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The Chemistry of Antimycin A. V. Synthesis of Antimycic Acid Methyl Ester Methyl Ether and its Analogs[1]

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N-(3-Amino-2-methoxybenzoyl)-L-threonine methyl ester (natural antimycic acid methyl ester methyl ether) (VIb) has been prepared from 3-nitrosalicylic acid methyl ether (Ia). The synthesis of N-(3-amino-2-methoxybenzoyl)-DL-threonine (Va), N-(4-amino-2-methoxybenzoyl)-DL-threonine (Vc) and N-(5-amino-2-methoxybenzoyl)-DL-threonine (Vd) also has been achieved by the same method.

The antibiotic antimycin A was isolated, in 1949, from an unidentified species of *Streptomyces* by Dunshee, *et al.*[2] It was found by degradation studies[3] that antimycic acid, one of the hydrolytic products of antimycin A, has the structure N-(3-aminosalicyloyl)-L-threonine.

Recently blastmycic acid, one of the hydrolytic products of blastmycin,[4] was shown to be N-(3-formylaminosalicyloyl)-L-threonine by Yonehara and co-workers.[5] Blastmycin appears to be a member of the antimycin complex, and very probably consists essentially of antimycin A_3.[6]

During the course of synthetic studies on antimycic acid,[7] many unsuccessful attempts were made to synthesize N-(3-nitro-salicyloyl)-DL-threonine by the condensation of 3-nitrosalicylic acid or O-acetyl- or O-carbobenzoxy- or O-carboallyloxy-3-nitrosalicylic acid or their acid chlorides with DL-threonine or the ethyl ester of DL-threonine. Similar routes starting with 3-aminosalicylic acid were also fruitless.[7] In addition, unsuccessful efforts to synthesize N-(3-nitrosalicyloyl)-DL-threonine by the condensation of acetaldehyde with N-(3-nitrosalicyloyl)-glycine have been reported.[8] Another synthetic approach, *viz.*, bromination of N-(acetylsalicyloyl)-DL-threonine and then nitrosation and catalytic reduction also was tried, but the chemical behavior of the resulting product was not completely identical with that of antimycic acid.[7]

Recently we found that O-methylsalicyloyl chloride and its nitro derivatives are much more easily condensed with threonine than are the corresponding O-acetyl compounds. Antimycic acid methyl ester methyl ether (VIb, Fig. 1) and related compounds now have been prepared successfully by using this method as outlined in Fig. 1.

Methylation of 3-nitrosalicylic acid[9] with diazomethane followed by saponification afforded 3-nitrosalicylic acid methyl ether (Ia); (Ia) was refluxed with thionyl chloride to yield the acid chloride IIa which was condensed with DL-threonine in sodium hydroxide solution to give N-(3-nitro-2-methoxybenzoyl)-DL-threonine (IIIa) in 89% yield; (IIIa) was converted into N-(3-nitro-2-methoxybenzoyl)-aminocrotonic azlactone (IVa) in 85% yield by the usual method with acetic anhydride; (IIIa) also was reduced catalytically with Pd–C in methanol solution to give N-(3-amino-2-methoxybenzoyl)-DL-threonine (Va) in 98% yield. The esterification of Va with diazomethane gave N-(3-amino-2-methoxybenzoyl)-DL-threonine methyl ester (DL-antimycic acid methyl ester methyl ether) (VIa) in 60% yield; VIa could also be obtained by esterification of IIIa with diazomethane followed by catalytic reduction with Pd–C of the methyl ester VIIa.

For synthesis in the natural antimycic acid series, N-(3-nitro-2-methoxybenzoyl)-L-threonine (IIIb) was obtained by condensation of the acid chloride IIa with L-threonine. This product could not be crystallized, but N-(3-amino-2-methoxybenzoyl)-L-threonine (L-antimycic acid methyl ether) (Vb) was obtained from it in 83% yield in crystalline form by catalytic reduction with Pd–C in methanol solution. The esterification of Vb with diazomethane produced the desired product, N-(3-amino-2-methoxybenzoyl)-L-threonine methyl ester (L-antimycic acid methyl ester methyl ether) (VIb) in 78% yield; VIb had the same melting point as antimycic acid methyl ester methyl ether obtained by methylation of natural antimycic acid with diazomethane and the mixed melting point showed no depression. Furthermore the infrared absorption spectra of the two substances were identical.

According to Tener, *et al.*,[3] when natural antimycic acid is heated with acetic anhydride and pyridine, it is converted into N-(3-acetamino-2-acetoxybenzoyl)-aminocrotonic azlactone; the resulting substance can be hydrolyzed with dilute sodium hydroxide to form N-(3-acetamino-2-hydroxybenzoyl)-aminocrotonic acid. Our synthetic products Va and Vb showed the same behavior and gave the same N-(3-acetamino-2-methoxybenzoyl)-aminocrotonic azlactone (VIIIa) in 84 and 78% yields, respectively. Hydrolysis of VIIIa with 0.08 *N* sodium hydroxide lead to N-(3-acetamino-2-methoxybenzoyl)-aminocrotonic acid (IXa).

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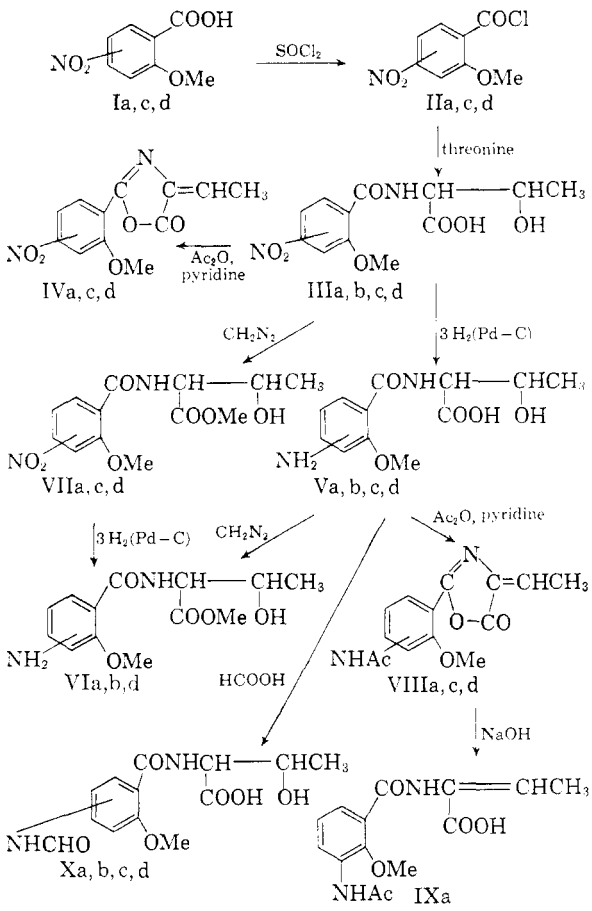

Fig. 1.—a, 3-substituted series or DL-3-substituted peptide; b, L-3-substituted peptide; c, 4-substituted series or DL-4-substituted peptide; d, 5-substituted series or DL-5-substituted peptide.

The above results thus fully confirm the correctness of the structure previously deduced for antimycic acid.

Attempts to synthesize N-formyl-DL- or L-antimycic acid methyl ether by formylation of Va or Vb with 78% formic acid were successful only in the DL-series. The product Xa was obtained in crystalline form in 73% yield from Va.

Two isomeric antimycic acids N-(4-amino-2-methoxybenzoyl)-DL-threonine (Vc) and N-(5-amino-2-methoxybenzoyl)-DL-threonine (Vd), respectively, were synthesized by the same method from 4- or 5-nitrosalicylic acid methyl ether (Ic, Id). The chemical behavior of these isomeric acids paralleled that of antimycic acid. Thus IIIc, IIId, Vc and Vd gave yellow or pale yellow azlactones IVc, IVd, VIIIc and VIIId, respectively, and the carboxyl group of IIIc, IIId and Vd could be esterified with diazomethane to give the esters VIIc, VIId and VId. The amino group of Vc and Vd was formylated with formic acid to produce Xc and Xd, respectively.

Experimental

N-(Nitro-2-methoxybenzoyl)-DL-threonine (III).—Two-*hundredths* mole of nitrosalicylic acid methyl ether (I) was refluxed with 20 g. of $SOCl_2$ until the solution became clear and then the excess of $SOCl_2$ was removed under reduced pressure. The residue (acid-chloride II) was dissolved in 40 to 50 ml. of absolute tetrahydrofuran and this solution was added in 2- to 3-ml. portions at intervals of 3 to 5 minutes to DL-threonine solution (0.023 mole of threonine in the calculated amount of *N* NaOH) with vigorous stirring in an ice-bath. During the reaction period, the solution was kept alkaline (thymol blue) with 2 *N* NaOH. After the addition of acid chloride, the stirring was continued for another hour and then the solution was acidified with concd. HCl and allowed to stand in an ice-box to crystallize. The product was filtered, washed with water and triturated with ether and then recrystallized (Table I).

N-(Amino-2-methoxybenzoyl)-DL-threonine (V) and Methyl Ester VIa.—To the 50–100 ml. of methanol solution of 1–2 g. of N-(nitro-2-methoxybenzoyl)-DL-threonine (III) or the methyl ester VIIa was added 0.15–0.3 g. of Pd–C (5%) and the mixture shaken in a hydrogen atmosphere for 15–30 minutes to absorb 3 moles of hydrogen. When the reduction was finished, the catalyst was filtered off and the filtrate concentrated to 3 to 4 ml. under reduced pressure at room temperature. Addition of a large amount of ether then caused the separation of a crystalline precipitate which was recrystallized (Table II).

N-(3-Amino-2-methoxybenzoyl)-L-threonine (L-Antimycic Acid Methyl Ether) (Vb).—Three and one-half grams of 3-nitrosalicylic acid methyl ether (Ia) was condensed with 2.31 g. of L-threonine as described above to give an oily product (IIIb) which was dissolved in 150 ml. of methanol and catalytically reduced with 0.65 g. of Pd–C (5%) over a period of 6 hours. During this time 1020 ml. of hydrogen was absorbed. The catalyst was filtered off and methanol removed under reduced pressure at room temperature. When the oily residue was dissolved in 30–50 ml. of ethyl acetate, crystals separated and a second crop was obtained from the mother liquor by the same treatment. The total yield was 3.95 g. (83%). Recrystallization from ethanol gave colorless thin plates, m.p. 83–86°. When the substance was kept in a desiccator, its melting point rose gradually. The second recrystallization from ethyl acetate gave long plates, m.p. 123.5–124.5°, $[\alpha]^{28}D$ +14° (*c* 1.82, ethanol).

Anal. Calcd. for $C_{12}H_{16}O_5N_2$: N, 10.45. Found: N, 10.28, 10.27.

N-(Nitro-2-methoxybenzoyl)-DL-threonine Methyl Ester (VII) or N-(Amino-2-methoxybenzoyl)-threonine Methyl Ester (VI).—N-(Nitro-2-methoxybenzoyl)-DL-threonine (III) or N-(amino-2-methoxybenzoyl)-threonine (V) was dissolved (or suspended if difficultly soluble) in a small amount of methanol and ethereal diazomethane added little by little, cooling with ice, until the color of the latter remained. Then the excess of diazomethane and the solvent were removed under reduced pressure and the residue recrystallized (Table III).

N-(Nitro-2-methoxybenzoyl)-aminocrotonic Azlactone (IV) or N-(Acetamino-2-methoxybenzoyl)-aminocrotonic Azlactone (VIII).—A mixture of 0.1–0.2 g. of N-(nitro-2-methoxybenzoyl)-DL-threonine (III) or N-(amino-2-methoxybenzoyl)-threonine (V) with 0.3 to 0.5 ml. of acetic anhydride and 3–5 drops of pyridine was heated for 1 to 3 minutes. After cooling the mixture was allowed to stand in order to crystallize, water being added if necessary, then filtered and the product recrystallized (Table IV).

N-(3-Acetamino-2-methoxybenzoyl)-aminocrotonic Acid (IXa).—Twenty-five ml. of 0.08 *N* NaOH was added to 0.47 g. of N-(3-acetamino-2-methoxybenzoyl)-aminocrotonic azlactone (VIIIa) and the mixture warmed to 60–70° until the solid dissolved. After cooling, the solution was adjusted to *p*H 2.5 and concentrated to about 2 ml. under reduced pressure. The oily product crystallized on cooling and then was filtered off and washed with a minimum amount of water. The product weighed 0.22 g. and another 0.14 g. was obtained from the mother liquor. The total yield was 73%. Recrystallization from acetone gave needles, m.p. 195.5–196.5°.

Anal. Calcd. for $C_{14}H_{16}O_5N_2$: N, 9.59. Found: N, 9.66.

N-(Formylamino-2-methoxybenzoyl)-threonine (X).—One- to three-tenths of a gram of N-(amino-2-methoxybenzoyl)-threonine (V) was boiled with 1–2 ml. of 78% formic acid for 10 minutes and the excess of formic acid then was removed completely under reduced pressure. The resulting oily product was dissolved in 1–1.5 ml. of water and chilled in an ice-box to separate the crystals, which were filtered,

TABLE I

N-(NITRO-2-METHOXYBENZOYL)-DL-THREONINES

Starting compd.	Product, 2-methoxy-(benzoyl)-DL-threonine	M.p., °C.	Recrystn. solvent	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found
Ia	N-(3-Nitro- (IIIa)	Pale yellow long plates, 144.5–145.5	Ethyl acetate	89	$C_{12}H_{14}O_7N_2$	9.39	9.38
Ic	N-(4-Nitro- (IIIc)	Pale yellow needles, 200.5–201 d.	Acetone or methanol	81	$C_{12}H_{14}O_7N_2$	9.39	9.46
Id	N-(5-Nitro- (IIId)	Pale yellow needles, 210–211 d.	Ethanol	87.5	$C_{12}H_{14}O_7N_2$	9.39	9.48

TABLE II

N-(AMINO-2-METHOXYBENZOYL)-DL-THREONINES

Starting compd.	Product, 2-methoxy-benzoyl)-DL-threonine	M.p., °C.	Recrystn. solvent	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found
IIIa	N-(3-Amino- (Va)	Colorless long plates, 163–164 d.	Ethanol	98	$C_{12}H_{16}O_5N_2$	10.45	10.53
IIIc	N-(4-Amino- (Vc)	Hygroscopic[a] crude solid, 60–70	....	Quant.	.....	...	...
IIId	N-(5-Amino- (Vd)	Colorless long plates, 214–215 d.	Water	75	$C_{12}H_{16}O_5N_2$	10.45	10.66[b]
VIIa	N-(3-Amino- methyl ester (VIa)	Colorless needles, 128.5–129.5	Ethyl acetate	91	$C_{13}H_{18}O_5N_2$	9.93	10.09

[a] Readily soluble in water, alcohols; insoluble in *n*-hexane, ether, ethyl acetate. [b] Dried for 1 hour at 95–100° (1 mm.) over P_2O_5.

TABLE III

METHYL ESTERS OF N-(NITRO-2-METHOXYBENZOYL)- AND N-(AMINO-2-METHOXYBENZOYL)-DL-THREONINES

Starting compd.	Product, threonine methyl ester	M.p., °C.	Recrystn. solvent	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found
IIIa	N-(3-Nitro-2-methoxy-benzoyl)-DL- (VIIa)	Pale yellow needles, 92.5–93.5	Benzene–*n*-hexane	87	$C_{13}H_{16}O_7N_2$	8.98	9.17
IIIc	N-(4-Nitro-2-methoxy-benzoyl)-DL- (VIIc)	Pale yellow needles, 115.5–116.5	Benzene	90	$C_{13}H_{16}O_7N_2$	8.98	8.93
IIId	N-(5-Nitro-2-methoxy-benzoyl)-DL- (VIId)	Pale yellow long plates, 147–148	Ethyl acetate	82	$C_{13}H_{16}O_7N_2$	8.98	9.15
Va	N-(3-Amino-2-methoxy-benzoyl)-DL- (VIa)	Colorless needles, 128.5–129.5	Ethyl acetate	60	$C_{13}H_{18}O_5N_2$	9.93	9.92
Vb	N-(3-Amino-2-methoxy-benzoyl)-L- (VIb)	Colorless[a] needles, 155–156	Ethanol or ethyl acetate	78	$C_{13}H_{18}O_5N_2$	C, 55.32 H, 6.43 N, 9.93	C, 55.27 H, 6.54 N, 10.09
Vd	N-(5-Amino-2-methoxy-benzoyl)-DL- (VId)	Colorless needles, 127–128	*s*-Butyl alcohol	51	$C_{13}H_{18}O_5N_2$	9.93	10.17

[a] $[\alpha]^{28}D$ +10° (*c* 2.05, ethanol); no depression of melting point mixed with natural antimycic acid methyl ester methyl ether.

TABLE IV

N-(NITRO-2-METHOXYBENZOYL)- AND N-(ACETAMINO-2-METHOXYBENZOYL)-AMINOCROTONIC AZLACTONES

Starting compd.	Product, 2-methoxybenzoyl)-aminocrotonic azlactone	Reaction conditions[a]	M.p., °C.	Recrytsn. solvent	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found
IIIa	N-(3-Nitro- (IVa)	A	Colorless needles, 175–176 d.	Ethyl acetate	85	$C_{12}H_{10}O_5N_2$	10.68	10.70
IIIc	N-(4-Nitro- (IVc)	B	Yellow needles, 159–160 d.	Ethyl acetate	75	$C_{12}H_{10}O_5N_2$	10.68	10.79
IIId	N-(5-Nitro- (IVd)	B	Pale yellow needles, 157–158 d.	Acetic acid	81	$C_{12}H_{10}O_5N_2$	10.68	10.69
Va	N-(3-Acetamino- (VIIIa)	B	Colorless prisms, 136.5–137.5	Ethanol	84	$C_{14}H_{14}O_4N_2$	10.22	10.45
Vb		B			78			10.46
Vc	N-(4-Acetamino- (VIIIc)	B	Yellow needles, 196–197 d.	Acetic anhydride	46	$C_{14}H_{14}O_4N_2$	10.22	10.32
Vd	N-(5-Acetamino- (VIIId)	C	Yellow needles, 177–178 d.	Ethanol	56	$C_{14}H_{14}O_4N_2$	10.22	10.37

[a] Reaction conditions: A, = Ac_2O, 100–110°, 3 minutes; B = Ac_2O, pyridine, 90°, 3 minutes; C = AcOH–Ac_2O–pyridine (20:10:1), 90°, 0.5–1 minute.

TABLE V

N-(FORMYLAMINO-2-METHOXYBENZOYL)-THREONINES

Starting compd.	Product, threonine	M.p., °C.	Recrystn. solvent	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found
Va	N-(3-Formylamino-2-methoxybenzoyl)-DL- (Xa)	Colorless needles, 183–184	Water	73	$C_{13}H_{16}O_6N_2$	9.46	9.61
Vb	N-(3-Formylamino-2-methoxybenzoyl)-L- (Xb)	Crude oil[a]	....	Quant.	.....	..	..
Vc	N-(4-Formylamino-2-methoxybenzoyl)-DL- (Xc)	Colorless needles, 145–146	Water	61	$C_{13}H_{16}O_6N_2$	9.46	9.35
Vd	N-(5-Formylamino-2-methoxybenzoyl)-DL- (Xd)	Colorless needles, 182.5–183.5	Water	67	$C_{13}H_{16}O_6N_2$	9.46	9.40

[a] Readily soluble in water, alcohols.

washed with water and recrystallized from a small quantity of water. For analysis the crystals were dried at 1–2 mm. and 50–60° for one hour (Table V).

Natural Antimycic Acid Methyl Ester-methyl Ether.—Seventy-five mg. of natural antimycic acid was suspended in 1 ml. of methanol and to this mixture diazomethane solution was added until the color of the latter remained. The solution was set aside for one hour and the excess of diazomethane and the solvent then removed under reduced pressure. The product was recrystallized from ethyl acetate to give a yield of 26 mg. (31%) of m.p. 155–156°.[2]

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Some Derivatives of 2,3-Dihydro-4H-1,4-thiazin-3-one and 1,4-Thiazane

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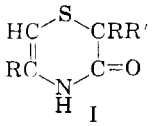
A series of dialkylmercaptoacetamides has been prepared and condensed with α-halocarbonyl compounds to give intermediate cyclic keto alcohols which were dehydrated to 2,2-dialkyl-2,3-dihydro-4*H*-1,4-thiazin-3-ones. Some of these in turn were oxidized to the sulfone and, in case of hydrogen at position 5, also to the epoxide.

Dialkylmercaptoacetic acids and amides previously have been condensed with an α-haloacetamide to give the corresponding amide acid and the diamide,[1] both of which were converted to thiomorpholinediones. In the present work the dialkylmercaptoacetamides were condensed with α-chloroacetaldehyde and α-haloketones to form the



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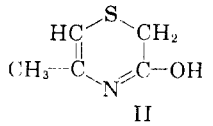


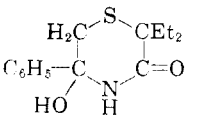
II

corresponding 2,3-dihydro-4*H*-1,4-thiazin-3-ones (I). These compounds are not known, but a monoalkyl derivative believed to have the lactim structure has been reported (II).[2]

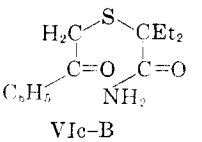
Only the dialkylmercaptoacetamide resulting from the alkaline hydrolysis of a 5,5-dialkyl-2-iminothioaolidone was used (Fig. 1) in the preparation of I. The mercaptoamide was therefore separated from the mercapto acid before use. The yield of the thioazolidone from the interaction of thiourea and the acid bromide was improved by lowering the temperature and extending the period of reaction. Hydrolysis of the thiazolidone with 5% sodium hydroxide for a shorter time (8–30 hours) gave better conversion to the mercaptoamide. When the hydrolysis of IIIa was continued for less than 16 hours, a third product was isolated which was identified as 5,5-diethyl-2,4-thiazolidinedione by comparing it with an authentic sample prepared by the acid hydrolysis of IIIa.[3,4]

When Clemmensen and Heitman[5] hydrolyzed IIIa with barium hydroxide, they obtained an oil and a solid which they believed to be X and VII, respectively (Table I). The solid was crystallized from water (m.p. 147°). Pennington and coworkers,[6] who prepared VII by another method, reported it to be a low melting solid which they did not purify. They postulated that Clemmensen and Heitman had obtained the disulfide of diethylmercaptoacetamide. We have prepared this disulfide by air oxidation of VII and have found it to melt at 159–160°.

Several of the products from the condensation of VII, VIII and IX with chloroacetaldehyde, chloroacetone and phenacyl bromide were oils. During the distillation of these oils water was evolved indicating that the compounds of general formula I were formed by the dehydration of corresponding intermediates. In every condensation using pure VII a solid product precipitated from the reaction mixture. The reaction of VII with chloroacetaldehyde and chloroacetone, respectively, gave intermediates which were unstable at room temperature. The first lost one mole of water on standing in a desiccator over calcium chloride to yield Ia (Table II). The second yielded Ib upon standing at room temperature in a closed vial. The intermediate VIc from phenacyl bromide was stable at room temperature. However, it lost one mole of water to give Ic when refluxed in ethanol. The compound VIc has the empirical formula $C_{14}H_{19}NO_2S$ and could conceivably be VIc-A or VIc-B.



VIc-A



VIc-B

The infrared spectra of both VIa and VIc showed OH bands at 2.8 and 2.9 μ, respectively, which were absent in the dehydrated products Ia and Ic. Also, the spectra of VIa and VIc showed carbonyl bands at 6.1 and 6.0 μ respectively, which were still present in Ia and Ic (see Table III). In an attempt to prepare the *p*-nitrobenzoyl derivative of VIc the only product which could be iso-

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