tract was filtered, washed with water, and dried (magnesium sulfate). Solvent was removed under vacuum at 40–45° leaving a dark red residue which was shaken vigorously with 250 ml. of petroleum ether followed by 250 ml. of benzene. The residue, after decanting the benzene solution, was triturated with 100 ml. of ether and divided into ether-soluble and -insoluble portions. The ether-insoluble portion was chromatographed on a column of 100 mesh silicic acid packed in chloroform. Continuous change of solvent from chloroform to ethyl acetate eluted first mitorubrin and then mitorubrinol. Fractional crystallization of the ether-soluble portion from ethyl acetate–ether afforded further quantities of mitorubrinol.

Mitorubin was recrystallized from ethyl acetate to give orange-yellow prisms: m.p. 218°; $[\alpha]^{25}D$ −405° (*c* 1.02, dioxane); mol. wt. 382 (mass spectrum); λ_{max}^{EtOH} 216 mμ (ε 18,200), 266 (18,200), 292 (10,100), and 346 (16,100); λ_{max}^{NaOH} 246 mμ (ε 20,200), 320 (23,600), 346 (28,600), and 485 (5600); ν_{max}^{KBr} 3400 (broad), 1715, 1660–1600 (many bands), 1545, 1505, 1450, 1380, 1345, 1315, 1270, 1240, 1220, 1160, 1130, 1115, 1075, 979, 960, 921, 916, 884, 872, 860, and 801 cm.$^{-1}$. Recrystallization of mitorubrinol from ethyl acetate–ether gave yellow microcrystalline needles: m.p. 219–221°; $[\alpha]^{25}D$ −375° (*c* 1.70, dioxane); ultraviolet spectrum identical with that of mitorubrin: ν_{max}^{KBr} 3400 (broad), 1715, 1650–1580 (many bands), 1540, 1445, 1365, 1320, 1260, 1235, 1200, 1165, 1105, 1075, 997, 972, 937, 881, 858, and 799 cm.$^{-1}$.

Deuterium Exchange with Mitorubrin. To a sample of 40 mg. of mitorubrin dissolved in 0.2 ml. of d_7-dimethylformamide was added 0.04 ml. of D_2O. The solution was allowed to stand at room temperature for intervals of 5 min., 12 hr., and 72 hr. After each period, the solvent was removed under vacuum and replaced with 0.2 ml. of fresh d_7-dimethylformamide, and the n.m.r. spectrum was determined.

Mitorubramine. Mitorubrin (9 mg.) was added to 1 ml. of a 1:1 mixture of 0.880 ammonium hydroxide and water. The pigment slowly dissolved to form a dark red solution which, on acidification with 10% hydrochloric acid, precipitated an orange colored solid. The precipitate was collected, washed with water, and dried *in vacuo* to yield 8 mg. of mitorubramine: m.p. 196–199° dec.; λ_{max}^{EtOH} 212 mμ (ε 25,800), 275 (32,600), 293 (shoulder), and 365 (18,500); $\lambda_{max}^{10\% NaOH}$ 240 mμ (ε 13,500), 297 (43,800), and 335 (18,500); mass spectrum *m/e* (381), 337, 229, 215, 214, 200, 189, 150, 124, and 123.

Orcylaldehyde (**6**). This substance was prepared according to the method of Adams[10] and after purification by sublimation had m.p. 183.5° (lit.[10] 178–180°); ν_{max}^{Nujol} 3150, 1630, 1600, 1390, 1295, 1270, 1230, 1205, 1165, 999, 989, 877, 836, and 821 cm.$^{-1}$. The n.m.r. spectrum of **6**, in d_7-dimethylformamide, showed two very broad signals at 11.0 and 12.5 p.p.m. for the hydroxyl protons, a singlet at 10.2 p.p.m. for the aldehyde proton, and a three proton singlet at 2.55 p.p.m. corresponding to the methyl group. The two aromatic protons gave rise to an AB quartet, with chemical shifts of 6.28 and 6.37 p.p.m. and a coupling constant of 2 c.p.s.

Methyl Orsellinate (**8**). Addition of 1 equiv. of diazomethane to an ice-cold solution of orsellinic acid (**7**) in anhydrous ether gave a quantitative yield of methyl orsellinate (**8**). The ester was obtained, after recrystallization from aqueous ethanol, as a microcrystalline solid: m.p. 135–138° dec. (lit.[12] m.p. 138–139°); λ_{max}^{EtOH} 216 mμ (ε 18,100), 264 (12,400), and 297 (5100); λ_{max}^{NaOH} 242 mμ (ε 8300), and 306 mμ (ε 17,900); ν_{max}^{Nujol} 3400, 3100–2500 (broad), 1650–1605 (many bands), 1580, 1500, 1315, 1260, 1215, 1200, 1170, 1160, 1115, 1065, 1005, 998, 957, 858, 840, 802, and 704 cm.$^{-1}$. The n.m.r. spectrum, in d_7-dimethylformamide, showed signals at 11 (2 H, broad), 6.36 (2 H, singlet), 3.93 (3 H, singlet), and 2.46 p.p.m. (3 H, singlet).

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686-04) for financial support.

Transformation of L-Serine Peptides to L-Cysteine Peptides[1]

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Contribution from the Laboratory of Organic Chemistry, University of Athens, Athens, Greece. *Received April 17, 1965*

The serine moieties of the peptides N-carbobenzoxy-L-serylglycine ethyl ester and N-carbobenzoxyglycyl-L-serylglycine ethyl ester were O-tosylated to give the corresponding O-tosyl derivatives IV and VI, respectively. Displacement of the O-tosyl groups of IV and VI by thiobenzoate anion afforded in excellent yields N-carbobenzoxy-S-benzoyl-L-cysteinylglycine ethyl ester (Va) and N-carbobenzoxyglycyl-S-benzoyl-L-cysteinylglycine ethyl ester (VIIa), respectively. A similar displacement by thioacetate anion afforded N-carbobenzoxy-S-acetyl-L-cysteinylglycine ethyl ester (Vb) and N-carbobenzoxyglycyl-S-acetyl-L-cysteinylglycine ethyl ester (VIIb).

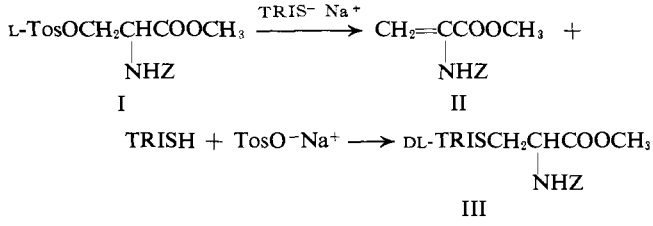
Introduction

Previous communications from this laboratory dealt with the possibility of the transformation of L-serines incorporated into a peptide chain to L-cysteine residues.[2] This should be brought about by conversion of the O-tosyl group of serine to an easily removable S-protected

(1) This investigation was supported in part by grants from the National Institutes of Health, U. S. Public Health Service, Grant TW 00107-01, and the Royal Hellenic Research Foundation.

(2) L. Zervas and I. Photaki, *Chimia* (Aarau), **14**, 375 (1960).

group of cysteine.[2] Using N-carbobenzoxy-O-tosyl-L-serine methyl ester as a model compound, it has been shown that by the interaction of this O-derivative with the sodium salt of tritylthiocarbinol, S-trityl-N-carbobenzoxycysteine methyl ester was formed.[3,4] During this reaction, though, complete racemization occurred. Apparently, in the above replacement reaction, a β-elimination is first brought about by the action of the alkaline sodium mercaptide on compound I and this is followed by the addition of tritylthiocarbinol to the dehydroalanine derivative II, leading to the formation of the DL-derivative III.

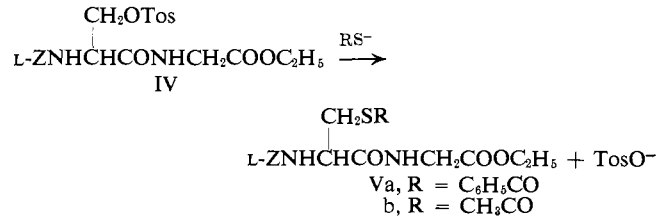


Tos = p-$CH_3C_6H_4SO_2$, Z = $C_6H_5CH_2OCO$, TRI = $(C_6H_5)_3C$

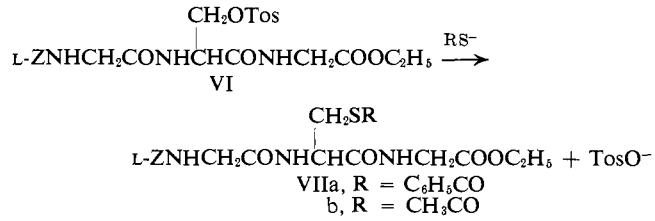
As a matter of fact O-tosyl[4] and O-diphenylphosphoryl serine derivatives[4,5] undergo quickly β-elimination under the action of 0.1 N alkali or even of diethylamine in nonpolar solvents. Following these findings Koshland, *et al.*,[6] succeeded in preparing a "tosylchymotrypsin" and converting it to "anhydro-chymotrypsin." This transformation involved the serine residue at the "active site" of chymotrypsin. On the other hand, conversion of L-serine residues[6,7] present at or near the active site of many enzymes to L-cysteinyl residues would be very useful for the study of the role of serine in the specific activity of these enzymes.

Further experiments carried out in this laboratory[8] proved that O-tosyl serine peptides could be readily transformed[9] to S-acyl cysteine peptides under conditions which do not affect the existing configuration of the serine residue. The removal of the S-acyl groups presents no difficulties since it can be effected under mild conditions which, in addition, exclude β-elimination reactions.[10] As a matter of fact S-acyl cysteines have been widely used in this laboratory for the synthesis of polypeptides containing cysteine residues.[3,10-12]

N-Carbobenzoxy-O-tosyl-L-serylglycine ethyl ester[4] was allowed to react with various salts (potassium, triethylammonium, diethylammonium, imidazolium) of thiobenzoic and thioacetic acid in solvents such as alcohol, ethyl acetate, or dimethylformamide, and N-carbobenzoxy-S-benzoyl-L-cysteinylglycine ethyl ester (Va) and N-carbobenzoxy-S-acetyl-L-cysteinylglycine ethyl ester (Vb) were isolated in excellent yields. The S-acyl peptides thus formed were identical with authentic samples prepared as described in previous communications from this laboratory.[10]



The displacement of O-tosyl groups by sulfur nucleophiles such as thiobenzoate or thioacetate anions has been extended to peptides bearing the serine moiety between two other amino acid residues as in the tripeptide carbobenzoxylglycyl-L-serylglycine ethyl ester. This peptide has been converted to its O-tosyl derivative VI, in the manner already described for the preparation of IV, *i.e.*, in absolute pyridine solution by addition of tosylchloride at -5 to 0°. The O-tosyl tripeptide VI has been converted to the corresponding S-benzoyl (VIIa) and S-acetyl (VIIb) cysteinyl tripeptides, in 75–80% yields of optically and analytically pure products.



Peptide VIIa was proved to be identical with the product obtained by coupling of carbobenzoxyglycine with S-benzoyl-L-cysteinylgylcine ethyl ester.

Experimental

Anhydrous reactants and dry solvents were used throughout this work. Evaporations were carried out *in vacuo* at 30–35°. The melting points are not corrected.

Prior to analysis the compounds were dried at 56° under high vacuum over phosphorus pentoxide.

The R_f values were determined by thin layer chromatography[13] in toluene–pyridine–acetic acid (80:10:1). The development of N-protected peptide derivatives was performed with iodine. The S-acyl derivatives were also developed with aqueous sodium nitroprusside solution after a short time treatment with sodium methoxide solution.

N-Carbobenzoxy-S-benzoyl-L-cysteinylglycine Ethyl Ester (Va). *A.* To a solution of 0.24 g. (0.0005 mole) of N-carbobenzoxy-O-tosyl-L-serylglycine ethyl ester[4] (IV) in 2.5 ml. of ethanol, 0.45 g. of potassium thiobenzoate was added. After allowing it to stand for 10 hr. at 20° (or for 3 hr. at 50°) the mixture was cooled and the precipitate was filtered and washed with a small quantity of cold ethanol to give Va, m.p. 150–153°, in almost quantitative yield.[14] After re-

(3) L. Zervas, I. Photaki, A. Cosmatos, and N. Ghelis, "Peptides: Proceedings of the Fifth European Symposium," G. T. Young, Ed., Pergamon Press Ltd., Oxford, 1963, p. 27.
(4) I. Photaki, *J. Am. Chem. Soc.*, **85**, 1123 (1963).
(5) G. Riley, J. Turnbull, and W. Wilson, *J. Chem. Soc.*, 1373 (1957).
(6) D. H. Strumeyer, W. N. White, and D. E. Koshland, Jr., *Proc. Natl. Acad. Sci. U. S.*, **50**, 931 (1963).
(7) D. E. Fahrney and A. M. Gold, *Biochemistry*, **3**, 783 (1964); J. Kallos and D. Rizok, *J. Mol. Biol.*, 7, 599 (1963).
(8) I. Photaki and V. Bardakos, *Experientia*, in press; by the time our note had been accepted for publication, we were notified of a preliminary report on similar results published by C. Ziourdrou, M. Wilchek, M. Sokolovsky, and A. Patchornik, *Israel J. Chem.*, **2**, 326 (1964).
(9) For examples of conversion of O-tosyl groups to S-acyl groups, *cf.* D. Horton and D. H. Hutson, *Advan. Carbohydrate Chem.*, **18**, 123 (1963).
(10) L. Zervas, I. Photaki, and N. Ghelis, *J. Am. Chem. Soc.*, **85**, 1337 (1963).
(11) I. Photaki, *Experientia*, **20**, 487 (1964).
(12) L. Zervas, I. Photaki, A. Cosmatos, and D. Borovas, to be published.
(13) M. Brenner and A. Niederwieser, *Experientia*, **16**, 378 (1960).
(14) The yield was lower (50%) if 0.1 g. (0.0006 mole) of potassium thiobenzoate was used.

crystallization from ethanol (recovery 85%) the melting point was 153.5° (lit.[10] m.p. 153°), $[\alpha]^{18}D$ −58.8° (*c* 1, dimethylformamide) (lit.[10] $[\alpha]^{18}D$ −58.5° (*c* 1, dimethylformamide)) R_f 0.5.

B. Interaction of IV and potassium thiobenzoate was carried out in dimethylformamide instead of ethyl alcohol. The reaction mixture was diluted with ethyl acetate and the solution was washed with cold water, potassium hydrogen carbonate solution, and again with water, dried over sodium sulfate, and evaporated to dryness. The crystalline residue was triturated with ether and filtered. The yield was 0.17 g. (77%) regardless of the temperature at which the reaction took place, *i.e.*, either at 20° (10 hr.), or at 50° (3 hr.); m.p. 152–153°, $[\alpha]^{18}D$ −58.3° (*c* 1, dimethylformamide).

C. To a solution of 0.35 g. of thiobenzoic acid and 0.35 ml. of triethylamine (or 0.25 ml. of diethylamine) in 2 ml. of ethyl acetate, 0.24 g. of IV was added and the solution was allowed to stand for 48 hr. at 20° (or for 3 hr. at 50°). It was diluted with ethyl acetate and was worked up as described under B. The yield was *ca.* 0.16 g. (70%), m.p. 152–153°, $[\alpha]^{18}D$ −58.2° (*c* 1, dimethylformamide).

D. To a solution of 0.35 g. of thiobenzoic acid and 0.16 g. of imidazol in 2 ml. of ethyl acetate, 0.24 g. of IV was added and the mixture was allowed to stand for 24 hr. at 20°. Va, which separated out, was filtered, washed with ether, and recrystallized from ethanol. The yield was 0.16 g. (72%), m.p. 152–153°, $[\alpha]^{18}D$ −58.6° (*c* 1, dimethylformamide).

*N-Carbobenzoxy-S-acetyl-*L*-cysteinylglycine Ethyl Ester (Vb).* *A.* To a solution of 0.24 g. of N-carbobenzoxy-O-tosyl-L-serylglycine ethyl ester[4] (IV) in 2 ml. of ethanol, 0.29 g. of freshly prepared potassium thioacetate was added. After allowing it to stand for 24 hr. at 20°, the solution was diluted with ethyl acetate and washed with cold water, potassium hydrogen carbonate solution, and water. It was dried over sodium sulfate and evaporated to dryness. The crystalline residue was triturated with ether and filtered. The yield was 0.13 g. (68%), m.p. 135–136° (lit.[10] m.p. 135–136°), $[\alpha]^{18}D$ −48.6° (*c* 1, dimethylformamide) (lit.[10] $[\alpha]^{18}D$ −48.4° (*c* 1, dimethylformamide)), R_f 0.5.

B. To a solution of 0.20 ml. of thioacetic acid in 2 ml. of ethyl acetate, 0.35 ml. of triethylamine (or 0.25 ml. of diethylamine, or 0.16 g. of imidazol) and 0.24 g. of IV were added. After allowing the mixture to stand for 24 hr. at 20° (or for 3 hr. at 50°), it was diluted with ethyl acetate and worked up as described above under A. The yield was 0.14–0.15 g. (75–80%),[15] m.p. 134–135°, $[\alpha]^{18}D$ −48.4° (*c* 1, dimethylformamide).

L-Serylglycine Ethyl Ester Hydrochloride. N-Carbobenzoxy-L-serylglycine ethyl ester[16] (3.25 g., 0.01 mole) was suspended in 22 ml. of 0.5 *N* alcoholic hydrogen chloride and catalytically (Pd) hydrogenated in the usual way. The catalyst was filtered and the filtrate was evaporated to dryness. To the residue ethanol was added and evaporated again. The oily residue was triturated with ether, the ether was decanted, and fresh ether was added. The hydrochloride crystallized by allowing the mixture to stand overnight at −10°. It was filtered and washed with ether. The yield was 2 g. (89%), m.p. 55–58°, $[\alpha]^{18}D$ +28° (*c* 2, dimethylformamide), R_f 0.36 (thin layer chromatography[13] in *n*-butyl alcohol–acetic acid–water (100:10:30)[17]).

Anal. Calcd. for $C_7H_{15}ClN_2O_4$: N, 12.36; Cl, 15.64. Found: N, 12.55; Cl, 15.60.

*N-Carbobenzoxyglycyl-*L*-serylglycine Ethyl Ester.* To a cold (0°) solution of 1.13 g. (0.005 mole) of L-serylglycine ethyl ester hydrochloride and 1.05 g. of carbobenzoxylglycine in 5 ml. of dimethylformamide, 1.1 g. of N,N′-dicyclohexylcarbodiimide was added followed by the dropwise addition of 0.7 ml. of triethylamine. The mixture was allowed to stand at room temperature overnight and the insoluble precipitate of N,N′-dicyclohexylurea and triethylamine hydrochloride was removed by filtration. The filtrate was diluted with ethyl acetate and washed successively with cold water, 1 *N* sulfuric acid, water, potassium hydrogen carbonate solution, and water. The solution was dried over sodium sulfate and concentrated to dryness. The residue was recrystallized from ethyl acetate; 0.91 g. (48%) of the product was obtained, m.p. 153–155°, $[\alpha]^{18}D$ +1.48° (*c* 2, dimethylformamide), R_f 0.02.

Anal. Calcd. for $C_{17}H_{23}N_3O_7$: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.77; H, 5.84; N, 10.70.

*N-Carbobenzoxyglycyl-O-tosyl-*L*-serylglycine Ethyl Ester (VI).* To a solution of 0.38 g. (0.001 mole) of N-carbobenzoxyglycyl-L-serylglycine ethyl ester in 3 ml. of anhydrous pyridine, precooled to −5°, 0.48 g. of tosyl chloride was added and the mixture was stirred at −5 to 0° for 1 hr. Cold water (20 ml.) was added with stirring. Upon seeding and scratching, crystalline VI separated out. The yield was 0.4 g. (75%), m.p. 99–101°. After one recrystallization from acetone–water, the melting point was raised to 102–103°, $[\alpha]^{19}D$ +4.25° (*c* 2, dimethylformamide), R_f 0.15.

Anal. Calcd. for $C_{24}H_{29}N_3O_9S$: C, 53.82; H, 5.46; N, 7.84; S, 5.99. Found: C, 54.06; H, 5.48; N, 7.72; S, 5.69.

*N-Carbobenzoxyglycyl-S-benzoyl-*L*-cysteinylglycine Ethyl Ester (VIIa).* *A.* To a solution of 0.16 g. (0.0003 mole) of VI in 2 ml. of ethanol, 0.27 g. of potassium thiobenzoate or 0.21 g. of thiobenzoic acid and 0.21 ml. of triethylamine (or 0.15 ml. of diethylamine) were added. After allowing it to stand for 48 hr. at 20° (or for 3 hr. at 50°) it was filtered from some undissolved material and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed with cold 1 *N* sulfuric acid, water, potassium hydrogen carbonate solution, and water. It was dried over sodium sulfate and evaporated to dryness. Acetone was added and it was evaporated again to dryness. The residue was crystallized by dissolving it in acetone and adding petroleum ether. The yield was 0.11–0.12 g. (75–80%), m.p. 105–108°, unaltered after recrystallization from acetone–petroleum ether, $[\alpha]^{18}D$ −30.6° (*c* 2, dimethylformamide), R_f 0.3.

Anal. Calcd. for $C_{24}H_{27}N_3O_7S$: C, 57.47; H, 5.43; N, 8.38; S, 6.39. Found: C, 57.80; H, 5.55; N, 8.47; S, 6.22.

B. A solution of 1.35 g. (0.003 mole) of N-carbobenzoxy-S-benzoyl-L-cysteinylglycine ethyl ester[10] (Va) and 0.6 g. of phenol in 4.5 ml. of trifluoroacetic

(15) If ethanol or dimethylformamide was used instead of ethyl acetate, the yield was 50–60%.

(16) J. S. Fruton, *J. Biol. Chem.*, **146**, 463 (1942).

(17) R. Schwyzer and H. Kappeler, *Helv. Chim. Acta*, **44**, 1991 (1961).

acid[18] was refluxed on a steam bath for 30 min. and then was evaporated to dryness. Upon dissolving the residue in ether and adding ether saturated with hydrogen chloride, S-benzoyl-L-cysteinylglycine ethyl ester hydrochloride separated as an oil. The supernatant liquor was decanted and the hydrochloride was washed several times with ether, each washing being followed by decantation. The remaining solvent was removed by evaporation. In the meantime, a solution containing 0.63 g. (0.003 mole) of carbobenzoxyglycine, 25 ml. of chloroform, and 0.42 ml. of triethylamine was cooled to −5° and 0.39 ml. of isobutyl chloroformate was added. The solution of the anhydride was allowed to stand at −5° for 15 min. and was added to the dipeptide hydrochloride, followed by the dropwise addition of 0.42 ml. of triethylamine. After being allowed to stand at room temperature overnight, the solution was diluted with chloroform and washed successively with 1 *N* hydrochloric acid, potassium hydrogen carbonate solution, and water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from acetone–petroleum ether; the yield was 0.73 g. (49%), m.p. 105–108°, $[\alpha]^{18}D$ −30.8° (*c* 2, dimethylformamide).

(18) F. Weygand and W. Steglich, *Z. Naturforsch.*, **14b**, 472 (1959).

Anal. Found: C, 57.77; H, 5.56; S, 6.22.

N-Carbobenzoxyglycyl-S-acetyl-L-cysteinylglycine Ethyl Ester (VIIb). To a solution of 0.10 ml. of thioacetic acid in 1 ml. of ethyl acetate, 0.175 ml. of triethylamine and 0.135 g. (0.00025 mole) of O-tosyltripeptide VI were added. The solution was allowed to stand at 20° for 24 hr. It was diluted with ethyl acetate and washed with cold 1 *N* sulfuric acid, water, potassium hydrogen carbonate solution, and water, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from acetone–petroleum ether yielded 0.091 g. (83%) of VIIb, m.p. 90–95°. After recrystallization from acetone–petroleum ether (recovery 80%), the melting point was 92–95°, $[\alpha]^{19}D$ −28.6° (*c* 1.5, dimethylformamide), R_f 0.15.

Anal. Calcd. for $C_{19}H_{25}N_3O_7S$: C, 51.93; H, 5.73; N, 9.56; S, 7.29. Found: C, 51.92; H, 5.98; N, 9.66; S, 6.89.

Acknowledgments. The authors wish to thank Dr. H. Mantzos for the microanalyses and Dr. G. C. Stelakatos for help in preparing the manuscript.

Glutarimide Antibiotics. VII. The Synthesis of *dl*-Neocycloheximide and the Determination of the Cyclohexanone Ring Stereochemistry of Cycloheximide, Its Isomers,[1] and Inactone

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Contribution from The Dow Chemical Company, Eastern Research Laboratory, Framingham, Massachusetts. *Received March 6, 1965*

The Nielsen condensation of dl-cis-2,4-dimethylcyclohexanone with 3-glutarimidylacetaldehyde has been examined as a synthetic approach to compounds having the gross structure of cycloheximide (I). The sole crystalline product from the reaction is a new isomer of I and has been named dl-neocycloheximide. A combination of chemical methods and n.m.r. spectroscopy has been used to elucidate completely the cyclohexanone ring stereochemistry of cycloheximide and its stereochemical isomers naramycin-B, isocycloheximide, and neocycloheximide. The skeletal structure of inactone has been confirmed and its stereochemistry has been elucidated. Comments on the stereochemistry of E-73 and streptovitacin-A are noted.

Introduction

The glutarimide antibiotics constitute a truly fascinating group of mold products. Their diverse spectrum of biological activity alone serves to place them in a unique category insofar as naturally occurring organic compounds are concerned. To date twelve distinct substances belonging to this class have been isolated, the best known of these being cycloheximide[2] (I). This particular compound not only is a highly effective fungicide,[2,3] having excellent systemic activity against tomato late blight, cherry leaf spot rust, and white pine blister rust, but is also the most potent rodent repellent known.[4] It also shows toxicity toward algae,[5] protozoa,[6] higher plants,[7] and animals.[8] In addition it has marked antitumor activity[9] but suffers from being somewhat too toxic to the host to be used in this respect. Recently it has been shown that one of

(1) A preliminary account of this work has appeared: F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1167, 1173 (1962).

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(3) J. R. Vaughn, *Phytopathology*, **41**, 36 (1951); T. T. McLure, *ibid.*, **42**, 14 (1952); H. D. Wells and B. P. Robinson, *ibid.*, **44**, 509 (1954); D. Cation, *Am. Fruit Grower*, **74**, 29 (1954); J. M. Hamilton and M. Szkolnik, *Proc. N. Y. State Hort. Soc.*, 58 (1955).

(4) J. F. Welch, *J. Agr. Food Chem.*, **2**, 142 (1954).

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(6) J. B. Loefer and T. S. Matney, *Physiol. Zool.*, **25**, 272 (1952).

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(8) J. H. Ford and B. E. Leach, *J. Am. Chem. Soc.*, **70**, 1223 (1948).

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