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Synthesis of Albonoursin

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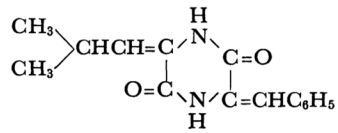
Treatment of the ester of 2-(2-chloroacetamido)-2-alkenoic acid with ammonia led to the formation of 3-alkylidene-2,5-piperazinedione. By using this method, total synthesis of albonoursin was accomplished. 2-(2-Chloroacetamido)-4-methyl-2-pentenoic acid, derived from the condensation of 4-methyl-2-oxopentanoic acid with chloroacetonitrile or the pyrolysis of 2,2-bis(2-chloroacetamido)-4-methylpentanoic acid, was converted to the ethyl ester, which was treated with ammonia to give 3-isobutylidene-2,5-piperazinedione. The piperazinedione was also synthesized by the esterification of 2-(2-aminoacetamido)-4-methylpentenoic acid, followed by a cyclization of the ester. Condensation of the piperazinedione with benzaldehyde yielded 3-benzylidene-6-isobutylidene-2,5-piperazinedione, and its physical constants are virtually identical with those recorded for the natural albonoursin.

In 1963, Khoklov and Lokshin isolated a new product from the culture filtrates of two *Streptomyces* species, *i.e.*, *St. albus var. fungatus* and *St. noursei*, and designated it as albonoursin.[1] Before the year, Brown and Kelley had reported that *St. noursei* produced a substance, "component 2."[2] Also Rao and Cullen isolated a substance "B-73," from the culture filtrate of *St. albus*.[3] These two substances have been revealed to be identical with albonoursin.[1] The structural investigations were made independently by Khoklov and Lokshin,[1] Brown *et al.*,[4] and Vondracek and Vanek,[5] respectively, and all of them have assigned the 3-benzylidene-6-isobutylidene-2,5-piperazinedione structure (I) for albonoursin.



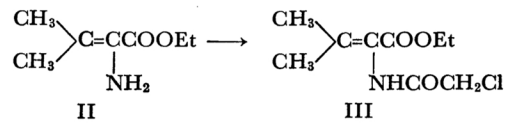
I

Although albonoursin has no special biological activity, it seems of much interest to investigate the synthetic method, since the structure may be regarded as the first cyclic dehydrodipeptide isolated from a natural origin.

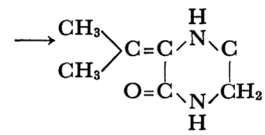
In a previous paper,[6] we have described a method for the synthesis of 3-isopropylidene-6-aralkylidene-2,5-piperazinediones. The method consists in the treatment of methyl 2-amino-3-methylcrotonate with phthaloylglycyl chloride, giving methyl 3-methyl-2-phthaloylglycylaminocrotonate, which, after removal of the phthaloyl group, was cyclized to yield 3-isopropylidene-2,5-piperazinedione. The condensation of the piperazinedione with aromatic aldehydes gave 3-isopropylidene-6-aralkylidene-2,5-piperazinediones.

It was also shown, however, that methyl 2-amino-3-methylcrotonate could be obtained by the reduction of the corresponding 2-nitro compound with aluminum amalgam, while analogous reduction of other 2-nitro-2-alkenoic acid esters resulted in the formation of the 2-oximino-alkanoic acid esters as the isolated products.

In the present paper, we wish to report an alternative and more general route for the synthesis of 3-alkylidene-2,5-piperazinediones and the total synthesis of albonoursin.[7]



II III



IV

1) A. S. Khoklov and G. B. Lokshin, *Tetrahedron Letters*, **1963**, 1881.

2) R. Brown and C. Kelley, *Annual Report of the New York State Department of Health Albany*, 10 (1957), 47 (1958), 52 (1959), 50 (1960), 40 (1961).

3) K. U. Rao and W. P. Cullen, *J. Am. Chem. Soc.*, **82**, 1127 (1960).

4) R. Brown, C. Kelley and S. E. Wiberley, *J. Org. Chem.*, **30**, 277 (1965).

5) M. Vondracek and Z. Vanek, *Chem. & Ind.*, **1964**, 1686.

6) C. Shin, M. Masaki and M. Ohta, *J. Org. Chem.*, **32**, 1860 (1967).

7) A part of this work was preliminarily communicated: C. Shin, Y. Chigira, M. Masaki and M. Ohta, *Tetrahedron Letters*, **1967**, 4601.

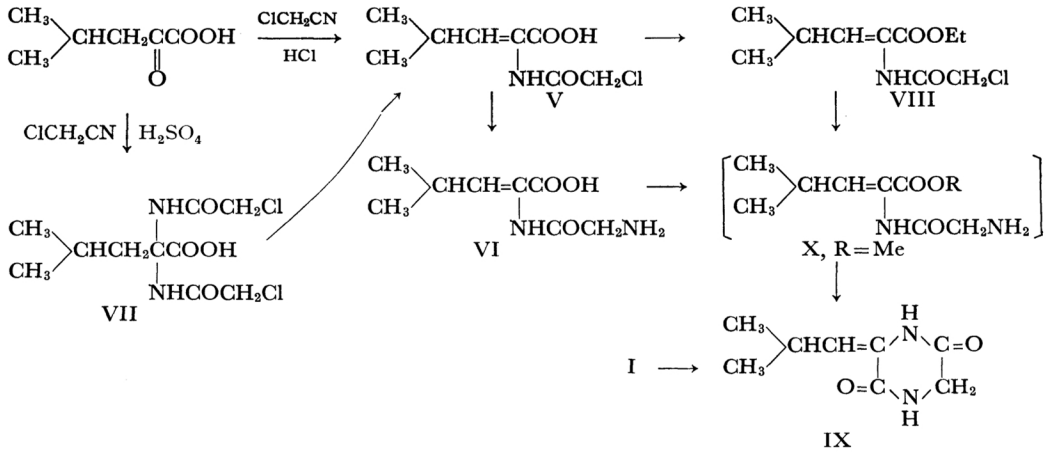


TABLE 1. PHYSICAL CONSTANTS OF 3-BENZYLIDENE-6-ISOBUTYLIDENE-2,5-PIPERAZINEDIONE

Product	Mp, °C	Infrared ν_{max}, cm^{-1}	Ultraviolet λ_{max}, mμ (log ε)
Synthesized	271—271.5	3180, 3080—3030, 1680, 1635, 1420, 1355, 690[a]	320.5 (4.4)[b]
Natural	272[c]	3184, 3080—3030, 1680, 1638, 1424, 1358, 690[c]	234 (3.9), 318 (4.4)[c]
	275—276[d]		
	263—265[e]		201, 236, 316[e]

a) In KBr. b) In dimethylformamide. c) Reference 4. d) Reference 3.
e) Reference 5.

Treatment of ethyl 2-amino-3-methylcrotonate (II) with chloroacetyl chloride in an aqueous solution in the presence of sodium hydrogencarbonate afforded ethyl 2-(2-chloroacetamido)-3-methylcrotonate (III) in 47% yield. When the ester III was treated with ammonia in methanol at room temperature for 2 days, the amination and the subsequent or spontaneous cyclization reactions occurred to yield 3-isopropylidene-2,5-piperazinedione (IV).

In an extension of this method to the synthesis of albonoursin, the ester of 2-(2-chloroacetamido)-4-methyl-2-pentenoic acid is required. Meister and Greenstein have reported that the condensation reaction of α-ketoisocaproic acid with chloroacetonitrile in the presence of hydrogen chloride gave a mixture of 2-(2-chloroacetamido)-4-methyl-2-pentenoic acid (V) and chloroacetamide. The acid V has not been isolated but characterized by its conversion to 2-(2-aminoacetamido)-4-methyl-2-pentenoic acid (VI).[8] However, our modification of the method led to the isolation of V in a pure state (see Experimental). The acid V was also obtained by heating 2,2-bis(2-chloroacetamido)-4-methylpentanoic acid (VII) in acetic acid for 3 hr. The acid V was identified by a comparison with the sample obtained in the preceding paper[9] from 2-chloromethyl-4-isobutylidene-5-oxazolone.

The acid V was transformed into the corresponding ethyl ester (VIII) in 26% yield by heating in ethanol in the presence of sulfuric acid and *p*-toluenesulfonic acid.[10] Treatment of the ester with ammonia in methanol afforded 3-isobutylidene-2,5-piperazinedione (IX).

In an alternative route, 2-(2-aminoacetamido)-4-methyl-2-pentenoic acid (VI) derived from V was refluxed in methanol in the presence of hydrogen chloride to give the corresponding methyl ester (X). By heating in aqueous solution, the ester X gave also the piperazinedione IX in 28% yield.

When the piperazinedione IX was condensed with benzaldehyde in the presence of acetic anhydride and sodium acetate, 3-benzylidene-6-isobutylidene-2,5-piperazinedione (I) was obtained in 56% yield. The identity of the product was confirmed by elemental analysis as well as infrared and ultraviolet spectra. The spectral data and other properties indicate the identity of the natural albonoursin, as shown in Table 1.

Experimental[11]

Ethyl 2-(2-Chloroacetamido)-3-methylcrotonate

8) A. Meister and J.P. Greenstein, *J. Biol. Chem.*, **195**, 849 (1952).

9) H. Kurita, Y. Chigira, M. Masaki and M. Ohta, This Bulletin, **41**, 2758 (1968).

10) In general, the esterification of this type of compounds is difficult. *N*-Acetyl-dehydroalanine has been reported to be esterified by means of the use of diazomethane in 10% yield and of dimethyl sulfate or methyl iodide in 40—50% yield: T. Wieland, G. Ohnacker and W. Ziegler, *Chem. Ber.*, **90**, 194 (1957).

11) All melting points were determined in a liquid bath and are uncorrected.

(III). Chloroacetyl chloride (0.8 g) was added portionwise, with vigorous stirring at room temperature, to ethyl 2-amino-3-methylcrotonate (1 g) suspended in a solution of sodium hydrogencarbonate (0.6 g) in water (15 ml). After stirring for 30 min, crystalline precipitates were collected and washed with water. Recrystallization from 50% aqueous ethanol afforded colorless needles (0.7 g, 47%), mp 117—118°C. The product was identical in melting point and infrared spectrum with the sample obtained in the preceding paper.[9]

3-Isopropylidene-2,5-piperazinedione (IV). A solution of III (0.6 g) in methanol (15 ml) was saturated with dry gaseous ammonia under cooling. When the solution was allowed to stand at room temperature for 3 days, crystalline substance precipitated. The methanol was evaporated under reduced pressure and the residual crystalline product was washed with cold water. Recrystallization from water afforded colorless prisms (0.26 g, 61%), mp 260°C (decomp.). The infrared spectrum was superimposable on that of the authentic 3-isopropylidene-2,5-piperazinedione.[6]

2,2-Bis(2-chloroacetamido)-4-methylpentanoic Acid (VII). The same directions were followed as that used for 2,2-bis(2-chloroacetamido)propionic acid.[12]

By a reaction of 4-methyl-2-oxopentanoic acid (5 g) and chloroacetonitrile (6 g) in concentrated sulfuric acid (30 ml), followed by a recrystallization of the crude product from water, there were obtained colorless prisms (5.6 g, 50%), mp 183—184°C (lit.[13] mp 134°C).

Found: C, 40.41; H, 5.34; N, 9.20%. Calcd for $C_{10}H_{16}N_2O_4Cl_2$: C, 40.13; H, 5.35; N, 9.36%.

2-(2-Chloroacetamido)-4-methyl-2-pentenoic Acid (V). *A) From 4-Methyl-2-oxopentanoic Acid.* The procedure was modified from the method of Meister and Greenstein.[8] A mixture of 4-methyl-2-oxopentanoic acid (4 g) and chloroacetonitrile (2 g) was saturated with dry hydrogen chloride at 0°C, and then allowed to stand in a refrigerator for 3 days. The mixture was treated with dry ether and the crystalline substance, chloroacetamide, was filtered off. The filtrate was concentrated to give a yellow viscous residue (*residue A*), which was dissolved in water (20 ml). The pH of the solution was adjusted to 8 with a sodium bicarbonate solution and an insoluble oil formed was removed by extraction with ether. The aqueous layer was acidified to pH 3 with 3 N hydrochloric acid and well extracted four times with ether. The ethereal extract was dried over anhydrous sodium sulfate and then evaporated. Addition of di-*n*-butyl ether to the residual oil gave a crystalline product. Recrystallization from di-*n*-butyl ether afforded colorless needles (0.7 g, 14%), mp 128—129°C. The product was identical with the sample prepared in the preceding paper.[9]

B) From VII. A suspension of VII (3 g) in acetic acid (12 ml) was gently refluxed for 3 hr, and the resultant dark brown solution was concentrated under reduced pressure to give a yellow viscous residue, which was treated in the same manner as for the *residue A* in the method A, giving colorless needles (0.7 g, 36.8%), mp 128—129°C. The product was identical, in melting point and infrared spectrum, with the sample obtained by the method A.

Ethyl 2-(2-Chloroacetamido)-4-methyl-2-pentenoate (VIII). A suspension of V (4.8 g) in ethanol (20 ml) and benzene (20 ml) was refluxed in the presence of concentrated sulfuric acid (0.5 g) and *p*-toluenesulfonic acid (0.5 g) for 5 hr. The resultant solution was concentrated under reduced pressure to give an oily residue. Ether was added to the residue and then the insoluble *p*-toluenesulfonic acid was filtered off. The ethereal solution was washed successively with aqueous sodium bicarbonate and with water, and dried over anhydrous sodium sulfate. After evaporation of the ether, the residue was distilled to give a colorless viscous oil (1.4 g, 25.6%), bp 135—137°C/2 mmHg. Upon addition of petroleum ether, the oil gradually solidified. Recrystallization from petroleum ether afforded colorless prisms, mp 64—67°C.

Found: C, 51.36; H, 6.68; N, 6.10%. Calcd for $C_{10}H_{16}NO_3Cl$: C, 51.39; H, 6.85; N, 6.00%.

2-(2-Aminoacetamido)-4-methyl-2-pentenoic Acid (VI). The procedure was modified from the method of Meister and Greenstein.[8] A solution of V (2.0 g) in methanol (30 ml) was saturated with gaseous ammonia under ice cooling and then left to stand at room temperature overnight. The solution was concentrated under reduced pressure: the residual oily product solidified partially upon addition of methanol to give colorless needles (0.5 g), mp 266—267°C (decomp.).[14]

3-Isobutylidene-2,5-piperazinedione (IX). *A) From VIII.* A solution of VIII (0.6 g) in methanol (10 ml) was saturated with gaseous ammonia and the resultant mixture was treated in a manner analogous to the case of IV. Recrystallization from water gave colorless needles (0.25 g, 59%), mp 277—278°C (decomp.). ν_{max}^{KBr} 3170, 3050, 1700 and 1640 cm^{-1}. λ_{max}^{KBr} 220 mμ (ε =16600), 240 (14100).

Found: C, 56.81; H, 7.01; N, 16.85%. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66%.

B) From X. A suspension of VI (0.4 g) in methanol (15 ml) was refluxed, while dry hydrogen chloride was passed through the mixture for 2 hr. The solution was concentrated under reduced pressure to dryness giving the methyl ester hydrochloride (X·HCl) as a crystalline residue, which was used without further purification. A solution of the crude X and sodium bicarbonate (0.1 g) in water (10 ml) was heated on a steam bath for 3 hr. Crystals gradually precipitated from the solution. The precipitates were collected and recrystallized from 50% aqueous methanol to give colorless needles (0.1 g) mp 277—278°C. The product was identical, in melting point and infrared spectrum, with the sample obtained in method A.

3-Benzylidene-6-isobutylidene-2,5-piperazinedione (I). A mixture of IX (0.05 g) and benzaldehyde (0.2 g) in acetic anhydride (2 ml) was heated at 140°C for 5 hr. The mixture was treated with water (4 ml) and ether (2 ml), giving crystalline precipitates. The precipitates were collected, dissolved in acetic acid and then reprecipitated by addition of water. Recrystallization from acetone afforded colorless needles (0.03 g, 40%).

Found: C, 70.02; H, 6.39; N, 11.00%. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%.

12) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids", Vol. 2, John Wiley and Sons, Inc., New York, 1961, p. 849.

13) S.-C. J. Fu, L. Levintow, V. E. Price and J. P. Greenstein, *Arch. Biochem.*, **28**, 440 (1950); *Chem. Abstr.*, **45**, 5625g (1951).

14) Unfortunately the mp was not recorded in literature 13.