UDC 542.91+615.779.9

COMPLETE SYNTHESIS OF SERRATAMOLIDE

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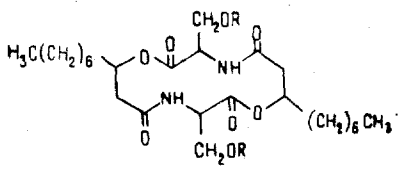
Khimiya Prirodnykh Soedinenii, Vol. 3, No. 4, pp. 267-272, 1967

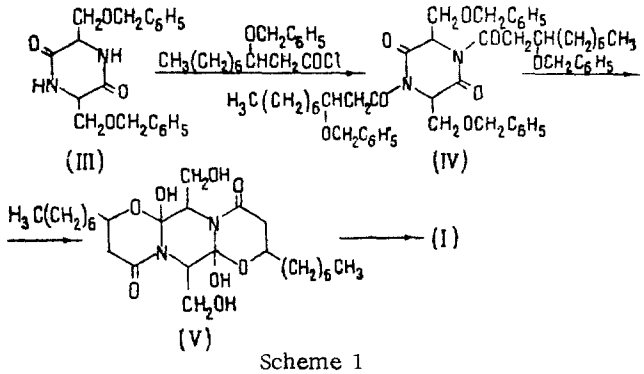
In 1961, Wasserman et al. isolated from the products of the metabolism of a culture of Serratia marcescens a new antibiotic serratamolide possessing a marked activity with respect to a number of bacteria, yeasts, and pathogenic fungi [1]. A study of the products of chemical degradation and of a number of physicochemical properties of serratamolide permitted the structure of a cyclotetradepsipeptide (I) constructed of regularly alternating L-serine and D-β-hydroxydecanoic acid residues to be assigned to it. During the work directed to establishing its structure, a number of its derivatives were prepared, including O, O'-diacetylserratamolide (II).



(I) R = H

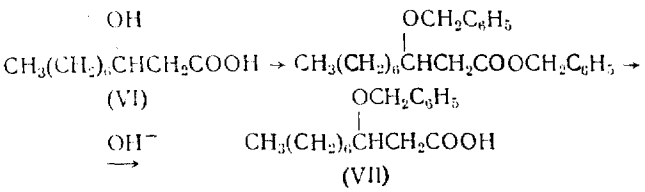
(II) R = CH_3CO

To confirm the proposed structure of serratamolide, we have carried out its synthesis. Previously, in the synthesis of cyclodepsipeptides containing α-hydroxy acid residues (enniatine, Valinomycin, sporidesmolides, etc.), we achieved the best results by cyclizing the corresponding linear compounds under conditions of high dilution (see, for example [2-4]). For serratamolide, however, which contains β-hydroxy acid residues, it proved to be better to use another general method for the synthesis of cyclodepsipeptides that we have proposed based on the inclusion of the hydroxy acids in cyclic amides and, in particular, of β-hydroxy acids in diketopiperazines [5].



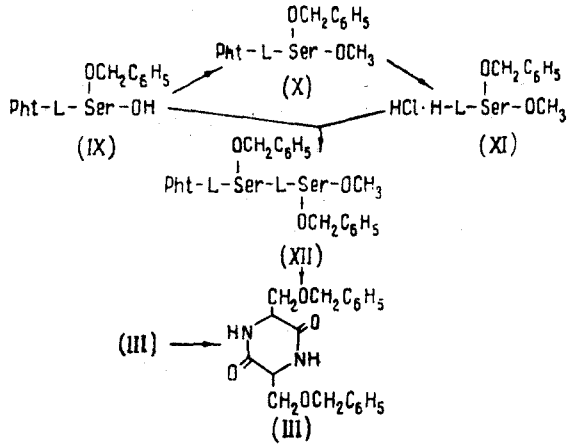
Scheme 1

Initially, we planned to obtain serratamolide (I) directly via the biscyclol (V), which could be formed by the acylation of L, L-3, 6-bis (benzyloxymethyl)-2, 5-diketopiperazine (III) with the chloride of D-β-benzyloxydecanoic acid with subsequent elimination of the protecting groups from the diacyl derivative (IV) by catalytic hydrogenolysis (scheme 1). For this route, we needed, in the first place, D-β-benzyloxydecanoic acid (VII) and the diketopiperazine (III). The first of these compounds was synthesized by the action of benzyl bromide and silver oxide on D-β-hydroxydecanoic acid (VI) obtained, in its turn, by the separation of the corresponding racemic acid into its antipodes by means of quinine and cinchonidine (scheme 2).



Scheme 2

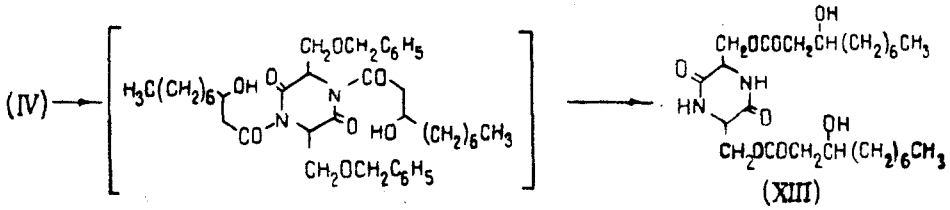
The diketopiperazine (III) was synthesized in the following way (scheme 3). Phthalylation of O-benzyl-DL-serine by the action of phthalic anhydride in dioxane led to N-phthalyl-O-benzyl-DL-serine (VIII). By separating the latter into its



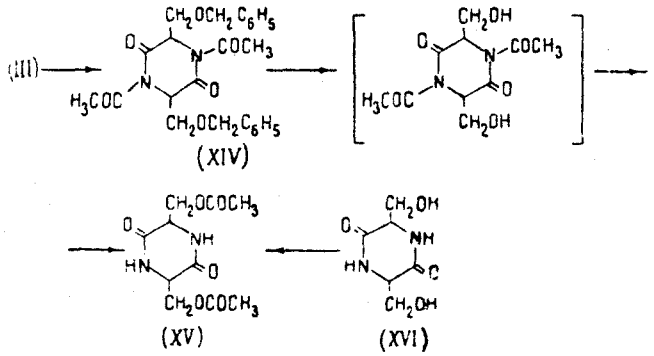
Scheme 3

antipodes via its morphine salt we obtained crystalline N-phthalyl-O-benzyl-L-serine (IX) (this compound was obtained in the form of an oil with considerable contamination by the racemate by De Haas [6] by a different method). This compound was methylated with diazomethane to give the methyl ester (X) which, under the action of hydrazine, furnished a high yield of the methyl ester of O-benzyl-L-serine (XI), which was isolated in the form of the hydrochloride. Condensation of the hydrochloride with N-phthalyl-O-benzyl-L-serine (IX) by means of N, N'-dicyclohexylcarbodiimide gave a quantitative yield of the corresponding dipeptide (XII), which was converted by treatment with hydrazine hydrate into the diketopiperazine (III).

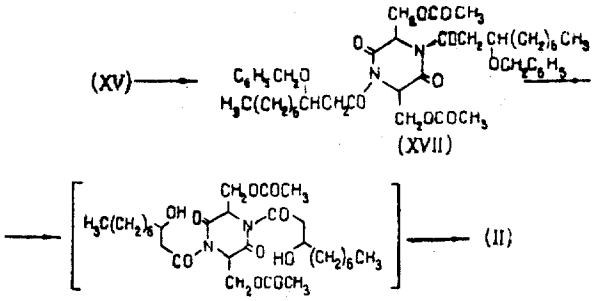
Acylation of the diketopiperazine (III) with D-β-benzyloxydecanoyl chloride in boiling toluene led to the diacyldiketopiperazine (IV). Without being isolated in the pure state, the latter was subjected to hydrogenolysis in tetrahydrofuran solution in the presence of palladium black. A substance was isolated from the reaction mixture with a yield of 50% which, however, differed in all its properties from serratamolide [mp 170–172° C; $[\alpha]_D^{20}$ 22.5° (c 0.8, acetic acid)]. Its IR spectrum was characterized by the absence of a second amide band and the presence of a band corresponding to an ester group (1730 cm^{-1}) This compound underwent alkaline hydrolysis extremely readily, forming as the sole reaction products β-hydroxydecanoic acid and the diketopiperazine of serine (XVI). These results permit the assumption that the reaction product was L, L-3, 6-bis (D-β-hydroxydecanoyloxymethyl)-2, 5-diketopiperazine (XIII), formed by the N → O migration of the D-β-hydroxydecanoic acid residue during hydrogenolysis.



This assumption was confirmed by a study of the behavior of L, L-N, N'-diacetyl-3, 6-bis (benzyloxymethyl)-2, 5-diketopiperazine (XIV) obtained by the acetylation of the diketopiperazine (III) with acetyl chloride in boiling benzene (scheme 4). When XIV was hydrogenolyzed, N → O migration of the acyl residue again took place, and the L, L-3, 6-bis (acetoxymethyl)-2, 5-diketopiperazine (XV) so formed was isolated with a yield of 85%. For identification, a sample of the latter was also synthesized by the acetylation of the diketopiperazine of L-serine (XVI) with acetic acid in the presence of hydrogen chloride or with acetyl chloride in acetic acid.

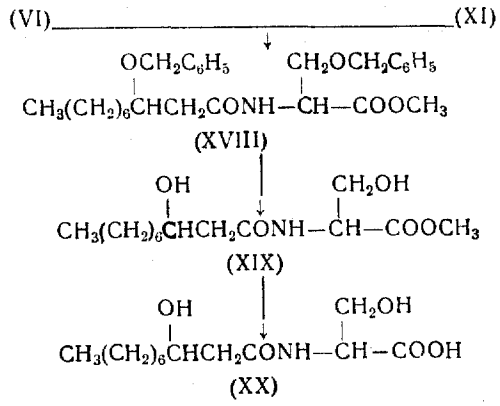


Scheme 4



Scheme 5

In order to exclude the possibility of N → O migration in the synthesis of serratamolide it was obviously necessary before acylation to block the reactive hydroxy groups of the diketopiperazine of L-serine (XVI) by means of a protective group stable to hydrogenolysis. For this purpose we used the acetyl residue. The acylation of the diketopiperazine (XV) with D-β-benzyloxydecanoyl chloride gave N, N'-bis (D-β-benzyloxydecanoyl)-3, 6-bis (acetoxymethyl)-L, L-2, 5-diketopiperazine (XVII) which, without isolation, was then subjected to catalytic hydrogenolysis (scheme 5). A compound was isolated from the reaction mixture with a yield of about 30% which had properties agreeing with those of O, O'-diacetylserratamolide (II). The structure of this compound was shown definitively by its spectral characteristics, by a molecular weight determination (by the thermoelectric method and by mass spectrometry), and, finally, by its conversion on alkaline hydrolysis into serratamic acid (XX), which is the product of the alkaline hydrolysis of serratamolide [1, 7]. For identification, we obtained a sample of serratamic acid by independent synthesis according to scheme 6, by condensing D-β-benzyloxydecanoic acid (VI) with the methyl ester of O-benzyl-L-serine (XI) by the carbodiimide method, by eliminating the benzyl group from the amide formed (XVIII) by catalytic hydrogenolysis, and subsequently by hydrolyzing the resulting methyl ester of serratamic acid (XIX).



Scheme 6

Selective elimination of the acetyl groups from diacetylserratamolide (II) was performed successfully by the action of methanolic hydrogen chloride at 20° C. The compound obtained was identical with serratamolide in regard to its physical properties (mp, mixed mp, specific rotation, IR spectrum, chromatographic behavior) and in its antimicrobial activity. Thus, the synthesis that we have performed has enabled the correctness of the structure of serratamolide proposed by Wasserman et al. to be definitively confirmed.

Experimental

Separation of DL-β-hydroxydecanoic acid into its antipodes. A mixture of 15 g (0.08 mole) of DL-β-hydroxydecanoic acid and 27 g (0.071 mole) of anhydrous quinine was dissolved in 200 ml of methyl ethyl ketone with heating. The solution was cooled and left at 0° C for 24 hr. The salt that separated out (15.5 g) was filtered off and recrystallized from methyl ethyl ketone. This gave 10 g (49%) of the salt of L-β-hydroxydecanoic acid and quinine, mp 102–104° C, $[\alpha]_D^{20}$ −131° (c 1.2; methanol).

Found, %: C 70.48; H 8.79; N 5.44. Calculated for $C_{30}H_{44}O_5N_2$, %: C 70.28; H 8.65; N 5.46.

A mixture of 5.14 g (0.01 mole) of the quinine salt of L-β-hydroxydecanoic acid, 20 ml of 2 N hydrochloric acid, and 30 ml of ether was shaken until the solid matter dissolved, and then the ethereal layer was separated off and the aqueous layer was extracted with ether. The combined ethereal solution was dried with magnesium sulfate and evaporated in vacuum. This gave 1.8 g (96%) of L-β-hydroxydecanoic acid, mp 48–48.5° C; $[\alpha]_D^{20}$ +21.5° (c 1.3; chloroform).

The filtrate after the separation of the quinine salt of L-β-hydroxydecanoic acid was evaporated in vacuum, and the residue was treated with 50 ml of water, 10 ml of concentrated hydrochloric acid, and 50 ml of ether. The mixture

was shaken until the salt dissolved and then the ethereal layer was separated off and the aqueous layer was extracted with ether. The D-β-hydroxydecanoic acid (8.9 g) obtained from the combined ethereal solution was dissolved in 100 ml of ethyl acetate, 12.3 g (0.042 mole) of cinchonidine was added to the solution, and the mixture was heated until it dissolved. The solution was left at 0° C for a day, and the salt that separated out was filtered off and thrice recrystallized from ethyl acetate. This gave 13.6 g (60%) of the cinchonidine salt of D-β-hydroxydecanoic acid, mp 119–120° C; $[\alpha]_D^{20}$ −83° (c 1.5; chloroform) (cf. [7]). Under conditions analogous to those for the isolation of L-β-hydroxydecanoic acid from its quinine salt, 4.8 g (0.01 mole) of the cinchonidine salt of D-β-hydroxydecanoic acid gave 1.85 g (98%) of D-β-hydroxydecanoic acid, mp 48–49° C; $[\alpha]_D^{20}$ −20.8° (c 1; chloroform).

D-β-Benzyloxydecanoic acid (VII). To a solution of 27 g (0.143 mole) of D-β-hydroxydecanoic acid (VI) in 500 ml of dry ether was added 70 g (0.3 mole) of silver oxide and, with stirring, over 5 hr, 71 ml (0.6 mole) of benzyl bromide. The mixture was stirred for another 24 hr at room temperature and then the precipitate of silver salt was filtered off and the filtrate was evaporated in vacuum. The residue was chromatographed on neutral alumina in the hexane-benzene system (gradient elution), and four main fractions were isolated. The first fraction consisted of a mixture of unchanged benzyl bromide and dibenzyl ether, and the second (34.2 g; 65%) was the benzyl ester of D-β-benzyloxydecanoic acid; $[\alpha]_D^{20}$ −0.5° (c 2; chloroform).

Found, %: C 78.10; H 8.60. Calculated for $C_{24}H_{32}O_3$, %: C 78.22; H 8.75.

The third fraction (10 g; 25%), consisted of the benzyl ester of D-β-hydroxydecanoic acid; $[\alpha]_D^{20}$ −17.8° (c 2.5; chloroform).

Found, %: C 73.37; H 9.31. Calculated for $C_{17}H_{26}O_3$, %: C 73.34; H 9.41.

Finally, the fourth fraction consisted of benzyl alcohol.

A solution of 18.5 g (0.05 mole) of benzyl D-β-benzyloxydecanoate in 200 ml of 0.6 N caustic soda in 90% ethanol was left at 20° C for 24 hr. The alcohol was distilled off in vacuum and the residue was treated with water, the aqueous solution then being washed with ether and acidified with hydrochloric acid. The oil which separated was extracted with ether. This gave 11.9 g (85%) of D-β-benzyloxydecanoic acid (VII); $[\alpha]_D^{20}$ −5.6° (c 1.2; chloroform).

Found, %: C 73.30; H 9.35. Calculated for $C_{17}H_{26}O_3$, %: C 73.34; H 9.41.

N-Phthalyl-O-benzyl-DL-serine (VIII). A mixture of 50 g (0.256 mole) of O-benzyl-DL-serine, 37 g (0.25 mole) of phthalic anhydride, and 300 ml of dry dioxane was boiled with stirring for 10 hr. The mixture was cooled and diluted with 1 *l* of ether, and the resulting solution was washed with 2 N hydrochloric acid and with water and was dried over magnesium sulfate and evaporated. This gave 80 g (96%) of N-phthalyl-O-benzyl-DL-serine (VIII), mp 93–95° C (from dipropyl ether-hexane).

Found, %: C 66.59; H 4.67; N 4.32. Calculated for $C_{18}H_{15}O_5N$, %: C 66.45; H 4.65; N 4.31.

N-Phthalyl-O-benzyl-L-serine (IX). To a boiling solution of 175 g (0.54 mole) of N-phthalyl-O-benzyl-DL-serine (VIII) in 1.5 *l* of acetone was added 145 g (0.48 mole) of morphine monohydrate. The mixture was boiled with stirring until all the morphine had dissolved and it was left at 0° C for 3 days. The crystals that deposited (190 g) were filtered off and recrystallized three times from the minimum amount of absolute ethanol. This gave 99 g (60%) of the morphine salt of N-phthalyl-O-benzyl-L-serine, mp 182–183° C (decomp.); $[\alpha]_D^{20}$ −95° (c 0.9; methanol). The salt obtained was stirred with 2.5 *l* of water, 0.5 *l* of ether, and 200 ml of concentrated hydrochloric acid until it had dissolved completely. The ethereal layer was separated off and the aqueous layer was extracted with ether. Evaporation of the combined ethereal solution gave 52 g (98.5%) of N-phthalyl-O-benzyl-L-serine (IX), mp 84–86° C (from dipropyl ether-hexane); $[\alpha]_D^{20}$ −62.5° (c 1.5; ethanol); −60° (c 12; chloroform).

Found, %: C 66.57; H 4.63; N 4.12. Calculated for $C_{18}H_{15}O_5N$, %: C 66.45; H 4.65; N 4.31.

Methyl ester of N-phthalyl-O-benzyl-L-serine (X). At 0° C, an ethereal solution of diazomethane was added to a solution of 32.5 g (0.1 mole) of N-phthalyl-O-benzyl-L-serine (IX) in 200 ml of ether until a persistent yellow coloration appeared. After an hour, the excess of diazomethane was decomposed with formic acid and the ethereal solution was washed with bicarbonate solution, dried over magnesium sulfate, and evaporated. This yielded 32.5 g (96%) of the methyl ester of N-phthalyl-O-benzyl-L-serine (X), mp 67–68° C (from isopropanol); $[\alpha]_D^{20}$ −66° (c 1; methanol).

Found, %: C 67.54; H 5.13; N 4.15. Calculated for $C_{19}H_{17}O_5N$, %: C 67.25; H 5.05; N 4.13.

Hydrochloride of the methyl ester of O-benzyl-L-serine (XI). A solution of 30 g (0.088 mole) of the methyl ester of N-phthalyl-O-benzyl-L-serine (X) and 4.6 g (0.094 mole) of hydrazine hydrate in 300 ml of methanol was left at 20° C for 24 hr. Then 1 *l* of ether and a solution of 10 g of sodium carbonate in 300 ml of water were added. The mixture was shaken until the precipitate of phthalyl hydrazide dissolved, and the ethereal layer was separated off, washed with water, and dried with magnesium sulfate. The drying agent was filtered off, and the filtrate was acidified with methanolic hydrochloric acid (to Congo Red) and evaporated in vacuum. Recrystallization of the residue from acetoni-

trile gave 15 g (69%) of the hydrochloride of the methyl ester of O-benzyl-L-serine (XI), mp 165–166° C; $[\alpha]_D^{20}$ +6.9° (c 1; methanol).

Found, %: C 53.82; H 6.73; N 6.03; Cl 14.37. Calculated for $C_{11}H_{16}O_3NCl$, %: C 53.77; H 6.56; N 5.70; Cl 14.43.

Methyl ester of N-phthalyl-O-benzyl-L-seryl-O-benzyl-L-serine (XII). A solution of 1 g of sodium carbonate in 10 ml of water was added to a suspension of 2.46 g (10 mmole) of the hydrochloride of the methyl ester of L-benzyl-L-serine (XI) in 10 ml of CH_2Cl_2, and the mixture was shaken for 2 min. The organic layer was separated off and dried over $MgSO_4$. The resulting solution of the methyl ester of O-benzyl-L-serine was treated with 3.25 g (10 mmole) of N-phthalyl-O-benzyl-L-serine (XI), the mixture was cooled to −10° C, and then 2.27 g (11 mmole) of dicyclohexylcarbodiimide was added. The mixture was kept at 0° C for 24 hr, and then 1 ml of 50% acetic acid was added, it was shaken for 20 min, and the precipitate was filtered off. The filtrate was washed with 2 N hydrochloric acid, with water, and with saturated sodium bicarbonate solution, dried with magnesium sulfate, and evaporated in vacuum. This gave 5.2 g (100%) of the dipeptide (XII) in the form of an oil. The substance was used subsequently without additional purification. A sample for analysis was purified by chromatography on neutral alumina in the benzene-ethyl acetate system; $[\alpha]_D^{20}$ −4.5° (c 2; methanol).

Found, %: C 67.31; H 5.43; N 5.20. Calculated for $C_{29}H_{28}O_7N_2$, %: C 67.43; H 5.46; N 5.42.

Diketopiperazine of O-benzyl-L-serine (III). A solution of 5.16 g (0.01 mole) of the methyl ester of N-phthalyl-O-benzyl-L-seryl-O-benzyl-L-serine (XII) and 2 ml (0.04 mole) of hydrazine hydrate in 20 ml of methanol was boiled for 5 hr. The mixture was evaporated and the residue was treated with 200 ml of chloroform and 100 ml of 5% sodium hydrogen carbonate solution, with shaking until it dissolved. The chloroform extract was washed with 2 N hydrochloric acid and with water and was dried over $MgSO_4$ and evaporated. This gave 2.5 g (70%) of the diketopiperazine (III), mp 166–167° C (from C_2H_5OH); $[\alpha]_D^{20}$ −79° (c 1; chloroform).

Found, %: C 67.89; H 6.20; N 7.93. Calculated for $C_{20}H_{22}O_4N_2$, %: C 67.78; H 6.26; N 7.91.

Acylation of the diketopiperazine of O-benzyl-L-serine (III) with D-β-benzyloxydecanoic acid. A mixture of 2.9 g (10.4 mmole) of D-β-benzyloxydecanoic acid (VII) and 15 ml of $SOCl_2$ was boiled for 1 hr. The reaction mixture was evaporated in vacuum and the residual acid chloride was dissolved in 20 ml of dry toluene; 1.77 g (5 mmole) of the diketopiperazine (III) was added and the mixture was boiled for 15 hr. The solution was evaporated and the residue was dissolved in 30 ml of dry tetrahydrofuran and hydrogenated in the presence of a palladium catalyst (from 0.1 g of PdO). The catalyst was filtered off, the filtrate was evaporated in vacuum, and the residue was dissolved in 10 ml of absolute ethanol and left for a day at 0° C. The crystals that deposited were filtered off and recrystallized from absolute ethanol. This gave 1.29 g (50%) of the diketopiperazine of O-D-β-hydroxydecanoyl-L-serine (XIII), mp 170–172° C; $[\alpha]_D^{20}$ −22.5° (c 0.8; acetic acid).

Found, %: C 60.49; H 8.89; N 5.60. Calculated for $C_{26}H_{46}O_8N_2$, %: C 60.68; H 9.01; N 5.44.

Acylation of the diketopiperazine of O-benzyl-L-serine (III) with acetyl chloride. Under the conditions of the preceding experiment, 3.2 g (9 mmole) of the diketopiperazine (III) and 2.1 ml (30 mmole) of acetyl chloride in 30 ml of benzene gave 2.0 g (86%) of the diketopiperazine of O-acetyl-L-serine (XV), identical with that described in the following experiment.

Synthesis of an authentic sample of the diketopiperazine of O-acetyl-L-serine (XV). A. A suspension of 1.74 g (10 mmole) of the diketopiperazine of L-serine (XVI) in 150 ml of anhydrous acetic acid was saturated with hydrogen chloride. The solution was left at room temperature for 5 hr and was evaporated to dryness in vacuum, and the residue was recrystallized from water. This gave 2.3 g (89%) of the diketopiperazine of O-acetyl-L-serine (XV), mp 228–230° C; $[\alpha]_D^{20}$ −7° (c 0.9; acetic acid).

Found, %: C 46.50; H 5.45; N 10.87. Calculated for $C_{10}H_{14}O_6N_2$, %: C 46.51; H 5.47; N 10.85.

B. A mixture of 3.0 g (17.2 mmole) of the diketopiperazine of L-serine (XVI), 10 ml of acetyl chloride, and 300 ml of glacial acetic acid was stirred at 20° C until the solid matter dissolved and was then treated as described in experiment A, to give 4.1 g (92%) of the diketopiperazine (XV), identical with that described in the preceding experiment.

O, O'-Diacetylserratamolide (II). A mixture of 2.5 g (9 mmole) of D-β-benzyloxydecanoic acid (VII) and 15 ml of thionyl chloride was boiled for 1 hr and evaporated in vacuum, the residue was dissolved in 20 ml of dry toluene, 1.03 g (4 mmole) of the diketopiperazine from O-acetyl-L-serine (XVI) was added, and the mixture was boiled for 25 hr. After cooling, the unchanged diketopiperazine (0.25 g) was filtered off and the filtrate was evaporated in vacuum. The residue was dissolved in 40 ml of dry tetrahydrofuran and was hydrogenated in the presence of a palladium catalyst (from 0.2 g of PdO). The catalyst was filtered off, the filtrate was evaporated in vacuum, the residue was dissolved in 10 ml of chloroform, and hexane was added to this solution until opalescence appeared. After 7 days, the crystals that had deposited were filtered off and recrystallized from absolute ethanol. This gave 0.5 g (27%, calculated on the diketopiperazine (III) that had reacted) of O, O'-diacetyl-serratamolide (II), mp 222–223° C; $[\alpha]_D^{20}$ +8° (c 0.5; chloroform).

Found, %: C 60.30; H 8.47; N 4.74; mol. wt. 578 (thermoelectrically in CF_3COOH). Calculated for $C_{30}H_{50}O_{10}N_2$, %: C 60.18; H 8.42; N 4.68; mol. wt. 598.7.

Alkaline hydrolysis of O-O'-diacetylserratamolide. A mixture of 79 mg (0.13 mmole) of (II) and 10 ml of 0.5 N caustic soda in 5% ethanol was boiled for 30 min. The solution was cooled, evaporated in vacuum, diluted in water to a volume of 3 ml, and acidified with hydrochloric acid. The crystals that deposited (43 mg; 60%) were filtered off and dried in vacuum. The substance obtained was identical with the serratamic acid described below.

Synthesis of serratamic acid. A. Methyl ester of D-β-benzyloxydecanoyl-O-benzyl-L-serine (XVIII). At −10° C, 2.3 g (8.3 mmole) of D-β-benzyloxydecanoic acid (VI) and 2.5 g (12 mmole) of dicyclohexylcarbodiimide were added to a solution of the methyl ester of O-benzyl-L-serine (XI), obtained as described in the synthesis of the methyl ester of N-phthalyl-O-benzyl-L-seryl-O-benzyl-L-serine (XII), from 2.46 g (10 mmole) of its hydrochloride, in 20 ml of methylene chloride. The mixture was left at 0° C for 48 hr, the excess of carbodiimide was decomposed with 1 ml of 50% acetic acid, and the precipitate of dicyclohexylurea was filtered off. The filtrate was washed with 2 N hydrochloric acid, with water, and with a saturated solution of sodium hydrogen carbonate, dried with $MgSO_4$, and evaporated in vacuum. This gave 3.9 g (100%) of the amide (XVIII) in the form of an oil. The substance was used subsequently without further treatment. A sample for analysis was purified by chromatography on alumina in the hexane-ether system; $[\alpha]_D^{20}$ +9.7° (c 1.9; methanol).

Found, %: C 71.40; H 8.30; N 3.10. Calculated for $C_{28}H_{39}O_5N$, %: C 71.61; H 8.37; N 2.98.

B. Methyl ester of serratamic acid (XIX). A solution of 2.35 g (5 mmole) of the methyl ester of D-β-benzyloxydecanoyl-O-benzyl-L-serine (XVIII) in 40 ml of methanol was hydrogenated in the presence of a palladium catalyst (from 0.4 g of PdO) until the theoretical amount of hydrogen had been adsorbed. The catalyst was filtered off, the filtrate was evaporated in vacuum, and the residue was recrystallized from di-n-propyl ether. This gave 1.23 g (85%) of the methyl ester of serratamic acid (XIX), mp 94–95° C; $[\alpha]_D^{20}$ −2.5° (c 0.9; ethanol).

Found %: C 58.09; H 9.47; N 4.94. Calculated for $C_{14}H_{27}O_5N$, %: C 58.11; H 9.41; N 4.84.

C. Serratamic acid (XX). A mixture of 578 mg (2 mmole) of the methyl ester of serratamic acid (XIX) and 5 ml of 0.5 N caustic soda was stirred at room temperature until the ester had dissolved (about 10 hr). The solution was acidified with hydrochloric acid and the crystals were filtered off and recrystallized from water. This gave 495 mg (90%) of serratamic acid (XX), mp 137–138° C; $[\alpha]_D^{20}$ +10° (c 2; ethanol) (cf. [7]).

Found, %: C 56.75; H 9.29; N 5.11. Calculated for $C_{13}H_{25}O_5N$, %: C 56.70; H 9.15; N 5.09.

Serratamolide. A suspension of 0.105 g (0.176 mmole) of diacetylserratamolide (II) in 30 ml of 10% methanolic hydrochloric acid was left with periodic shaking for 2 hr (20° C). The diacetylserratamolide gradually went into solution. The resulting solution was evaporated in vacuum and the residual oil was subjected to preparative thin-layer chromatography on plates of hydrated silica (layer thickness 2 mm) in the acetone-chloroform-ethyl acetate (1:2:6) system. The product was eluted from the chromatogram with ethyl acetate, the solvent was evaporated off, and the residue was recrystallized from alcohol. The yield of serratamolide was 46 mg (51%), mp 149–150° C, $[\alpha]_D^{20}$ +7.7° (c 1; chloroform). The compound obtained was identical with the natural antibiotic in respect of its IR spectrum and chromatographic behavior. A mixture with natural serratamolide gave no depression of the melting point.

Summary

The complete synthesis of the antibiotic serratamolide has been effected, definitively demonstrating its structure.

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26 July 1966

Institute of the Chemistry of Natural Compounds
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