remained. The dichloroalanine **13** thus obtained showed the following nmr spectral data: nmr (TFA) $\delta$ 1.79 (s, 3 H, acetyl), 3.73 and 4.41 (AB doublets, $J$ = 12 Hz, 2 H, $CH_2$); nmr (DMSO-$d_6$) 1.90 (s, 3 H, acetyl), 3.93 (s, 2 H, $CH_2$). After the solution was stirred for 10 min, hydrgen sulfide was bubbled in rapidly for 10 min. After an additional 10 min, the solvent was removed *in vacuo*. Trituration four times with small portions of diethyl ether gave 0.65 g (85%) of a white solid: mp 113–114° dec; nmr (TFA) $\delta$ 2.36 (s, 4 H, acetyl, SH), 4.36 and 4.74 (AB doublet, $J$ = 12 Hz, 2 H, $CH_2$), and 7.80 (broad s, 1 H, NH); nmr (DMSO-$d_6$) $\delta$ 1.87 (s, 4 H, acetyl, SH), 3.89 (s, 2 H, $CH_2$).

*Anal.* Calcd for $C_5H_8ClNO_3S$ (197.7): C, 30.39; H, 4.07; N, 7.09. Found: C, 30.39; H, 4.07; N, 7.04.

Similar results, as evidenced by nmr spectral data, were obtained when the dibromo compound **14** was treated with hydrogen sulfide in trifluoroacetic acid. However, the product was an unstable oil and attempts to effect purification were unsuccessful.

***N*-Acetyl-2-acetylthio-3-bromo-DL-alanine (16).**—2-Acetamidoacrylic acid (**5**) (0.30 g, 2.33 mmol) was suspended in 9 ml of glacial acetic acid. A solution of bromine in acetic acid was added until the bromine color was no longer discharged. An excess of thiolacetic acid was added and the reaction mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated *in vacuo* and the solid residue was triturated with diethyl ether to yield 0.47 g (70%) of crystalline material. Recrystallization from ethyl acetate gave material melting at 127–129° dec: tlc $R_{fA}$ 0.62; nmr (trifluoroacetic acid) $\delta$ 1.80 (s, 3 H, acetyl), 1.95 (s, 3 H, acetyl), 3.43 and 4.27 (AB doublet, $J$ = 11 Hz, $CH_2$, 2 H), 7.70 (s, 1 H, amide proton).

*Anal.* Calcd for $C_7H_{10}BrNO_4S$ (284.2): C, 29.6; H, 3.53; N, 4.94. Found: C, 29.5; H, 3.71; N, 4.91.

***N*-Benzyloxycarbonyl-2-mercapto-DL-alanine (18).**—2-(Benzyloxycarbonylamino)acrylic acid (17)[9] (500 mg, 2.26 mmol) was stirred in 3 ml of trifluoroacetic acid while hydrogen chloride gas was passed in for 10 min. After the solution was stirred for an additional 10 min, hydrogen sulfide was introduced into the reaction mixture for 15 min. The solvent was removed at reduced pressure followed by a vacuum of <1 mm. Ether was added slowly to the resulting oil until no more solid precipitated (~20 ml). Filtration and removal of solvent gave an oil with a structure apparently that of an impure sample of the thiol **18**: nmr ($CDCl_3$) $\delta$ 1.86 (s, 3 H, $CH_3$), 2.35 (s, 0.8 H, SH), 5.10 (s, 2.5 H, $CH_2$), and 7.60 (s, 8.5 H, phenyl). The instability of the product precluded further purification; however, tlc showed a major component ($R_{fC}$ 0.60) with only minor impurities.

**2-Mercapto-DL-alanine Hydrobromide (19).**—A solution of *N*-benzyloxycarbonyl-2-mercaptoalanine (**18**) was prepared as above but in acetic acid. To this solution was added 6 ml of a saturated solution of hydrogen bromide in acetic acid. Within 5 min, gas evolution began. After the solution was stirred for 1 hr, the mixture was filtered and the solvent was reduced *in vacuo* to 1/3 its original volume. The slow addition of 40 ml of diethyl ether, while cooling the mixture, gave a small amount of white solid ($NH_4Br$) which was filtered off. Removal of the solvent from the filtrate gave a viscous and somewhat unstable oil: nmr (DMSO-$d_6$) $\delta$ 1.58 (s, $CH_3$), 2.38 (s, SH), and 7.40 (t, $J$ = 51 Hz, $NH_3^+$). Further attempts at purification of **19** led to loss of ammonium bromide.

An impure sample of freshly prepared **19** in pyridine cooled to 0° was treated with acetic anhydride and allowed to stand in a refrigerator for 2 days. Following work-up of the reaction mixture, no evidence for the presence of **9** or **11** was detected by tlc or nmr. The crude product obtained consisted of several components as shown by tlc.

**Registry No.**—**9**, 36871-62-2; **11**, 36871-63-3; **12**, 36871-64-4; **15**, 36871-65-5; **16**, 36871-66-6; **18**, 36871-67-7.

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# Reaction of Hexafluoroacetone with Certain Simple Peptides and Related Compounds

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Hexafluoroacetone in dimethyl sulfoxide reacts with simple *N*-glycyl peptides and glycine esters to form fluorinated derivatives which contain an oxazolidine ring. When the N-terminal residue of the peptide is $\alpha$-methylalanyl, the product is a polyfluorinated imidazolidinyl peptide.

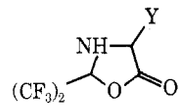
For the last four years, our research group has been concerned with the interaction of aldehydes and ketones with amino acids and simple peptides and their derivatives. Thus far, we have studied a fairly general reaction between carbonyl compounds (acetone, cyclohexanone, cyclopentanone, or isobutyraldehyde) and dipeptides[1] which has afforded novel imidazolidine ring systems. In general, polyhalogenated ketones react quite differently from other carbonyl compounds with amino acids, peptides, and their derivatives. Hexachloroacetone and *sym*-trichlorotrifluoroacetone afforded *N*-trichloroacetyl[2] and *N*-trifluoroacetyl[3] derivatives, respectively. Hexafluoroacetone condenses with amino acids to yield 2,2-bistrifluoromethyl-5-oxazolidones (**1**).[4] All of the foregoing reactions of polyhalogenated ketones were run with dimethyl sulfoxide as the solvent. The interaction of hexafluoroacetone with certain low-molecular-weight peptides in dimethyl sulfoxide is the subject of the present paper.

Hexachloroacetone and *sym*-trichlorotrifluoroacetone both suffered facile cleavage during reactions with simple peptides. In both cases, the trichloromethyl-to-carbonyl carbon bond was ruptured and chloroform was the by-product. Under identical reaction conditions, the cleavage of a carbon–carbon bond of hexafluoroacetone was never observed. Instead, one or two molecules of hexafluoroacetone condensed with the peptides studied in this work and produced relatively nonpolar and volatile peptide derivatives.

When glycylglycine was treated with hexafluoroacetone in dimethyl sulfoxide at −28 to +25°, a crystalline product was obtained, the solubility of which indicated that it was less polar than the parent dipeptide. Elemental analysis indicated that two hexafluoroacetone molecules condensed with one molecule of glycylglycine with the loss of a molecule of water.

(1) C. A. Panetta and M. Pesh-Imam, *J. Org. Chem.*, **37**, 302 (1972).
(2) C. A. Panetta and T. G. Casanova, *ibid.*, **35**, 2423 (1970).
(3) C. A. Panetta and T. G. Casanova, *ibid.*, **35**, 4275 (1970).
(4) F. Weygand, K. Burger, and K. Engelhardt, *Chem. Ber.*, **99**, 1461 (1966).

Spectral data (ir and nmr) provided evidence for carboxyl and amide carbonyl groups and for amine, amide, methylene, and methine hydrogen atoms. The acidity of the product and its apparent carboxyl carbonyl stretching absorption ruled out involvement of the carboxyl moiety (which was involved in the case of the reaction of hexafluoroacetone with amino acids[4] referred to above). The observation of an amide NH deformation absorption band[5] was strong proof that the amide group was not affected during the reaction. The only sites remaining on the dipeptide for the attachement of the two hexafluoroacetone molecules were the amino and methylene groups. Both of these groups, when present in separate molecules, are known to add to hexafluoroacetone.[6] Using the above information and other data which we obtained on similar fluorinated products derived from ethyl glycylglycinate and methyl and ethyl glycinate (see below), the structure of the condensation product



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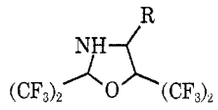
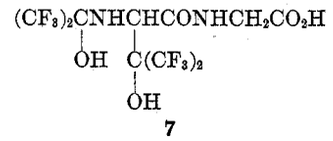


2, R = -CONHCH$_2$CO$_2$H
3, R = -CONHCH$_2$CO$_2$Et
4, R = -CONHCH$_2$CONHCH$_2$CO$_2$Me
5, R = -CO$_2$Et
6, R = -CO$_2$Me

was established as that of **2**. The polytrifluoromethylated oxazolidine ring probably resulted from the loss of water from the two hexafluoroacetone adduct moieties in **7**. The location of one of the hexafluoroacetone



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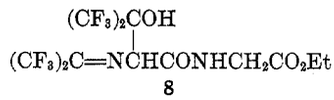

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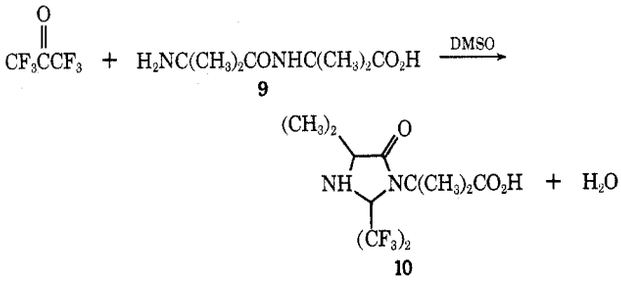
residues on what was originally the amino-end rather than the carboxyl-end methylene group was deduced from the mass spectral fragmentation patterns obtained on the ethyl glycylglycinate–hexafluoroacetone condensation product.

The condensation of glycylglycine ethyl ester with hexafluoroacetone afforded two isomeric products which were distillable, but were actually separated by chromatography on a column of silicic acid. An elemental analysis of a mixture of these isomers showed, as in the case of glycylglycine, that two molecules of hexafluoroacetone had condensed with a molecule of the dipeptide ester and that a molecule of water was lost. The major product (80% of the isomeric mixture) was very similar in its spectral properties with **2**. A mass spectrum of it confirmed the structural relationship and resulted in the assignment of structure **3** to this product. The minor (~20%) constituent of the isomeric mixture was tentatively assigned structure **8**. This was established mainly from infrared (C=N stretching band), nmr (alcohol proton), and mass spectral data.

Triglycine methyl ester has also been treated with hexafluoroacetone under conditions which are identical with those described above for glycylglycine ethyl ester. Elemental analysis and spectral evidence indicated that the fluorinated product also had the oxazolidine structure, **4**.

To obtain further support for the polyfluorinated oxazolidinyl peptide structures (**2**, **3**, and **4**) proposed above, we undertook the investigation of the action of hexafluoroacetone on the ethyl and methyl esters of glycine. Originally, we assumed that these reagents, when dissolved in DMSO, would combine to form 5-oxazolidones (**1**) similar to the reaction of zwitterionic amino acids with hexafluoroacetone.[4] However elemental analysis showed that, as with the peptides, two molecules of hexafluoroacetone condensed with each molecule of ethyl or methyl glycinate with the concomitant loss of a molecule of water. The spectral data on the oily products were in complete accord with structures **5** and **6**.

Imidazolidinyl peptides are commonly formed from the interaction of dipeptides and nonhalogenated aldehydes and ketones.[1] With hexafluoroacetone, an imidazolidinyl peptide was formed when the $\alpha$-carbon atom at the amino end of the peptide was completely substituted. This fact was demonstrated in the reaction of $\alpha$-methylalanyl-$\alpha$-methylalanine (**9**) with hexafluoroacetone. The two reactants condensed in a 1:1 molar ratio to afford an acidic, but relatively nonpolar, product the infrared spectrum of which lacked the amide NH deformation absorption band[5] that was present in the spectrum of the parent dipeptide. The polyfluorinated imidazolidinyl peptide product, **10**, was characterized by elemental analysis and by its infrared and proton magnetic resonance spectra.



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Thus, hexafluoroacetone in dimethyl sulfoxide condenses with N-terminal glycyl peptides and glycine esters in a 2:1 ratio to afford fluorinated products which contain an oxazolidine ring. When the N-terminal residue is $\alpha$-methylalanyl, equimolar amounts of reactants combine to yield a polyfluorinated imidazolidinyl peptide.

## Experimental Section

**Reaction of Glycylglycine with Hexafluoroacetone. Preparation of 2.**—A solution of 0.698 g (5.3 mmol) of glycylglycine in 15 ml of DMSO was placed in a dry flask which was equipped with a drying tube containing Drierite, a Dry Ice cooled condenser, and a magnetic stirrer. Anhydrous hexafluoroacetone gas was introduced to the flask in a steady stream; this was continued until a persistent reflux rate of the condensed gas was obtained. The reaction mixture soon froze. The entire apparatus was left unattended (in a hood, and usually overnight),

(5) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co. Ltd., London, 1968, pp 286, 287.

(6) For a review of these and other reactions see C. G. Krespan and W. J. Middleton, *Fluorine Chem. Rev.*, **1**, 145 (1967).

during which time the Dry Ice sublimed and the reaction mixture slowly warmed to ambient temperature. The resultant yellow solution was poured into about 100 ml of ice–water. The aqueous solution was extracted thrice with 30-ml portions of *n*-BuOH, and the butanol solvent was removed by distillation under reduced pressure. The residue weighed 0.573 g and was chromatographed on silicic acid (160 g, Mallinckrodt, 100 mesh) using MeOH as the solvent. This procedure removed the last traces of DMSO from the product, and the resultant homogeneous oil (0.379 g, 16%) crystallized during storage. The product, **2**, was soluble in 1 *N* NaOH, acetone, or methyl isobutyl ketone, but was insoluble in water, benzene, or hexane. It was recrystallized from methyl isobutyl ketone and benzene: mp 135.0–135.5°; ir (Nujol) 3400, 3260 (NH,OH), 1743–1715 (carboxyl C=O), 1670 (amide C=O), 1538 (amide NH); nmr (acetone-$d_6$) 4.12 (m, 2, methylene H), 5.1 (m, 2, methine H and amide H), 6.9 (broad, 1, amine H), 8.0 (broad, 1, carboxyl H).

*Anal.* Calcd for $C_{10}H_6F_{12}N_2O_4$ (**2**): C, 26.92; H, 1.36; F, 51.10; N, 6.28. Found: C, 26.88; H, 1.47; F, 48.47; N, 6.32.

**Reaction of Glycylglycine Ethyl Ester with Hexafluoroacetone. Preparation of 3 and 8.**—A solution of 0.983 g (5.0 mmol) of the hydrochloride of glycylglycine ethyl ester in 25 ml of DMSO was treated with 0.535 g (5.3 mmol) of triethylamine. This mixture was then treated with an excess of hexafluoroacetone in exactly the same manner as that described above for glycylglycine. An oil was obtained which weighed 0.444 g (18.8%), bp 96–110° (0.23 mm).

*Anal.* Calcd for $C_{12}H_{10}F_{12}N_2O_4$ (**3** or **8**): C, 30.40; H, 2.13; F, 48.08; N, 5.91. Found: C, 30.60; H, 2.27; F, 47.08; N, 5.81.

In a later run, the above oily product was found to contain two isomers, **3** and **8**. The minor product (**8**) was obtained in only 2.8% yield, tlc $R_f$ 0.8 [$C_6H_6$–EtOAc (9:1), silica gel]. The major oily product (**3**) was isolated in 12.7% yield, $R_f$ 0.4 [$C_6H_6$–EtOAc (9:1), silica gel]. The ir, nmr, and mass spectra of both of these isomers were consistent with the proposed structures.

**Reaction of Glycylglycylglycine Methyl Ester Hexafluoroacetone. Preparation of 4.**—The hydrochloride of glycylglycylglycine methyl ester[7] (mp 196–197°) was treated with hexafluoroacetone according to the same procedure that was used on glycylglycine ethyl ester hydrochloride (see above). The yield of crystalline product (**4**) was 27.8%: mp 150.5–151.0° (from hot $CH_2Cl_2$ or benzene); ir (Nujol) 3484, 3356, 3165 (NH), 1757 (ester C=O), 1689, 1667 (amide C=O), 1536 (amide NH), 1227 (C-F), 1183 (C–O–C); nmr (acetone-$d_6$) 2.8 (s, 2, amide, $H_2O$), 3.67 (s, 3, methyl), 4.02 (m, 4, methylene), 4.95 (broad, ~1, methine), 5.2 (broad, ~1, NH, partly exchanged); mass spectrum *m/e* (rel intensity) 517 (3, $M^+$), 486 (26, $M^+ - OCH_3$), 448 (60, $M^+ - CF_3$), 429 (7, $M^+ - NHCH_2CO_2CH_3$), 402 (100, $M^+ - CONHCH_2CO_2CH_3$), 351 (4, $M^+$ – hexafluoroacetone), 344 (21, $M^+ - CONHCH_2CONHCH_2CO_2CH_3$), 173 (100, $CONHCH_2CONHCH_2CO_2CH_3$), 88 (29, $NHCH_2CO_2CH_3$), 85 (25, $NH{=}CHCONH{=}CH_2$).

*Anal.* Calcd for $C_{13}H_{11}F_{12}N_3O_5$ (**4**): C, 30.12; H, 2.14; F, 44.08; N, 8.12. Found: C, 29.98; H, 2.08; F, 43.82; N, 8.14.

**Reaction of Glycine Ethyl and Methyl Esters with Hexafluoroacetone. Preparation of 5 and 6.**—The hydrochlorides of glycine ethyl and methyl esters were treated with hexafluoroacetone in separate experiments according to the procedure used on glycylglycine ethyl ester hydrochloride. The ethyl ester product, **5**, was obtained in 16.3% yield, bp 84° (23 mm).

*Anal.* Calcd for $C_{10}H_7F_{12}NO_3$ (**5**): C, 28.79; H, 1.69; F, 54.65; N, 3.36. Found: C, 28.60; H, 1.79; F, 54.44; N, 3.54.

The methyl ester product, **6**, was obtained in 44.5%, bp 78° (25 mm). The ir and nmr spectra of both of these products were consistent with the proposed structures.

**Reaction of α-Methylalanyl-α-methylalanine (9) with Hexafluoroacetone. Preparation of 10.**—A mixture of 0.37 g (1.80 mmol) of α-methylalanyl-α-methylalanine[8] and 5 ml of DMSO was treated with an excess of hexafluoroacetone in the same manner as that described above for glycylglycine. A solid precipitated when the reaction mixture was poured into ice–water. It weighed 0.31 g and was crystallized from aqueous acetone to afford 25 mg (4.1%) of pure **10**, mp 88.5°. The ir and nmr spectra supported structure **10** for this product. It was insoluble in water, but soluble in 1 *N* NaOH solution.

*Anal.* Calcd for $C_{11}H_{14}F_6N_2O_3$ (**10**): C, 39.29; H, 4.20; F, 33.90; N, 8.33. Found: C, 39.05; H, 4.13; F, 34.15; N, 8.32.

**Registry No.**—**2**, 36871-69-9; **3**, 36871-70-2; **4**, 36901-03-8; **5**, 36871-71-3; **6**, 36871-72-4; **8**, 36871-73-5; **10**, 36871-74-6; hexafluoroacetone, 684-16-2.

**Acknowledgment.**—Support of this work under a National Institutes of Health Research Project Grant No. AM 12761-03 is gratefully acknowledged.

(7) H. N. Rydon and P. W. G. Smith, *J. Chem. Soc.*, 2542 (1955).

(8) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R.C. Sheppard, *Tetrahedron*, **11**, 39 (1960).

# Crystal and Molecular Structure of 5a,11a-Dibromojanusene

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The crystal structure of 5a,11a-dibromojanusene has been solved by the heavy-atom method. The strain between the apposed aromatic rings results in corresponding carbon atoms in the two rings being separated by amounts ranging from 2.99 Å for 11b and 12b to 4.09 Å in the case of 14 and 19. The dihedral angle between the apposed rings is 26.6°. The molecular geometry is discussed in detail.

Janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene) was first synthesized by Cristol and Lewis in 1967.[1] The compound was synthesized in order to study the physical and chemical effects arising from the π-electron interactions between two apposed aromatic rings, forced by the rigidity of the system to approach each other very closely. The structural formula, and the atom numbering system, are shown in Figure 1. A Dreiding model of janusene shows that the apposed or face (F) rings (in the terminology of Cristol and Lewis) would be parallel to each other and separated by about 2.5 Å, in the absence of any repulsion between the two π-electron clouds. Considerable repulsion is, of course, to be expected. The X-ray analysis of 5a,11a-dibromojanusene (DBJ) (Figure 2) was undertaken in order to determine how the molecular structure accommodates the strains imposed by the π-electron interaction.

(1) S. J. Cristol and D. C. Lewis, *J. Amer. Chem. Soc.*, **89**, 1476 (1967).

## Discussion

The bond lengths and angles in DBJ, as determined in this analysis, are given in Tables I and II, respectively, together with the corresponding standard deviations. Since none of the hydrogen atoms was located, data are given only for the bonds involving the carbon atoms and the bromine atoms.

The carbon–carbon bond lengths are all well within the expected limits. The carbon–bromine bond length