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# CONDENSATION OF 1,4-DIACETYLPIPERAZINE-2,5-DIONE WITH ALDEHYDES

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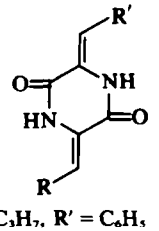
**Abstract**—Condensation of 1,4-diacetylpiperazine-2,5-dione with aldehydes has been applied to the synthesis of albonoursin and unsymmetrical 3,6-diarylidenepiperazine-2,5-diones. The reaction has been extended to 1,4-diacetyl-3,6-dimethylpiperazine-2,5-dione, which gives derivatives of 2-methyl-3-phenylserine. The mechanism and stereochemistry are discussed; *cis* 1-acetyl-3-isobutylidene-piperazine-2,5-dione has been isolated.

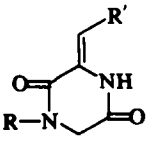
Some arylidene and alkylidene derivatives of piperazine-2, 5-dione, namely albonoursin(**1**),[1] 3, 6 - dibenzylidenepiperazine - 2, 5-dione(**2**),[1] and 3 - anisylidene - 6 - benzylidenepiperazine - 2, 5 - dione(**3**)[2] have been isolated from culture filtrates of *Streptomyces* species. While the synthesis of **2** and **3** was achieved by the method of Sasaki,[3] albonoursin required an independent approach[4] owing to the failure of this reaction when applied to the aliphatic aldehydes. In a recent letter[5] we reported a modification of the method of Sasaki which allows ready access to both monoarylidene and monoalkylidene piperazine-2,5-diones. The present paper deals with the general conditions devised for this reaction, its use in the synthesis of the natural products **1** and **3**, its mechanism and stereochemistry.

*Conditions, use and limitations of the method.* The suggestion[6] that N-acetylation of piperazine-2,5-dione should precede its condensation in the presence of acetic anhydride and sodium acetate, and the finding[4] that 1, 4 - diacetyl - 3 - isopropylidenepiperazine - 2, 5 - dione condenses with benzaldehyde in the presence of triethylamine, prompted us to study the condensation of aldehydes with 1, 4 - diacetylpiperazine - 2, 5 - dione(**8**). The technique of reacting the activated **8** instead of the simple piperazine-2,5-dione offers the advantage that several base-solvent combinations suitable for aldol condensation can be tested.

Preliminary experiments showed that aromatic aldehydes condense with **8** in the presence of triethylamine to give 1 - acetyl - 3 - arylidene-piperazine - 2, 5 - diones **6a-c** or 3, 6 - diarylidene-piperazine - 2, 5 - diones **2** and **5**, depending on the reaction conditions, while the aliphatic terms failed to react even at high temperatures. Stronger bases were therefore taken into consideration, and the bulky t-butoxide ion was chosen owing to the acylating properties of the CO—N—CO system of **8**. In fact four aliphatic aldehydes were successfully condensed with **8**, in the presence of tBuOK, with DMF as solvent, to give the parent monoalkylidene derivatives **6d-g** (Table 1). Attempts of monocondensation with ketones or double condensation with aliphatic aldehydes resulted in poor yields and are not described in this paper. An improvement of the reaction conditions, mainly by the



**1**: R = $iC_3H_7$, R′ = $C_6H_5$
**2**: R = $C_6H_5$, R′ = $C_6H_5$
**3**: R = $C_6H_4OCH_3p$, R′ = $C_6H_5$
**4**: R = $C_6H_4NO_2p$, R′ = $C_6H_5$
**5**: R = $C_6H_4NO_3p$, R′ = $C_6H_4NO_2p$



**6**: R = $COCH_3$
**7**: R = H

**a**: R′ = $C_6H_5$
**b**: R′ = $C_6H_4OCH_3p$
**c**: R′ = $C_6H_4NO_2p$
**d**: R′ = $CH_3$
**e**: R′ = $C_2H_5$
**f**: R′ = $nC_3H_7$
**g**: R′ = $iC_3H_7$

Table 1. 1-Acetyl-3-arylidene(alkylidene)piperazine-2,5-diones

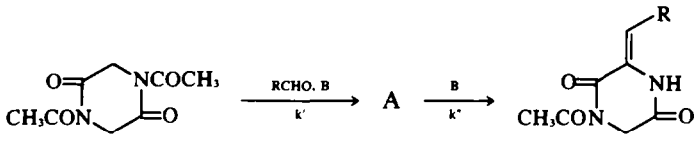
| Compounds | Yield* % | M.p. °C | Solvent | Formula | Analysis%† C | H | N | UV(EtOH) $\lambda_{max}$ nm | $\epsilon$ | IR($CHCl_3$), $cm^{-1}$ NH | lactame C=O | C=C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | 75 | 200–201 | EtOH | $C_{13}H_{12}N_2O_3$ | 63·86<br>63·93 | 5·00<br>4·95 | 11·40<br>11·47 | 229<br>316 | 14500<br>15300 | 3370 | 1700 | 1632 |
| **6b** | 66 | 179–180 | EtOH | $C_{14}H_{14}N_2O_4$ | 61·39<br>61·31 | 5·18<br>5·14 | 10·15<br>10·21 | 230<br>334 | 15800<br>20900 | 3370 | 1700 | 1628 |
| **6c** | 82 | 213–215 | EtOAc | $C_{13}H_{11}N_3O_5$ | 54·04<br>53·98 | 3·95<br>3·83 | 14·46<br>14·53 | 229<br>331 | 13300<br>15500 | 3370 | 1705 | 1635 |
| **6d** | 28 | 182–184 | $C_6H_6$ | $C_8H_{10}N_2O_3$ | 52·50<br>52·74 | 5·51<br>5·53 | 15·24<br>15·38 | 222 | 14100 | 3382<br>3190 | 1690 | 1641 |
| **6e** | 75 | 154–156 | $C_6H_6$ | $C_9H_{12}N_2O_3$ | 55·00<br>55·09 | 6·14<br>6·16 | 14·31<br>14·28 | 222 | 14600 | 3385<br>3190 | 1695 | 1641 |
| **6f** | 75 | 137–138 | $C_6H_6$<br>n-hexane | $C_{10}H_{14}N_2O_3$ | 56·94<br>57;13 | 6·65<br>6·71 | 13·30<br>13·32 | 222 | 14500 | 3380<br>3180 | 1690 | 1635 |
| **6g** | 80 | 146–147 | i-Propyl ether | $C_{10}H_{14}N_2O_3$ | 57·08<br>57·13 | 6·74<br>6·71 | 13·31<br>13·32 | 222 | 14200 | 3390<br>3190 | 1695 | 1642 |
| **14** | 6·9 | 108–110 | i-Propyl ether | $C_{10}H_{14}N_2O_3$ | 57·03<br>57·13 | 6·79<br>6·71 | 13·21<br>13·32 | 222 | 24000 | 3380<br>3190 | 1693 | 1627 |

*Of purified products.
†Upper figures, found; lower figures, calc.

Table 2. PMR data* of 1-acetyl-3-arylidene(alkylidene)piperazine-2,5-diones and deacetylated products

| Compounds | Solvent | Aromatic | Vinylic | CO–$CH_2$–N | $CH_3CO$ | NH | Allylic |
|---|---|---|---|---|---|---|---|
| **6a** | A | 7·66m | 7·14s | 4·47s | 3·36s | 10·45b | |
| **7a** | A | 7·55m | 6·71s | 4·06d(J 2) | | 9·82b 8·30b | |
| **6b** | A | 7·41dd | 7·06s | 4·43s | 3·32s | 10·45b | |
| **7b** | A | 7·34dd | 6·77s | 4·05d(J 2) | | 9·82b 8·26b | |
| **6c** | A | 8·15dd | 7·13s | 4·46s | 3·33s | 10·76b | |
| **7c** | A | 8·08dd | 6·85s | 4·08d(J 2) | | 10·55b 8·47b | |
| **6d** | B | | 6·52q(J 8) | 4·51s | 2·63s | 9·37b | 1·91d(J 8) |
| **7d** | A | | 5·89q(J 8) | 3·96d(J 2) | | 10·00b 8·10b | 1·73d(J 8) |
| **6e** | B | | 6·46t (J 8) | 4·50s | 2·63s | 9·38b | 2·31m |
| **7e** | A | | 5·82t (J 8) | 3·98t (J 8) | | 10·00b 8·12b | 2·21m |
| **6f** | B | | 6·53t (J 8) | 4·53s | 2·65s | 9·63b | 2·25m |
| **7f** | A | | 5·83t (J 8) | 3·96d(J 2) | | 10·00b 8·15b | 2·12m |
| **6g** | B | | 6·28d(J 10·5) | 4·47s | 2·61s | 9·64b | 2·76m |
| **7g** | A | | 5·59d(J 10·5) | 3·98d(J 2) | | 9·96b 8·13b | 2·83m |
| **14** | B | | 5·63d(J 10) | 4·41s | 2·60s | 9·73b | 3·53m |

*$\delta$(ppm) values relative to TMS as internal standard; coupling constants in Hz. Intensities of the signals in accordance with the numbers of protons. A: hexadeuterio DMSO, B: deuteriochloroform, s: singlet, d: doublet, dd: double doublet, t: triplet, q: quartet, m: multiplet, b: broad signal.



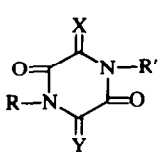

SCHEME 1

use of other bases, widely employed to generate enolate anions, should lead to better results. The deacetylated derivatives **7a-g** were prepared, for comparison[7] purposes, by hydrazinolysis of the parent 1 - acetyl - 3 - alkylidene(arylidene)piperazine - 2, 5 - diones. PMR data of both classes of compounds are reported in Table 2.

An important feature of our modification is that, for a given set of conditions, the reactivity of **8** is greater than that of monocondensed products. Therefore monoarylidene(alkylidene) derivatives can be obtained easily when an equivalent of base is used. A second condensation can be induced with aromatic aldehydes forcing sometimes the conditions in order to enhance the reaction rate. This technique has been employed for a facile synthesis of the natural products **1** and **3** and of the unsymmetrical diarylidenepiperazine - 2, 5 - dione **4** (Table 3).

*Mechanism.* Our efforts to elucidate the mechanism of the reaction were applied to the recognition of the aldol intermediate A (Scheme 1).

The finding of Shemyakin[8] that hydrogenolysis of the 1, 4 - diacetylpiperazine - 2, 5 - dione **9** gave bis O-acetylserine anhydride (**10**) suggested that A should contain an acetate function. All attempts to detect the acetate bands in the IR spectra of the reaction mixtures failed. As the rate of elimination k'' could well be larger than k', we decided to carry out the reaction in a solvent where A was supposed to be practically insoluble, in order to allow low concentration of A in the solution, slowing down the elimination reaction. Eventually it was found that 1 - acetyl - 3 - *p* - nitrobenzylidenepiperazine - 2, 5 - dione(**6c**) reacts with *p*-nitrobenzaldehyde in THF solution, in the presence of triethylamine, to give a yellow crystalline precipitate. Attempts to recrystallize the product from DMF resulted in a complete transformation into the brown-red condensation product **5**. It was therefore analysed without purification. The structure **11** was attributed on the basis of the following evidence: elemental analysis correct for $C_{20}H_{16}N_4O_8$ . 1/2 THF; UV (95% aqueous DMF), $\lambda_{max}$: 354 ($\epsilon$ 14800) and




| | X | Y | R | R' |
|---|---|---|---|---|
| **8:** | $H_2$ | $H_2$ | $CH_3CO$ | $CH_3CO$ |
| **9:** | $H,CH_2OCH_2C_6H_5$ | $H,CH_2OCH_2C_6H_5$ | $CH_3CO$ | $CH_3CO$ |
| **10:** | $H,CH_2OCOCH_3$ | $H,CH_2OCOCH_3$ | H | H |
| **11:** | $H,CHC_6H_4NO_2p$ (OCOCH₃) | $CHC_6H_4NO_2p$ | $CH_3CO$ | H |

Table 3. 3,6-Diarylidene(arylidene, alkylidene)piperazine-2,5-diones

| Compounds | Yield % | M.p. °C | Formula | Analysis%* C | H | N | UV $\lambda_{max}$ nm | $\epsilon$ | IR(KBr), cm$^{-1}$ NH | lactame C=O | C=C |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 52[d] | 265–267 | $C_{15}H_{16}N_2O_2$ | 70·20<br>70·29 | 6·30<br>6·29 | 10·89<br>10·93 | 237[a]<br>319[a] | 8000<br>24500 | 3180 | 1680 | 1635 |
| 2 | 87[d] | 298–300 | $C_{18}H_{14}N_2O_2$ | 74·36<br>74·47 | 4·92<br>4·86 | 9·63<br>9·65 | 343[b] | 27800 | 3170 | 1675 | 1620 |
| 3 | 90[d] | 265–dec | $C_{19}H_{16}N_2O_3$ | 71·13<br>71·24 | 5·10<br>5·03 | 8·78<br>8·74 | 358[c] | 33000 | 3190 | 1675 | 1625 |
| 4 | 70[d] | >360 | $C_{18}H_{13}N_3O_4$ | 64·21<br>64·47 | 3·99<br>3·91 | 12·55<br>12·53 | 310[b]<br>373[b] | 10700<br>17400 | 3230 | 1680 | 1625 |
| 5 | 100 | >360 | $C_{18}H_{12}N_4O_6$ | 56·77<br>56·85 | 3·32<br>3·18 | 14·87<br>14·73 | 354[b]<br>505[b] | 13800<br>1840 | 3260 | 1684 | 1628 |

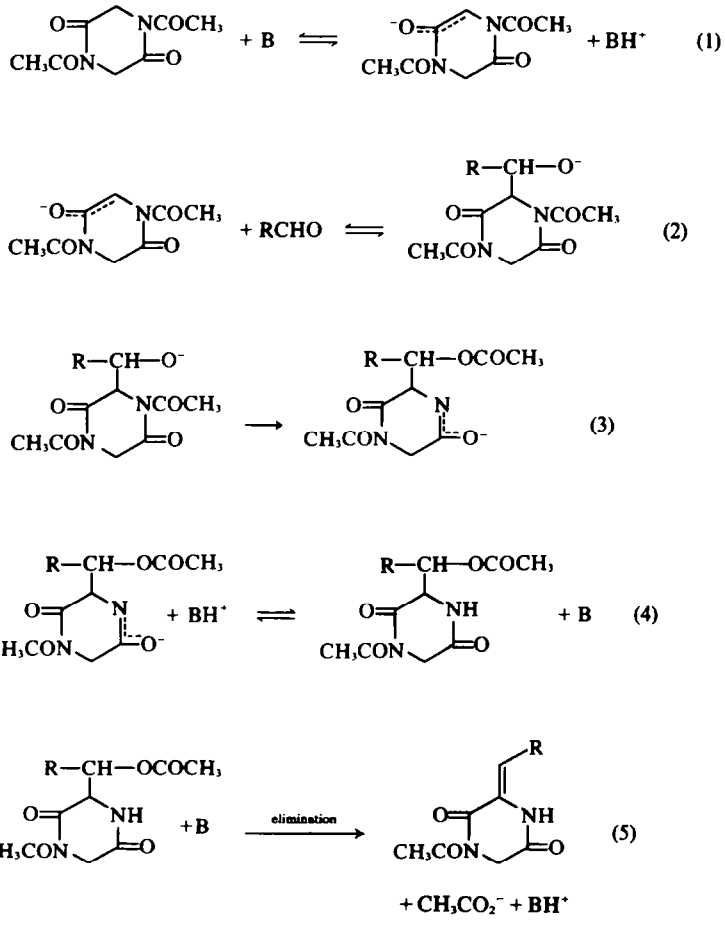
*Upper figures, found: lower figures, calc.
[a]for solution in EtOH.
[b]for solution in 95% acqueous DMF.
[c]for solution in $CHCl_3$.
[d]yields of purified products.

505 nm (ε 1900); IR (KBr), $\nu_{max}$: 3270, 3190 (lactame NH), 1738, 1040 (acetate CO), 1685 (lactame CO) and 1634 $cm^{-1}$ (C=C); mass spectrum, significant peaks at *m/e* 440: $M^+$, 0·13% relative abundance; 410: $M^+$—NO, 0·37%; 380: $M^+$—$C_2H_4O_2$, 17·5%; 60: $C_2H_4O_2^+$, base peak, in addition to the peaks at 350: $M^+$—$C_2H_4O_2$—NO, 4·9%; 334: $M^+$—$C_2H_4O_2$—$NO_2$, 1·5% found also in the spectrum of **5** and to the peaks of THF at 72, 71, 42 and 41. In the reaction mixture from which **11** was obtained only the reagents could be detected (TLC). Eventually **11** was promptly converted into the condensation product (**5**) by treatment with triethylamine in DMF at room temperature. These findings suggest that the condensation should proceed, in general, through the following steps (Scheme 2).

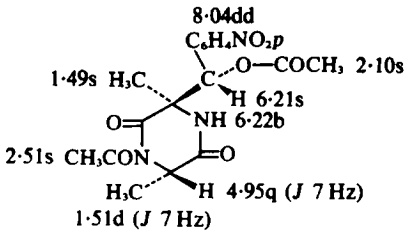
When triethylamine is used as base, the equilibria (1) and (2) are largely unfavourable. Step (3), on the other hand, represents a kinetically favoured intramolecular acyl transfer to which the success of the reaction should be attributed.[9] With stronger bases and under the Sasaki conditions (piperazine-2,5-dione, aromatic aldehyde and acetic anhydride–sodium acetate at 130–160°), the same mechanism should also intervene. In the last case, N-acetylation should precede the condensation. Substituted derivatives, *e.g.* 3 - methylpiperazine - 2, 5 - dione,[10] which undergo monocondensation, are expected to be deactylated at the N atom near the methylene engaged in the condensation. Steric strain prevents the free amide group from reacylation.

*Stereochemistry*

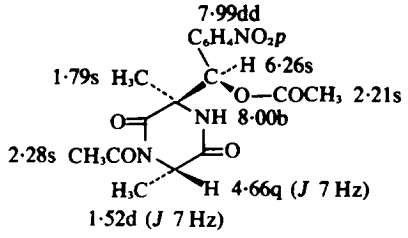
(a) *Aldol intermediate.* One or both diastereoisomers may be present in the aldol intermediate **11**. Our first attempts to elucidate this point showed that the study of this product was not convenient in view of its low solubility and stability. The reaction between *p*-nitrobenzaldehyde and 1, 4- diacetyl - 3, 6 - dimethylpiperazine - 2, 5 - dione was therefore considered. In this case, two products were isolated, and the structures **12** (*threo*) and **13** (*erythro*) have been assigned: elemental




SCHEME 2



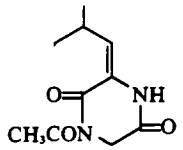

12 One of the enantiomers only shown




13

PMR data: chemical shifts as $\delta$ values relative to TMS as internal standard, for solutions in $CDCl_3$; intensities of the signals in accordance with the numbers of protons; s: singlet; d: doublet; dd: double doublet; b: broad signal.

analysis, IR and PMR spectra in accordance. Acid hydrolysis of the products gave respectively *threo* and *erythro* 2 - methyl - 3 - *p* - nitrophenylserines.[11] The configuration at the third center of asymmetry is thermodynamically controlled in the reaction conditions employed; the isolated products are therefore expected to correspond to the most stable diastereoisomers shown by the formulae **12** and **13**. The *erythro*/*threo* ratio of the isolated products was 18/82.* As the stereochemistry of the serine moiety is kinetically controlled (step 3 of Scheme 2 irreversible and k″ larger than k′ in Scheme 1) also




14

in the case of 1, 4 - diacetylpiperazine - 2, 5 - dione, the intermediate aldol product will be, in general, a mixture of both diastereoisomers.

(b) *Condensation products. Trans* geometry has been recently attributed[10] to the products of the Sasaki reaction. This finding was to be expected according to the conclusions drawn by Zimmerman[12] about the stereochemistry of the Perkin reaction and related condensation reactions. We have carefully examined the products of monocondensation obtained by our modification. A single spot was always observed in TLC chromatograms of the mother liquors of the aromatic derivatives **6a-c**, while a second product could be detected in the case of the aliphatic derivatives **6d-g**. This second component was isolated (6·9% yield) from the mother liquors of **6g**. The structure **14** was assigned on the basis of elemental analysis, IR, UV and PMR spectra; the vinylic proton of the geometrical isomer **6g** is deshielded (0·65 $\delta$) relative to the equivalent proton of **14**, while the allylic proton of **14** is deshielded (0·75 $\delta$) relative to the equivalent proton of **6g**. *Cis* ageometry was thus attributed to **14** according to the findings of Sammes.[10] To our knowledge, **14** is the first example of *cis* alkylidene derivative of this class of compounds. Taking into account that the condensation products come from a mixture of two diastereoisomeric aldol intermediates, the stereochemical outcome of the reaction should be the result of a stereoselective elimination (step 5), as in the case of the previously quoted paper[12] of Zimmerman. It is not surprising that the selectivity of the reaction is less complete for the aliphatic derivatives where the alkyl–C=O steric interaction is energetically less important than the equivalent phenyl–C=O interaction.

## CONCLUSIONS

We believe that our findings have clarified the mechanism and the stereochemistry of the Sasaki reaction and of the modification devised by us. It is worthwhile to point out, in the meantime, that the parent enolate anions can be generated from 1, 4 - diacetylpiperazine - 2, 5 - diones in the presence of tBuOK–DMF or other base–aprotic solvent combinations. They are expected to take part, besides the reported condensations, to other general reactions of enolate anions.

## EXPERIMENTAL

M.ps were measured with a Büchi oil bath apparatus; UV spectra were recorded on a Cary 14 instrument, IR spectra on a Perkin–Elmer 521 spectrophotometer, PMR spectra on a Varian A60D spectrometer. Mass spectra were determined on a A.E.I.MS12 spectrometer (direct inlet technique, 70 eV, 70° source temp).

1 - *Acetyl* - *arylidene*(*alkylidene*)*piperazine* - 2, 5 - *diones* (**6a-g**) were prepared according to the methods previously[5] reported. The *cis* isomer **14** of **6g** has been isolated by preparative TLC (silicagel Merck, 0·5 mm thickness, $CHCl_3$–acetone 9:1): 2·33 g of raw material was

*70/30[11] in the condensation of *p*-nitrobenzaldehyde with D,L-alanine methyl ester. The different stereochemical outcome of the two reactions should be attributed to the different mechanisms. In the last case the stereochemistry may be thermodynamically controlled; furthermore a linear rather than a cyclic transition state is operative.

crystallized from EtOAc to give 900 mg of pure **6g**. The residue, after TLC separation, gave an additional amount of 470 mg of **6g** and 160 mg of **14**.

3 - *Arylidene(alkylidene)piperazine* - 2, 5 - *diones* (**7a-g**). Equivalent amounts of **6** (0·03 moles) and hydrazine hydrate were reacted in 10 ml of DMF at room temp, for 2 hr. Evaporation of the solvent and washing with water gave almost quantitative yields of the deacylated derivatives **7**. M.ps and spectra, taken on recrystallized samples, of **7a**,[12] UV(EtOH): $\lambda_{max}$ 227 nm, $\epsilon$ 14300 and 297 nm, $\epsilon$ 18300, and **7d-g**[13] are in accordance with reported data. Compound **7b**: m.p. 278–280° (AcOH–$H_2O$); UV (EtOH): $\lambda_{max}$ 225 nm, $\epsilon$ 16400 and 316 nm, $\epsilon$ 20800; IR (KBr): $\nu_{max}$ 3250, 3050, 1665 and 1622 $cm^{-1}$. (Found: C, 62·06; H, 5·21; N, 12·02. $C_{12}H_{12}N_2O_3$ requires: C, 62·06; H, 5·21; N, 12·06%). Compound **7c**: m.p. 275–280° (AcOH–$H_2O$); UV (EtOH): $\lambda_{max}$ 226 nm, $\epsilon$ 12600 and 340 nm, $\epsilon$ 14900; IR (KBr): $\nu_{max}$ 3250, 3110, 1680 and 1625 $cm^{-1}$. (Found: C, 53·45; H, 3·71; N, 16·99. $C_{11}H_9N_3O_4$ requires: C, 53·44; H, 3·67; N, 17·00%).

*Albonoursin* (**1**). A soln of tBuOK (0·5 N) in tBuOH (1·5 ml) was added slowly, with stirring to a soln of 1 - acetyl - 3 - isobutylidenepiperazine - 2, 5 - dione (315 mg) and benzaldehyde (159 mg) in 3 ml of DMF at 0°. After 14 h at room temp the solvent was evaporated, the residue washed with water and diethyl ether, dried and crystallized from AcOH–acetone to give 200 mg of purified product.

3, 6 - *Dibenzylidenepiperazine* - 2, 5 - *dione* (**2**). A soln of 1, 4 - diacetylpiperazine - 2, 5 - dione (198 mg), benzaldehyde (106 mg) and triethylamine (205 mg) in 2 ml of DMF was heated at 130° for 2 h. Evaporation of the solvent and washing with water and diethyl ether gave a residue which was crystallized from AcOH–$H_2O$.

3 - *Benzylidene* - 6 - *anisylidenepiperazine* - 2, 5 - *dione* (**3**). A soln of 1 - acetyl - 3 - anisylidenepiperazine - 2, 5 - dione (247 mg), benzaldehyde (110 mg) and triethylamine (205 mg) in 4 ml DMF was kept 6 h at 130°. Evaporation of the solvent and washing with water and diethyl ether gave the product which was crystallized from AcOH–$H_2O$.

3 - *p - Nitrobenzylidene* - 6 - *benzylidenepiperazine* - 2, 5- *dione* (**4**). A soln of 1 - acetyl - 3 - benzylidenepiperazine - 2, 5 - dione (244 mg), *p*-nitrobenzaldehyde (151 mg) and triethylamine (105 mg) in 2 ml DMF was kept 2 days at room temp. The ppt was recrystallized from DMF.

3,6 - *Di - p - nitrobenzylidenepiperazine* - 2, 5 - *dione* (**5**)

(a) A soln of 1, 4 - diacetylpiperazine - 2, 5 - dione (198 mg), *p*-nitrobenzaldehyde (300 mg) and triethylamine (205 mg) in 2 ml DMF was kept 24 h at room temp. The dark-brown mass was filtered and the solid washed with water and diethyl ether.

(b) The aldol product **11** (12 mg) was dissolved in a 0·1 N soln of triethylamine in DMF (0·6 ml) at room temp. After 2 h the mixture was filtered and the solid washed with water and diethyl ether to give 7 mg of **5** identified by its IR spectrum.

N - (*p - Nitrophenyldehydroalanyl*) - 0 - *acetyl* - 3 *p - nitrophenylserine anhydride* (**11**). A soln of 1 - acetyl - 3 - *p* - nitrobenzylidenepiperazine - 2, 5 - dione (200 mg), *p* - nitrobenzaldehyde (110 mg) and triethylamine (70 mg) in 8 ml THF was kept at room temp for 2 days. Filtration and washing with THF gave 42 mg of the product as yellow crystals. Mixtures of **11** and **5** (IR) were obtained after longer reaction times.

*Reaction of p-nitrobenzaldehyde with* 1, 4 - *diacetyl* - 3, 6 - *dimethylpiperazine* - 2, 5 - *dione*. To a soln of 1, 4 - diacetyl - 3, 6 - dimethylpiperazine - 2, 5 - dione (4·24 g) and *p*-nitrobenzaldehyde (2·83 g) in 20 ml DMF at 0°, a 0·5 N soln of tBuOK in tBuOH (3·6 ml) was added slowly, with stirring. The mixture was kept at room temp for 15 h, quenched with AcOH, and the solvent evaporated. A soln of the residue in EtOAc was washed with saturated brine, dried over $Na_2SO_4$ and evaporated to give 4·2 g of an oily residue. Crystallization from EtOAc–n-hexane gave 400 mg of **12**. Preparative TLC (silicagel Merck, 0·5 mm thickness, $CHCl_3$–$Et_2O$ 1:1) of the material recovered from the mother liquors gave a further amount of the same product. The two crops were collected and recrystallized from EtOAc–n-hexane to give 690 mg of **12**: m.p. 209–211°; IR ($CHCl_3$): $\nu_{max}$ 3370, 1747, 1690 $cm^{-1}$. (Found: C, 53·99; H, 5·03; N, 11·18. $C_{17}H_{19}N_3O_7$ requires: C, 54·11; H, 5·08; N, 11·14%).

The slow moving isomer **13** required further purification by preparative TLC ($CHCl_3$–EtOAc 8:2). Eventually 170 mg of pure **13** was obtained after crystallization from EtOAc-n-hexane: m.p. 178–179°; IR ($CHCl_3$): $\nu_{max}$ 3375, 1760 and 1685 $cm^{-1}$. (Found: C, 54·08; H, 5·12; N, 11·08. $C_{17}H_{19}N_3O_7$ requires: C, 54·11; H, 5·08; N, 11·14%).

*Acid hydrolysis of the* 2 - *methyl* - 3 - *p - nit - rophenylserine derivatives* **12** *and* **13**. The isomer **12** (200 mg) was heated to reflux in a mixture of MeOH (5 ml) and 35% HCl (5 ml) for 18 h. The solvent was evaporated at reduced pressure, the residue taken up with water and passed through a column (8 mm diam) filled with 6 g charcoal (Merck active charcoal for gaschromatography, 35–50 mesh ASTM). D,L-alanine was completely removed by washing with water, while the aromatic amino acid was recovered by elution with 1:1 $H_2O$–acetone soln. Evaporation of the solvent and recrystallization from water gave 70 mg of pure D,L-*threo* - 2 - methyl - 3 - *p* - nitrophenylserine: m.p. 205–207°; PMR (for solns of the hydrochloride in $D_2O$), $\delta$ (ppm relative to DSS as internal standard): 8·11 (4H, dd), 5·44 (1H,s) and 1·50 (3H,s).

D,L - *Erythro* - 2 - methyl - 3 - *p* - nitrophenylserine (45 mg) was obtained from the isomer **13** (100 mg) by the same procedure, m.p. 201–202°, PMR, $\delta$ (ppm): 8·05 (4H,dd), 5·30 (1H,s) and 1·70 (3H,s).

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