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SYNTHESES AND CONFIGURATIONAL ASSIGNMENTS OF ALBONOURSIN AND ITS THREE GEOMETRIC ISOMERS

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Albonoursin (1) was isolated from *Streptomyces (St.) albus var. fungatus* and *St. noursei* by Brown and Kelley[1] and by other workers,[2] and recently from *Actinomyces tumemacerance* by Fukushima *et al.*[3] The structure was determined to be 3-benzylidene-6-isobutylidene-2,5-piperazinedione, independently, by Khokhlov and Lokshin[4] and by other workers.[5,6] Although the total synthesis of 1 was accomplished,[7,8] no report on the configurational assignment of 1, for which possible four geometric isomers exist as shown in Fig 1, has been appeared in the literature.

On the other hand, concerning the physiological activity, it has been recently reported that the naturally occurring 1 exhibited antibacterial activity and inhibited the growth of transplantable solid tumors in mice.[3]

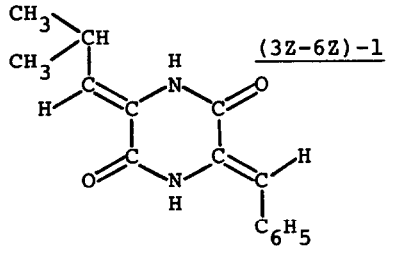
Because of the pharmacological and the configurational interests in the relation between the naturally occurring 1 and its three stereochemical isomers, in this paper, the enthusiastic syntheses of the four isomers were pursued successfully and the configurational assignments of the four structures were established on the basis of the NMR spectroscopic analysis and chemical determination.

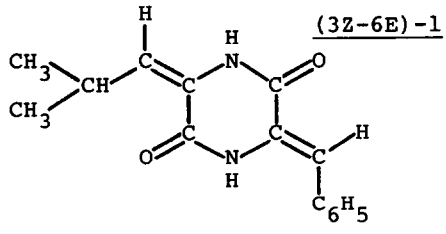
The starting 3-(Z)-isobutylidene-1-acetyl ((Z)-2)-, 3-(E)-isobutylidene-1,4-diacetyl ((E)-3)-, 3-(Z)-benzylidene-1-acetyl ((Z)-4)- and 3-(E)-benzylidene-1,4-diacetyl-2,5-piperazinediones ((E)-5) were obtained by acetylation of pure 3-(Z)-isobutylidene (mp 269-271°C, NMR (CF_3COOH); δ 8.46, 9.78 (NH), 6.44 (vinyl))-, 3-(E)-isobutylidene (mp 258-259°C, 8.24, 9.72 (NH), 5.90 (vinyl))-, 3-(Z)-benzylidene (mp 260-262°C, 8.44, 9.31 (NH), 7.41 (vinyl), 7.50 (phenyl sharp s))- and 3-(E)-benzylidene-2,5-piperazinediones (mp 270-271°C, 8.14, 9.84 (NH), 6.96 (vinyl), 7.41 (phenyl broad m)), respectively, which derived from the cyclization of individual (Z)- and (E)-methyl 2-chloroacetylamino-4-methyl-2-pentenoates (mp 68-69°C, NMR ($CDCl_3$); δ 7.74 (NH), 6.62 (vinyl), 2.63 (3-proton) and bp 107-110°C/1 mmHg, 8.45 (NH), 6.94 (vinyl), 3.42 (3-proton)) and (Z)- and (E)-ethyl 2-chloroacetyl-

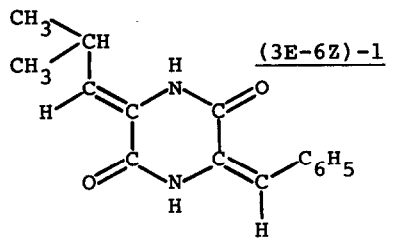
aminocinnamates (mp 103-104°C, 8.00 (NH, phenyl and vinyl) and bp 117-118°C/1 mmHg, 8.67 (NH), 7.89 (vinyl)) with ammonia.[9] The configurational assignments of all the above isomers were determined by the methods recently reported.[10-12]

Treatment of (Z)-2 with benzaldehyde in the presence of Et_3N at 100°C for 1 hr gave a pure condensation product, which was identical with that prepared by condensation of (Z)-4 with isobutylaldehyde in t-BuOH in the presence of t-BuOK at room temperature for 12 hr, according to the method reported by Gallina and Liberatori.[13] This fact indicates that the configuration of the product resulting from the two routes is to be 3-(Z)-benzylidene-6-(Z)-isobutylidene-2,5-piperazinedione ((3Z-6Z)-1). On the other hand, the analogous condensation of (E)-3 with benzaldehyde by the latter method gave also a pure product, the geometric structure of which was readily determined by comparing the chemical shifts of the two exocyclic vinyl protons of the product with those of (3Z-6Z)-1, to be 3-(Z)-benzylidene-6-(E)-isobutylidene-2,5-piperazinedione ((3Z-6E)-1). It is observed that the chemical shift of vinyl proton in the 3-benzylidene group of (3Z-6E)-1 is almost equal to that of (3Z-6Z)-1, but the vinyl proton in the isobutylidene group of (3Z-6Z)-1 shifts to lower field by 0.44 ppm than that of (3Z-6E)-1 by deshielding effect of the carbonyl function on the exocyclic vinyl proton,[12] as shown in Table 1.

Furthermore, analogous condensation of (E)-5 with isobutylaldehyde gave two isomeric products as a mixture, one of which could be separated purely by recrystallization from boiling glacial acetic acid. Similarly, the comparison of the chemical shifts of vinyl proton in the two isobutylidene groups of the products with that of (3Z-6E)-1 indicated that the pure one is 3-(E)-benzylidene-6-(E)-isobutylidene-2,5-piperazinedione ((3E-6Z)-1) and the another to be 3-(E)-benzylidene-6-(E)-isobutylidene-2,5-piperazinedione ((3E-6E)-1), respectively. From the intensity of the vinyl proton signals, the yielding ratio of (3E-6Z)-1







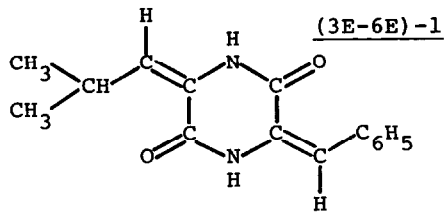


Fig 1

Scheme 1

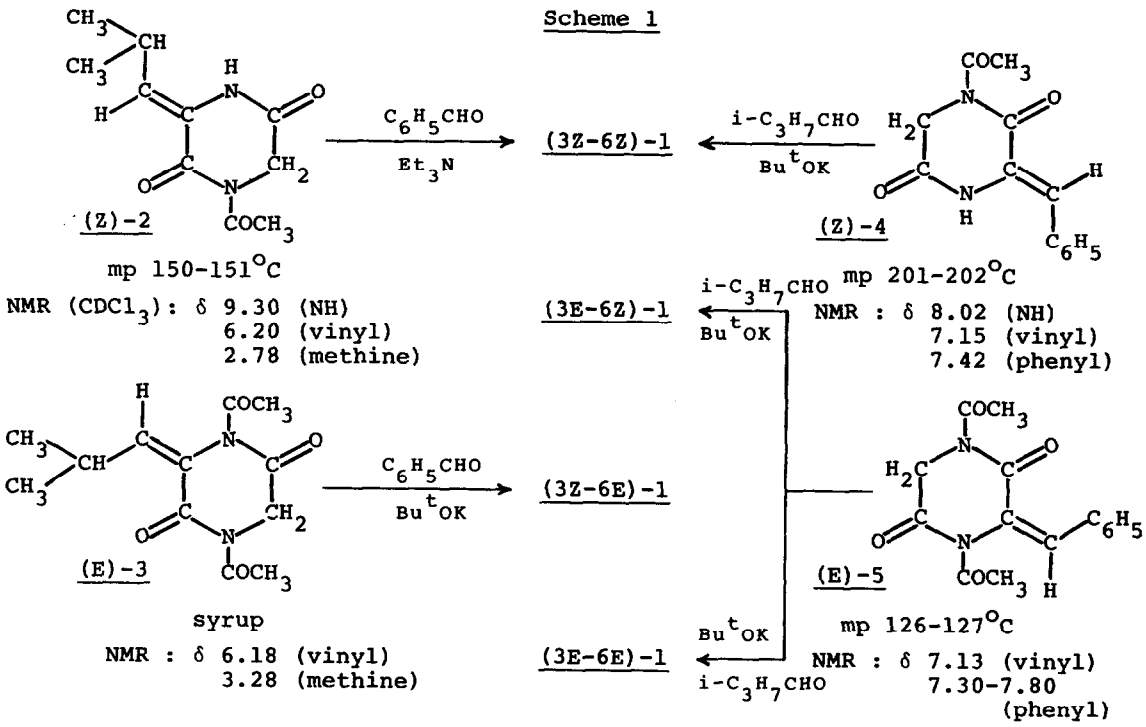
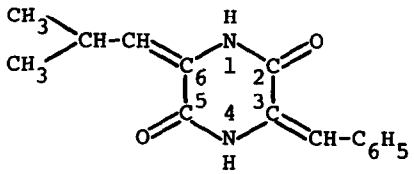


Table 1. Physical constants and spectral data of 1



Compound	Yield (%)	Mp °C (dec.)	^{1}H NMR spectrum, δ, in CF_3COOH NH[e]	3-vinyl	6-vinyl (J_{Hz})	$(CH_3)_2$-	C_6H_5- (CH-)	UV spectrum[d]
(3Z-6Z)-1	58.9[a] 52.3[b]	271-271.5	9.76	7.32s	6.40d (10)	1.19s 1.25s	7.45s[f] (2.87m)	234(3.90) 317(4.33)
(3E-6Z)-1	54.6[c]	277-278	10.00	6.89s	6.33d (10)	1.16s 1.24s	7.34m[g] (2.83m)	232(3.93)[h] 238(3.92)
(3E-6E)-1			10.08	6.83s	5.87d (10)	1.11s 1.18s	7.42m[g] (3.75m)	323(4.30)
(3Z-6E)-1	43.8	252-253	9.56	7.24s	5.96d (10)	1.13s 1.20s	7.46s[f] (3.76m)	231(3.82)[h] 237(3.80) 317(4.32)

a) From (Z)-2. b) From (E)-3. c) Mixture of (3E-6Z)-1 and (3E-6E)-1. d) In 95% EtOH, nm (log ε). e) Broad singlet. f) Sharp singlet. g) Broad multiplet. h) Shoulder.

and (3E-6E)-1 was determined to be 2 : 1. These facts show that (Z)-substituent predominantly introduced in the course of chemical syntheses.

It will be noteworthy that phenyl protons of exocyclic benzylidene group trans to the carbonyl function appears as a sharp singlet, while that of cis position as a broad multiplet or singlet due to a restricted free-rotation, as shown in Table 1 and 3-benzylidene-2,5-piperazinedione.

The yields, physical constants, NMR and UV spectra data of 1 are summarized in Table 1.

Consequently, it was found that the configuration of the naturally occurring albonoursin was identified to be (3Z-6Z)-geometry, from the results that the melting point, IR and UV spectra of albonoursin (mp 272°C, IR: 3180, 3080-3030, 1680, 1638, 1424, 1358, 690 cm^{-1}, UV: 234 (log ε=3.9), 318 (4.4) nm)[5] were in excellent agreement with that of (3Z-6Z)-1 prepared here. This conclusion will be supported by the facts that the biosynthesis of 3-alkylidene-2,5-piperazinediones such as mycelianamide,[14] cryptoechinuline A,[15] neoechinuline,[16] by incorporation of L-tyrosine or L-triptophan into cyclic dipeptide and subsequent stereoselective dehydrogenation give preferentially (Z)-isomer.

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