α,β-Unsaturated Carboxylic Acid Derivatives. Part 18.[1] Syntheses of Geometric Isomers of 3,6-Dibenzylidene- and 3-*p*-Anisylidene-6-benzylidene-2,5-piperazinediones

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Naturally occurring 3,6-dibenzylidene- and 3-*p*-anisylidene-6-benzylidene-2,5-piperazinediones and their geometric isomers were synthesized by the condensation of 1-acetyl or 1,4-diacetyl derivative of (*E*)- and (*Z*)-benzylidene- or *p*-anisylidene-2,5-piperazinediones with an appropriate aldehyde. The configuration of these compounds were assigned on the basis of the spectroscopic analyses, and those of natural products were determined to be (3*Z*,6*Z*).

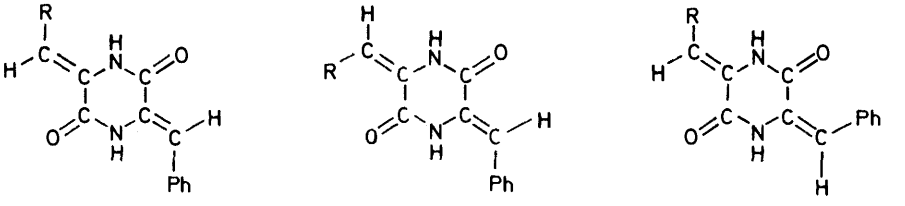
3,6-DIBENZYLIDENE- (1) and 3-*p*-anisylidene-6-benzylidene-2,5-piperazinedione (2) (2,5-piperazinedione = PDO) were isolated, together with the antibiotic albonoursin (3-benzylidene-6-isobutylidene-PDO),[2-6] from the culture filtrate of *Streptomyces noursei* [7] and *S. thioluteus*.[8]

Syntheses of these compounds [8-10] and many analogues [11] have been accomplished by several research groups, but the configurational assignments of the above natural products had not been accomplished until the four isomers of albonoursin were synthesized by us.[12]

In this paper, we synthesized two of three possible isomers of (1) and three of four possible isomers of (2), and determined the configurations of (1) and (2) to be (3*Z*,6*Z*).

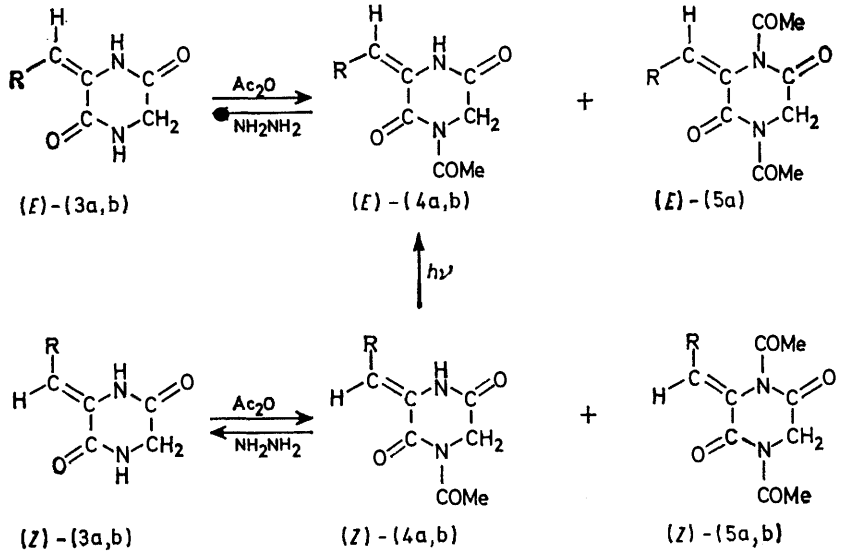
RESULTS AND DISCUSSION

1-Acetyl and 1,4-diacetyl derivatives of (*E*)- and (*Z*)-benzylidene-PDO [(*E*)-(3a) and (*Z*)-(3a),[13] which were synthesized by cyclization of ethyl (*E*)- and (*Z*)-2-(chloroacetylamino)cinnamates with ammonia] were obtained by refluxing (*E*)- or (*Z*)-(3a) with acetic anhydride for a short period. It is noteworthy that (*E*)-(3a) gave predominantly the 1,4-diacetyl derivative



(3*Z*, 6*Z*)-(1); R = Ph (3*E*, 6*Z*)-(1); R = Ph (3*Z*, 6*E*)-(2); R = C_6H_4OMe-*p*

(3*Z*, 6*Z*)-(2); R = C_6H_4OMe-*p* (3*E*, 6*Z*)-(2); R = C_6H_4OMe-*p*



(*E*)-(3a,b) (*E*)-(4a,b) (*E*)-(5a)

(*Z*)-(3a,b) (*Z*)-(4a,b) (*Z*)-(5a,b)

a; R = Ph, b; R = C_6H_4OMe-*p*

(*E*)-(5a),[14] whereas (*Z*)-(3a) gave the 1-acetyl derivative (*Z*)-(4a) [12] as the main product. Although the prolonged reaction of (*Z*)-(3a) for 3 h increased the yield of the 1,4-diacetyl derivative (*Z*)-(5a) to *ca.* 20%, the ratio (*Z*)-(4a): (*Z*)-(5a) was still 2.7 : 1. This general phenomenon [15] in the acetylation of mono-alkylidene-PDO is diagnostic in similar way, (*E*)-(5a) was successfully condensed with *p*-anisaldehyde to give (3*Z*)-*p*-anisylidene-(6*E*)-benzylidene-PDO [(3*Z*,6*E*)-(2)]. However, compounds (1) and (2) in the (3*E*,6*E*)-configuration could not be obtained, because only (*Z*)-substituents were introduced by condensation with an aromatic aldehyde. As in the

TABLE 1

Yields, physical constants, and ^{1}H n.m.r. spectral data for (1) and (2)

Compound	Yield (%)	Procedure	M.p. (°C) (decomp.)	^{1}H N.m.r. spectra [a] (δ) NH	3-Vinyl	6-Vinyl	C_6H_4-X	OMe
(3*Z*,6*Z*)-(1)	73.4 [b]	A	283—284	10.28		6.82	7.36—7.66 (m)	
	65.5 [c]	A	(295)					
(3*E*,6*Z*)-(1)	69.0 [d]	B	270—272 (281)	10.08 10.85	6.54	6.76 (s)	7.18—7.66 (m)	
(3*Z*,6*Z*)-(2)	49.5 [e]	A	263—265	10.16		6.80	6.97—7.63 (m)	3.85
	60.0 [b]	A	(270)					
(3*E*,6*Z*)-(2)	53.2 [f]	B	252—253 (258)	10.02 10.75	6.52	6.72 (s)	6.86—7.70 (m)	3.81
(3*Z*,6*E*)-(2)	61.5 [d]	B	253—254 [g]	9.97 10.77	6.74	6.56 (s)	6.97—7.63 (m)	3.85

[a] Measured in [$^2H_6$]DMSO. [b] From (*Z*)-(4a). [c] From (*Z*)-(5a). [d] From (*E*)-(5a). [e] From (*Z*)-(4b). [f] From (*E*)-(4b). [g] Colourless powder from boiling acetic acid; others were pale yellow powders.

distinguishing the geometry of the parent compound, even when only one isomer is available.

On the other hand, the photoisomerization of 1-acetyl-(3*Z*)-*p*-anisylidene-PDO [(*Z*)-(4b)] [16] by the method of Porter and Sammes [14] gave the corresponding (*E*)-isomer, (*E*)-(4b), in low yield. Deacetylation of (*Z*)-(4b) and (*E*)-(4b) with hydrazine [16] gave the deacetylated products (*Z*)-(3b) and (*E*)-(3b) in quantitative yields, respectively, and prolonged acetylation of (*Z*)-(4b) gave the corresponding 1,4-diacetyl derivative (*Z*)-(5b) in 31% yield.

For the preparation of (1) and (2), the above acetyl derivatives (3)—(5) were condensed with benzaldehyde or *p*-anisaldehyde in the presence of sodium acetate [9] or triethylamine [17] at elevated temperatures (Procedure A) or in the presence of potassium t-butoxide at 0 °C (Procedure B).[16] Condensation of (*Z*)-(4a) and (4b) with benzaldehyde by procedure A gave (3*Z*,6*Z*)-dibenzylidene-PDO [(3*Z*,6*Z*)-(1)] and (3*Z*)-*p*-anisylidene-(6*Z*)-benzylidene-PDO [(3*Z*,6*Z*)-(2)], respectively. Similar condensation of (*E*)-(3a) and (*Z*)-(5a) gave the same (3*Z*,6*Z*)-(1), indicating the thermal isomerization of (*E*)-(5a) under these reaction conditions.

As expected, treatment of (*E*)-(5a) or (*E*)-(4b) with benzaldehyde by procedure B gave (3*E*,6*Z*)-dibenzylidene-PDO [(3*E*,6*Z*)-(1)] and (3*E*)-*p*-anisylidene-(6*Z*)-benzylidene-PDO [(3*E*,6*Z*)-(2)], respectively. In a condensation of isobutyraldehyde by procedure B,[12] the formation of the (*E*)-substituent could not be detected.

The physical and spectral data for the isomers of (1) and (2) are listed in Tables 1 and 2. The previous observations that vinyl protons in the (*E*)-configuration resonate at higher field than those in the (*Z*)-configuration [12,18] support the structures of the geometric isomers shown in Table 1. From the physical properties of the geometric isomers summarized in Tables 1 and 2, the configurations of naturally occurring (1) and (2) could be identified unambiguously as having (3*Z*,6*Z*)-geometry, since the decomposition points, and the i.r. and u.v. spectra reported for (1) and (2) were in excellent agreement with those of (3*Z*,6*Z*)-(1) and (3*Z*,6*Z*)-(2), respectively. This conclusion is supported by the fact that the biosynthesis of 3-alkylidene- or arylidene-PDO such as mycelianamide,[19] cryptoechinuline A,[20] and neoechinuline,[21] by incorporation of L-tryptophan into a cyclic dipeptide and subsequent stereoselective dehydrogenation, gives predominantly the (*Z*)-isomer.

TABLE 2

I.r. and u.v. spectral data for (1) and (2) *

	$\nu_{max.}$ (KBr)/cm^{-1} NH	NHCO	C=C	$\lambda_{max.}$ (95% EtOH)/nm (log ε)	
(3*Z*,6*Z*)-(1)	3 200	1 695	1 635	233 (3.95)	338 (4.47)
(3*E*,6*Z*)-(1)	3 170	1 695	1 630	232 (3.89)	337 (4.30)
(3*Z*,6*Z*)-(2)	3 200	1 690	1 635	236 (3.95)	352 (4.45)
(3*E*,6*Z*)-(2)	3 190	1 690	1 638	234 (3.93)	352 (4.40)
(3*Z*,6*E*)-(2)	3 170	1 682	1 625	235 (3.96)	352 (4.47)

* Compound (1); m.p. 298—300 °C, $\lambda_{max.}$ 234 (log ε 3.9) and 338 nm (log ε 4.3) (ref. 7): (2); m.p. 270—273 °C, $\lambda_{max.}$ 350, and 398 nm (ref. 8).

EXPERIMENTAL

M.p.s were taken with a Yamato micro-apparatus (MP-21) (capillary method). I.r. spectra were recorded with a Hitachi EPI-G3 spectrometer, u.v. spectra with a Shimadzu UV-100 spectrometer, and n.m.r. spectra with a JNM-PS-100 spectrometer (tetramethylsilane as the internal standard, in deuteriochloroform unless otherwise stated).

Chemical shifts and coupling constants were recorded in δ and Hz units, and i.r. frequencies in cm^{-1}.

Acetylation of (*E*)-(3a).—The acetylation of (*E*)-(3a) [13] (170 mg, 0.84 mmol) with acetic anhydride (5 ml) was carried out by the usual procedure by heating at 130 °C for 0.5 h. After removal of excess of acetic anhydride under reduced pressure, the residual semi-solid, consisting of two components, was chromatographed on a silica gel column [benzene–acetone (25 : 1 v/v)] to give (*E*)-(5a) (160 mg, 66.7%) and (*E*)-(4a) (10 mg, 4.8%), both as colourless prisms after recrystallization from ethanol. (*E*)-(5a), m.p. 126—127 °C (lit.,[14] syrup); δ 2.60 and 2.65 (2 × Ac), 4.59 (CH_2; s), 7.13 (vinyl-H; s), and 7.30—7.80 (Ph; m) (Found: C, 63.05; H, 4.9; N, 10.1. $C_{15}H_{14}N_2O_4$ requires C, 62.93; H, 4.93; N, 9.79%). (*E*)-(4a), m.p. 157—158 °C (lit.,[14] m.p. 178—179 °C); δ 2.57 (Ac), 4.42 (CH_2; s), 6.58 (vinyl H; s), 7.12—7.48 (Ph; m), and 10.04 (NH) (Found: C, 64.1; H, 5.05; N, 11.45. $C_{13}H_{12}N_2O_3$ requires C, 63.92; H, 4.95; N, 11.47%).

Acetylation of (*Z*)-(3a) *and* (*Z*)-(4b).—Acetylation of (*Z*)-(3a) [13] and (*Z*)-(4b) [16] was performed in a similar manner as described above. From (*Z*)-(3a) (330 mg, 1.63 mmol) and acetic anhydride (10 ml), (*Z*)-(4a) and (*Z*)-(5a) were obtained in 90.0% (358 mg) and 6.7% (30 mg) yield, respectively. When the reaction was continued for 3 h, the above yields were 57.7% and 24.4%, respectively. (*Z*)-(4a), m.p. 201—202 °C (lit.,[16] m.p. 200—201 °C). (*Z*)-(5a): m.p. 151—152 °C; δ 2.48 and 2.60 (2 × Ac), 4.60 (CH_2; s), 7.34 (Ph; s), and 7.50 (vinyl H; s) (Found: C, 62.9; H, 4.8; N, 9.65. $C_{15}H_{14}N_2O_4$ requires C, 62.93; H, 4.93; N, 9.79%).

Acetylation of (*Z*)-(4b) (680 mg, 2.48 mmol) with acetic anhydride (20 ml) for 3 h gave (*Z*)-(5b) (250 mg, 31.1%) as colourless prisms from ethanol, along with starting material (46.3% recovered); (*Z*)-(5b): m.p. 159—160 °C; δ 2.53 and 2.59 (2 × Ac), 4.48 (CH_2; s), 7.06 (Ph; s), 7.44 (vinyl H; s) (Found: C, 60.85; H, 5.0; N, 8.8. $C_{16}H_{16}N_2O_5$ requires C, 60.75; H, 5.10; N, 8.86%).

Preparation of (*E*)-(4b).—A solution of (*Z*)-(4b) (200 mg, 0.73 mmol) in methanol (100 ml) was irradiated with a high-pressure mercury lamp under a nitrogen atmosphere at room temperature for 3 h. The resulting solution was concentrated to give crystals, which were chromatographed on a silica gel column with chloroform–acetone (10 : 1 v/v) as eluant to give (*E*)-(4b) (30 mg, 15.1%) as colourless prisms from methanol, along with starting material (65% recovered) (*E*)-(4b), m.p. 173—174 °C; δ 2.59 (Ac), 4.43 (CH_2; s), 6.50 (vinyl H; s), 7.12 (Ph; s), and 9.60 (NH) (Found: C, 61.2; H, 5.35; N, 10.2. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.15; N, 10.21%).

Deacetylation of (*E*)-(4b) *and* (*Z*)-(4b).—A solution of (*E*)-(4b) or (*Z*)-(4b) (274 mg, 1 mmol) in hydrazine hydrate (100 mg, 2 mmol) and dimethylformamide (3 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into ice–water (10 ml) and the crystals that separated were collected, washed with water, and recrystallized from boiling acetic acid to give (*E*)-(3b) or (*Z*)-(3b), respectively, as a colourless powder in quantitative yield. (*E*)-(3b), m.p. 258—260 °C (decomp); δ 4.50 (CH_2; s), 6.90 (vinyl H; s), 7.28 (Ph; s), and 8.18 and 9.86 (2 × NH), (Found: C, 62.0; H, 5.3; N, 12.1. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21; N, 12.06%). (*Z*)-(3b), m.p. 243—245 °C (decomp.) (lit.,[16] m.p. 278—280 °C).

Preparation of (1) *and* (2).—Preparation of (1) and (2) was performed by the condensation of (3)—(5) with the appropriate aldehyde by procedure A [9,17] or B; [16] the results are presented in Table 1. Elemental analyses were in agreement with theoretical values.

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