ChemResearch) in a flask equipped with a Dry Ice condenser. The refluxing mixture was stirred for 4–6 hr, after which time it was allowed to warm slowly to room temperature. It was then extracted thrice with anhydrous ether and the ether solution was distilled. The CFA fraction began to distil immediately after the ether fraction. The main portion boiled between 83.5 and 84.5°: wt 28.0 g (67%); ir (liquid film) 1790 (C=O), homogenous according to glc. CFA was stored in a tightly stoppered bottle and was used in the following experiments without further purification.

General Procedure for the Preparation of *N*-Trifluoroacetylamino Acids.—A mixture of the amino acid (6.0–9.0 mmol), 10 ml of DMSO, and a threefold excess of CFA was stirred for 24 hr in a flask protected from atmospheric moisture. A complete solution was usually obtained within the first hour. The progress of the reaction was followed by taking samples periodically and submitting them to gas–liquid chromatographic analysis. The area under the chloroform peak varied in proportion with the yield of the TFA–amino acid. The reaction mixture was poured into 50 ml of ice water and the resultant mixture was extracted thrice with *n*-BuOH. The organic phase was concentrated *in vacuo* and the residual oil, which contained the TFA–amino acid and DMSO, was placed on a silicic acid (100 mesh) column. The eluting solvent was benzene–acetone–methanol (50:40:10) and the TFA–amino acid fraction was further purified as shown in Table I. If a second run through a column was required, the eluting solvent was changed to benzene–acetone (90:10). All TFA–amino acids were identified by comparison of tlc's, melting points, and infrared spectra with those of authentic samples. Physical constants for the TFA–amino acids are found in Table I.

***N*-Trifluoroacetylglycylglycine (4).**—A mixture of 1.035 g (7.85 mmol) of glycylglycine (Nutritional Biochemicals Corporation, Aldrich Chemical Co.), 15 ml of DMSO, and 5.15 g (24.0 mmol) of CFA was stirred for 24 hr in a flask equipped with a drying tube filled with Drierite. The product was extracted and isolated with the same procedure that was used with the TFA–amino acids (above). Final purification solvent and physical constants are listed in Table I.

Anal. Calcd for $C_6H_7F_3N_2O_4$: C, 31.58; H, 3.07; F, 25.00; N, 12.28. Found: C, 31.46; H, 3.28; F, 25.22; N, 12.16.

***N*-Trifluoroacetylprolylglycine Ethyl Ester (6).**—A mixture of 1.00 g (5.8 mmol) of L-prolylglycine in 40 ml of EtOH was treated with dry HCl gas for 1 hr. The resulting solution was stored for 16 hr at room temperature. The ethanol was removed by distillation under reduced pressure. The residue was dissolved in water and the pH of the solution was adjusted to 6.0. The solution was extracted twice with CH_2Cl_2. The organic layer was separated, dried, and concentrated *in vacuo* to an oil: 0.9 g; ir (liquid film) 1760 (ester C=O).

The above prolylglycine ethyl ester (4.74 mmol) was treated with 3.0 g (13.9 mmol) of CFA in 10 ml of DMSO. The mixture was stirred for 24 hr under a dry atmosphere. The product was extracted and isolated as in the foregoing procedures. An impure product (1.05 g) was obtained after one pass through a silicic acid column. Attempts were made to crystallize this oily product, but they were without success. A sample of it (0.33 g) was placed on a second silicic acid column using the same elution solvent system that was used in other procedures (see above). Three fractions were collected: (1) wt 30 mg, tlc, one zone (benzene:acetone:HOAc, 50:45:5), R_f ~0.9; (2) 110 mg, tlc showed several zones, R_f of most intense spot was ~0.8; (3) 110 mg, tlc, one zone, R_f ~0.8. Part of the third fraction crystallized and was identified as *N*-trifluoroacetylprolylglycine ethyl ester (6) (yield and other data are in Table I). Characterizations of the components of the other two fractions were not made.

Registry No.—L-Valine, 72-18-4; DL-phenylalanine, 150-30-1; L-phenylalanine, 63-91-2; L-leucine, 61-90-5; L-tyrosine, 60-18-4; L-proline, 147-85-3; DL-alanine, 302-72-7; glycylglycine, 556-50-3; L-prolylglycine ethyl ester, 26347-43-3; *sym*-trichlorotrifluoroacetone, 758-42-9; dimethyl sulfoxide, 67-68-5.

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β-(β′-Aminoalkyl)-α-tetronic Acids. An Extension of the Schinz α-Tetronic Acid Synthesis

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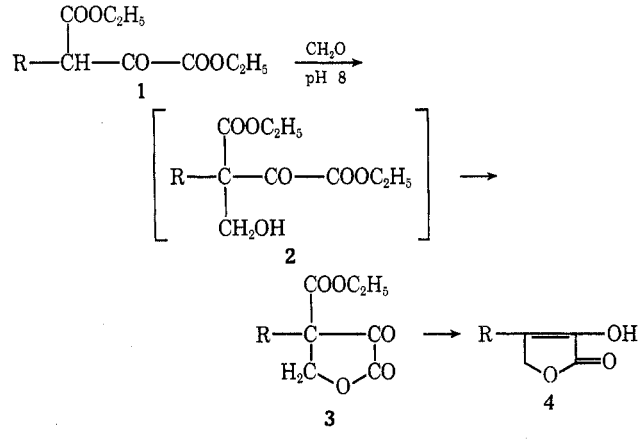
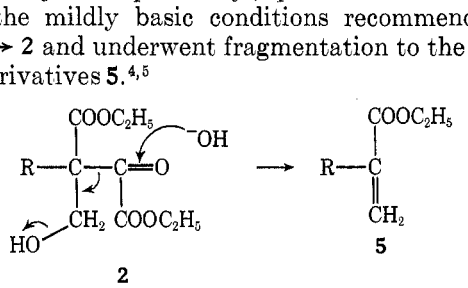
The field of α-tetronic acids, after a thorough synthetic exploration in the Forties by Schinz and coworkers,[1] has gained in interest recently as its representatives were encountered among the degradation products of the important antibiotic, cephalosporin C,[2] and were subsequently utilized as intermediates in the total synthesis of the Cephalosporin C_e nucleus.[3]

On the preparation of such intermediates, a serious limitation of the original Schinz scheme **1** → **2** → **3** → **4**



was recognized and went on record.[3c,d] The intermediary hydroxymethyl products **2**, which gave the ketoparaconic esters **3** in good yields in all cases where R represented an alkyl group, with substituents like R = benzylmercaptomethyl, proved to be unstable under the mildly basic conditions recommended for step **1** → **2** and underwent fragmentation to the acrylic ester derivatives **5**.[4,5]



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(1) (a) H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1439 (1947). (b) A. Rossi and H. Schinz, *ibid.*, **31**, 473, 1954 (1948); **32**, 1967 (1949). (c) F. Fleck, A. Rossi, M. Hinder, and H. Schinz, *ibid.*, **33**, 130 (1950).

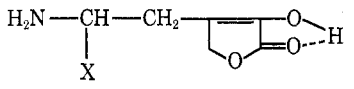
(2) For a review, see E. P. Abraham, *Quart. Rev.*, **21**, 231 (1967).

(3) (a) E. Galantay, A. Szabo, and J. Fried, *Tetrahedron Lett.*, 415 (1963). (b) A. G. Long and A. F. Turner, *ibid.*, 421 (1963). (c) E. Galantay, H. Engel, A. Szabo, and J. Fried, *J. Org. Chem.*, **29**, 3560 (1964). (d) D. M. Green, A. G. Long, P. J. May, and A. F. Turner, *J. Chem. Soc.*, 766 (1964). (e) G. C. Barrett, S. H. Eggers, T. R. Emerson, and G. Lowe, *ibid.*, 788 (1964). (f) R. Heymès, G. Amiard, and G. Nominé, *C. R. Acad. Sci., Ser. C*, **263**, 170 (1966). (g) J. E. Dolfini, J. Schwartz, and F. Weisenborn, *J. Org. Chem.*, **34**, 1582 (1969).

(4) Schinz himself noted[1a] that he could not isolate **3**, R = phenyl or α-naphthyl, and that he obtained the corresponding **5** instead, as he then thought, from the room temperature thermolysis of the initially formed **3**. Compounds **3**, R = alkyl, can in fact be thermolyzed, at 250–320° to **5**, CO and CO_2.[5]

(5) M. Hinder, H. Schinz, and C. F. Seidel, *Helv. Chim. Acta*, **30**, 1495 (1947).

This tendency of the hydroxymethyl–ethoxalyl esters **2** to fragmentation presented itself even more drastically in the present work which aimed at the preparation of the novel aminoalkyl tetronic acid derivatives **6**, compounds attractive to us because of



6a, X = H

b, X = CH_3

their interesting structural relationship to the biologically important catecholamines.[6]

The easily available ethoxyalyl ester **1**, R = β-phthalimidoethyl, on its reaction with formaldehyde at pH 8.2 and 0°, gave again the fragmentation product in 86% yield. Since the phthalimid functionality is separated here by two methylene groups from the quaternary carbon atom in the initially formed **2**, it is surprising to find such a cleancut difference from say, the R = ethyl case where no fragmentation occurs.

This unwanted[7] fragmentation we could subsequently avoid by carrying out the hydroxymethylation step under acid catalysis.[8] By refluxing the ethoxalyl ester **1** (R = β-phthalimidoethyl) and paraformaldehyde in trifluoroacetic acid, the corresponding ketoparaconate ester **3** was formed (tlc, spectra). Attempts to isolate this intermediate by crystallization proved unsuccessful but also unnecessary; after heating the crude hydroxymethylation product with HCl–AcOH, which treatment effected not only decarboxylation but also removal of the protective phthalyl group, the desired aminoethyl tetronic acid **6a** hydrochloride could be directly obtained by crystallization, in 33.6% overall yield. The homolog **6b**, analogously prepared, was isolated as its sparingly soluble tetraphenylboronate complex which in turn was converted into the hydrochloride salt.

As this example suggests, the Schinz scheme, with our modification which not only expands its scope but also shortens the overall operation, may be tried with confidence whenever the synthesis of a β-substituted α-tetronic acid is contemplated.

Experimental Section

γ-Phthalimidobutyric Acid.—A mixture of 1650 g of potassium phthalimide, 770 g of γ-butyrolactone, and 2500 ml of DMF was heated under reflux for 37 hr. After cooling and addition of 300 ml of benzene, the potassium salt of the product, which separated as a solid, was filtered and washed with several portions of benzene and ether. The title product was obtained by dissolving the potassium salt in 5 l. of water, washing the aqueous solution with ethyl acetate, and then acidifying with concentrated hydrochloric acid. The filtered and washed solids (1450 g, mp 104–108°) were recrystallized from acetone–petroleum ether to yield 1350 g or 65% of the pure product, mp 114–115° (lit.[9] 117–118°).

The **ethyl ester** was obtained by saturating, at 10°, a stirred suspension of 280 g of the acid in 3 l. of absolute ethanol, with hydrogen chloride. A solution was formed from which, on standing for 18 hr at 5°, 287 g (92%) of the ester separated in crystalline form, mp 73–74° (lit.[9] 71–72°).

(6) E. Galantay, U. S. Patent 3,474,112 (Oct 21, 1969).

(7) Unwanted, that is, from the stand point of obtaining α-tetronic acids. This fragmentation reaction has obvious utility in the preparation of substituted acrylic esters of the type **5**. See also ref 5.

(8) Acid-catalyzed hydroxymethylation reactions (paraformaldehyde–cc? H_2SO_4) in not unrelated systems were studied by S. Olson and coworkers; see, *e.g.*, S. Olsen and G. Havre, *Acta Chem. Scand.*, **8**, 47 (1954).

(9) S. Gabriel and R. Colman, *Ber.*, **41**, 513 (1908).

Ethyl α-Ethoxalyl-γ-phthalimidobutyrate.—To a stirred suspension of 24.0 g of sodium hydride (from 43.7 g of a 55% mineral oil suspension) in 200 ml of absolute benzene, there was added 146 g of diethyl oxalate and 0.5 ml of absolute ethanol, followed dropwise by a solution of 261 g of ethyl γ-phthalimidobutyrate in 1200 ml of benzene. Stirring at room temperature was maintained for 60 hr until all the sodium hydride disappeared and a brown solution was formed. Then the mixture was extracted with ice water (three 700-ml portion). After backwashing with benzene, the aqueous solution was acidified to pH 2 with concentrated hydrochloric acid and the product (crystallizing oil, 280 g) obtained by chloroform extraction. For analysis, a small sample was distilled (135° bath temperature, 0.001 mm).

Anal. Calcd for $C_{18}H_{19}O_7N$: C, 59.8; H, 5.3; O, 31.0. Found: C, 60.0; H, 5.6; O, 30.8.

β-(β′-Aminoethyl)-α-tetronic Acid Hydrochloride.—A mixture consisting of 122.2 g of ethyl α-ethoxalyl-γ-phthalimidobutyrate, 21.8 g of paraformaldehyde and 213 g of trifluoroacetic acid was refluxed for 2 hr, then evaporated to dryness. The residual oil (147.9 g, $FeCl_3$ test negative) was heated under reflux with a mixture of 200 ml of glacial acetic acid, 500 ml of 11 *N* HCl, and 200 mg of hydroquinone for 2 hr. On concentration to 200 g *in vacuo* and subsequent storage at 5° overnight, 54.8 g of solid material mp 173–175°, mostly phthalic acid) crystallized and was subsequently removed by filtration. The filtrate was evaporated to an oil (28 g) which on treatment with absolute ethanol gave the product, 20.4 g (33.6%), mp 172–175°. An analytical sample, mp 175–177°, was obtained on recrystallization from methanol–ether: λ_{max}^{KBr} 1775, 1760 cm^{-1} (lactone), 1720 (–C=C–); λ_{max}^{EtOH} 231.5 mμ (ε 9520); $FeCl_3$ reaction purple.

Anal. Calcd for $C_6H_9O_3N \cdot HCl$: C, 40.1; H, 5.6; N, 7.8; O, 26.7; Cl, 19.7. Found: C, 40.3; H, 5.7; N, 8.0; O, 26.3; Cl, 19.3.

Ethyl α-Methylene-γ-phthalimidobutyrate.—On addition at 0° of 8.6 g of 37% formaldehyde solution to an aqueous solution (110 ml, pH 8.2) of the sodium salt of ethyl α-ethoxalyl-γ-phthalimidobutyrate (from 18 g of the free ester) an almost immediate separation of oily material and of some colorless crystals could be observed. After 2 hr, the mixture was extracted with benzene and the oily extract (13 g) distilled (135–144° bath temperature, 0.001 mm) to give 11.6 g (86%) of the title product: λ_{max}^{neat} 1775, 1725, 1715, 1400, 1185, 725 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}O_4N$: C, 65.9; H, 5.5; N, 5.1; O, 23.4. Found: C, 65.7; H, 5.7; N, 5.2; O, 23.4.

Comparison of the tlc and spectra prior and after distillation excluded the possibility that a ketoparaconate ester was nevertheless formed but pyrolyzed during distillation.

Ethyl γ-Phthalimidovalerate.—A solution of 29.2 g of ethyl γ-bromovalerate in 90 ml of DMF was added dropwise (30 min) to a stirred suspension of 25.8 g of potassium phthalimide in 150 ml of DMF at 50°. After stirring for 18 hr, the temperature was shortly raised to 150°. The recooled mixture was poured on ice and extracted with chloroform. The oily extract was dissolved in 60 ml of benzene and percolated through a column of 100 g of alumina (activity grade III). Evaporation of the benzene solution and washings yielded 27.9 g (73%) of the title product, mp 47–50°. For analysis a small sample was distilled in a micro apparatus.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1; O, 23.2. Found: C, 65.1; H, 6.6; N, 5.1; O, 23.2.

Ethyl α-Ethoxalyl-γ-phthalimidovalerate.—A mixture consisting of 88.3 g of diethyl oxalate, 158.0 g of ethyl γ-phthalimidovalerate, 900 ml of absolute benzene, and 26.1 g of 53.3% sodium hydride–mineral oil suspension was stirred at room temperature and under nitrogen for 3 days. The sodium salt of the title product, which separated as a yellow solid, was filtered, washed with benzene, and dried at room temperature, 121.9 g, mp 218–220° dec.

Anal. Calcd for $C_{19}H_{19}NO_7Na$: N, 3.5; O, 28.2. Found: N, 3.4; O, 27.9.

The free ester was obtained as a yellow viscous oil on acidification of the aqueous solution of above salt and chloroform extraction.

β-(B′-Aminopropyl)-α-tetronic Acid Hydrochloride.—A mixture of 52.9 g of ethyl α-ethoxalyl-γ-phthalimidovalerate, 10.6 g of paraformaldehyde, and 106 g of trifluoroacetic acid was heated under reflux for 2½ hr, then evaporated *in vacuo* to 69.4 g of an oily residue. Latter was refluxed, after addition of 200 mg of hydroquinone, with a mixture of 176 ml of glacial acetic acid and 440 ml of 11 *N* HCl for 4 hr. On standing overnight,

the mixture deposited 11.96 g of phthalic acid and an additional 0.52 g was obtained on concentration of the filtrate. The final concentrate, 32 g of an oil, was dissolved in 600 ml of water and the solution was filtered clear, buffered with 150 ml of 10% sodium acetate solution to a pH of 5.5, washed with 100 ml of ethyl acetate, and then treated with a solution of 64.0 g of sodium tetraphenylboronate in 800 ml of water. A gummy precipitate was formed which was filtered, washed with water, air-dried, and then further washed with ether. The colorless tetraphenylboronate weighed 12.4 g, mp 113–115° dec, λ_{max}^{KBr} 1750, 1700 sh.

Anal. Calcd for $C_{31}H_{31}NO_3B$: C, 78.2; H, 6.6; N, 2.9. Found: C, 77.8; H, 6.9; N, 3.0.

The above tetraphenylboronate (12.00 g) was dissolved in a mixture of 400 ml of 95% ethanol and 100 ml of acetone and treated with a solution of 3.46 g of cesium chloride in 400 ml of 87% aqueous alcohol. The cesium tetraphenylboronate precipitate (9.0 g) as well as the additional solids (2.1 g) formed on concentration of the mixture were removed by filtration. Final evaporation to dryness resulted in 3.82 g of a colorless foam which, on crystallization with methanol–ether, yielded 3.20 g of the pure β-(β′-aminopropyl)-α-tetronic acid hydrochloride: mp 176–179° dec; $FeCl_3$ reaction purple; λ_{max}^{KBr} 1750, 1705; λ_{max}^{EtOH} 231.5 mμ (ε 9340).

Anal. Calcd for $C_7H_{11}NO_3 \cdot HCl$: C, 43.4; H, 6.2; N, 7.2; O, 24.5; Cl, 18.3. Found: C, 43.7; H, 6.4; N, 6.9; O, 24.4; Cl, 18.4.

Registry No.—Ethyl α-ethoxalyl-γ-phthalimidobutyrate, 25739-35-9; β-(β′-aminoethyl)-α-tetronic acid hydrochloride, 25739-36-0; ethyl α-methylene-γ-phthalimidobutyrate, 24249-90-9; ethyl γ-phthalimidovalerate, 10264-78-5; ethyl α-ethoxalyl-γ-phthalimidovalerate, 25739-39-3; β-(β′-aminopropyl)-α-tetronic acid tetraphenylboronate complex, 25776-64-1; β-(β′-aminopropyl)-α-tetronic acid hydrochloride, 25739-40-6.

One-Step Synthesis of Quinoxaline 1,4-Dioxides and Related Compounds

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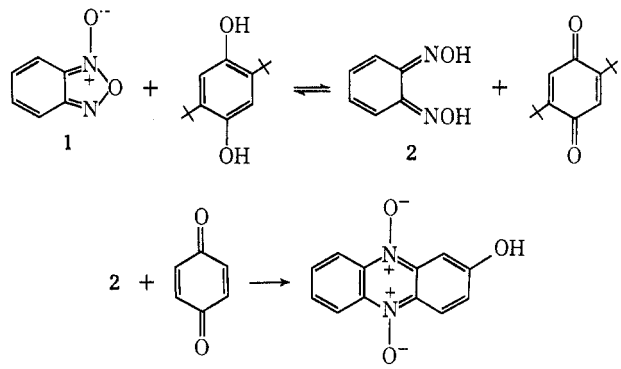
An elegant one-step synthesis of quinoxaline 1,4-dioxides, which comprised the reaction of benzofurazan 1-oxide (1) (BFO) with enamines or enolate anions, was reported in 1965.[2,3] With this method, a wide variety of quinoxaline 1,4-dioxides were prepared in good yields. α-Diketones, *e.g.*, biacetyl, did not react in the expected manner, and under a variety of conditions no 2-acetylquinoxaline 1,4-dioxide was isolated.[4] In the present work a probable explanation is offered for this failure which resulted in the discovery of a new method for the preparation of 1-hydroxyquinoxalin-2-one 4-oxides and quinoxaline 1,4-dioxides.

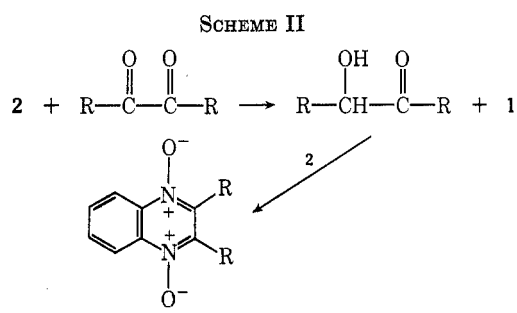
Studies in our laboratories have shown that *o*-quinone dioxime (2) was produced when BFO oxidized 2,5-di-*tert*-butyl hydroquinone to the corresponding *p*-quinone. This dioxime reacted with *p*-benzoquinone under neutral conditions to give 2-phenazinol 5,10-dioxide[5] (Scheme I).

SCHEME I



This discovery prompted us to investigate the reaction of biacetyl with *o*-quinone dioxime, two compounds of higher and lower oxidation states than the reactants used in the reactions of BFO mentioned earlier. The product isolated, 2,3-dimethylquinoxaline 1,4-dioxide, was of a lower oxidation state than expected had the two reactants simply combined. It was therefore assumed that an initial oxidation–reduction reaction took place in which the dioxime was oxidized to BFO[6] with simultaneous formation of α-hydroxy ketone, which then reacted with another molecule of *o*-quinone dioxime to give the observed products (Scheme II). Support for

SCHEME II



the above assumption was provided by the formation of BFO in this reaction. Furthermore when α-hydroxy ketones were substituted for α diketones, quinoxaline 1,4-dioxides were obtained. The reactions carried out are outlined in Table I.

A possible mechanism for the reactions of α-hydroxy ketones and α-hydroxy aldehydes with the dioxime is outlined in Scheme III. Even though ionic intermediates are presented, a radical ionic pathway cannot be excluded at this time.

Extension of this reaction to α-ketoaldehydes resulted in the formation of hydroxamic acids, **8a** and **8b**, in 50–60% yields (Scheme IV). A similar mechanism accounts for the formation of these products without invoking an initial oxidation–reduction reaction.

This synthetic method is not superior to present methods for the preparation of quinoxaline 1,4-dioxides. However, it represents a major improvement over ear-

(1) Department of Pharmaceutical Chemistry, College of Pharmacy, University of Rhode Island, Kingston, R. I. 02881.

(2) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965).

(3) M. J. Haddadin and C. H. Issidorides, *J. Org. Chem.*, **31**, 4067 (1966).

(4) J. D. Johnston, unpublished results.

(5) B. W. Dominy, unpublished work.

(6) *o*-Quinone dioxime has been oxided to benzofurazan 1-oxide: T. Zincke and P. Schwarz, *Justus Liebigs Ann. Chem.*, **307**, 39 (1899).