16. Influence of N,N′-Substituents on the $FeCl_3$-Catalyzed Photo-oxidation of 2,5-Dibenzylpiperazine-3,6-diones

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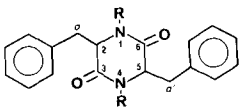
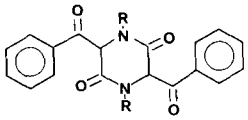
Reactions carried out on benzoyl (**2**) and hydroxybenzyl (**10**) derivatives of L-phenylalanine-cycloanhydride **1** lead to the conclusion that the structure **3**, previously proposed for picroroccellin (a metabolite from the lichen *Roccella fuciformis*), should be revised to **6**. While the $FeCl_3$-catalyzed photo-oxidation of **1** gives **2**, the *N,N′*-dimethyl derivative **7** leads to *N,N′*-dimethyl-2-benzylpiperazine-3,5,6-trione (**9**). *N,N′*-diacetyl-L-phenylalanine-cycloanhydride **11** remains unchanged. It is established that *N,N′*-substitutions of 2,5-dibenzylpiperazines-3,6-diones considerably influence their photo-oxidations under the reported conditions.

Introduction. – Methylene groups in α-position of aromatic structures can be transformed into the corresponding oxo functions through a $FeCl_3$-catalyzed photo-oxidation in acetone/H_2O [1]. This reaction was recently applied to the synthesis of analogues of septorine [2], a biologically active pyrazine isolated from the fungus *Septoria nodorum* BERK [3]. 2,5-Dibenzylpiperazine-3,6-dione ('L-phenylalanine cycloanhydride' (**1**), s-*cis*-isomer according to [10]) gave under these conditions the dibenzoyl derivative **2** [4]. Hydroxylations represent the initial step of this reaction as exemplified by the isolation of septorinol and other derivatives [2] [4], or of the unstable α-hydroxybenzylpiperazine-3,6-diones. The identification of benzaldehyde [1] or of anisaldehyde (in the case of *p*-methoxy-substituted compounds [2] [4]) indicated that further photo-oxidations of the oxo products could occur through *Norrish*-type-I cleavage [5].

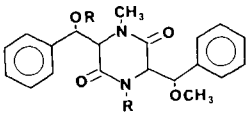
More than a century ago, *Stenhouse* and *Groves* [6] reported the isolation of picroroccellin, a bitter substance from the lichen *Roccella fuciformis*. In 1922, *Forster* and *Saville* [7] proposed, after analysis of the rest of the same sample, the structure **3** for this substance, in which the relative positions of the Me groups were still not established. Since that time, in spite of intensive investigations, and striking enough [8], this molecule has never been found again in all samples of *Roccella fuciformis*. This lichen had been seriously identified by botanists as species of *Roccella fuciformis* D.C. growing on trees of the West African coast. Recently, the synthesis of the tetramethylderivative **5** was reported [9]. This substance shows the same m.p. as described for 'dimethyl-picroroccellin'. A proposal was made to revise structure **3** to **6** for the natural compound. Because of the relationships between *Forster* and *Saville*'s 'dimethyl-picroroccellin' **4** and the dibenzoyl derivative **2**, we decided to perform the synthesis of 'dimethyl-picroroccellin' by reduction and subsequent methylation. However, all attempts failed due to the unstability of the products submitted to $NaBH_4$ reduction and to methylations by different methods. Therefore, it was decided to accomplish the synthesis through the *N,N′*-dibenzoyl derivative **8**, which was thought to be accessible by photo-oxidation of *N,N′*-dimethyl derivative **7** according to our reaction. But in contrast to previous observations, the main



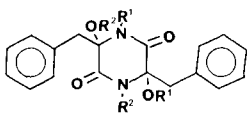
1 R = H
7 R = CH_3
11 R = $-\overset{O}{\overset{\|}{C}}-CH_3$



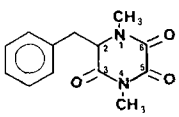
2 R = H
8 R = CH_3



3 R = H
4 R = CH_3



5 $R^1 = R^2 = CH_3$
6 $R^1 = CH_3$, $R^2 = H$



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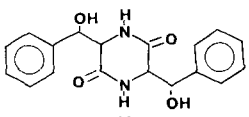

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product formed was the *N,N'*-dimethyl-2-benzylpiperazine-3,5,6-trione (**9**) obtained in a yield of 30%. As the photo-oxidation of an acetylated benzyl-pyrazine lead [2] to the corresponding acetate of the benzylic alcohol through transacetylation, the photo-oxidation of *N,N'*-diacetyl derivative **11** was attempted. However, this acetylated product turned out to be very stable, establishing the great influence of the *N,N'*-substituents on the course of the photo-oxidation of the benzyl group in **1**.

Results and Discussion. – *The Structure of 'Picroroccellin', a Substance Isolated from the Lichen* Roccella fuciformis. In presence of $FeCl_3$, H_2O, and acetone, the photo-oxidation of **1**, (s-*cis*-isomer [10]) with sunlight, led to the corresponding dibenzoyl derivative **2** [4]. Starting from this substance, we tried to synthesize *Forster* and *Saville*'s 'dimethyl picroroccellin' **4** [7] by $NaBH_4$ reduction and methylation. Preparative TLC of the mixture of the reduced compounds to isolate the diol **10** gave only unidentified products. Small amounts of **10** were previously shown to be present (according to MS) among the products issued from the photo-oxidation of **1** to **2**. Methylations were then carried out directly in the mixture of benzyl, benzoyl, and hydroxybenzyl derivatives. By applying the procedure in [7] for the methylation of picroroccellin ($(CH_3)_2SO_4$ and NaOH/EtOH), no methylated product could be observed (TLC and MS). The starting material was completely degraded to a series of non-identifiable molecules. Similar results were observed by using MeI in presence of freshly prepared Ag_2CO_3. It was not possible to isolate any defined compound except *N,N'*-dimethyl derivative **7** (issued from **1**) by treatment with NaH/DMF and MeI [11]. It could be concluded hence, that benzylic alcohols in this series are very sensitive to experimental conditions, as previously noticed in the case of septorine [2] [3]. This could be further demonstrated by the impossibility to isolate such benzylic alcohols by preparative TLC, and the subsequent formation of benzaldehyde after workup. The treatment of **3** with $(CH_3)_2SO_4$ in presence of NaOH would obviously not give the tetramethyl derivative **4** as expected by the authors.

These findings support the suggestion that **6** might represent the structure of 'picroroccellin' according to [9]. 'Dimethyl-picroroccellin' would then be **5**, obtained by synthesis as described. However, it remains very striking that, since more than a century and in spite of serious investigations [8], picroroccellin has not been found again in the lichen *Roccella fuciformis*. Because of the great amount isolated first (methylation of the original 'picroroccellin' has been reported [7] on 10 g of crystallin substance), we assume that the product could originate from the bark on which the lichen was fixed. The identification of 'picroroccellin' and the determination of its configuration will remain a difficult problem due to lack of direct comparison between natural and synthetic products.

Synthesis of 1,4-Dimethyl-2-benzylpiperazine-3,5,6-trione (**9**). During the $FeCl_3$-catalyzed photo-oxidation of **7**, a new compound was observed on TLC, exhibiting a stronger UV absorption than the starting material. The increasing amount of this new substance was matched with the disappearance of **7** and with the formation of benzaldehyde from further degradations. Preparative TLC gave a colourless substance (yield 30%): $C_{13}H_{14}N_2O_3$ (elemental analysis; MS: 246 (M^+), 231 ($M^+ - 15$), 203 ($M^+ - 15 - 28$), 155 ($M^+ - 91$), 91 (base peak, tropylium ion). The ^{1}H- and ^{13}C-NMR spectra were in agreement with the structure of **9** (3.00 (*s*, CH_3N); 3.25 (*s*, CH_3N); 3.30 (*dd*, $J = 4$, CH_2); 4.45 (*t*, $J = 4$, CH); 6.6 (*m*, 2 arom. H); 7.05 (*m*, 3 arom. H). ^{13}C-NMR: results are presented in the *Table*). The signals observed in the ^{13}C-NMR spectrum for the Me groups and the carbonyl functions were compared with the reported values for dimethyl-uracile [12] and assignments for the CH_2 and CH corroborated by the similar signals in the spectra of phomamide [13] and **7**.

Table. *^{13}C-NMR Data of* **7** *and* **9**

7			**9**		
C(2,5)	64.2	(CH)	C(2)	64.3	(CH)
C(3,6)	165.4	(CO)	C(3)	168.2	(CO)
C(α,α′)	39	(CH_2)	C(5)	155.8	(CO)
C(1′,1″)	137		C(6)	153.1	(CO)
C(2′,6′,2″,6″)	129.6		CH_2	38.7	(CH_2)
C(3′,5′,3″,5″)	128.8		C(1′)	132.8	
C(4′,4″)	127.2		C(2′,6′)	129.3	
CH_3-N(1,4)	33.4	(CH_3N)	C(3′,5′)	129	
			C(4′)	128.4	
			CH_3–N(1)	26.5	(CH_3N)
			CH_3–N(4)	33	(CH_3N)

Thus, the photo-oxidation of **7** differs from that of **1** observed previously. As noticed in the case of *N,N′*-dibenzylpiperazinedione [4], the photo-oxidation does not affect the second benzyl substituent, leading in both cases to mono-oxo derivatives. Compound **7** appears to be more sensitive to the *Norrish*-type-I photo-degradation [5] and it is transformed into **9** with elimination of the benzoyl group as benzaldehyde as soon as a mono-oxo product is formed.

The trione **9** behaves as a triamide; it does not react with 2,4-dinitrophenylhydrazine, and it is comparably stable towards sunlight. The results so far observed in the series of dibenzyl-piperazinediones may be related to a previous photo-enolization of an oxo group (positions 2,3 or 5,6), leading to an activated corresponding CH_2 group (α or α′).

The lack of photo-oxidation of **9** could be due to the fact that the molecule exists only in its oxo structure. When the photo-oxidation is performed in acetone/D_2O, isolated **9** shows no D-incorporation at C(2) or elsewhere. Similarly, boiling **9** in D_2O does not lead to an uptake of deuterium as evidenced by MS determinations.

The *1,4-diacetyl-2,5-dibenzylpiperazine-3,6-dione* (**11**; m.p. 147–149°, R_f 0.30 (SiO_2, TLC in hexane/AcOEt 8:2)) was prepared according to [10] and submitted to the $FeCl_3$-catalyzed sunlight photo-oxidation. However, the starting material was recovered quantitatively, and not a trace of benzaldehyde (always present from further photo-degradations otherwise) could be detected among the reaction products. It can be concluded that the Ac groups in **11** stabilize the molecule against the photo-oxidation. Thus, if *N*-methyl substitution induces the formation of **9** by photo-induced *Norrish*-I-type cleavage, the acetylation to **11** stabilizes the product. These results establish the neccessity of the presence of free NH groups for the sunlight photo-oxidation of both benzyl substituents to yield the corresponding benzoyl groups in compounds of type **1**. As previously observed [4], the use of a UV lamp instead of sunlight considerably increased the degradations.

Experimental Part

General. M.p.: *Kofler* microscope, not corrected. TLC: *Schleicher-Schüll* SiO_2 fluorescent films for anal. purposes, UV observation or I_2-vapour visualization, on 1-mm thick plates for prep. procedure. ^1H- and ^{13}C-NMR: *CAMECA* 240-MHz spectrometer, in $CDCl_3$, δ(ppm) with respect to TMS. MS: *AEI MS 50* apparatus.

Compound **2** was prepared according to [4] and **7** by NaH/CH_3I/DMF methylation of **1** according to [11].

1,4-Dimethyl-2-benzylpiperazine-3,5,6-trione (**9**). Compound **7** (161 mg, 0.5 mmol) was dissolved in dry acetone (150 ml, distilled over $KMnO_4$), and $FeCl_3$ (162 mg, 1 mmol) was added in H_2O (2 ml). The soln. was submitted to sunlight under TLC control (performed every 30 min, development by AcOEt). For this purpose, an aliquot was extracted twice with CH_2Cl_2 after addition of an equal volume of H_2O. The extracts were combined and dried (Na_2SO_4), then concentrated *in vacuo*. Compound **9** appeared (UV observation) at R_f 0.50 while **7** had R_f 0.45. Isolation was performed by prep. TLC (layer: 1 mm SiO_2) and extraction of the compounds with CH_2Cl_2. Substance **9** amounted to 30% (36 mg) and was recrystallised from acetone/hexane: 18 mg (15%). M.p. 170–174°. Anal. calc. for $C_{13}H_{14}N_2O_3$: C 63.40, H 5.73, N 11.38; found: C 63.34, H 5.74, N 11.54.

1,4-Diacetyl-2,5-dibenzylpiperazine-3,6-dione (**11**) was obtained according to [10] by reflux of **1** during 5 h in $AcOH/Ac_2O$ (1:1), hydrolysis on ice, filtration, and crystallisation from Et_2O.

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