of 1 ml. of dibutylchloroamine, the solution was irradiated at 0° in a quartz test-tube with a mercury arc lamp under a stream of nitrogen for 2.5 hours. The dark solution was poured over ice, made alkaline with sodium hydroxide, and concentrated somewhat by warming *in vacuo*. The basic solution was extracted twice with ether. The ether extract was dried over sodium sulfate and concentrated to 69.8 mg. of black solid which was refluxed with dilute ethanolic potassium hydroxide for 5 minutes. The alcoholic solution was diluted with water and extracted with ether. Removal of the ether *in vacuo* gave 37.4 mg. of dark oil which was chromatographed on 4 g. of Woelm neutral alumina. The 15.7 mg. of yellow oil which was obtained on elution with 3:1 benzene–ether failed to yield a pure compound.

3β-Dimethylamino-20α-methylaminoallopregnane (XIV).—Platinum oxide (300 mg.) was hydrogenated in 15 ml. of acetic acid, and to the pre-reduced catalyst was added a solution of 600 mg. (1.672 mmoles) of 3β-dimethylamino-20α-methylaminopregnane-5 in 15 ml. of glacial acetic acid containing 4 drops of water. The theoretical quantity of hydrogen was taken up in 4.5 hours, and the solution was filtered, poured over ice, and made basic with sodium hydroxide. The product was extracted into ether, and the ethereal solution was dried over sodium sulfate. Removal of the ether *in vacuo* gave 552.7 mg. (92%) of crystalline 3β-dimethylamino-20α-methylaminoallopregnane. Crystallization from aqueous acetone gave plates, m.p. 103.5–104.5°, $[\alpha]^{27}D$ +27.5° (chloroform, *c* 0.95).

Anal. Calcd. for $C_{24}H_{44}N_2$: C, 79.93; H, 12.30; N, 7.77. Found: C, 79.23; H, 12.06; N, 7.80.

Dihydroconessine (XVII). A. With Dibutylchloroamine Carrier.—3β-Dimethylamino-20α-methylaminoallopregnane (103.7 mg., 0.2875 mmole) and 40.8 mg. (0.305 mmole) of N-chlorosuccinimide were covered with 4 ml. of dry ether and swirled occasionally. After one-half hour the solution was diluted with a little ether–pentane, washed three times with water, dried over sodium sulfate, and concentrated *in vacuo* to 107.5 mg. of white N-chloro-3β-dimethylamino-20α-methylaminoallopregnane. The chloroamine was dissolved in 10 ml. of 90% sulfuric acid at 0°. To the resulting orange-yellow solution was added 100 mg. of dibutylchloroamine. The solution was irradiated in a quartz test-tube at 0° with a mercury arc lamp under a stream of nitrogen. After 70 minutes, the solution was poured over ice and made alkaline with sodium hydroxide while keeping the temperature close to 0° by addition of ice. The product was extracted into ether, and the ether solution was washed with sodium chloride solution, dried over sodium sulfate, concentrated *in vacuo*, and heated at about 80° to remove N-butylpyrrolidine. The residue (84.4 mg.) appeared to be an amine salt—it was insoluble in ether and gave a Beilstein test for halogen. The residue was dissolved in methanol, and ammonium hydroxide solution was added. The product was extracted with ether–pentane. After drying over potassium carbonate the solvent was removed, and the oily residue (70 mg.) was chromatographed on 7 g. of Woelm neutral alumina (activity grade 1). Elution with 3:1 benzene–ether gave 57.4 mg. (56% based on starting diamine) of semi-crystalline material which crystallized readily from aqueous acetone as flat needles, m.p. 100.5–101°, mixture m.p. with dihydroconessine (m.p. 99–100°) 99.5–100.5°, mixture m.p. with 3β-dimethylamino-20α-methylaminoallopregnane (m.p. 103.5–104.5°) 72.5–86° (lit.[22] m.p. 105–105.5° for dihydroconessine); $[\alpha]^{26}D$ +53.5° (chloroform, *c* 0.8) (lit.[3] $[\alpha]D$ +51.8°). The infrared spectrum of the synthetic dihydroconessine was identical in all respects with that of dihydroconessine prepared by hydrogenation of conessine.

B. Without Carrier.—N-Chloro-3β-dimethylamino-20α-methylaminoallopregnane (90 mg., 0.228 mmole) was dissolved in 10 ml. of 90% sulfuric acid at 0°. The resulting solution was irradiated in a quartz test-tube at 0° with a mercury arc lamp under a stream of nitrogen. After 70 minutes the solution was poured over ice, made alkaline with sodium hydroxide, and extracted with ether. The ether was evaporated, and the residue was refluxed with 10 ml. of ethanol containing 1 g. of potassium hydroxide for 0.5 hour. The solution was diluted with water and extracted with ether. The ether solution was dried over sodium sulfate and concentrated *in vacuo* to a slightly yellow semi-solid (80.3 mg.) which was chromatographed on 7.5 g. of Woelm neutral alumina. Elution with 2:1 benzene–ether gave 64.4 mg. of oil (79%) which crystallized from aqueous acetone as flat needles, m.p. 101.5–102.5°, mixture m.p. with authentic dihydroconessine, 100.5–102°.

(22) E. Späth and O. Hromatka, *Ber.*, **63**, 126 (1930).

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

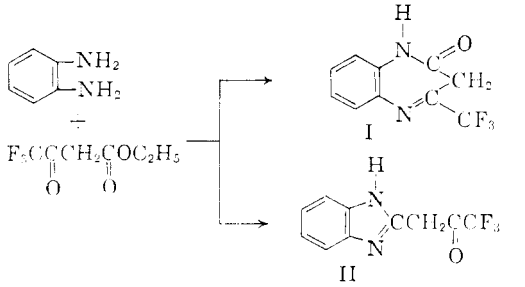
A Study of the Condensation of Ethyl γ,γ,γ-Trifluoroacetoacetate with *o*-Phenylenediamine[1]

BY FRANCES BAIRD WIGTON AND MADELEINE M. JOULLIÉ[2]

RECEIVED FEBRUARY 28, 1959

The reactions of *o*-phenylenediamine with γ,γ,γ-trifluoroacetoacetate has been studied under various conditions. The structure and nature of the products formed was investigated by both chemical and physical methods.

Earlier investigators have studied the condensation of ethyl acetoacetate with *o*-phenylenediamine under several conditions.[3] A number of products were reported, but their identity was not completely established in all cases. The present study is concerned with the condensation of ethyl γ,γ,γ-trifluoroacetoacetate and *o*-phenylenediamine. The primary objectives of this work were to establish the nature of the products formed as well as to observe the effects of the fluorine atoms on the reaction and on the reaction products. Theoretically, the reaction between these two compounds could lead to the formation of either one or both of two cyclic products, namely, 4-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3*H*)-one (I) and 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone (II). The condensation was carried out under



(1) Presented before the Division of Organic Chemistry at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) To whom all inquiries should be addressed.

(3) (a) O. Hinsberg and P. Koller, *Ber.*, **29**, 1500 (1896); (b) S. Coffey, J. Thompson and F. Wilson, *J. Chem. Soc.*, 856 (1936); (c) L. Monti, *Gazz. chim. ital.*, **70**, 648 (1940); (d) W. Sexton, *J. Chem. Soc.*, 303 (1942).

neutral, slightly alkaline and acid conditions. In the first two cases, compound I was isolated. Under acidic conditions, II was obtained.

The identity of I as a cyclic amide was established by a series of chemical tests and from infrared and ultraviolet spectra.

Compound I did not react with 2,4-dinitrophenylhydrazine and did not give a positive ferric chloride test characteristic of an enolic structure. No evidence for a haloform type of cleavage could be obtained when the product was treated with aqueous sodium hydroxide. Davidson[4] reported that cyclic amides undergo cleavage when heated with hydroxylamine hydrochloride to yield hydroxamic acid derivatives. When I was treated with hydroxylamine hydrochloride and sodium acetate in aqueous alcohol, 3-(*o*-aminophenylimino)-butyrohydroxamic acid was obtained. The presence of a primary amino group in this product was proved by the fact that the compound gave a positive test with a solution of nickel chloride and 5-nitrosalicylaldehyde in aqueous triethanolamine. It also gave a positive Hinsberg test. When 3-(*o*-aminophenylimino)-butyrohydroxamic acid was refluxed with dilute sulfuric acid for a short time, it was reconverted to I. The infrared spectrum of 3-(*o*-aminophenylimino)-butyrohydroxamic acid showed two sharp bands at 2.90 and 3.03μ, which could be associated with the NH stretching of a primary amine, and a strong band at 6.03 μ probably associated with the carbonyl group of a hydroxamic acid.[5]

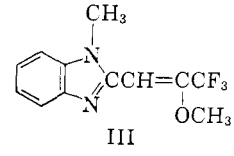
Further information concerning the nature of I was obtained from its hydrolysis by acids and bases. The hydrolysis of 4-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3*H*)-one with 10% sulfuric acid yielded a mixture of two products which were identified as *o*-phenylenediamine and II. The hydrolysis of I with 10% sodium hydroxide yielded a product which was identified as 2-methylbenzimidazole.

The infrared spectrum of I was studied as a potassium bromide disk and in chloroform solution. In the solid state, a broad band in the 3.0–3.6μ region was observed and ascribed to CH stretching and to NH stretching of a secondary amide group. In chloroform solution, a band at 2.94μ and a broad band in the 3.0–3.5μ region were observed. A number of secondary amides are known to absorb at 3.25μ, and this band, associated with NH modes, is supposed to vanish in dilute solutions being replaced by a band at 2.92 μ.[5] A strong band at 6.05μ which could be identified with the carbonyl group of an amide was present in the infrared spectrum of I in the solid state. This band was shifted to 5.88μ in chloroform, as expected. An ill-defined band at 14.15μ, present in the spectrum of this compound in the solid state, was associated with an out-of-plane NH deformation and consequently should have disappeared with dilution. This band was absent in the spectrum of I in chloroform solution. Bands at 6.23, 6.35 and 6.76μ were present in the spectra of I both in the solid state and in solution. These bands may be associated with the presence of a phenyl group. The C=N band is a difficult one to identify since this group is conjugated with a C=C bond. The frequencies of these two groups are so close that it is doubtful whether they can be distinguished. A single band at 13.24μ in the spectrum of compound I in the solid state indicates the presence of a disubstituted benzene ring. A similar band at 13.38μ was also observed in the spectrum of 3-(*o*-aminophenylimino)-butyrohydroxamic acid. It should be noticed that in the spectrum of this compound a band around 6.30μ is not observed. Such a band often indicates a benzene ring conjugated with another group and is present in the spectrum of I.

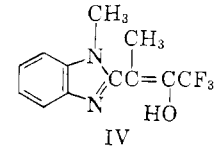
Compound II was shown to have the same elemental analysis as compound I, although its melting point was much higher than I. It seemed logical to assume that it could have the structure of a benzimidazolyl ketone that could possess considerable enolic character. No carbonyl derivative could be obtained from II with 2,4-dinitrophenylhydrazine, hydroxylamine hydrochloride or even with 2-diphenylacetyl-1,3-indandione-1-hydrazone,[6] but the compound gave an intense violet color with ferric chloride solution. These results indicated the presence of an enol structure and the enol content of this compound, determined by a Kurt-Meyer titration, was found to be 69%.

When II was heated with aqueous sodium hydroxide, 2-methylbenzimidazole was obtained, indicating that a haloform cleavage had occurred. The sodium salt of 2-benzimidazoleacetic acid undergoes decarboxylation under the conditions used, which is not surprising in view of the ease of decarboxylation of this compound.

It was hoped that by using sodium ethoxide instead of aqueous sodium hydroxide, an ester might be isolated instead of the salt, since similar reactions are known to occur.[7] However, it was found that II reacts with sodium ethoxide to form a stable disodium salt which could be hydrolyzed by water to the starting material. The nature of the disodium salt was established by alkylation with methyl iodide, whereupon a dimethyl derivative was formed. Two possible structures may be postulated for this product.



III



IV

The fact that the dimethylated product gave a strong positive test with ferric chloride seemed to indicate structure IV. This was confirmed by the infrared spectrum of this compound in the solid state, which showed a well-defined absorption band at 3.08μ. This band may be ascribed to the OH stretching frequency of a hydrogen bonded hydroxyl group. The deformation mode of a methyl group attached to a nitrogen atom might be expected to give a band of reasonably characteristic frequency. The dimethylated derivative shows a

(4) D. Davidson, *J. Chem. Ed.*, **17**, 81 (1940).

(5) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(6) R. A. Braun and W. A. Mosher, THIS JOURNAL, **80**, 3048 (1958).

(7) H. Meerwein and H. Sönke, *Ber.*, **64**, 2375 (1931).

band at 7.08μ which could be associated with this deformation mode A band at 7.62μ could be associated with the C–N stretching band of a tertiary amine.[5] Both bands are absent in the infrared spectrum of II.

The infrared spectrum of II, as a potassium bromide disk, shows a very intense band at 6.12μ which may be attributed to the carbonyl band of a conjugated ketone similar to the bands exhibited by ketones such as acetylacetone and dibenzoylmethane, which are known to exist largely in their enol forms. A band at 8.0μ may be attributed to the stretching vibration of the =C—O group. The infrared spectra of III and IV show a broad band in the 6.2–6.5μ region and a band at 6.74μ which may be related to the presence of a phenyl group. A band in the 13.2μ region is also present in both spectra.[5]

The bands observed in the ultraviolet spectra of I and II, and their relative intensities are shown in Table I

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Solvent	Compound I λ, mμ	Compound I log ε	Compound II λ, mμ	Compound II log ε
Water	218	4.96	..	..
(1×10^{-4} M soln.)	242	3.66	..	..
	276	3.60	..	..
Absolute ethanol	..	..	330	4.36
(3.3×10^{-5} M soln.)	..	..	260	3.74
	..	..	225	3.73
	..	..	205	4.07
Dioxane				
(2×10^{-5} M soln.)	..	..	339	4.39
	..	..	265	3.60
	..	..	228	3.80

Experimental

General Information.—All analytical samples were recrystallized four or five times from the appropriate solvent, once with the aid of decolorizing carbon. All compounds were dried *in vacuo* in an Abderhalden drying pistol for 24 to 40 hours, while heating at 80 or 110° depending on the melting point of the compound and the solvent used in its recrystallization. The microanalyses for all compounds were performed by the Galbraith Laboratories, Knoxville, Tenn. All of the melting points which are reported are uncorrected.

All ultraviolet absorption spectra were determined with a Beckman DU spectrophotometer equipped with a recorder model RS-3.

All infrared spectra were determined with a Perkin–Elmer infrared spectrophotometer model 21.

1. Condensation of Ethyl Trifluoroacetoacetate with *o*-Phenylenediamine under Basic Conditions. Preparation of the 4-(Trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3H)-one (I).—A solution of 10.8 g. (0.1 mole) of *o*-phenylene-diamine in 70 ml. of xylene was placed in a two-neck flask equipped with a 50-ml. addition funnel and a Dean-Stark tube; 0.5 ml. of 0.5 N potassium hydroxide in absolute ethanol was added to the solution, and the mixture was heated to boiling. Ethyl trifluoroacetoacetate (20.9 g., 0.114 mole) which had been previously treated with solid anhydrous sodium carbonate to remove all traces of acid, was dissolved in 10 ml. of xylene and added dropwise to the boiling solution over a half-hour period. The reaction mixture was heated for an additional hour and then allowed to cool overnight. The product crystallized in long needles and was removed by filtration, yield 80%, m.p. 183–185°. The compound was recrystallized from benzene to a constant melting point, 184–185°.

Anal. Calcd. for $C_{10}H_7N_2F_3O$: C, 52.59; H, 3.09; N, 12.27. Found: C, 52.97; H, 3.19; N, 12.02.

2. Condensation of Ethyl Trifluoroacetoacetate with *o*-Phenylenediamine under Neutral Conditions.—The procedure described in 1 was followed, omitting the addition of the alcoholic potassium hydroxide. The product was precipitated from the cooled reaction mixture and removed by filtration, yield 88%, m.p. 184–185°. A mixture of this compound with the product obtained in 1 showed no depression in melting point.

The filtrate was extracted with 100 ml. of 10% aqueous sodium hydroxide, and the extracts were acidified. No product was isolated.

3. Condensation of Ethyl Trifluoroacetoacetate with *o*-Phenylenediamine under Acidic Conditions. Preparation of 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone (II).—To a mixture of 5.4 g. (0.05 mole) of *o*-phenylenediamine and 10.5 g. (0.057 mole) of ethyl trifluoroacetoacetate, 50 ml. of 4 N hydrochloric acid was added, and the resulting solution was refluxed for one hour. A solid formed upon cooling and was removed by filtration. When this product was treated with sodium bicarbonate, it yielded *o*-phenylenediamine, yield 20%, m.p. 103–104°. The filtrate was neutralized with sodium bicarbonate, and the solid which formed was removed by filtration. This product decomposed at 270° and gave an intense purple color when treated with ferric chloride solution. This compound was found to be 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone. It was obtained in approximately 15% yield. The characterization and another method of preparation of this compound are described in procedure 6.

4. Reaction of 4-(Trifluoromethyl)-1H-1,5-benzodiazepine-2(3H)-one with Hydroxylamine Hydrochloride. Preparation of 3-(*o*-Aminophenylimino)-butyrohydroxamic Acid.—A solution of 4.6 g. (0.025 mole) of 4-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2-(3*H*)-one in 70 ml. of absolute ethanol was mixed with a solution of 1.75 g. (0.025 mole) of hydroxylamine hydrochloride and 2.05 g. (0.025 mole) of anhydrous sodium acetate in 20 ml. of water. The resulting solution was allowed to stand overnight in the cold. A small crop of crystals formed and was removed by filtration. More product was obtained by the addition of water to the filtrate. This compound was recrystallized from water to constant melting point, 158–159° dec. The yield of 3-(*o*-aminophenylimino)-butyrohydroxamic acid was 75%.

Anal. Calcd. for $C_{10}H_{10}N_3F_3O_2.\frac{1}{2}H_2O$: C, 44.44; H, 4.10; N, 15.55. Found: C, 44.50; H, 4.16; N, 15.24.

5. Basic Hydrolysis of 4-(Trifluoromethyl)-1H-1,5-benzodiazepin-2-(3H)-one.—A solution of 1 g. (0.004 mole) of 4-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3*H*)-one in 20 ml. of 10% aqueous sodium hydroxide was refluxed for 30 minutes. The resulting solution was cooled and neutralized with concentrated hydrochloric acid. A solid formed and was collected by filtration. The product was recrystallized from benzene, and the melting point of the pure product was 178–180°. A mixture of this product with starting material showed a depression in melting point. A mixture of this product with 2-methylbenzimidazole showed no depression in melting point. The infrared spectrum of this product proved to be identical to the infrared spectrum of a known sample of 2-methylbenzimidazole.

6. Acid Hydrolysis of 4-(Trifluoromethyl)-1H-1,5-benzodiazepin-2-(3H)-one. Preparation of 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone (II).—4-(Trifluoromethyl)-1*H*-1,5-benzodiazepin-2-(3*H*)-one (5 g., 0.022 mole) was refluxed in 100 ml. of 10% aqueous sulfuric acid for one hour. The solution was cooled and neutralized with 10% aqueous sodium hydroxide. The solid which formed was removed by filtration. The product was recrystallized from 50% aqueous ethanol, m.p. 270° dec., yield 60%.

Anal. Calcd. for $C_{10}H_7N_2F_3O$: C, 52.59; H, 3.09; N, 12.27. Found: C, 52.40; H, 3.21; N, 12.35.

The filtrate from the above reaction was extracted with ether, and the extracts were evaporated under reduced pressure. A solid was obtained which melted at 100–103°. A mixture of this solid and *o*-phenylenediamine showed no depression in melting point.

7. Basic Hydrolysis of 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone.—A solution of 0.5 g. (0.002 mole) of 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone in 10 ml. of 10% aqueous sodium hydroxide was refluxed for 30 minutes. The solution was cooled and neutralized with concentrated hydrochloric acid. A solid formed which was removed by filtration, m.p. 175°. It was recrystallized from benzene. A mixture of this compound with 2-methylben-

zimidazole showed no depression in melting point. The infrared spectrum of this product proved to be identical with the infrared spectrum of 2-methylbenzimidazole.

8. **Reaction of 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone with Sodium Ethoxide.**—A solution of 0.19 g. (0.0086 mole) of sodium metal in 20 ml. of absolute ethanol was mixed with 1 g. (0.0043 mole) of 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone, and the mixture was heated under reflux for 30 minutes. After the resulting solution was cooled, concentrated hydrochloric acid was added dropwise until the neutral point was reached. The sodium chloride which formed was removed from the precipitate by extracting with 100 ml. of water. The product was then removed by filtration and dried, m.p. 270° dec. A mixture of this product with the starting material showed no depression in melting point.

9. **Methylation of 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone. Preparation of 3-(1-Methyl-2-benzimidazolyl)-1,1,1-trifluoro-2-hydroxy-2-butene (IV).**—A solution of 0.19 g. (0.0086 mole) of sodium in 20 ml. of absolute ethanol was mixed with 1 g. (0.0043 mole) of 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone, and the mixture was heated in a water-bath at 50° for 30 minutes; 4 ml. (0.06 mole) of methyl iodide was added gradually to the solution with shaking during the heating period. After the addition of methyl iodide was completed, the solution was heated for an additional 15 minutes. The ethanol and excess methyl iodide were removed by distillation, and the residue was treated with 100 ml. of cold water. The product which formed was collected by filtration and recrystallized from 50% aqueous ethanol, yield 91%, m.p. 178° dec.

Anal. Calcd. for $C_{12}H_{11}N_2F_3O$: C, 56.24; H, 4.32; N, 10.93. Found: C, 56.04; H, 4.21; N, 11.06.

10. **Determination of the Enolic Content of 3-(2-Benzimidazolyl)-1,1,1-2-propanone.**—A solution of 0.001 mole of 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone in 50 ml. of absolute methanol was cooled to −5°, and an excess of approximately 0.1 *N* bromine in absolute methanol was added with stirring. A slight excess of di-isobutylene was added until the red color of the bromine disappeared. The time consumed in adding the bromine and decolorizing the solution was approximately 15 seconds. Then, 5 ml. of 10% aqueous potassium iodide was added and the mixture warmed to 30° by dipping the flask in hot water. The solution was allowed to stand for 10 minutes to make sure that the reaction was completed. The solution was titrated with stirring, with standard 0.1 *N* sodium thiosulfate solution until the color became light yellow. At this point 200 ml. of water and 5 ml. of starch solution were added, and the titration continued until the blue color which formed disappeared.

The exact amounts of the compounds used and the results obtained are

Sample, g.	Ml. of 0.1 *N* bromine soln.	Ml. of 0.1 *N* thiosulfate soln.	Enol, % present
0.2286	25	16.54	69.93
.2288	25	16.92	68.49
.2284	25	16.52	69.93

11. **Qualitative Tests for the Structure Analysis of 4-(Trifluoromethyl)-1H-1,5-benzodiazepin-2(3H)-one, 3-(*o*-Aminophenylimino)-butyrohydroxamic Acid and 3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone.**—The qualitative tests for structure analysis were carried out according to the procedures described by Shriner, Fuson and Curtin[8] unless otherwise noted.

(8) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF ENGINEERING, UNIVERSITY OF TOKUSHIMA]

The Chemistry of Antimycin A. VII. Synthesis of Antimycic Acid and its Analogs

BY F. SHIGEO OKUMURA, MITSUO MASUMURA AND TOKUNARU HORIE

RECEIVED MARCH 19, 1959

N-(3-Aminosalicyloyl)-L-threonine (natural antimycic acid) (VIb) has been prepared from 3-aminosalicylic acid benzyl ether (I). The synthesis of N-(3-aminosalicyloyl)-DL-threonine (VIa) also has been achieved by the same method.

In a previous paper[1] it was reported that the synthesis of L- or DL-antimycic acid-methyl ester-methyl ether was successfully achieved by condensation of nitrosalicylic acid methyl ether with L- or DL-threonine and that the synthetic L-peptide was identical with natural antimycic acid-methyl ester-methyl ether.

More recently we have found that 3-nitrosalicylic acid benzyl ether[2] (I) can be prepared in good yield by benzylation of 3-nitrosalicylic acid methyl ester[3] in dimethylformamide solution.

The synthesis of natural antimycic acid from 3-nitrosalicylic acid benzyl ether (I) has been carried through by almost the same procedure described in the preceding paper[1] as shown in Fig. 1.

The benzyl ether I was converted into the corresponding acid chloride II by heating with thionyl chloride, and this product was condensed with DL-threonine to give N-(3-nitro-2-benzyloxybenzoyl)-DL-threonine (IIIa). Compound IIIa was converted into N-(3-nitro-2-benzyloxy-benzoyl)-α-aminocrotonic azlactone (IV) by heating with acetic anhydride and pyridine. Compound IIIa also was converted easily into colorless plates of N-(3-aminosalicyloyl)-DL-threonine (DL-antimycic acid)(VIa) by catalytic reduction with palladium-on-charcoal in methanol solution. The infrared spectrum of this compound (VIa) was nearly identical with that of natural antimycic acid.[4] Furthermore VIa could be converted with diazomethane into a methyl ester-methyl ether VIIa identical with the sample previously synthesized.[1]

For the synthesis of natural antimycic acid N-(3-nitro-2-benzyloxybenzoyl)-L-threonine (IIIb) was obtained by condensation of the acid chloride II with L-threonine. Recrystallization from benzene gave long needles of a solvated product containing one mole of benzene. Compound IIIb gave the same azlactone IV as that derived from the DL-threonine peptide (IIIa) by the usual method. L-Antimycic acid (N-(3-aminosalicyloyl)-L-threonine) (VIb) was obtained from

(1) F. S. Okumura, M. Masumura, T. Horie and F. M. Strong, THIS JOURNAL, **81**, 3753 (1959).

(2) The syntheses of nitrosalicyclic acid benzyl ether, N-(substituted-2-benzyloxybenzoyl)-glycine and -leucine have been reported by W. O. Foye and R. L. Hull, *J. Amer. Pharm. Assoc.*, **42**, 50 (1953).

(3) Prepared by esterification of 3-nitrosalicylic acid, which was obtained from Eastman Organic Chemicals.

(4) G. M. Tener, F. M. Bumpus, B. R. Dunshee and F. M. Strong, THIS JOURNAL, **75**, 1100 (1953).