

SYNTHESES OF BENZOYLPIPERAZINE DIONES FROM THEIR BENZYL COUNTERPARTS

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Abstract- The first synthesis of 2,5-dibenzoylpiperazine-3,6-diones through a selective $\text{FeCl}_3\text{-H}_2\text{O-UV}$ promoted photooxidation of the corresponding benzyl methylene groups is reported. This reaction has been also applied to NN'-dibenzylpiperazine-2,5-dione and to a p-methoxy-benzyl-substituted hydantoin chosen as a model, resulting in the expected product. By modifying the experimental conditions, the unsymmetrically substituted benzyl-benzoyl derivatives may be obtained.

The selective photooxidation of benzylic methylene groups to oxo derivatives in aromatic structures has been recently reported from this laboratory¹. Consequently, we have extended this reaction to heterocyclic substances in order to provide a hitherto unreported synthesis of benzoylpiperazine-diones. Z-2,5-Dibenzyl-3,6-dioxo-piperazine (L-phenylalanine anhydride 1²) has been submitted to sunlight in an acetone- $\text{H}_2\text{O-FeCl}_3$ solution, leading to the formation of the dibenzoyl product 2. SiO_2 column chromatography gave (22%) a mixture of the two substances 2 and 3 in the ratio 93:7 according to MS determination. The final isolation was carried out by preparative TLC and the structures of the products established on the basis of their MS in high resolution. When performed with a 330W-Hanau-UV lamp under control by TLC, the reaction stopped after 3 h led to a 1:1 mixture of 2 and 3. By using sunlight or the UV-lamp, in both cases the formation of benzaldehyde and benzoic acid through degradation was observed and the yields could not be improved by changing the exposures or modifying the proportions of the reagents.

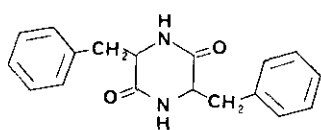
In similar conditions, NN'-dibenzylpiperazine-2,5-dione 4 led by sunlight irradiation to a single product identified as the monobenzoyl derivative 5 (21% yield). Irradiation with the UV-lamp gave 12% of a 1:1 mixture of 5 with the dibenzoyl derivative 6 (MS and ¹H NMR establish the presence in 5 of the original benzyl group and of the

benzoyl substituent). The formation of these products has always been accompanied by benzaldehyde and benzoic acid issued from further degradations.

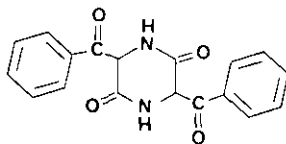
The methylated hydantoin 7 was prepared by prolonged treatment of tyrosylhydantoin³ with a solution of diazomethane. MS and ¹H NMR confirmed the structure of this substance, in particular the introduction of the N-methyl group in position 1 of the hydantoin⁴. Sunlight exposure of 7 furnished 12% of the expected 8 together with some anisaldehyde and anisic acid, while the UV-lamp gave 8% of this product with abundant amounts of anisaldehyde and anisic acid.

This reaction occurs very likely through the intermediate introduction of a hydroxy group at the benzylic methylene site, as exemplified by a short photooxidation of 1 which led to a mixture of mono and dihydroxy compounds (MS determination carried out directly on the reaction mixture). These hydroxy derivatives are quite unstable in these conditions and we failed to isolate them by using the usual procedures.

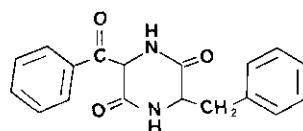
Naturally occurring compounds in this series are rare, as septorine⁵ (a p-hydroxybenzoylpyrazine from the fungus *Septoria nodorum*) or picrorocellin⁶ (from the lichen *Roccella fuciformis*) the structure of which has been however recently⁷ contested.



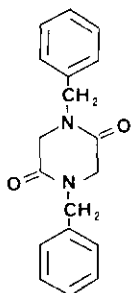
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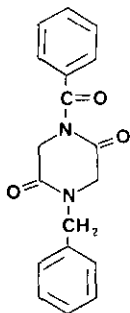
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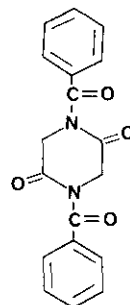
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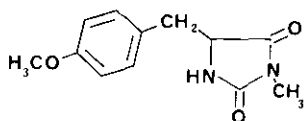
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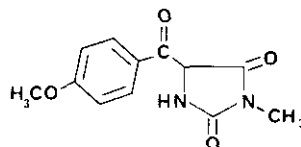
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7



8

EXPERIMENTAL

Mps have been determined with a Kofler apparatus under the microscope and are corrected. Mass spectrometry has been carried out on an AEI MS 50 apparatus, ^1H NMR on CAMECA 240, Bruker 90 and 400 MHz, CDCl_3 , zero TMS, δ ppm.

2,5-Dibenzoylpiperazine-3,6-dione 2 : in a typical experiment, 276 mg 1² (1 mM) was dissolved in 1L boiling acetone and after return to room temperature, 325 mg (2 mM) FeCl_3 added in 2ml water. Sunlight exposure of the mixture was followed by SiO_2 TLC (hexane-AcOEt 1:1, Schleicher-Schüll fluorescent film, UV observation). The formation of spots at Rf 0.50 and 0.47 was matched with the growing with time intensity of the benzaldehyde (Rf 0.95, 2, 4-DNP, Rf, mp, direct comparison with an authentic substance) issued from further degradations. The photooxidation was stopped after 12-15 h, the bulk of the acetone concentrated under vacuo, H_2O added, the product extracted with AcOEt (thrice) the organic layer washed with water and dried over Na_2SO_4 prior to final concentration. SiO_2 column chromatography developed with hexane-AcOEt 1:1 (TLC monitoring) gave the mixture of substances 2 and 3 as colourless crystals (22%), MS indicating a 93:7 ratio. The final isolation was obtained through preparative TLC, leading to 50 mg 2 and 4 mg 3 (extraction of the scrapped SiO_2 with AcOEt), 2: mp 108-112°C, MS, m/z 322.0956, M^+ , calc. for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4$ 322.0953, 105, $\text{C}_6\text{H}_5\text{CO}^+$. When carried out with a 330W-Hanau-UV lamp, 4 h, cooling by ice, 1 (138 mg, 0.5 mM) gave 48 mg (15%) of a 1:1 mixture of 2 and 3, leading by preparative TLC to 20 mg 2 and 18 mg 3.

2-Benzyl-5-benzoylpiperazine-3,6 dione 3 : This substance was obtained from the preceding experiment as an amorphous powder, MS, m/z 308.1167, M^+ , calc. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ 308.1160, 105, $\text{C}_6\text{H}_5\text{CO}^+$, 91, C_7H_7^+ , tropylium ion.

N-Benzyl-N'-benzoylpiperazine-2,5-dione 5 : In similar conditions, NN'-dibenzylpiperazine-2,5 dione 4 (a commercially available ABC Aldrich compound) led by sunlight irradiation to the monobenzoyl derivative 5, (21% yield). The UV-lamp gave a 1:1 mixture of 5 with NN'-dibenzoylpiperazine-2,5 dione 6 (12%). Preparative TLC in hexane-AcOEt 1:1 afforded the two substances, Rf 0.25 and 0.30 respectively. 5 : mp 175-180°C, prisms (AcOEt), MS, m/z 308.1159, M^+ , calc. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ 308.1160, 105.0345, calc. for $\text{C}_6\text{H}_5\text{CO}^+$ 105.0340, 91.0551, calc. for C_7H_7^+ 91.0547, tropylium ion. ^1H NMR, 4.70 (s, 2H, NCH_2CO), 5.05 (s, 2H, $\text{C}_6\text{H}_5\text{CONCH}_2\text{CO}$), 4.20 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_5$) 7.4-7.6 (10H, aromatic protons); 4 had $\text{NCH}_2\text{C}_6\text{H}_5$ at 4.10 (s, 4H) and NCH_2CO at 4.70 (s, 4H).

NN'-Dibenzoylpiperazine-2,5 dione 6 : This product was obtained as an amorphous powder, MS, m/z 322, M⁺, 217, M-C₆H₅CO⁺, 105, C₆H₅CO⁺; ¹H NMR, 5.05 (s, 4H), 7.4-7.6, aromatic protons (10H).

p-Methoxybenzoyl-l-methylhydantoin 8 : Tyrosylhydantoin³ in MeOH was treated overnight with an ether-MeOH solution of diazomethane, resulting in colourless prisms through concentration, yield 90%, homogenous substance in TLC hexane-AcOEt-MeOH 7:3:1. This substance was identified as p-methoxybenzyl-l-methylhydantoin 7, mp 139-140°C (MeOH), Anal.: Found: C, 61.52; H, 6.02; N, 11.96; calc. for C₁₂H₁₄N₂O₃ : C, 61.31; H, 6.18; N, 11.96; MS, m/z 234, M⁺, 121, CH₃OC₆H₄CH₂⁺, ¹H NMR, 3.90 (s, 3H, OCH₃), 6.10, (bs, 1H, NH), 2.80-3.20 (m, 2H, CH₂), 4.3 (m, 1H, CH), 3.05 (s, 3H, 1-N-CH₃)⁴, aromatic protons at 6.8-7.4 (4H). The FeCl₃-H₂O promoted photooxidation of 7 in acetone by using the same conditions as for 1, furnished 12% of 8 by irradiation with sunlight. The substance was isolated by preparative TLC developing with hexane-AcOEt-MeOH 7:3:1 in which it had R_f 0.30 while the starting material was at R_f 0.20. Anisaldehyde and anisic acid are formed in the reaction (R_f, 2,4-DNP, mp, direct comparison with the authentic substances) and their yields are increasing with time indicating the degradation of the products. 8 : amorphous powder, MS, m/z 248, M⁺, 135, CH₃OC₆H₄CO⁺; ¹H NMR id. 7 except for the lacking CH₂ benzyl group signals and for the CH hydantoin signals being now shifted to 4.80. In this case, the use of the UV-lamp led to a 8% yield in the substance 8, with increased amounts of anisaldehyde and anisic acid.

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