reported previously,[8] m.p. 232°.

Anal. Calcd. for $C_{24}H_{25}O_4N_3S$: C, 63.8; H, 5.58; N, 9.31; S, 7.10. Found, in material dried at 90°: C, 63.9; H, 5.69; N, 9.24; S, 7.12.

The use of 50% aqueous tetrahydrofuran as the solvent for this reaction gave an 80% yield of recrystallized product, identified as the dianilide by its m.p. and mixed m.p. with authentic material.

Tosyl-L-pyroglutamyl Chloride (III). A. Decomposition of the Dichloride by Fusion.—Tosyl-L-glutamyl dichloride (8.0 g.) was fused at 90°. There was vigorous evolution of a fuming gas, and the melt rapidly resolidified. Removal of the hydrogen chloride was completed by the application of a water-pump vacuum for a few minutes, and the solid was cooled and powdered. The yield of material having m.p. 106–107° was almost quantitative. Recrystallization from ether–hexane gave the acid chloride as long prisms, m.p. 106.5–107°; lit.[8,9] m.p. 83–85° and 105–106°.

Anal. Calcd. for $C_{12}H_{12}O_4NSCl$: Cl, 11.8. Found, in material dried at 50°: Cl (by hydrolysis), 11.7.

Treatment of the compound with excess ethanol during 18 hr. at room temperature gave ethyl tosyl-L-pyroglutamate as long prisms, m.p. 114–115° from ethyl acetate–hexane; lit.[8] m.p. 115–116°. The ester was recovered unchanged after treatment with ethanol containing 5% of hydrogen chloride for 40 hr. at room temperature.

(12) J. Rudinger, J. Honzl and M. Zaoral, *Coll. Czech. Chem. Commun.*, **21**, 202 (1956).

(13) Capillary melting points were determined for all compounds and are corrected. Samples recorded as melting with decomposition were placed in the bath at 10° below the m.p. and heated at 3–4° per minute.

(14) Tosyl-L-glutamic acid was prepared by the method of Harington and Moggridge (see ref. 7) from glutamic acid having $[\alpha]^{22.5}D$ +31.5 ± 0.5° (*c* 1, 6 *N* HCl). Before isolation of the product from ethyl acetate, it was washed with water to remove strong acids which could cause transesterification (see ref. 8). The material had m.p. 128.5–129°, sometimes resolidifying and melting again at 144–145°, $[\alpha]^{24}D$ +20.1 ± 1.0° (*c* 1, dry ethyl acetate). The rotation was increased by the presence of moisture in the solvent.

(15) F. Knoop and H. Oesterlin, *Z. physiol. Chem.*, **170**, 186 (1927)

B. From Tosyl-L-pyroglutamic Acid.—The preparation was carried out as described in the literature,[7] by treating tosyl-L-pyroglutamic acid in ether with phosphorus pentachloride and crystallizing the product by the addition of hexane. The yield of material having m.p. 106.5–107° was 58%.

C. Decomposition of the Dichloride in Benzene (Preparative Method).—Tosyl-L-glutamic acid (25 g.) was suspended in dry ether (250 ml.) and cooled in ice, and phosphorus pentachloride (50 g.) was added in one portion. The mixture was swirled with cooling until most of the acid had dissolved and then allowed to come to room temperature and filtered to remove excess reagent. The total reaction time was 35 minutes. The filtrate was evaporated under reduced pressure from a bath at 40° to a crystalline residue. Dry benzene (250 ml.) was added and a portion (50–100 ml.) was distilled under reduced pressure; the bath was then replaced by a heating mantle, and more of the benzene was distilled at atmospheric pressure during 5 minutes. The residue was cooled rapidly by evaporating the remaining benzene under reduced pressure to leave a viscous, pale yellow oil. The addition of ether (100 ml.) caused rapid deposition of the crystalline product. Crystallization was completed by the addition of hexane (100 ml.) and storage at 0° for 30 minutes. The yield was 22.3 g. (89%) of m.p. 106.5–107°. Occasionally, the compound crystallized as slender prisms, m.p. 85.5–86.5°, raised to the usual value by admixture of a little of the high melting form. This metastable form was unsuitable for use in the preparation of tosyl-L-glutaminyl-L-asparagine because of its tendency to go into matted aggregates of crystals during the coupling process.

Tosyl-L-pyroglutamic Acid Anilide (Vb).—Tosyl-L-pyroglutamyl chloride in chloroform was treated with aniline, and the product was isolated as described by Rudinger,[8] to give a 97% yield of material having m.p. 253.5–254.5°, after previous softening. Recrystallization from 90% acetic acid gave the anilide as long plates, m.p. unchanged; the literature[8] gives m.p. 230–232°, presumably a different crystalline form.

Anal. Calcd. for $C_{18}H_{18}O_4N_2S$: C, 60.3; H, 5.06; N, 7.82; S, 8.95. Found, in material dried at 90°: C, 60.5; H, 5.19; N, 7.85; S, 8.86.

The use of ice-cold 50% aqueous tetrahydrofuran as the reaction medium gave a 54% yield of recrystallized product, identified with the above by m.p. and mixed m.p.

Reactions of Tosyl-L-glutamyl Dichloride and Tosyl-L-pyroglutamyl Chloride with Ammonia. A. In Chloroform.—To a stirred ice-cooled solution of dry ammonia (0.5 g.) in chloroform (20 ml.) was added portionwise tosyl-L-glutamyl dichloride (1.00 g.). The mixture, from which a white precipitate separated immediately, was stirred for 30 minutes at room temperature and evaporated to dryness under reduced pressure. The residue was washed with water to leave a yield of 0.70 g. of tosyl-L-pyroglutamamide (Vc) (84%), having m.p. 193–194°. Recrystallization from ethanol gave large elongated prisms, m.p. 195–195.5°. The literature[7] reports a m.p. of 196°.

Anal. Calcd. for $C_{12}H_{14}O_4N_2S$: N, 9.93. Found, in material dried at 90°: N, 9.87.

The use of tosyl-L-pyroglutamyl chloride in the above preparation gave a 65% yield of recrystallized material, identified as tosyl-L-pyroglutamamide by m.p. and mixed m.p. with the product described in the preceding paragraph.

B. In Concentrated Aqueous Ammonia.—Tosyl-L-pyroglutamyl chloride (0.403 g.) was added to ice-cold concentrated aqueous ammonia (25 ml.). The solid went into solution when the mixture was allowed to come to room temperature. After 1 hr., most of the ammonia was removed by evaporation under reduced pressure, whereupon the product precipitated from solution. It was stored for 1 hr. at 0°, collected and washed with ice-cold water. The yield of tosyl-L-glutamide (VIc) was 0.260 g. (65%), melting to a blue liquid at 220–221° dec., after softening from 215°. The compound was obtained as long prisms, with the same m.p., by recrystallization from ethanol: $[\alpha]^{22}D$ +16.2° ± 0.5° (*c* 1.8, acetic acid). The addition of a little water to the solution had no marked effect on the rotation. The value previously reported,[2] $[\alpha]^{21}D$ +8.3° (*c* 1.7, acetic acid), for material melting between 210° and 220° is apparently incorrect.

Anal. Calcd. for $C_{12}H_{17}O_4N_3S$: N, 14.0. Found, in material dried at 70°: N, 13.8.

A sample prepared similarly from tosyl-L-glutamyl dichloride was indistinguishable from the above product by m.p., mixed m.p. or optical rotation.

Reactions of Tosyl-L-glutamyl Dichloride and Tosyl-L-pyroglutamyl Chloride with Cyclohexylamine. A. In Chloroform.—Tosyl-L-glutamyl dichloride (0.50 g.) was added portionwise to an ice-cooled stirred solution of cyclohexylamine (1.5 ml.) in chloroform (10 ml.), and stirring was continued for 30 minutes at room temperature. The clear solution was cooled in ice, extracted with dilute hydrochloric acid and evaporated under reduced pressure to a gum, which was dissolved in acetonitrile (10 ml.). The small quantity of solid which precipitated was collected after the solution had stood for 1 hr. at room temperature and washed with a little acetonitrile. This material had m.p. 253–255° (not depressed by admixture of authentic tosyl-L-glutamic acid dicyclohexylamide, prepared as described subsequently). The yield was 45 mg. (6.6%). The acetonitrile filtrate and washings were diluted with water (40 ml.), the resulting oil crystallized by scratching and the solid collected after storage at 0° for 4 hr. The yield of tosyl-L-pyroglutamic acid cyclohexylamide (Vd) was 0.44 g. (82%), melting at 184.5–185.5° after softening at 162°. Recrystallization from ethyl acetate–hexane gave the material as plates, m.p. 162–163°. The compound was dimorphous, some samples resolidifying and melting again at 184.5–185.5°.

Anal. Calcd. for $C_{18}H_{24}O_4N_2S$: C, 59.3; H, 6.64; N, 7.69; S, 8.80. Found, in material dried at 90°: C, 59.6; H, 6.74; N, 7.53; S, 8.85.

Treatment of this compound with cyclohexylamine (20 parts) for 10 minutes on the steam-bath gave a 93% yield of tosyl-L-glutamic acid dicyclohexylamide (VId) as small needles, m.p. 256–256.5°, from 75% acetic acid.

Anal. Calcd. for $C_{24}H_{37}O_4N_3S$: C, 62.2; H, 8.05; N, 9.06; S, 6.92. Found, in material dried at 90°: C, 62.1; H, 8.15; N, 9.07; S, 6.85.

Tosyl-L-pyroglutamyl chloride (0.50 g.) was treated with cyclohexylamine in chloroform under identical conditions, and the products were separated in the same way. The yields were 0.53 g. (88%) of tosyl-L-pyroglutamic acid cyclohexylamide, melting at 184.5–185.5° after softening at 162°, and 33 mg. (4.3%) of tosyl-L-glutamic acid dicyclohexylamide, m.p. 253–255°. The identities of both compounds were confirmed by mixed m.p. with the authentic substances.

B. In Benzene.—Tosyl-L-glutamyl dichloride (0.50 g.) was added portionwise to a stirred ice-cooled solution of cyclohexylamine (1.5 ml.) in benzene (10 ml.). The mixture, which rapidly became semi-solid, was allowed to stand for 30 minutes at room temperature, diluted with benzene to give a mobile suspension, cooled in ice and extracted with dilute hydrochloric acid. Ethyl acetate was added to the organic phase, but the solid did not dissolve and was removed by filtration. The filtrate was evaporated under reduced pressure to a gum, which was fractionated as before by the use of acetonitrile. The yield of tosyl-L-pyroglutamic acid cyclohexylamide was 0.36 g. (67%), melting at 184–185° after softening at 162°. The m.p. was not depressed by admixture of authentic material. The two insoluble fractions, from benzene–ethyl acetate and from acetonitrile, were combined and recrystallized from 70% acetic acid to give 0.124 g. (18%) of a product, m.p. 256.5–257°, undepressed by mixture with authentic tosyl-L-glutamic acid dicyclohexylamide.

Tosyl-L-pyroglutamyl chloride (0.50 g.) was treated with cyclohexylamine in benzene and the products isolated by the procedure already described. A small quantity of solid was deposited from the reaction mixture but dissolved on the addition of ethyl acetate after removal of the excess amine by extraction with hydrochloric acid. The yield of tosyl-L-pyroglutamic acid cyclohexylamide was 0.50 g. (83%), m.p. 184–185° (not depressed by mixture with the authentic substance). The fraction which was insoluble in acetonitrile amounted to 39 mg. (5.1%), m.p. 253–255° (undepressed by mixture with authentic tosyl-L-glutamic acid dicyclohexylamide).

C. In Aqueous Tetrahydrofuran.—Tosyl-L-glutamyl dichloride (0.50 g.) was added portionwise to a stirred ice-cooled solution of cyclohexylamine (1 ml.) in tetrahydro-

furan (10 ml.) and water (10 ml.). The clear solution was stirred at 0° for a total reaction time of 10 minutes, brought to *p*H 1 with hydrochloric acid and partially evaporated under reduced pressure to remove most of the tetrahydrofuran. An oil separated and rapidly crystallized. The crude product was fractionated as described previously, but only a trace of solid separated from the acetonitrile solution, even on seeding with the dicyclohexylamide. The yield of tosyl-L-pyroglutamic acid cyclohexylamide was 0.47 g. (87%), melting at 184.5–185.5° after softening at 162°. The identity of the substance was confirmed by a mixed m.p. with the authentic compound.

The use of tosyl-L-pyroglutamyl chloride (0.50 g.) in this reaction gave 0.54 g. (89%) of tosyl-L-pyroglutamic acid cyclohexylamide, m.p. 162–163°. A mixture with the authentic material melted at 184.5–185.5°, after softening at 162°. There was only a trace of product insoluble in acetonitrile.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Preparation and Cleavage of Some Codeine Glycols[1]

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Osmium tetroxide oxidation of codeine and a number of codeine derivatives gave the corresponding 7,8-dihydroxydihydrocodeines, except in the case of codeinone. Yields in this hydroxylation were quite sensitive to the nature of the substituent at carbon 6, and with codeinone dimethyl ketal oxidation of the tertiary amine to a formyl derivative also occurred. Cleavage of the glycols with periodate took place readily, and with those compounds which had no hydrogen at position 6, the cleavage product existed in part as an internal enol hemiacetal. When a hydrogen was present at position 6, introduction of a carbonyl at 7 by periodate oxidation presumably led to an α,β-unsaturated carbonyl compound and oxide ring opening by β-elimination.

As part of a general program directed to the study of morphine and codeine metabolism, we undertook the preparation of a number of codeine glycols both for their interest as possible metabolites and also for their potential use in the synthesis of specifically labeled morphine derivatives. For the latter purpose a method was sought by which ring C could be opened and then reconstituted after replacement of one of the carbons by radioactive carbon.

Ozonolysis is of no avail, since it has been found to attack the aromatic ring A at least as rapidly as the alicyclic double bond in ring C.[2a] Initiation of ring-opening by epoxidation with perbenzoic or monoperphthalic acids also was rejected because these reagents have been shown to form amine oxides first and then to attack the aromatic nucleus as well as the ring C double bond.[2b] This aromatic oxidation apparently is avoidable with performic acid,[3] but the strong acid conditions required were considered unsuitable for some of the contemplated compounds.

An attractive possibility that appeared to have the necessary specificity was oxidation with osmium tetroxide. A series of compounds was chosen all having the Δ^7-double bond and differing only in the substituents at position 6. These were Δ^7-desoxycodeine, codeine, 6-methylcodeine, codeinone dimethyl ketal and codeinone. The hydroxylations were carried out in ether solution at room temperature in the presence of pyridine, and the precipitated osmate esters were cleaved to the corresponding glycols. While the three procedures in the literature for cleaving osmate esters[4–6] gave substantially the same yield, ethanolic sodium sulfite[4] was the method of choice since it gave the most easily purified product.

The results are shown in Table I, and it is interesting to note the strong effect of the 6-substituent on the yield. This is in the expected direction with increasing electronegativity, and codeinone under these conditions, as might be expected, gave no isolable glycol. In those cases, namely, codeinone dimethyl ketal and codeinone, where the yield was poor, only part of the unconverted starting material was recovered, indicating competitive reaction at sites other than the Δ^7-double bond. In the case of codeinone dimethyl ketal, the most thoroughly investigated, oxidation by osmium tetroxide definitely was established to occur alpha to the nitrogen.

From a typical oxidation of codeinone dimethyl ketal with osmium tetroxide, 75% of the starting material was accounted for as glycol IV (11% conversion) and as recovered ketal (64%). The remaining 25% consisted of a number of products only one of which was identified. This was obtained pure by careful chromatography on alumina and was found to contain an additional oxygen (as compared to codeinone dimethyl ketal). That it was not the amine oxide was shown by comparison with an authentic sample of codeinone dimethyl ketal-N-oxide, prepared by oxidation with monoperphthalic acid. Strong absorption in the infrared at 5.98 μ indicated the osmium tetroxide product most likely was an amide, and this was

(1) Supported in part by a grant from the National Institutes of Health, Bethesda, Md.

(2) (a) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 41; C. H. Lovell, Thesis, Univ. of California, Berkeley, 1955. (b) H. Rapoport and E. C. Galloway, THIS JOURNAL, **77**, 5753 (1955).

(3) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

(4) A. Butenandt J. Schmidt-Thomé and H. Paul, *Ber.*, **72**, 1112 (1939).

(5) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(6) D. H R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).