$n^{19}D$ 1.5685 (lit.[7] $n^{20}D$ 1.5680); ir (neat) 3025, 2920, 1683, 1603, 1496, 1450, 1380, 853, 755, and 691 cm^{-1}.

4-Phenylamino-3-methyl-2-buten-1-ol (IV).—To a solution of Ia (0.50 g, 0.0029 mol) in ether (10 ml) and acetic acid (25 ml) was added zinc powder (6.0 g, 0.092 g-atom) gradually and the mixture was stirred for 4 days at room temperature. After removal of inorganic solids, the mixture was diluted with water and extracted with ether (five 50-ml portions). Combined ether extracts were neutralized with sodium bicarbonate and dried over sodium sulfate and potassium hydroxide. Removal of ether gave a crude product which was passed through an alumina column with benzene to give IV as an oil (0.13 g, 26%): $n^{18}D$ 1.5780 (lit.[7] $n^{20}D$ 1.5765); ir (neat) 3400, 3030, 2924, 1675, 1600, 1500, 1445, 1383, 751, and 690 cm^{-1}.

2-Phenyl-4-chloro-3,6-dihydro-1,2-oxazine (IIa).—Chloroprene (5.9 g, 0.067 mol) in xylene (10 ml) was treated similarly with nitrosobenzene (3.6 g, 0.033 mol) in dry benzene (40 ml). Distillation under reduced pressure afforded IIa (3.8 g, 58%) as an oil: bp 101–105° (0.8 mm) [lit.[8] bp 87–88° (0.5 mm)]; $n^{21}D$ 1.5766 (lit.[8] $n^{20}D$ 1.5788); ir (neat) 3060, 2880, 2830, 1662, 1600, 1495, 1455, 1431, 1354, 1278, 1214, 760, and 691 cm^{-1}.

4-Phenylamino-3-chloro-2-buten-1-ol (V).—To a solution of IIa (1.0 g, 0.0051 mol) in ether (10 ml) and acetic acid (10 ml) was added zinc powder (3.0 g, 0.046 g-atom) gradually and the mixture was stirred for 1 day at room temperature. Work-up as above afforded a crude product which was purified by a silica gel column, eluting with benzene–methanol to give analytically pure V as an oil (0.70 g, 71%): $n^{21}D$ 1.5835; ir (neat) 3400, 3040, 2920, 1645, 1603, 1503, 1432, 1320, 1253, 755, and 691 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; N, 6.12; H, 7.09. Found: C, 60.77; H, 6.14; N, 7.06.

2-Phenyl-4-(4-methyl-3-pentenyl)-3,6-dihydro-1,2-oxazine (IIIa) and 2-Phenyl-5-(4-methyl-3-pentenyl)-3,6-dihydro-1,2-oxazine (IIIb).—Myrcene (9.2 g, 0.067 mol) was treated with nitrosobenzene (3.6 g, 0.033 mol) similarly. The product was distilled under reduced pressure to give IIIa (2.4 g, 30%) and IIIb (1.3 g, 16%), both of which were further purified on an alumina column eluting with *n*-hexane to give analytically pure samples.

Compound IIIa exhibited the following properties: bp 113–115° (0.3 mm); $n^{19}D$ 1.5539; ir (neat) 3030, 2924, 1664, 1632, 1600, 1497, 1455, 1379, 1218, 1086, 1033, 756, and 688 cm^{-1}; mass spectrum *m/e* (rel intensity) 243 (35.4), 198 (28.0), 162 (100), 156 (54.2), 144 (55.4), 136 (16.7), 135 (28.1), 121 (29.2), 119 (29.2), 109 (36.5), 107 (99.8), 105 (60.4), 104 (62.5), 93 (85.8), 91 (60.8), 79 (70.8), 78 (50.0), 77 (65.8), 69 (93.3), 67 (60.8), and 55 (52.5).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.44; H, 8.55; N, 6.09.

IIIb was analyzed as follows: bp 122–124° (0.3 mm); $n^{19}D$ 1.5520; ir (neat) 3020, 2924, 1673, 1600, 1494, 1451, 1377, 1214, 1082, 1028, 753, and 686 cm^{-1}; mass spectrum *m/e* (rel intensity) 243 (97.5), 198 (22.5), 182 (50.8), 168 (50.0), 156 (44.2), 154 (44.2), 153 (40.8), 149 (41.7), 136 (15.9), 135 (25.8), 107 (57.5), 105 (42.5), 93 (94.2), 77 (100), 73 (91.7), 69 (91.7), 57 (34.2), and 55 (25).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.97; H, 8.59; N, 5.97.

4-Phenylamino-3-(4-methyl-3-pentenyl)-2-buten-1-ol (VI).—IIIa (1.0 g, 0.0041 mol) in ether (10 ml) and acetic acid (25 ml) was reduced with zinc powder (7.5 g, 0.11 g-atom) at room temperature for 5 days. Work-up as above afforded crude VI which was purified by silica gel and alumina columns successively to give pure VI (0.29 g, 29%) as an oil: $n^{19}D$ 1.5030; ir (neat) 3380, 2924, 1660, 1603, 1504, 1435, 1375, 746, and 689 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.22; H, 9.22; N, 5.77.

Registry No.—Ia, 26332-63-8; IIa, 26332-64-9; IIIa, 26332-65-0; IIIb, 26332-66-1; IV, 26332-67-2; V, 26332-68-3; VI, 26332-69-4; nitrosobenzene, 586-96-9; isoprene, 78-79-5; chloroprene, 126-99-8; myrcene, 123-35-3.

(8) O. Wichterle and M. Kolinsky, *Chem. Listy*, **47**, 1787 (1953); *Chem. Abstr.*, **49**, 201 (1955).

Trifluoroacetylation of Amino Acids and Peptides under Neutral Conditions

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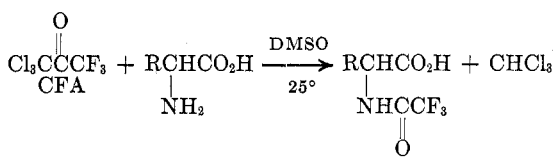
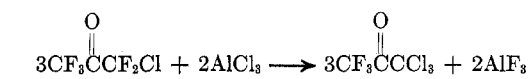
The trifluoroacetyl group has been employed as an alkali-sensitive amino-protecting group[2] for amino acids. Perhaps of more importance, is its use in the preparation of *N*-trifluoroacetylamino acid esters from amino acids derived from natural protein hydrolyzates. These derivatives are volatile and can be analyzed rapidly and quantitatively by gas–liquid chromatography.[3,4] Most recently, rapid chemical and stereochemical analyses of *N*-trifluoroacetylamino acids and peptides using fluorine-19 nuclear magnetic resonance spectroscopy has been reported.[5a]

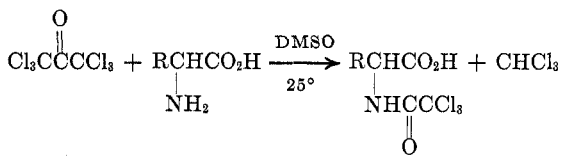
We have found that several amino acids (see Table I) can be easily *N*-trifluoroacetylated using *sym*-trichlorotrifluoroacetone (CFA) in dimethyl sulfoxide (DMSO). The conditions are mild and essentially neutral. The progress of the reaction can be followed by thin layer



chromatography or by gas–liquid chromatography. The latter method gives quantitative results when based on the size of the chloroform peak. CFA[5b] was easily prepared from commercially available chloropentafluoroacetone and aluminum chloride.



Although the actual mechanism of the reaction was not studied, the products showed that CFA was cleaved between the carbonyl carbon atom and the trichloromethyl moiety. Evidently, the trifluoromethyl group is a much poorer leaving group than is the trichloromethyl portion. This fact was established earlier by comparison of the reactions of hexachloroacetone and hexafluoroacetone with amino acids. The former work,[6] performed in this laboratory, found that *N*-trichloroacetylamino acids (**1**) were the major products.



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(1) To whom inquiries should be addressed.

(2) E. Schröder and K. Lübke, "The Peptides," Vol. I, "Methods of Peptide Synthesis," Academic Press, New York, N. Y., 1965, p 6–9.

(3) C. W. Gehrke, D. Roach, R. W. Zumwalt, D. L. Stalling, and L. L. Wall, "Quantitative Gas–Liquid Chromatography of Amino Acids in Proteins and Biological Substances," Analytical BioChemistry Laboratories, Inc., Columbia, Mo., 1968.

(4) B. Weinstein, *Methods Biochem. Anal.*, **14**, 203 (1966).

(5) (a) R. E. Sievers, E. Bayer, and P. Hunziker, *Nature*, **223**, 179 (1969). (b) Charles B. Miller and Cyril Woolf, U. S. Patent 2,807,646 (Sept 24, 1957); *Chem. Abstr.*, **52**, 2890*f* (1958).

(6) C. A. Panetta and T. G. Casanova, *J. Org. Chem.*, **35**, 2423 (1970).

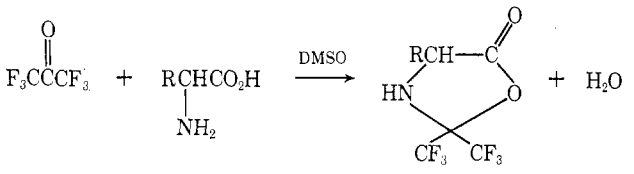
TABLE I

N-TRIFLUOROACETYLATION OF AMINO ACIDS AND DIPEPTIDES USING *sym*-TRICHLOROTRIFLUOROACETONE[a] AND DIMETHYL SULFOXIDE

Dipeptide or amino acid	TFA-amino acid or -dipeptide: Yield, %[b]	Mp, °C[c]	Purification	Lit. mp, °C[d]	[α], deg	Lit. [α],[e] deg	Trifluoroacetyl carbonyl stretch, ν (cm⁻¹)	Ml of DMSO per mmol of amino acid or dipeptide
L-Valine	94.0	88–89	From toluene then sublimation	86–88	−15.8 (2% H_2O)	−15.2		1.35
DL-Phenylalanine	51.5	126.5–127.0	From benzene and hexane	127–128				1.06
L-Phenylalanine	56.8	120–121	From benzene and hexane	120–122	+16.0 (2% EtOH)	+17.4		1.06
L-Leucine	Quantitative	Oil[f]	Distillation	72–75			1710 (neat)	1.06
L-Tyrosine	80.0	192.5–193.5	From water	192.5–193.5				1.07
L-Proline	Quantitative	Oil[f]	Distillation	46–48			1690 (neat)	1.31
DL-Alanine	20.0	118–119	Sublimation	120.5				1.31
Glycylglycine	42.5	184.7–185.0	From benzene and acetone	185[g]			1660 (Nujol)	1.91
L-Prolylglycine ethyl ester	23.4	109.5–110.5	From water	112–114[h]			1660 (Nujol)	1.91

[a] CFA (3 mol) was used per mole of amino acid or dipeptide. [b] No attempt was made to determine the optimum yields of the TFA–amino acids or TFA–dipeptides by this procedure. [c] Melting points are corrected. [d] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 932. [e] Reference *d*, pp 918–919. [f] Identity established by direct comparison with authentic material using thin layer chromatography and infrared spectroscopy. [g] F. Weygand and M. Reiher, *Chem. Ber.*, **88**, 26 (1955). [h] F. Weygand, P. Klinke, and I. Eigen, *ibid.*, **90**, 1896 (1957).

The reaction of hexafluoroacetone with amino acids,[7] on the other hand, afforded not the *N*-trifluoroacetylamino acids, but 2,2-bistrifluoromethyl-5-oxazolidones (**2**).



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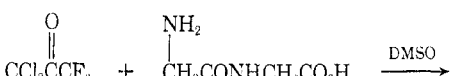
Other work[8] on the reaction of hexafluoroacetone with peptides in DMSO also showed no evidence for the rupture of carbonyl carbon–trifluoromethyl bond of the ketone.

The specific rotations of two *N*-trifluoroacetylamino acids (L-valine and L-phenylalanine), prepared by the present procedure, were determined and are provided with the published values for the corresponding optically pure compounds (see Table I).

Another advantage that CFA has over the conventional reagent, trifluoroacetic anhydride, is that it permits *N*-trifluoroacetylation of peptides without concomitant cleavage of the amide bond. Weygand and coworkers have reported[9] the partial cleavage of peptide bonds during trifluoroacetylation of peptides with trifluoroacetic anhydride. Two dipeptides (**3**, **5**) (see Table I) were acetylated with CFA in the present work.

Experimental Section[10]

The thin layer chromatograms of the TFA–amino acids and TFA–dipeptides were run on microscope slides coated with 250 μ layer of silica gel (J. T. Baker, 7G). Spotting was performed



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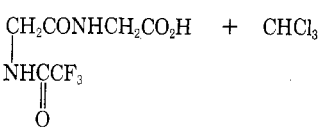

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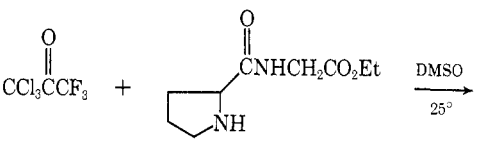

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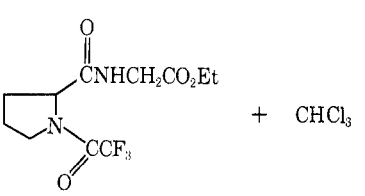

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using 0.5–1.0 μl of a 1% solution and the solvent system was either benzene–acetone–HOAc (50:45:5) or benzene–acetone (90:10). The zones were detected as yellow areas on a purple background after spraying with a 0.5% aqueous $KMnO_4$ solution sometimes followed with heating. Cited R_f values are approximate.

Gas–liquid chromatographic analyses of the chloroform byproduct in the following experiments were performed on a stainless steel column (0.25 in. × 2 m) packed with 20% dodecyl phthalate on GC-22, 60–80 mesh. The oven temperature was maintained at 90° and helium was the carrier gas.

***sym*-Trichlorotrifluoroacetone (CFA).**[11]—Fresh, anhydrous $AlCl_3$, 18.5 g (0.139 mol), was treated with 35.0 g (0.192 mol) of chloropentafluoroacetone (Allied Chemical Corp., Peninsular

(7) F. Weygand, K. Burger, and K. Engelhardt, *Chem. Ber.*, **99**, 1461 (1966).

(8) C. A. Panetta and T. G. Casanova, unpublished results.

(9) F. Weygand, R. Geiger, and U. Glocker, *Chem. Ber.*, **89**, 1543 (1956).

(10) Melting points are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(11) We are indebted to Mr. Cyril Woolf, Corporate Chemical Research Laboratory, Allied Chemical Corp., Morristown, N. J., whose advice and suggestions led to this procedure.

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.

Acknowledgment.—Support of this work under a National Institutes of Health Research Grant No. 5 R01 AM12761-02 MCHA is gratefully acknowledged.

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

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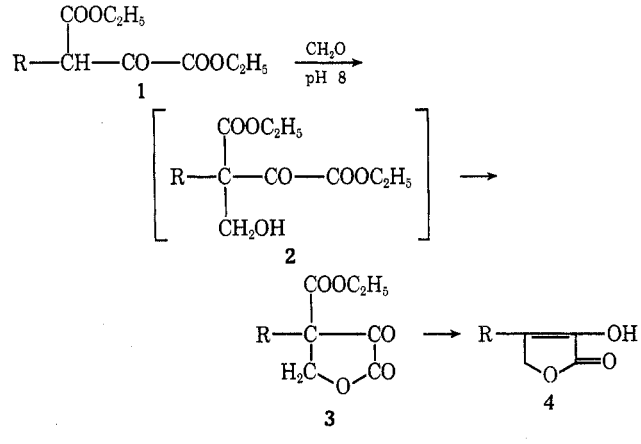
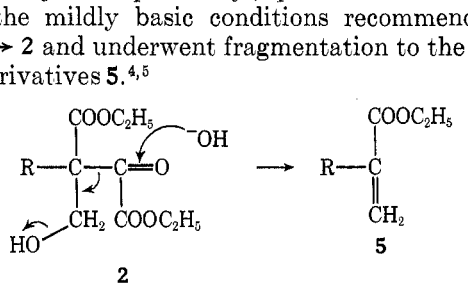
The field of α-tetronic acids, after a thorough synthetic exploration in the Forties by Schinz and coworkers,[1] has gained in interest recently as its representatives were encountered among the degradation products of the important antibiotic, cephalosporin C,[2] and were subsequently utilized as intermediates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



* Author to whom correspondence should be addressed.

(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).