Synthetic Studies Related to Cephalosporin C. Sulfur-Containing α-Tetronic Acids and α-Aminobutenolides[1]

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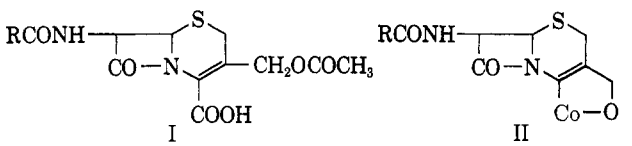
A number of sulfur-containing α-tetronic acids and α-aminobutenolides related to cephalosporin C have been synthesized from the Mannich condensation product X. The α-amino-β-thiomethylbutenolide IV, which in the chemistry of cephalosporin plays a role similar to that of D-penicillamine in penicillin chemistry, has been prepared in the form of its crystalline S-trityl derivative XXIV. Detritylation has been achieved by means of mercuric chloride to furnish the very reactive thiolamine IV, which undergoes self-condensation to XXV.

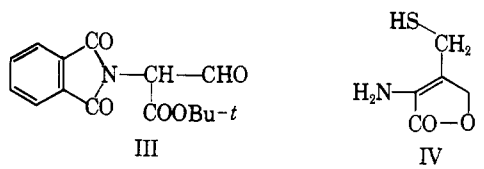
The antibiotic cephalosporin C (Ia), according to the outstanding investigations of Abraham and Newton,[3] possesses as its most characteristic feature a fused 3,6-dihydro-(2H)-1,3-thiazine-β-lactam ring system, which takes the place of the well-known thiazolidine-β-lactam system of the penicillins. It is quite evident that approaches to the total synthesis of this antibiotic or of the related, medicinally important acylaminocephalosporanic acids,[4] *e.g.*, Ib, must be concerned primarily with the construction of this unusual and little explored ring system.



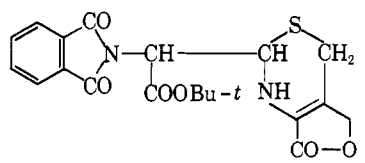
I II

a, R = D-HOOCCH(NH_2)(CH_2)$_3$–
b, R = α-thienylmethyl–

A rational approach, which would make maximum use of the wealth of experience accumulated by Sheehan and his collaborators[5] in the penicillin field, would aim at the synthesis of the 3,6-dihydro-(2H)-1,3-thiazine lactone V to be followed by a sequence of reactions leading to II, similar to those applied in the synthesis of the penicillins.[6] The advantage of an intermediate such as V lies in the fact that in it the allylic acetoxyl and carboxyl groups of cephalosporin C are joined in mutual protection to form a Δ^2-butenolide, the presence of which in fusion with the dihydrothiazine ring would, moreover, serve to stabilize the double bond in the 4,5-position of the latter. The fact that lactones obtained from cephalosporin C and other acylcephalosporanic acids (II) exhibited biological activity *per se* added to the attractiveness of the "lactone approach." Reopening of the lactone ring at an advanced stage of the synthesis was regarded a difficult but manageable step.

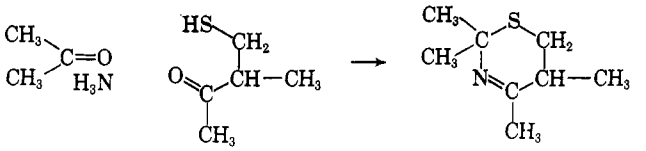


III IV



V

The chemistry of the 3,6-dihydro-(2H)-1,3-thiazine nucleus had received little attention until its presence was demonstrated in cephalosporin C. Stimulated by that discovery, two recent papers[7,8] have described the preparation of a simple representative, 2,5-dimethyl-3,6-dihydro-(2H)-1,3-thiazine-4-carboxylic acid (and its benzyl ester), and an interesting transformation of penicillin sulfoxides to dihydrothiazine-β-lactams has been reported by the Lilly group.[9] Our projected synthesis of the dihydrothiazine derivative V required the preparation of a moiety whose function in the construction of the cephalosporin ring system would be similar to that of penicillamine (β,β-dimethyl-D-cysteine) in the elaboration of the thiazolidine ring of the penicillins. Such a "cephalosporamine" is the butenolide derivative IV, which could then be condensed with carbonyl compounds to form the 3,6-dihydro-(2H)-1,3-thiazine ring, and particularly with the phthalimidomalonaldehydate ester III[10] to furnish the intermediate V. Consideration was also given to a somewhat simplified ring closure scheme, which was to utilize a procedure described by Asinger, Thiel, and co-workers[11,12] for the preparation of 5,6-dihydro-(2H)-1,3-thiazines. This procedure involves the condensation of a β-mercapto ketone with a ketone or aldehyde in the presence of ammonia. It was felt that by the use of β-mercaptomethyl-α-tetronic acid (VI) reacting as its



(1) For a preliminary publication, see E. Galantay, A. Szabo and J. Fried, *Tetrahedron Letters*, 415 (1963).

(2) The Ben May Laboratory for Cancer Research, The University of Chicago, Chicago 37, Ill.

(3) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961).

(4) R. R. Chauvette, E. H. Flynn, B. G. Jackson, E. R. Lavagnino, R. B. Morin, R. A. Mueller, R. P. Pioch, R. W. Roeske, C. W. Ryan, J. L. Spencer, and E. Van Heynigen, *J. Am. Chem. Soc.*, **84**, 3401 (1962).

(5) J. C. Sheehan and K. R. Henery-Logan, *ibid.*, **84**, 2983 (1962), and earlier references cited therein.

(6) In projecting such a course it was realized that the analogy between the cephalosporin and penicillin systems was not to be carried too far. For instance, the lower nucleophilicity of the enamine nitrogen in a 3,6-dihydro-(2H)-1,3-thiazine would be expected to offer greater resistance towards closure of the β-lactam ring in the cephalosporins.

(7) D. M. Green, A. G. Long, P. J. May, and A. F. Turner, *J. Chem. Soc.*, 766 (1964).

(8) G. C. Barrett, S. H. Eggers, T. R. Emerson, and G. Lowe, *ibid.*, 788 (1964).

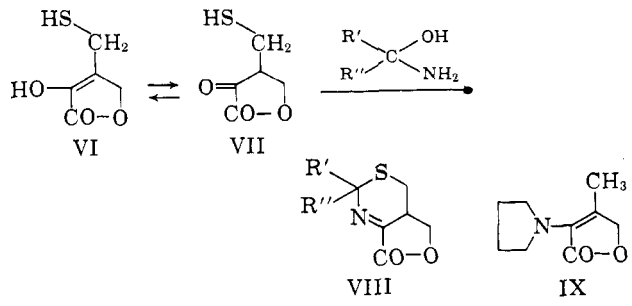
(9) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).

(10) J. C. Sheehan and D. A. Johnson, *ibid.*, **76**, 158 (1954).

(11) F. Asinger, M. Thiel, and W. Höringklee, *Ann.*, **610**, 1 (1957).

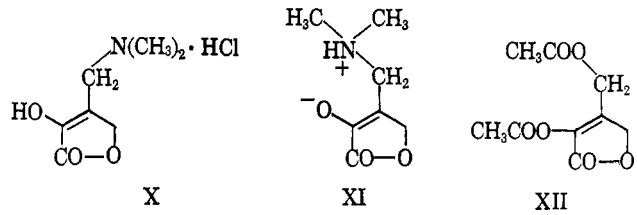
(12) M. Thiel, F. Asinger, and G. Trümpler, *ibid.*, **619**, 137 (1958); M. Thiel, F. Asinger, K. Häussler, and T. Körner, *ibid.*, **622**, 107 (1959).

α-keto lactone tautomer VII in an Asinger-type ring closure, prior introduction of the primary enamine grouping to form the "cephalosporamine" IV could be avoided. Shift of the double bond from the 3-position in the primary condensation product VIII to the desired 4-position (as in V) would then be expected to occur readily, if not spontaneously, with the formation of the more stable Δ^2-butenolide system. As is well known, α-tetronic acids are highly enolized and acidic substances[13] which fail to react with carbonyl reagents, *e.g.*, hydroxylamine or phenylhydrazine.[14] In a model experiment, however, it was found that β-methyl-α-tetronic acid[14] reacts smoothly with pyrrolidine to form the enamine IX under conditions[15] which convert ring ketones into enamines. This finding gave encouragement to the view that the projected β-mercaptomethyl-α-tetronic acid VI might undergo Asinger-type ring closure.

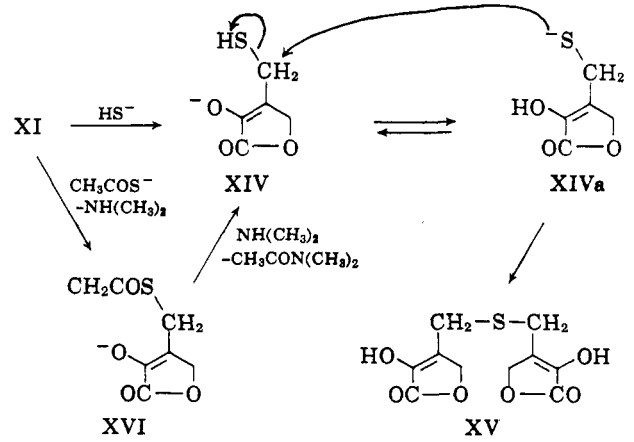


As a starting material we chose the readily available β-dimethylaminomethyl-α-tetronic acid hydrochloride (X), obtained by Mannich and Bauroth in a single step from pyruvic acid, dimethylamine hydrochloride, and formaldehyde,[16] and we introduced the sulfur function by nucleophilic substitution on the methylene carbon bearing the nitrogenous group.[17,18]

The hydrochloride X was converted into the "free base," which on the basis of its ultraviolet absorption maximum at 267 mμ (enolate of β-methyl-α-tetronic acid, 267 mμ)[8,14] has the zwitterion structure XI. Although the hydrochloride X was reported to be unstable in neutral or even slightly acidic solutions,[16] conversion into the zwitterion XI was achieved quantitatively by brief stirring of the cold aqueous solution of the hydrochloride with silver carbonate, removal of excess silver ion by hydrogen sulfide treatment, filtration, and lyophilization. The zwitterion XI was characterized by reconversion to the original hydrochloride, and by preparation of a tetraphenylboronate of m.p. 117°. Acetylation with acetylchloride gave the O-acetate of X and treatment with acetic anhydride in the presence of potassium acetate gave α-acetoxy-β-acetoxymethylbutenolide (XII). Compound XI readily underwent substitution reactions with the highly nucleophilic thiolate anions, most appropriately in highly polar solvents such as dimethylformamide and tetramethylene sulfone (sulfolane). The use of hydroxylic solvents, on the other hand, led to concurrent degradation by reverse-Mannich or reverse-aldol reactions and had to be carefully avoided.



Reaction of the zwitterion XI with sulfhydryl anion led to the sulfide XV rather than to the desired mercaptan. This dimerization reaction could not be suppressed, even when a steady excess of hydrogen sulfide was present so as to reduce the concentration of the S-dianion and to shift the equilibrium $2SH^- \rightleftarrows S^{-2} + H_2S$ in favor of the sulfhydryl anion.[19] The reaction is therefore interpreted to involve rapid equilibration between the initially formed enolate salt XIV and the S-anion XIVa, followed by nucleophilic attack of the latter on the former. The sulfide XV proved to be identical with "compound I" a degradation product obtained by Abraham and Newton[3] from cephalosporin C and assigned that structure by these authors on the basis of analytical and titration data.



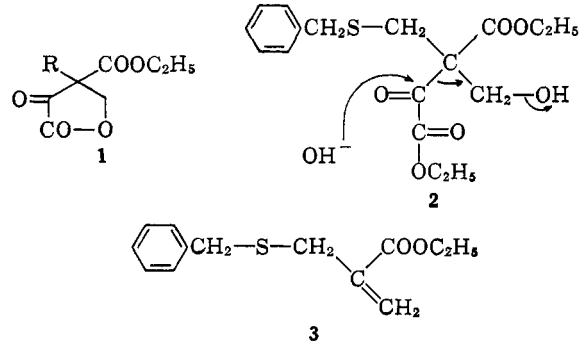
(13) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).

(14) H. Schinz and M. Hinder, *ibid.*, **30**, 1349 (1947).

(15) M. E. Herr and F. W. Weyl, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

(16) C. Mannich and M. Bauroth, *Ber.*, **27**, 1108 (1924).

(17) Prior to settling on this approach two other avenues were explored. One of these was patterned after the procedure of Schinz and Hinder,[14] which consists of treating an α-ethoxalyl ester with formaldehyde followed by acid-catalyzed decarboxylation of the intermediate α-keto-β-alkyl paraconate ester (**1**). Reaction of ethyl α-ethoxalyl-β-benzylmercaptopropionate with formaldehyde at pH 8 or with paraformaldehyde in pyridine gave instead of the expected ketoparaconic ester a good yield of ethyl α-benzylmercaptomethylacrylate (**3**) resulting from base-induced fragmentation of the intermediate hydroxymethyl derivative **2**.



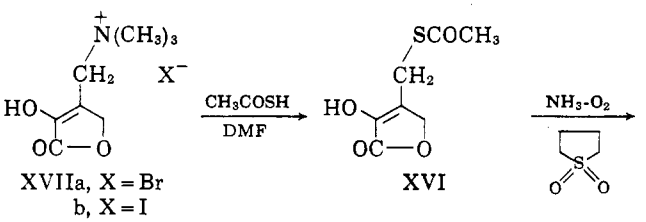
Another scheme to prepare derivatives of VI envisioned N-bromosuccinimide bromination of the methyl ether of β-methyl-α-tetronic acid to the bromomethyl compound. Instead, bromination of the ring took place as indicated by the n.m.r. spectrum of the resulting product. Similar results were obtained by Long, *et al.*,[7] with the acetate of β-methyl-α-tetronic acid.

(18) Approaches similar to the one described in this paper, which was first communicated in ref. 1, were reported by A. G. Long and A. F. Turner [*Tetrahedron Letters*, 421 (1963)] and by G. C. Barrett, V. V. Kane, and G. Lowe [*J. Chem. Soc.*, 783 (1964)].

(19) A Schöberl and A. Wagner, "Houben-Weyl, Methoden der Organischen Chemie," Vol. 9, VEB Georg Thieme Verlag, Stuttgart, 1955, p. 7.

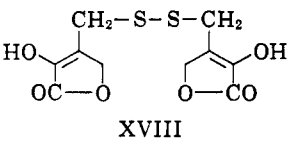
We then turned our attention to derivatives of the β-mercaptomethyl-α-tetronic acid VI, in which the sulfhydryl group is protected by a readily removable substituent. The S-acetyl derivative XVI appeared to be most attractive in this respect, since it presented the opportunity of generating the free mercaptan VI by ammonolysis, that is under the conditions of the Asinger dihydrothiazine condensation. When a solution of equivalent amounts of the zwitterion XI and potassium thioacetate in dimethylformamide was heated for 15 min. at 75° and the mixture was evaporated under high vacuum, the dipotassium enolate of the sulfide XV was again obtained in almost quantitative yield. The latter could be transformed into the pure sulfide in 84% yield by acidification and recrystallization. In the dimethylformamide distillate, 1 mole of dimethylacetamide was detected by vapor phase chromatography. Similar results were obtained with tetramethylene sulfone as the solvent. Obviously, the primary product, the enolate XVI had been aminolyzed *in situ* by the liberated dimethylamine to the tautomeric pair of monoanions XIV and XIVa to be followed by self-condensation to the monoenolate of XV. The latter, on evaporation (equilibration with SH^- and volatilization of H_2S), led to the dienolate of the sulfide XV.

To prevent this aminolysis and thus to obtain the S-acetyl compound the zwitterion XI was first quantitatively converted to the quaternary salt XVII by means of a large excess of methyl bromide or iodide at 5°. Reaction of the resulting quaternary salt[20] with an excess of thiolacetic acid in dimethylformamide afforded, after distillation, a 24% yield of the pure acetyl derivative XVI as a solid of m.p. 74°. The S-acetyl derivative XVI could be converted into the disulfide XVIII



XVIIa, X = Br
b, X = I

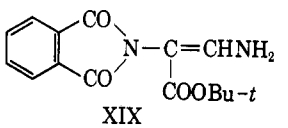
XVI



XVIII

by treating a tetramethylene sulfone solution of the former with dry ammonia in the presence of air. Under these conditions oxidation of the resulting S-monoanion XIVa was faster[21] than equilibration and condensation with XIV to form the sulfide XV, and the diammonium salt of the disulfide XVIII crystallized directly from the mixture. The free dienol disulfide XVIII m.p. 131–132°, was obtained by careful acidification of its aqueous solution. The over-all yield of XVIII from the zwitterion XI without isolation of intermediates was 27.6%.

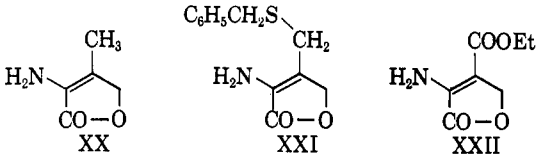
With the β-acetylthiomethyl-α-tetronic acid XVI in hand, attempts were made to effect an Asinger condensation to form the dihydrothiazine ring. When a solution of XVI was treated in acetone with dry ammonia, sublimation of ammonium hydrosulfide occurred immediately and a precipitate, found to be the diammonium salt of the sulfide XV, was formed. No condensation product with acetone could be detected by n.m.r. spectroscopy. Evidently, ammonolysis to the desired thiol VI occurred instantaneously but this was followed by rapid self-condensation of the monoanions XIV and XIVa. Equally disappointing was the ammonolysis reaction of XVI in the presence of *t*-butyl phthalimidomalonaldehydate III[10] in dimethylformamide, from which the sulfide XV, the disulfide XVIII, and *t*-butyl α-phthalimido-β-aminoacrylate XIX, but



XIX

no dihydrothiazine condensation product could be isolated. Similar results were obtained with the free mercapto lactone VI, obtained in low and erratic yields from the reaction of the quaternary salt XVII with hydrogen sulfide in dimethylformamide or the reaction of the zwitterion XI with sodium hydrosulfide.

At this point it was decided to elaborate the full "cephalosporamine" structure IV, to be used in our original ring closure scheme, III → V. The chemistry of α-aminobutenolides had not received attention until Abraham and Newton[3] isolated α-amino-β-methylbutenolide (XX) as a degradation product of cephalosporin

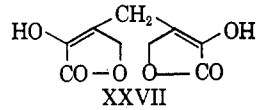


XX XXI XXII

C. Green, *et al.*,[7] subsequently synthesized this compound as well as the related benzylthio derivative XXI by fusion of the requisite β-substituted α-tetronic acids with ammonium acetate, a reaction reminiscent of the Bucherer transformation of naphthols into naphthylamines and having an analogy in the conversion of β-carbethoxy-α-tetronic acid into the α-aminobutenolide XXII.[22]

It was evident from the known lability of the allylic carbon–sulfur bond in the mercaptomethyltetronic acid VI and its derivatives that the synthesis of the mercaptoaminobutenolide IV, demanded the choice of a protecting group for the thiol function, which would not only withstand the drastic conditions of the ammonium

(20) Both the bromide and iodide salts XVIIa and b, when exposed to the atmosphere, deteriorated rapidly owing to their hygroscopicity and rapid reaction with water, to form a compound, $C_9H_8O_6$, m.p. 242°, to which the structure of a β,β′-methylenebis-α-tetronic acid (XXVII) was assigned



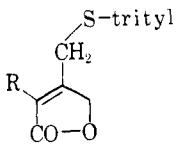
XXVII

on the basis of the n.m.r. spectrum of its dimethyl ether (diazomethane). This dilactone was first obtained by O. Kaltwasser [*Ber.*, **29**, 2273 (1896)] from the acid-catalyzed condensation of pyruvic acid and formaldehyde and correctly identified by Y. Asahina and S. Terada [*J. Pharm. Soc. Japan*, 57 (1923)]. *Cf.* also S. Olsen and G. Havre, *Acta Chem. Scand.*, **8**, 47 (1954). Comparison of this dilactone with the "$C_{15}H_{14}O_{10}$ acid" of Mannich and Bauroth[16] obtained as a side product in the Mannich condensation with pyruvic acid showed the two to be identical.

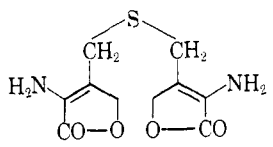
(21) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, **28**, 1311 (1963).

(22) M. Suquet, *Ann. chim.* (Paris), **8**, 545 (1953).

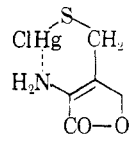
acetate fusion but at the same time require extremely mild and selective conditions for its removal. The above requirements appeared to be met by the triphenylmethyl group, which offered the additional advantage of being introduced with relative ease.[23] Reaction of the zwitterion XI with potassium triphenylmethylmercaptide or of the quaternary salt XVII with triphenylmercaptan in dimethylformamide yielded about 30% of the triphenylmethylthio-α-tetronic acid XXIII, which on ammonium acetate fusion according to Green, *et al.*,[7] afforded in 30% yield the desired α-aminobutenolide XXIV, separation from about 30% of unchanged starting material being achieved by chromatography on silica gel. Application of this latter reaction to the sulfide XV gave the diaminodibutenolide XXV. Attempts to remove the trityl group of XXIV with trifluoroacetic acid or with silver nitrate in pyridine[23] resulted in rupture of both the triphenylmethyl and allylic carbon–sulfur bonds, as evidenced by the formation of hydrogen sulfide and silver sulfide, respectively. The desired detritylation could, however, be achieved by means of mercuric chloride in 1,2-dimethoxyethane solution, which caused immediate and quantitative precipitation of the hydrochloride of the mercuric mercaptide XXVI. Selectivity of this reaction, is noteworthy, the corresponding α-tetronic acid XXIII being detritylated only very slowly under these conditions. The amino group in XXIV must therefore play a significant role in the reaction, possibly through coordination with the mercury atom, which will thereby be placed in a position favorable for attack on the sulfur atom. Treatment of a suspension of the mercaptide XXVI in methanol with hydrogen sulfide gave after evaporation of the solvent the dihydrochloride of the sulfide XXV, formed from 2 moles of cephalosporamine (IV), and demonstrating again the reactivity of the allylic thiol grouping also under acidic conditions. Liberation of IV under proper control of the acidity and polarity of the medium in the presence of appropriate aldehydes or ketones is envisioned to prevent dimerization by trapping the reactive thiol grouping with the formation of the desired 3,6-dihydro-(2H)-1,3-thiazine ring system.



XXIII, R = OH
XXIV, R = NH_2



XXV



XXVI

The disulfide XVIII had antimicrobial activity against a variety of organisms. Thus, it inhibited the growth of *Staphylococcus aureus* (209 P) at a concentration of 0.4 γ/ml.; that of penicillin-resistant *S. aureus* isolates at 1.6–1.8 γ/ml. and that of *Trichophyton mentagrophytes* at 0.7 γ/ml. The dimethyl ether of XVIII was active against *S. aureus* at 19 γ/ml. and the S-trityl derivative XXIII at 2.4 γ/ml. The monosulfide XV, the zwitterion XI, and the methylene-bridged bistetronic acid (XXVII) were inactive at 100 γ/ml.

(23) The usefulness of the triphenylmethyl group as a sulfhydryl-protecting group in peptide synthesis was demonstrated by G. Amiard, R. Heymes, and L. Velluz [*Bull. soc. chim. France*, 698 (1956)] and L. Zervas and I. Photaki [*J. Am. Chem. Soc.*, **84**, 3887 (1962)].

Experimental[24]

β-Dimethylaminomethyl-α-tetronic Acid Zwitterion (XI).—To a solution of 8.45 g. of silver nitrate (50 mmoles) in 75 ml. of water was added dropwise a solution of 2.83 g. of sodium carbonate (27.5 mmoles) in 75 ml. of water. The silver carbonate thus prepared was separated by centrifugation, washed five times with 150 ml. portions of water, and suspended in 75 ml. of iced water. To the efficiently stirred suspension was added at once an ice-cold solution of 7.40 g. of β-dimethylaminomethyl-α-tetronic acid hydrochloride (X, 37.6 mmoles)[16] in 75 ml. of iced water. After 5 min. of mixing evolution of carbon dioxide ceased and a small sample gave a negative test for chloride ion. The silver salts were removed by centrifugation, and the clear solution was saturated with hydrogen sulfide for 5 min. at 0°. The mixture was Seitz filtered and the filtrate was lyophilized. After drying over phosphorus pentoxide, 5.68 g. of the zwitterion XI was obtained as a light, colorless solid: m.p. 115–118° dec.; yield 96%; $\lambda_{max}^{H_2O}$ 267 mμ (ε 9000); $\lambda\lambda_{max}^{KBr}$ 5.80, 6.15, 7.60, 8.95, 9.80, 10.60, and 12.75 μ.

Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.46; H, 7.11; N, 8.96.

Tetraphenylboronate.—Solutions of equivalent amounts of XI and sodium tetraphenylboronate in 1% acetic acid were mixed and the resulting precipitate was recrystallized twice from methanol–water, m.p. 116–117°.

Anal. Calcd. for $C_{31}H_{32}BNO_3$: C, 77.95; H, 6.71; N, 2.93. Found: C, 77.53; H, 6.50; N, 3.00.

Acetate–Hydrochloride.—To 7 ml. of ice-cold acetyl chloride was added portionwise with stirring 1.57 g. of the zwitterion XI followed by an additional 14 ml. of acetyl chloride. After 24 hr. at room temperature the reagent was evaporated *in vacuo* and the residue was triturated with acetone. After separation of 692 mg. of β-dimethylaminomethyl-α-tetronic acid hydrochloride (X) the acetone solution was evaporated to dryness and the residue was dissolved in methanol. On slow diffusion of ether into the methanol solution at 5°, 450 mg. of the acetate–hydrochloride crystallized. Recrystallization from methanol–ether gave pure material: m.p. 132–134°; λ_{max}^{EtOH} 210 mμ (ε 9150); $\lambda\lambda_{max}^{KBr}$ 2.95, 3.45, 3.80, 5.65 and 8.50 μ.

Anal. Calcd. for $C_9H_{13}NO_4 \cdot HCl$: C, 45.82; H, 5.95; Cl, 15.10; N, 5.95; acetyl, 18.26. Found: C, 45.61; H, 6.11; Cl, 14.68; N, 5.57; acetyl, 24.00.

α-Acetoxy-β-acetoxymethyl-α,β-butenolide (XII).—A mixture of 3.00 g. of β-dimethylaminomethyl-α-tetronic acid hydrochloride (X, 15.55 mmoles), 1.27 g. of freshly fused sodium acetate (15.55 mmoles), and 50 ml. of acetic anhydride was heated to 80° for 10 min. After standing overnight at room temperature, the mixture was filtered from 1.00 g. of sodium chloride and evaporated (30° at 0.1 mm.) to 3.50 g. of a light brown oil. Distillation (Hickman flask, 150° bath temperature, 0.001 mm.) was accompanied by decomposition and yielded 1.26 g. of a brown oil. Repeated redistillation on a small scale (130–140° at 0.001 mm.) yielded the pure compound as a colorless, viscous oil: λ_{max}^{EtOH} 212 mμ (ε 12000); $\lambda\lambda_{max}^{KBr}$ 5.62, 5.73, 5.90, 8.17, and 8.46 μ.

Anal. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71; acetyl, 40.3. Found: C, 50.34; H, 4.61; acetyl, 40.1.

β-Dimethylaminomethyl-α-tetronic Acid Methiodide (XVIIb).—To an ice-cold suspension of 1.00 g. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI, 6.38 mmoles) in 25 ml. of anhydrous acetone was added 10.0 ml. of methyl iodide. After 20 hr. at 5°, the mixture was evaporated *in vacuo* to give 1.93 g. (100%) of an extremely hygroscopic solid.

β-Dimethylaminomethyl-α-tetronic Acid Methobromide (XVIIa).—Into a cooled (3–5°) suspension of 5.00 g. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI) in 100 ml.

(24) Melting points were taken on a Thomas–Hoover apparatus and are corrected for stem exposure. Ultraviolet spectra were determined on a Cary 11, infrared spectra on a Perkin-Elmer 21, and nuclear magnetic resonance spectra on a Varian A60 spectrometer in deuteriochloroform solution, unless indicated otherwise, with tetramethylsilane as internal standard. For paper chromatography Whatman No. 1 paper was used in the descendent manner using the solvent system *n*-butyl alcohol–acetic acid–water, 4:1:4, unless stated otherwise. For thin layer chromotography Excorna paper powder with $CaSO_4$ binder was used with the same solvent system. For less polar substances thin layers of silica gel G were used with varying proportions of chloroform–methanol as a solvent. Spots were developed by spraying with 2% Tollens reagent. Usually, sulfur-containing compounds showed brown spots immediately, whereas sulfur-free substances became visible only after 15 min. at 105°.

of anhydrous acetone methyl bromide gas was introduced. Within 30 min. the weight of the mixture had increased by 8.12 g. Sodium iodide (1 mg.) was then added and the mixture was allowed to stand at 5° for 18 hr. Evaporation yielded 7.73 g. (98%) of the methobromide as a colorless solid.

Anal. Calcd. for $C_8H_{14}BrNO_3$: Br, 31.55. Found: Br, 31.66.

β-Thiobismethylenebis-α-tetronic Acid (XV). A.—A mixture of 1.14 g. of potassium thioacetate (10 mmoles) and 1.57 g. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI, 10 mmoles) in 16 ml. of dry, dimethylamine-free dimethylformamide was stirred at room temperature in a reduced nitrogen atmosphere until dissolved, which required 10 min. The solution was then immersed for 10 min. into a bath held at 75°, the brown mixture was allowed to reach room temperature (30 min.), and the solvent was evaporated (30° at 0.05 mm.) to yield a deep yellow crystalline residue (3.02 g.). Trituration of this solid with 20 ml. of iced 1 *N* hydrochloric acid yielded 1.47 g. (84%) of sulfide XV in the form of white needles, m.p. 138–140°. Recrystallization from a large volume of methanol and prolonged drying (3 days, 78° at 0.04 mm., phosphorus pentoxide) yielded the pure compound: m.p. 147–148°; λ_{max}^{EtOH} 236 mμ (ε 13,700); λ_{max}^{NaOH} 281 mμ (ε 13,600); $\lambda\lambda_{max}^{KBr}$ 3.03, 5.75, 5.90, 8.77, and 12.83 μ. Mobility toward the anode in pH 7.0 collidine acetate buffer (0.05 *M* in acetate, 14 v./cm., 3 hr.) was 4.9 cm.

Anal. Calcd. for $C_{10}H_{10}O_6S$: C, 46.52; H, 3.90; S, 12.40. Found: C, 46.42; H, 4.02; S, 12.31.

The yellow crystals initially separating on evaporation of the dimethyl formamide reaction mixture constitute the **monopotassium salt** of XV: m.p. 194–200° dec.; $\lambda\lambda_{max}^{EtOH}$ 241 mμ (ε 13800), 263–270 mμ (ε 9420).

Anal. Calcd. for $C_{10}H_9KO_6S$: K, 13.2; S, 10.72. Found: K, 12.2; S, 9.76.

The dimethylformamide distillate was analysed by vapor phase chromatography. The formation of 1 mole of dimethyl acetamide was demonstrated.

B.—A mixture of 9.65 g. of β-dimethylaminomethyl-α-tetronic acid hydrochloride (X, 50 mmoles) and 11.20 g. of sodium hydrosulfide flakes (70% pure, 200 mmoles) in 50 ml. of dimethylformamide was kept at 100° for 10 min. in a reduced nitrogen atmosphere. The initial green color changed to red and from the mixture, yellow crystals (4.94 g.) separated. On trituration with 25 ml. of cold 1 *N* aqueous hydrochloric acid, 1.48 g. of needles with a double melting point (108° and 139–141°) was obtained in 23% yield. On recrystallization from methanol, the sulfide XV was obtained melting at 145–146.5°. From the dimethylformamide mother liquor, β-mercaptomethyl-α-tetronic acid VI was isolated (see below).

Dimethyl Ether of β-Thiobismethylenebis-α-tetronic Acid.—To a stirred suspension of 459 mg. of β-thiobismethylenebis-α-tetronic acid (XV, 1.775 mmoles) in 10 ml. of ice-cold methanol there was added 50 ml. of a 0.218 *M* ethereal solution of diazomethane. After 3.5 hr. at 0° the mixture was acidified with acetic acid and evaporated to dryness. Recrystallization of the residue (410 mg., m.p. 71–74°) from isopropyl alcohol yielded the pure **dimethyl ether**: m.p. 74.5–75°; λ_{max}^{EtOH} 229 mμ (ε 19,750); $\lambda\lambda_{max}^{KBr}$ 5.65, 6.00, 6.89, 7.88, 7.93, 11.42, 12.88, and 13.15 μ; n.m.r., six protons at τ 6.02 (OCH_3), four at 6.50 (bridge methylenes), and four at 5.22 (ring methylenes).

Anal. Calcd. for $C_{12}H_{14}O_6S$: C, 50.32; H, 4.94; S, 11.21; methoxyl, 21.67. Found: C, 50.06; H, 4.72; S, 11.00; methoxyl, 21.96.

β-Mercaptomethyl-α-tetronic Acid (VI). A.—The dimethylformamide mother liquor of thiobismethylenebis-α-tetronic acid (XV, from experiment B above) was treated with 11.0 ml. of concentrated hydrochloric acid and the mixture was evaporated (40° at 0.05 mm.) until it weighed 18 g. This material was dissolved in cold water and extracted with ethyl acetate to yield 4.24 g. of an oil, which gave positive ferric chloride and nitroprusside reactions. Paper chromatography indicated the presence of the sulfide (R_f 0.717) and of a faster moving compound (R_f 0.795). Part of the oil was short-path distilled in a horizontal tube (115° oven temperature, 0.0005 mm.). The small amount of viscous oil thus obtained was homogeneous by paper chromatography and represented the substance with R_f 0.795; positive ferric chloride and nitroprusside reactions; λ_{max}^{EtOH} 242 mμ (ε 8300); $\lambda\lambda_{max}^{neat}$ 2.92, 3.86, 5.67, 5.97, and 8.87 μ.

B.—One hundred milliliters of a 0.274 *N* solution of potassium *t*-butoxide in dimethylformamide was saturated with hydrogen sulfide at ice-bath temperature. To the green solution, 4.41 g. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI, 27.4 mmoles) was added and the mixture was stirred at room temperature for 3.5 hr., while a stream of hydrogen sulfide was passed through the solution. The cooled mixture was then carefully acidified with a total of 5.00 ml. of 12 *N* aqueous hydrochloric acid (color change from green through brown to yellow) and evaporated (40° at 0.1 mm.) until it weighed 11.43 g. Extraction with ethyl acetate yielded 3.28 g. of a yellow oil still containing dimethylformamide. The solid residue from the ethyl acetate extraction was dissolved in ice-water and the solution was extracted with ethyl acetate to give 2.00 g. of a more viscous oil. Both oils contained the desired product (VI), as shown by paper chromatography and color reactions. The second oil also contained some of the sulfide XV. On distillation of small samples at 80–100° at 0.001 mm. in horizontal tubes, most of the mixture decomposed, but 30–40-mg. samples of pale yellow, slowly crystallizing oils could be obtained, which were homogeneous by paper chromatography and could be stored in evacuated tubes.

β-Acetylmercaptomethyl-α-tetronic Acid (XVI).—Into a cooled (8°), stirred mixture of 5.00 g. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI, 32 mmoles) and 0.05 g. of sodium iodide in 92 ml. of anhydrous dimethylformamide there was introduced methyl bromide gas, until about 120 g. of methyl bromide had condensed. After 45 min., the excess methyl bromide was distilled off *in vacuo*. To the colorless suspension of the **methobromide XVIIa** thus obtained, there was added 9.0 ml. of thioacetic acid; the mixture was kept at 85° for 7 hr. in a nitrogen atmosphere. After cooling and standing in the refrigerator 0.97 g. of trimethylammonium salt was removed by filtration and the filtrate was evaporated (50° at 0.1 mm.) until it weighed 13.68 g. Exhaustive extraction with boiling dry ether yielded 3.96 g. of a yellow oil, which was fractionated from a small Claisen flask. After removing a lower boiling fraction (2.40 g., 41–46° at 0.005 mm.), which consisted essentially of dimethylthioformamide [$n^{22}D$ 1.5612; λ_{max}^{EtOH} 269 mμ (ε 14,900), 336 mμ (41.6); n.m.r., three protons at τ 6.66, three at 6.74, and one at 0.85], the residue (1.50 g., 24%) crystallized (m.p. 62–69°).

Anal. Calcd. for C_3H_7NS: C, 40.44; H, 7.92; N, 15.72; S, 35.92. Found: C, 41.23; H, 8.18; N, 16.01; S, 33.87.

On short-path distillation, the pure **β-acetylmercaptomethyl-α-tetronic acid (XVI)** was obtained: b.p. 120° (bath temperature at 0.005 mm.); m.p. 70–74°; λ_{max}^{EtOH} 240 mμ (ε 14,550); $\lambda\lambda_{max}^{KBr}$ 3.03, 5.80, 5.92, 7.95, and 8.70 μ; n.m.r., three protons at τ 7.60, two at 6.16, two at 5.30, and one at 2.63.

Anal. Calcd. for $C_7H_8O_4S$: C, 44.69; H, 4.29; S, 17.05; acetyl, 22.80. Found: C,44.81; H, 4.21; S, 17.34; acetyl, 22.66.

β-Dithiobismethylenebis-α-tetronic Acid (XVIII). A.—A mixture of 1.21 g. of β-dimethylaminomethyl-α-tetronic acid methobromide (XVIIa, 4.76 mmoles) and 2.00 ml. of thioacetic acid (Eastman) in 7.46 g. of redistilled tetramethylene sulfone ("Sulfolane," Shell) was kept at 85° in a nitrogen atmosphere for 60 min. To the cooled mixture was added 10 ml. of ether and the solid-containing lower layer was twice more extracted with ether (centrifuge). The ether extracts were concentrated *in vacuo*, and into the resulting purified tetramethylenesulfone solution of (XVI, 7.52 g.) ammonia gas was introduced for 1 hr. The temperature rose to 40°. Dry ether was then layered over the mixture and crystallization was allowed to proceed overnight at 5°. The yellow crystals formed were isolated and washed with ether and ethyl acetate by centrifugation. The crude **diammonium salt of XVIII** weighed 401 mg.: λ_{max}^{EtOH} 246 mμ (ε 14,500), sh 222 mμ (ε 10,250).

Anal. Calcd. for $C_{10}H_{10}O_6S_2$: C, 41.39; H, 3.47; S, 22.10. Calcd. for $C_{10}H_{16}N_2O_6S_2$: N, 8.64; S, 19.75. Found: N, 7.39; S, 18.00.

The **free disulfide (XVIII)** was obtained in the following way. The above diammonium salt was covered with 15 ml. of ethyl acetate followed by 12.5 ml. of 1 *N* hydrochloric acid. After brief shaking, the ethyl acetate layer together with an afterwash was washed three times with water, dried over magnesium sulfate, and evaporated to yield a crystallizing oil. All manipulations were carried out as fast as possible with the temperature of the mixture never exceeding 0°. Treatment of the above oil with a little chloroform eliminated an oily side product and left 282 mg. (27.6%) of the disulfide, m.p. 129–130°. After recrystallization from a small volume of *t*-butyl alcohol, the melting point rose to 131–132°; λ_{max}^{EtOH} 244 mμ (ε 22600); $\lambda\lambda_{max}^{KBr}$ 3.10, 5.80, 5.90, 8.00, 8.77, and 12.90 μ. Mobility toward the anode

in a pH 7.0 collidine acetate buffer (0.05 molar in acetate, 14 v./cm., 3 hr.) was 1.6 cm.

Anal. Calcd. for $C_{10}H_{10}O_6S_2$: C, 41.39; H, 3.47; S, 22.10. Found: C, 41.17; H, 3.97; S, 22.02.

The **dimethyl ether** of XVIII, prepared as described above for the dimethyl ether of XV and purified by thin layer chromatography, melted at 59° and showed the following n.m.r. spectrum: six protons at τ 5.95, four at 6.36, and four at 5.23.

B.—A mixture of 1.85 g. of β-dimethylaminomethyl-α-tetronic acid methiodide (XVIIb) prepared from 1.00 g. of the zwitterion XI (6.39 mmoles) and 2 ml. of thioacetic acid in 6.25 ml. of tetramethylene sulfone was stirred under nitrogen at room temperature for 40 min., then heated to 78° within 3 min., and kept between 78 and 86° for 20 min. From the cooled mixture 228 mg. of a solid by-product was isolated by centrifugation. The solid was washed three times with three 1-ml. portions of methylene dichloride, and the washings were added to the tetramethylene sulfone solution, from which the more volatile material was distilled off *in vacuo* (0.35 mm., room temperature). Ammonia was then introduced for 20 min., followed by 2 ml. of ether, and the mixture was kept at 5° overnight, whereupon 378 mg. of the diammonium salt crystallized. The salt was purified by trituration with ether, isopropyl alcohol, ethyl acetate, and ether, and the pure disulfide 195 mg. (20.6%) of m.p. 130–130.5 was recovered upon acidification as described above.

β-Methylenebis-α-tetronic Acid (XXVII).—A solution of 230 mg. of β-dimethylaminomethyl-α-tetronic acid methiodide (XVIIb) in 2 ml. of water soon deposited crystals. After 48 hr. at 5°, 96 mg. of a colorless solid could be obtained (m.p. 185–210°) which after sublimation (150° at 0.005 mm.) melted at 242°: λ_{max}^{EtOH} 241 mμ (ε 20,400); $\lambda\lambda_{max}^{KBr}$ 3.04, 5.80, 8.74, 10.06, 10.16, and 12.96 μ.

Anal. Calcd. for $C_9H_8O_6$: C, 50.95; H, 3.80. Found: C, 50.60; H, 3.73.

This product proved to be identical by mixture melting point and infrared spectrum with the substance described by Mannich and Bauroth[16] as the "$C_{15}H_{14}O_{10}$ acid."

The **dimethyl ether,** prepared with diazomethane in methanol, had m.p. 98.5–99.5°; n.m.r., six protons at τ 6.03, four at 5.33, and two at 6.60.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04; methoxyl, 25.84. Found: C, 54.77; H, 5.04; methoxyl, 26.00.

Reaction of *t*-Butylphthalimidomalonaldehydate with β-Mercaptomethyl-α-tetronic Acid (VI).—To a solution of β-acetylmercaptomethyl-α-tetronic acid (XVI) prepared from 5.0 mmoles of XI in 9 g. of tetramethylene sulfone was added 0.900 g. of *t*-butyl phthalimidomalonaldehydate.[10] Ammonia was passed in for 90 min., during which time the brown solution deposited 250 mg. of the diammonium salt of the disulfide XVIII, which could be converted to 202 mg. of the free disulfide (m.p. 128–132°) by acidification. Thin layer chromatography of the mother liquor (silica gel G, $CHCl_3$–MeOH, 5:1) revealed four compounds. Spot 1 (R_f 0.79) and spot 3 (R_f 0.46) corresponded to compounds which codistilled with tetramethylene sulfone under high vacuum and could not therefore be the desired ring closure product. Spot 2 (R_f 0.58) had the mobility of β-thiobismethylenebis(α-amino-α,β-butenolide) (XXV), see below, and spot 4 (R_f 0.28) had that of *t*-butyl α-phthalimido-β-aminoacrylate (XIX).

α-Pyrrolidino-β-methyl-α,β-butenolide (IX).—A solution of 3.025 g. of β-methyl-α-tetronic acid[14] (26.6 mmoles) and 3.50 ml. of dry benzene was heated in a nitrogen atmosphere under a Dean–Stark trap until 0.38 ml. of water had separated, which required 5 hr. On vacuum fractionation, 3.82 g. of a light green oil, b.p. 91–95° at 0.03 mm., $n^{23}D$ 1.5283, was obtained: λ_{max}^{EtOH} 290 mμ (ε 4660); $\lambda\lambda_{max}^{neat}$ 5.65–5.72, 6.03–6.09, 6.90, 7.13, 7.30, 7.43, 7.96, 8.86, 9.44, and 12.92 μ.

Anal. Calcd. for $C_9H_{13}NO$: N, 8.38. Found: N, 8.22.

α-Amino-β-methyl-α,β-butenolide (XX).—An intimate mixture of 302.8 mg. of β-methyl-α-tetronic acid (2.66 mmoles) and 558.4 mg. of ammonium acetate (7.22 mmoles) was heated at 120° for 60 min. under 1 atm. of nitrogen. The cooled crystalline mass was taken up in chloroform; the chloroform solution was dried over magnesium sulfate and evaporated to give 274 mg. of crystals, m.p. 134–137°. Recrystallization from chloroform–hexane followed by sublimation (78° at 0.10 mm.) yielded the pure compound: m.p. 144–145°; λ_{max}^{EtOH} 249 mμ (ε 7930); $\lambda\lambda_{max}^{HCl}$ 207 mμ (ε 7100), 249 mμ (ε 4700); $\lambda\lambda_{max}^{KBr}$ 2.94–3.01, 5.78, 5.95, 6.20, 7.07, 7.38, 8.10, 8.80, 9.68, 10.27, 10.90, and 12.89 μ; n.m.r. (in CD_3COOD), three protons at τ 8.11 and two at 5.38. Mobility towards the cathode in a pH 2.3 buffer was 2.5 cm. (isoleucine moved 6.5 cm).

Anal. Calcd. for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.20; H, 6.38; N, 12.44.

The **acetyl derivative** was prepared with acetic anhydride at room temperature. After sublimation (100° at 0.001 mm.) followed by recrystallization from ethyl acetate–hexane, the material had m.p. 115–116°; $\lambda\lambda_{max}^{EtOH}$ 217 mμ (ε 9520), sh 235 mμ (ε 8100); $\lambda\lambda_{max}^{KBr}$ 3.10–3.16, 3.33, 5.63, 5.70, 6.00, 6.50, 6.91, 7.53, 7.83, 8.85, 9.37, 9.87, and 12.99 μ.

β-Thiobismethylenebis(α-amino-α,β-butenolide) (XXV).—A mixture of 160 mg. of β-thiobismethylenebis-α-tetronic acid (0.62 mmoles) and 194 mg. (2.48 mmoles) of ammonium acetate was heated at 120° in a nitrogen atmosphere for 25 min. Chloroform extraction of the mixture yielded 53 mg. of a red solid: homogeneous on thin layer chromatography; m.p. 161–163°; λ_{max}^{EtOH} 268 mμ (ε 7800); $\lambda\lambda_{max}^{KBr}$ 2.90, 2.91, 5.73, 5.97, 6.23, 6.90, 8.80, 9.82, and 12.89 μ.

Anal. Calcd. for $C_{10}H_{12}N_2O_4S$: N, 10.93. Found: N, 10.75.

β-Triphenylmethylmercaptomethyl-α-tetronic Acid (XXIII).

A.—To 7 ml. of a 0.36 *N* solution of potassium *t*-butoxide in dimethyl formamide (2.60 mmoles of base) was added 392 mg. of β-dimethylaminomethyl-α-tetronic acid zwitterion (XI, 1.99 mmoles) and 557 mg. of triphenylmethyl mercaptan (1.99 mmoles) and the mixture was allowed to remain at room temperature under a vacuum of 30 mm. for 15 hr. After addition of 0.3 ml. of glacial acetic acid, the light yellow solution was evaporated (35° at 1 mm.) and the residue was extracted with 15 ml. of ethyl acetate. Evaporation of the solvent left 900 mg. of a residue, which showed a spot corresponding to the desired α-tetronic acid on thin layer chromatography ($R_{tritylmercaptan}$ 0.88 in $CHCl_3$–MeOH, 5:1, silica gel G). For isolation, see section D.

B.—A mixture of 1.93 g. of triphenylmethyl mercaptan (7.0 mmoles) and β-dimethylaminomethyl-α-tetronic acid methiodide (XVIIb), prepared from 1.01 g. (6.45 mmoles) of the zwitterion (XI) in 15 ml. of anhydrous dimethylformamide, was stirred for 1 hr. at room temperature and then heated at 85° for 30 min. The initial light suspension disappeared and a heavy precipitate formed. After cooling and filtration from 0.30 g. of solid material the mixture was evaporated *in vacuo*. The residue was extracted with methylene dichloride to yield 660 mg. of a yellow semisolid oil similar in composition to mixture A.

C.—To a mixture of 2.41 g. of β-dimethylaminomethyl-α-tetronic acid methiodide (XVIIb) prepared from 1.01 g. of the zwitterion (XI) and 1.76 g. of triphenylmethyl mercaptan there was added at room temperature 46 ml. of a 0.278 *N* solution of potassium *t*-butoxide in dimethylformamide (12.76 mmoles of base). After 60 min. at room temperature and *in vacuo* (30 mm., gas evolution) the orange mixture was concentrated *in vacuo* (35° at 0.1 mm.) until it weighed 5.30 g. (45 min.). Trituration with ether afforded 2.56 g. of an oil. The solid residue was dissolved in water, acidified, and extracted with ethyl acetate to yield an additional 1.0 g. of oil. The combined oily fractions (3.56 g.) on preparative thin layer chromatography of an aliquot (100 mg.) were found to contain 1.15 g. or 47.5% of β-triphenylmethylmercaptomethyl-α-tetronic acid (XXIII), m.p. 150–152°.

D. Isolation.—A solution of 2.55 g. of the crude mixtures obtained under A, B, and C in methylene chloride was applied to a column of 108 g. of 100–200-mesh Davison silica gel deactivated with 8 g. of water. Methylene dichloride eluted 1.09 g. of triphenylmethyl mercaptan. Subsequent elution with methylene dichloride containing 5% ethyl acetate yielded 577 mg. of an oil which on trituration with carbon tetrachloride crystallized, m.p. 155–157°. The pure tritylmercapto-α-tetronic acid XXIII, obtained on recrystallization from CH_2Cl_2–cyclohexane, had m.p. 182–183°; λ_{max}^{EtOH} 230 mμ (ε 17,500); $\lambda\lambda_{max}^{KBr}$ 2.97, 5.73, 5.86, 6.27, 6.72, 6.92, 7.20, 8.04, 8.82, 9.72, 13.00, 13.46, 14.30, and 14.88 μ; n.m.r., 15 protons at about τ 2.72, two at 5.63, two at 6.77, and one at 3.48.

Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 74.21; H, 5.19; S, 8.25. Found: C, 74.04; H, 5.01; S, 8.52.

α-Amino-β-triphenylmethylmercaptomethyl-α,β-butenolide (XXIV).—An intimate mixture of 1.482 g. of β-triphenylmercaptomethyl-α-tetronic acid (XXIII, 3.82 mmoles) and of 0.591 g. of ammonium acetate (7.72 mmoles) was heated at 116° under nitrogen for 30 min. From the resulting brown oil 1.482 g. of a gummy substance was extracted with chloroform. It was redissolved in methylene dichloride and chromatographed on a

column made up from 100 g. of 100–200-mesh Davison silica gel previously deactivated with 8 g. of water. Elution with methylene dichloride furnished, in addition to triphenylmethylmercaptan and unchanged starting material, 580 mg. of the pure aminobutenolide XXIV obtained as a foam which crystallized on trituration with ether: m.p. 124–125°; λ_{max}^{EtOH} 267 mμ (ε 10,900); λ_{max}^{HCl} 267 mμ (ε 10,000); $\lambda\lambda_{max}^{KBr}$ 2.92–2.99, 5.65–5.70, 5.90, 6.25, 6.72, 6.94, 7.22, 7.36, 8.86, 9.78, 13.18, 13.40, 14.25, and 14.88 μ; n.m.r., 15 protons at about τ 2.63, two at 5.60, two at 6.94, and two at 6.50.

Anal. Calcd. for $C_{24}H_{21}NO_2S$: C, 74.40; H, 5.46; N, 3.62; S, 8.29. Found: C, 74.05; H, 5.66; N, 3.77; S, 8.52.

α-Amino-β-mercaptomethyl-α,β-butenolide Mercuric Chloride Hydrochloride Salt (XXVI).—To a solution of 127 mg. of α-amino-β-triphenylmethylmercaptomethyl-α,β-butenolide (XXIV, 0.326 mmoles) in 0.17 ml. of peroxide-free 1,2-dimethoxyethane was added 0.46 ml. of a solution of 90 mg. of mercuric chloride (0.331 mmoles) in 1,2-dimethoxyethane. Pale yellow crystals separated immediately, which were washed with small amounts of 1,2-dimethoxyethane to give 99.2 mg. (79.5%) of the complex: $\lambda\lambda_{max}^{KBr}$ 2.95, 5.73, 8.85, and 9.80 μ, no bands in the 14-μ region.

Anal. Calcd. for $C_5H_7Cl_2HgNO_2S$: C, 14.41; H, 1.69; Cl, 17.02; N, 3.35; S, 7.69. Found: C, 12.32; H, 1.66; Cl, 17.30; N, 2.53; S, 7.58.

The mother liquor was treated with 1 ml. of water and evaporated to dryness. The residue (103 mg.) on vacuum sublimation (120° at 0.005 mm.) yielded 77 mg. (89%) of triphenylmethylcarbinol, m.p. 148° (infrared absorption spectrum indistinguishable from that of an authentic sample).

β-Thiobismethylenebis(α-amino-α,β-butenolide) Dihydrochloride.—Into a suspension of the above mercury complex in 5 ml. of methanol there was introduced hydrogen sulfide, whereupon black mercuric sulfide immediately precipitated. After 20 min., the centrifuged clear solution was evaporated to dryness to furnish β-thiobismethylenebis(α-amino-α,β-butenolide) dihydrochloride: λ_{max}^{EtOH} 268 mμ (ε 7800); $\lambda\lambda_{max}^{KBr}$ 3.00–3.80, 5.62–5.65, 5.85 sh, 6.62, 7.10, 7.38, 8.90, 9.75, and 13.20 μ.

Anal. Calcd. for $C_{10}H_{14}ClN_2O_4S \cdot CH_3OH$: Cl, 19.10; N, 7.51; S, 8.60. Found: Cl, 18.70; N, 7.52; S, 8.61.

α-Phthalimido-β-aminoacrylate (XIX).—To 40 ml. of liquid ammonia 500 mg. of *t*-butyl α-phthalimidomalonaldehydate[10] was added and the yellow solution was allowed to evaporate (1 hr.) to form 510 mg. of a red foam. The latter was dissolved in methylene dichloride; the solution was filtered and precipitated with diisopropyl ether to yield 460 mg. of α-phthalimido-β-aminoacrylate (XIX) as a yellow, amorphous powder, 80–100° dec. Thin layer chromatography on silica gel G ($CHCl_3$–MeOH, 5:1) showed the product to be homogeneous (R_f 0.28); λ_{max}^{EtOH} 237 mμ (ε 11,800) and 266 mμ (ε 13,700); $\lambda\lambda_{max}^{CHCl_3}$ 6.03 and 6.41 μ.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: N, 9.72. Found: N, 10.49.

Ethyl α-Ethoxalyl-β-benzylmercaptopropionate.—To a mixture of 22.5 g. of a 53.3% sodium hydride–mineral oil dispersion (0.5 mole) and 75.00 g. (0.513 mole) of diethyl oxalate in 150 ml. of ether was added with stirring under nitrogen over a 60-min. period 112 g. (0.5 mole) of ethyl β-benzylmercaptopropionate.[25] The reaction mixture was refluxed for an additional hour when the evolution of hydrogen ceased. After cooling, the mixture was poured into 500 ml. of ice–water containing 2.5 g. of sodium bicarbonate. The ether layer, along with two subsequent hexane extracts, was discarded and the aqueous layer was acidified with 100 ml. of 40% acetic acid and extracted with ether to obtain 96.0 g. of the oily product. For analysis, a small sample was subjected to short-path distillation (100–105° at 0.0001 mm.): red color with $FeCl_3$; $\lambda\lambda_{max}^{neat}$ 2.84, 5.69, 5.75, 6.03, and 7.98 μ.

Anal. Calcd. for $C_{16}H_{20}O_5S$: C, 59.26; H, 6.21; S, 9.88. Found: C, 59.27; H, 6.22; S, 9.87.

Ethyl α-Benzylmercaptomethyl Acrylate (3).—To a vigorously stirred emulsion of 7.25 g. of ethyl α-ethoxalyl-β-benzylmercaptopropionate (22.3 mmoles) in 10 ml. of water was added 1.70 ml. of a 40% formaldehyde solution (25.3 mmoles), and then over a period of 15 min. a solution of 3.08 g. (22.2 mmoles) of potassium carbonate in 10 ml. of water. The temperature was maintained at 20° by mild cooling. The yellow color of the mixture faded 5 min. after the addition was completed and the pH reached a constant value of 8.0. Extraction of the reaction mixture with ether yielded 4.44 g. (81%) of almost pure product: b.p. 150° (0.50 mm.); $n^{18}D$ 1.5425; $\lambda\lambda_{max}^{neat}$ 5.81, 6.12, and 8.37 μ; n.m.r., τ 8.72 triplet and 5.79 quadruplet (CH_3CH_2O), 6.75 (doublet CH_2), 6.37 (singlet CH_2), 4.44 (multiplet) and 3.80 (doublet) (vinyl protons), 2.74 (phenyl).

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.08; H, 6.83; S, 13.55; ethoxyl, 19.03. Found: C, 66.16; H, 6.83; S, 13.05; ethoxyl, 17.50.

N-Bromosuccinimide Bromination of β-Methyl-α-tetronic Acid Methyl Ether.—A mixture of 7.950 g. (62.3 mmoles) of β-methyl-α-tetronic acid methyl ether,[14] 11.10 g. (62.3 mmoles) of N-bromosuccinimide, and 0.05 g. of benzoyl peroxide in 70 ml. of carbon tetrachloride was refluxed for 2 hr. After cooling and filtration from 5.90 g. of succinimide, the solution was evaporated to give 13.1 g. of a red, light oil. On fractionation (5-in. Vigreux, 0.01 mm.) 8.23 g. of a fraction boiling between 65–70° was collected: $\lambda_{max}^{cyclohexane}$ 239 mμ (ε 6240); $\lambda\lambda_{max}^{neat}$ 5.56, 5.63, 7.50 9.51, and 9.80 μ; the n.m.r. spectrum showed an intact methyl group, three protons at τ 8.00.

Anal. Calcd. for $C_6H_7BrO_3$: C, 34.75; H, 3.38; Br, 38.55; methoxyl, 14.95. Found: C, 35.20; H, 3.57; Br, 38.15; methoxyl, 15.24.

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