View Article Online / Journal Homepage / Table of Contents for this issue

Published on 01 January 1970. Downloaded by Universiteit Utrecht on 26/10/2014 16:51:09.

On the Synthesis of 3-Benzylidenepiperazine-2,5-diones

By **A. E. A. Porter** and **P. G. Sammes,*** Chemistry Department, Imperial College, London S.W.7

Treatment of *N*-(chloroacetyl)phenylalanine with methylamine gives 3-*trans*-benzylidene-1-methylpiperazine 2,5-dione, also produced, with no acetyl group at position 4, by cyclisation of (*N*-acetyldehydrophenylalanyl)-sarcosine with acetic anhydride.

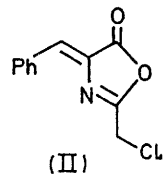
In view of the recent communication of Dominy and Lawton [1] on the synthesis of 3-benzylidenepiperazine-2,5-diones we wish to report a new synthesis, based on the route of Shin and his co-workers,[2] and to demonstrate that the product isolated by Dominy and Lawton was the 1-acetyl derivative [*i.e.* (I; $R^1 = H$, $R^2 = Ac$)] rather than the isomeric 4-acetyl compound.

Heating *N*-(dichloroacetyl)phenylalanine in acetic anhydride afforded the azlactone (II). Hydrolysis of

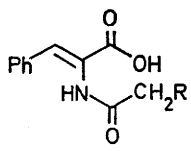
(I)

a; *trans* (shown)

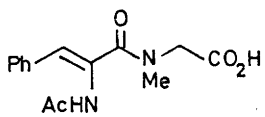
b; *cis*



(II)



(III)



(IV)

the azlactone in hot aqueous acetone gave *N*-chloroacetyldehydrophenylalanine (III; R = Cl), m.p. 195—197°, which reacted with methylamine to afford sarcosyldehydrophenylalanine (III; R = MeNH). Warming this in water, or even attempted crystallisation from water, caused spontaneous cyclisation to 1-methyl-3-*trans*-benzylidenepiperazine-2,5-dione (I; $R^1 = H$, $R^2 =$ Me), m.p. 142—143°. The same compound, with no acetyl group at position 4, was also isolated on attempted cyclisation of (*N*-acetyldehydrophenylalanyl)sarcosine (IV) with acetic anhydride under the conditions of Dominy and Lawton.[1] The loss of the *N*-acetyl group from position 4, either during the reaction or during isolation, is consistent with previous work on the condensation of aromatic aldehydes to give piperazine-2,5-diones in the presence of acetic anhydride.[3] The deacetylation could be a consequence of steric strain. On the basis of our results, the product isolated by Dominy and Lawton must be the 1-acetyl derivative rather than the 4-acetyl compound. This reassignment has been confirmed by comparison of the chemical shifts of the vinyl protons in these benzylidene compounds and in their photoisomers (Ib) (see Table).[3] The latter show a

^{1}H N.m.r. data (τ values) for 3-benzylidenepiperazine-2,5-diones [a]

Compound	CO·NH	C:CH	Ph
(Ia; $R^1 = H$, $R^2 = Ac$)	1·9br	2·84(s)	2·6br(s)
(Ia; $R^1 = H$, $R^2 = Me$)	2·0br	2·94(s)	2·6br(s)
(Ib; $R^1 = H$, $R^2 = Ac$)	0·14br	3·30(s)	2·3—2·7(m)
(Ib; $R^1 = H$, $R^2 = Me$)	0·39br	3·55(s)	2·4—2·8(m)
(Ib; $R^1 = R^2 = Ac$)		2·82(s)	2·2—2·7(m)

[a] At 60 MHz; *ca.* 10% solutions in $CDCl_3$; Me_4Si as internal reference.

vinyl proton signal at higher field than for the initial condensates, indicating the absence of a 4-acetyl function. Although the *trans*-condensates could not be further acetylated by acetic anhydride in the presence of sodium acetate, the photoisomer (Ib; $R^1 = H$, $R^2 = Ac$) gave a non-crystalline di-*N*-acetyl derivative (Ib; $R^1 = R^2 = Ac$) in which the vinylic proton is again deshielded, this time by the acetyl group at position 4.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined for solutions in chloroform, and u.v. spectra for solutions in ethanol unless otherwise specified.

N-(*Chloroacetyl*)*dehydrophenylalanine* (III; R = Cl).—

[1] B. W. Dominy and R. G. Lawton, *J. Org. Chem.*, 1969, **34**, 2013.

[2] C. Shin, Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Japan*, 1969, **42**, 191.

[3] K. W. Blake and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 980.

View Article Online

Published on 01 January 1970. Downloaded by Universiteit Utrecht on 26/10/2014 16:51:09.

2-Chloromethyl-4-benzylideneoxazolidin-5-one (II) [4] (3·0 g.) was heated in acetone (37 ml.) and water (19 ml.) under reflux for 1·5 hr. The cooled solution was then extracted with light petroleum. Concentration of the extract afforded the acid (III; R = Cl) (3·0 g., 92%), m.p. 195—197°, $\nu_{max.}$ (KBr) 3250, 3050—2500, 1690, and 1665 cm.$^{-1}$, τ [$(CD_3)_2SO$] 5·92 (2H, s), 2·3—2·9 (6H, m), and 0·46br (1H).

trans-3-*Benzylidene*-1-*methylpiperazine*-2,5-*dione* (Ia; R^1 = H, R^2 = Me).—*N*-(Chloroacetyl)dehydrophenylalanine (III; R = Cl) (1·0 g.) was suspended in 25% w/v aqueous methylamine (6 ml.) at room temperature. After 48 hr. the solution that formed was concentrated to dryness; the residue was triturated with ethanol to give material (0·67 g.), m.p. 180—184°, $\nu_{max.}$ (KBr) 3300—2300, 1690, 1650, 1605, and 1560—1540 cm.$^{-1}$, $\lambda_{max.}$ 279 nm. (ε 13,600), τ (D_2O) 7·26 (3H, s), 6·0 (2H, s), 2·72 (1H, s), and 2·58 (5H, s). On attempted crystallisation from water a different *compound* formed, m.p. 142—143°, $\nu_{max.}$ (KBr) 3375, 3070, 1690, 1640, and 1510 cm.$^{-1}$, $\lambda_{max.}$ 292 nm. (ε 18,600), τ ($CDCl_3$) 6·92 (3H, s), 5·86 (2H, s), 2·94 (1H, s), 2·62 (5H, s), and 2·0br (1H) (Found: C, 66·8; H, 5·6; N, 13·2. $C_{12}H_{12}N_2O_2$ requires C, 66·6; H, 5·6; N, 13·0%).

(N-*Acetyldehydrophenylalanyl*)*sarcosine* (IV).—Sarcosine (3·3 g.) in acetone (37 ml.) containing N-sodium hydroxide (37 ml.) was treated with 2-methyl-4-benzylideneoxazolidin-5-one (7 g.) at room temperature for 10 hr. Acidification with 1N-hydrochloric acid gave a yellow precipitate. This was collected, washed with water, redissolved in saturated potassium hydrogen carbonate solution, and reprecipitated with hydrochloric acid to give needles of the *peptide* (IV) (8·6 g., 83%), m.p. 205—207° (decomp.) (from ethanol), $\nu_{max.}$ (KBr) 3270, 3100—2400, 1710, 1660, 1600, and 1490—1530 cm.$^{-1}$, τ [100 MHz, $(CD_3)_2SO$] 8·08 (3H, s), 6·95 and 7·14 (3H), 5·84 and 6·02 (2H), 3·86 (1H, s), 2·66 (5H, m), and 0·26br (1H) (Found: C, 60·6; H, 5·6; N, 10·3. $C_{14}H_{16}N_2O_4$ requires C, 60·8; H, 5·8; N, 10·1%).

[4] M. Bergmann, V. Schmitt, and A. Miekeley, *Z. physiol. Chem.* 1930, **187**, 264.

Heating this peptide in acetic anhydride at 100° for 12 hr., followed by evaporation, gave a pale yellow solid. Trituration with benzene gave the piperazine-2,5-dione (Ia; R^1 = H, R^2 = Me) (2·8 g., 60%), m.p. and mixed m.p. 142—143°.

cis-3-*Benzylidene*-1-*methylpiperazine*-2,5-*dione* (Ib; R^1 = H, R^2 = Me).—The *trans*-isomer (0·2 g.) in methanol (30 ml.) was irradiated with light from a medium-pressure mercury lamp (125 w) for 3 hr. with a Pyrex filter. T.l.c. indicated a 7 : 3 ratio of product to the less polar starting material (silica gel; 95 : 5 chloroform–methanol). Preparative t.l.c. gave (from ethanol) the cis-*isomer* (76 mg.), m.p. 193—195°, $\nu_{max.}$ 3380, 1690, 1635, and 1400 cm.$^{-1}$, $\lambda_{max.}$ 298 nm. (ε 15,000), τ ($CDCl_3$) 6·96 (3H, s), 5·86 (2H, s), 3·65 (1H, s), and 2·4—2·8 (5H, n) (Found: C, 66·7; H, 5·8; N, 12·9. $C_{12}H_{12}N_2O_3$ requires C, 66·6; H, 5·6; N, 13·0%).

1-*Acetyl*-cis-3-*benzylidenepiperazine*-2,5-*dione* (Ib; R^1 = H, R^2 = Ac).—The *trans*-isomer (Ia; R^1 = H, R^2 = Ac) (0·2 g.) (prepared according to the method of Dominy and Lawton [1]) was photolysed in methanol (35 ml.) in a Pyrex vessel with a 125 w medium-pressure mercury lamp. After 3 hr. the products were separated by preparative t.l.c. (silica gel; 95 : 5 chloroform–methanol) to give the *photoisomer* (30 mg.), m.p. 178—179° (from methanol), $\nu_{max.}$ 3400, 1705, 1688, and 1630 cm.$^{-1}$, $\lambda_{max.}$ 320 nm. (ε 11,600), τ ($CDCl_3$) 7·43 (3H, s), 5·53 (2H, s), 3·3 (1H, s), 2·3—2·7 (5H, m), and 0·14 (1H, m) (Found: C, 63·7; H, 5·1; N, 11·6. $C_{13}H_{12}N_2O_3$ requires C, 63·9; H, 4·95; N, 11·5%).

Treatment of the photoisomer with acetic anhydride at 100° for 12 hr. gave a new compound. This was isolated by preparative t.l.c. (silica gel; 95 : 5 chloroform–methanol) to give a non-crystalline viscous oil, $\nu_{max.}$ 1700, 1625, 1375, and 1300 cm.$^{-1}$, τ ($CDCl_3$) 7·40 (3H, s), 7·34 (3H, s), 5·38 (2H, s), 2·82 (1H, s), and 2·2—2·7 (5H, m).

We thank the S.R.C. for a research studentship (to A. E. A. P.).

[0/1063 *Received, June 23rd,* 1970]