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TOTAL SYNTHESIS OF SERRATAMOLIDE

I. SYNTHESIS OF O,O'-DIACETYLSERRATAMOLIDE

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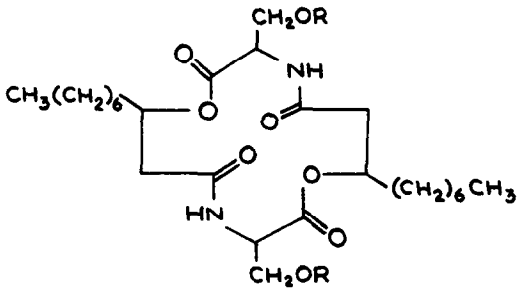
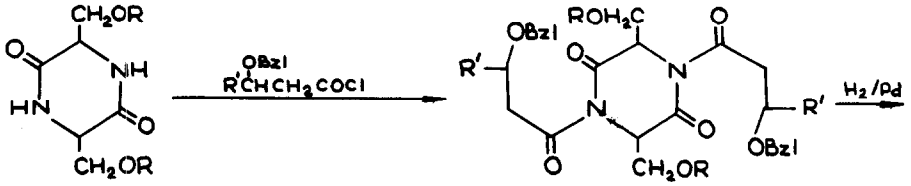
IN 1961 Wasserman et al. (1) isolated from a Serratia marcescens culture a new antibiotic, serratamolide, possessing appreciable activity against a number of bacteria, yeasts and pathogenic fungi. On the basis of the properties of this compound and the results of its degradative study, it was ascribed the cyclotetradepsipeptide structure (I), built up from L-serine and D-β-hydroxydecanoic acid residues. Several derivatives of the antibiotic, including O,O'-diacetylserratamolide (II) were obtained.



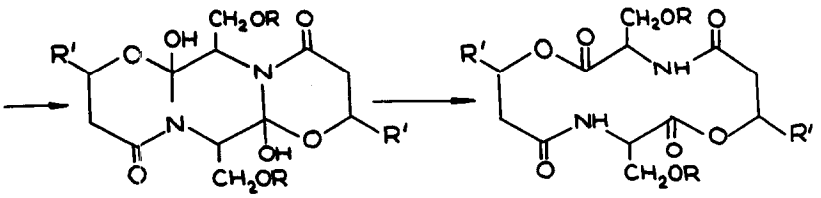
(I): R=H; (II): R=Ac.

In the course of our investigations into the chemistry of naturally occurring cyclodepsipeptides (2-7) we undertook the synthesis of serratamolide. Earlier, for the preparation of α-hydroxyacid-containing cyclodepsipeptides (enniatins A and B, valinomycin, sporidesmolides I and II and their analogs) successful use had been made of high dilution cyclization of the linear depsipeptides. Since, however, serratamolide contains residues of β-hydroxyacids, we considered it feasible for the synthesis of this antibiotic to utilize the general method of cyclodepsipeptide synthesis we had recently developed (8), based on the incorporation of hydroxy acids into cyclic amides, in particular, β-hydroxy acids into diketopiperazines.



(III):R=H;
(IV):R=Bzl;
(V):R=Ac;
(VI):R=D-β-hydroxydecanoyl.

(VII):R=Bzl, R'=$(CH_2)_6CH_3$;
(VIII):R=Ac, R'=$(CH_2)_6CH_3$;
(IX):R=Ac, R'=H.



(X)

(I):R=H, R'=$(CH_2)_6CH_3$;
(II):R=Ac, R'=$(CH_2)_6CH_3$;
(XI):R=Ac, R'=H.

We planned to arrive straightforwardly at serratamolide (I) via the bis-cyclol (X) which should have formed on acylation of L,L-3,6-bis-(benzyloxymethyl)-2,5-diketopiperazine (IV) by benzyloxydecanoyl chloride and removal of the protective groups from the N,N'-diacyl derivative (VII) by catalytic hydrogenolysis.

To accomplish this it was necessary to have D-β-benzyloxydecanoic acid (XII) and the diketopiperazine (IV). The first of these compounds we synthesized by reacting $C_6H_5CH_2Br$ and Ag_2O with D-β-hydroxydecanoic acid (XIII) obtained by quinine-cinchonidine resolution of the racemate. The diketopiperazine (IV) was synthesized as follows: Phthalylation of O-benzyl-DL-serine (9) with phthalic anhydride in dioxane afforded N-phthalyl-O-benzyl-DL-serine (yield 96%). Its resolution with morphine in acetone gave crystalline N-phthalyl-O-benzyl-L-serine (XIV).+ Methylation of this compound by CH_2N_2 in etheral solution yielded the corresponding methyl ester (XV) which was hydrazinolyzed in good yield to methyl O-benzyl-L-serinate (XVI) isolated as the hydrochloride. Condensation of (XIV) and (XVI) with dicyclohexylcarbodiimide led to N-phthalyl-O-benzyl-L-seryl-O-benzyl-L-serine methyl ester (XVII) in quantitative yield. The latter gave (IV) on treatment with hydrazine hydrate (yield 70%). The constants of the synthesized compounds are presented in Table 1.

+ This compound but in the form of an oil with considerable amounts of the racemate was obtained by De Haas (10) in another way.

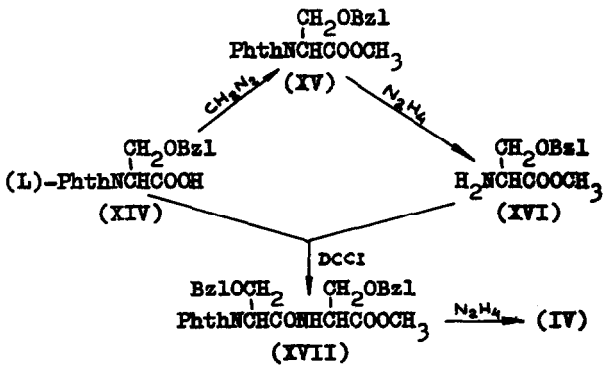
TABLE 1

Constants of Synthesized Compounds+

Compound	M.P. (°C)	$[\alpha]_D^{20}$
II	222-223	+20,0 (c=0,5; $CHCl_3$)
IV	166-167	-79.0 (c=1; $CHCl_3$)
V	228-230	-7,0 (c=0,9; CH_3COOH)
VI	170-172	-22,5 (c=0,8; CH_3COOH)
XI	242-243	-47,0 (c=0,14; 85% aq.HCOOH)
XII	oil	-5,6 (c=1,2; $CHCl_3$)
XIII	48-49	-20,8 (c=1; $CHCl_3$)
XIV	84-86	-62,5 (c=1,5; C_2H_5OH)
XV	67-68	-66,0 (c=1; CH_3OH)
XVI·HCl	165-166	+6,9 (c=1; CH_3OH)
XVII	oil	-4,5 (c=2; CH_3OH)
XVIII	oil	+9,7 (c=1,9; CH_3OH)
XIX	94-95	-2,5 (c=0,9; C_2H_5OH)
XX	137-138	+10,0 (c=2; C_2H_5OH)

+ In all cases the analytical data correspond to the required values.

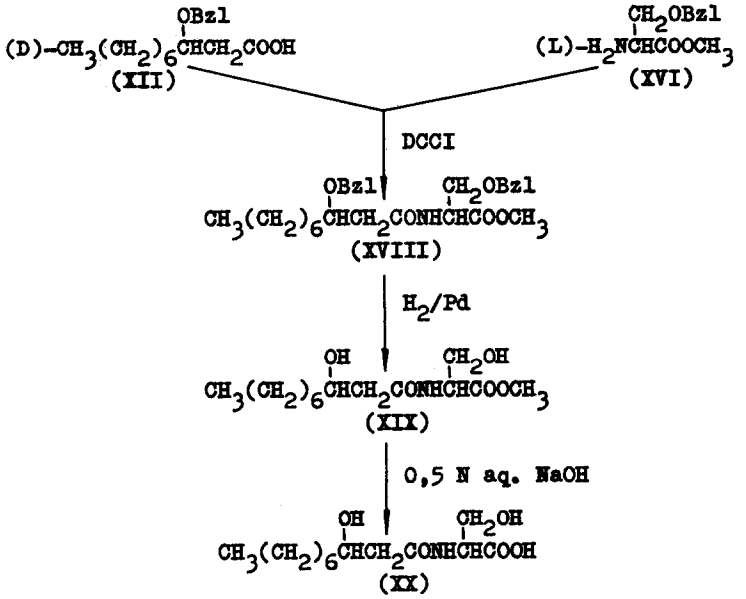
As was expected acylation of bis-(benzyloxymethyl)-diketopiperazine (IV) by D-β-benzyloxydecanoyl chloride in boiling toluene (15 hrs.) did give N,N'-diacyldiketopiperazine (VII). The latter, without isolation, was subjected to hydrogenolysis in tetrahydrofuran solution in the presence of Pd-catalyst. However, instead of the anticipated serratamolide (I) a crystalline substance was isolated in 50% yield



with m.p. 170-172°, $[\alpha]_D^{20}$ -22,5° (c=0,8; CH_3COOH) and with no amide II band in the i.r. spectrum but with a band 1730 cm^{-1} corresponding to an ester group. The compound yielded D-β-hydroxydecanoic acid (XIII) and seryl-seryl anhydride (III) on mild alkaline hydrolysis. It therefore followed that this compound was 3,6-bis-(D-β-hydroxydecanoyloxymethyl)-2,5-diketopiperazine (VI), formed by N→O migration of the D-β-hydroxydecanoic acid residue in the process of hydrogenolysis. This was confirmed by a study of the behavior of N,N'-diacetyl-3,6-bis-(benzyloxymethyl)-2,5-diketopiperazine prepared by acetylating the diketopiperazine (IV) with acetyl chloride in boiling benzene. When this N,N'-diacetyldiketopiperazine was hydrogenolyzed, N→O migration of the acetyl group was also observed, 3,6-bis-(acetoxymethyl)-2,5-diketopiperazine (V) being isolated in 85% yield. For identification purposes, the latter was synthesized by O-acetylation of (III) with acetic acid in the presence of hydrogen chloride.

In order to exclude N→O acyl migration in the synthesis of serratamolide the hydroxyl function of L-seryl-L-seryl anhydride (III) had to be protected by some hydrogenolysis-resistant group before carrying out the acylation. It was natural to first use for this the diacetyl derivative (V). The possibility of incorporating a β-hydroxyacid into the latter had been shown by us on the example of β-benzyloxypropionic acid. On acylating compound (V) with the chloride of this acid and then hydrogenolyzing the resultant N,N'-diacyl derivative (IX), a serratamolide analog, the cyclotetradepsipeptide (XI), was obtained. In turn, acylation of (V) by D-β-benzyloxydecanoyl chloride under the above condition gave rise to N,N'-bis-(D-β-benzyloxydecanoyl)-3,6-bis-(acetoxymethyl)-2,5-diketopiperazine (VIII), which without isolation was subjected to catalytic hydrogenolysis. As a result a crystalline compound was obtained from the reaction mixture in 30% yield, whose constants and properties coincided with those described by Wasserman (1) for O,O'-diacetylserratamolide. The structure of this compound was confirmed as follows. It possesses an i.r. spectrum characteristic of such type of depsipeptide macrocycles. Molecular weight determination by thermoelectric method gave a value corresponding to formula (II) (M.W. Found: 578. Calc. 599). Moreover alkaline hydrolysis yielded an acid which turned out to be identical with the earlier known serratamic acid (XX), an alkaline hydrolysis product of serratamolide (1, 11). In order to identify this acid we carried out

its counter synthesis according to the following scheme:



With the total synthesis of O,O'-diacetylserratamolide final proof is provided of the validity of Wasserman's formula for serratamolide.

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