Anodic Oxidation of 3,5-Dihalogenotyrosines as a Model Reaction for the Biogenesis of the Cavernicolins, Metabolites of the Verongid Sponge *Aplysina cavernicola*

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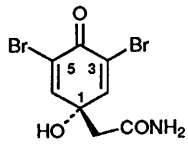
Anodic oxidation of 3,5-dibromo-4-methoxyphenylalanine methyl ester **3**, led to cavernicolin [3,3a,7,7a-tetrahydro-3a-hydroxyindole-2,6(1*H*)-dione] model compounds although equilibration to all four possible stereoisomers **4α**, **4β**, **5α** and **5β** was a special characteristic of the model compounds only. This may constitute a new model for the biogenesis of the cavernicolins as an alternative to a spirolactone route from oxidation of amino-protected tyrosines. Chemical oxidation gave poor results.

ortho-Halogen-bearing *p*-quinols, such as 3,5-dibromoverongiaquinol **1**, were isolated from various sponges of the order Verongida of tropical and temperate waters[1] whilst products of formal cyclization of these quinols, such as the mixture of the C-7 epimeric 5,7-dibromocavernicolins **2**, were isolated from a single species, the Mediterranean *Aplysina* [= *Verongia*] *cavernicola*.[1] It is still a matter of debate whether these compounds are produced *via* arene oxide[2,3] or phenol oxidative coupling,[1,4] and biosynthetic experiments have not been completed as yet.[5] We preferred phenol oxidative coupling *via* a spirolactone intermediate to arene oxide routes in order to rationalize the very low optical purity of both the cavernicolins and the chiral verongiaquinols.[1,4,6]



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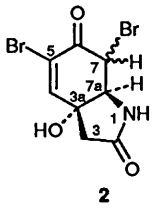

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All these sponge metabolites showed marked biological activities,[4] so that there is a two-fold scope in devising synthetic routes to them: to provide rare compounds of these series[7] and modified compounds, as well as to establish models for biogenesis.

Recently, in a synthetic route to verongiaquinols from halogenophenols, we have satisfactorily replaced low-yield Tl^{III} oxidations[1,8] with anodic processes.[7] This prompted us to address the question of whether or not anodic oxidation can be extended to the synthesis of the cavernicolins from halogenotyrosine precursors. The electrochemical background is as follows. In the area of non-halogenated tyrosines, anodic processes have been widely employed for cleaving tyrosyl-peptide bonds[9] whilst the formation of spirolactones from tyrosines constitutes a model for the biosynthesis of coumarins.[10] In contrast, very little is known about anodic processes with halogenotyrosines. We are aware only of an anodic-induced spirocarbocyclization of a substrate made of a 1-iminodien-4-one moiety linked at C-3 to 3,5-dibromotyramine in a route to discorhabdin C, an amino-acid metabolite of marine sponges.[11]

We report here our observations concerning anodic oxidation of halogenotyrosines.

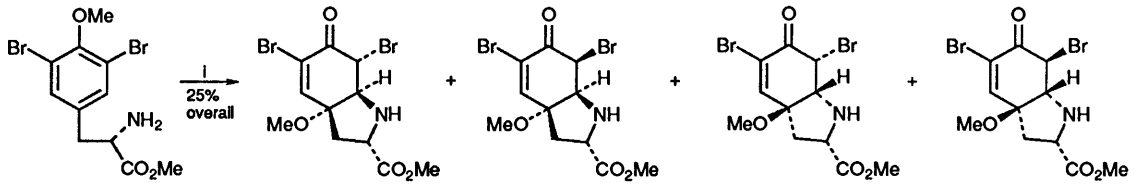
Results and Discussion

Failure to Produce Halogenated Spirolactones on Anodic Oxidation of N-*Acyltyrosines*.—Our initial plans for the synthesis of compounds having the skeleton of the cavernicolins focused on spirolactone intermediates following our initial biogenetic hypothesis.[1,4] However, upon anodic oxidation of *N*-acetyl-3,5-dibromotyrosine **6** only quinols (such as **7a** and **7b**, to be dealt with later) and benzenoids were obtained in modest yields.

Since spirolactones were previously obtained by anodic oxidation of nonhalogenated tyrosines,[9] we must admit that the presence of bromine atoms at the *ortho,ortho'*-positions of the tyrosine ring is detrimental to the efficiency of the desired lactonization processes.† This is not the case upon anodic oxidations of *o,o'*-dihalogeno-(*p*-acetamido)phenols to quinols, which were found to run efficiently.[7] On this basis, we decided to attempt a one-pot construction of the cavernicolin skeleton by relying on Michael-type intramolecular attack of a free amino group in quinol intermediates. The results were as follows.

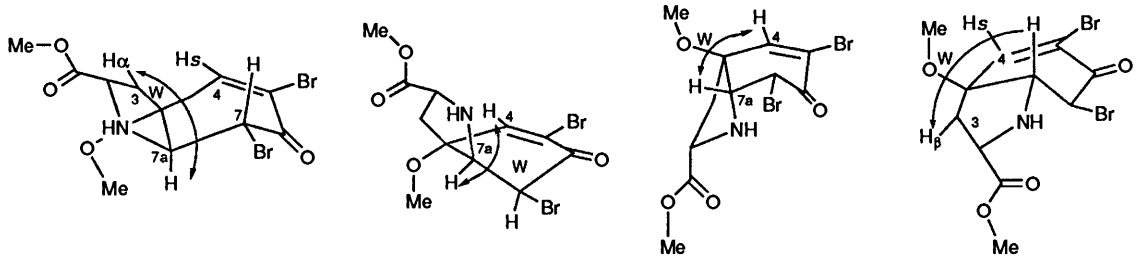
Intramolecular Michael-type Cyclization of Esterified Halogenotyrosines via *Anodically Generated* 3,5-*Dihalogenoquinols*.—In our attempts at one-pot cyclization of halogenotyrosine precursors toward compounds with the skeleton of the cavernicolins we needed a carboxy-blocked 3-chlorotyrosine. Treatment of 3-chlorotyrosine with excess of diazomethane in Et_2O–MeOH resulted also in methylation of the phenolic function, giving 3-chloro-4-methoxyphenylalanine methyl ester which, however, gave disappointing results in anodic treatment. That in this case protection of the OH group might have inhibited phenolic oxidation can be ruled out on the basis of the observations reported below with compound **3**. The fact that all previous examples of successful anodic formation of quinols (see above and ref. 7) involved *o,o'*-dihalophenols as substrates suggests rather that these anodic processes do not tolerate free conjugative positions at the phenolic ring; possibly intermolecular phenolic oxidative coupling occurred to give the tarry mixtures that we observed. On this presumption we turned to 3,5-dibromotyrosine, treated it with excess of diazomethane, and obtained 3,5-dibromo-4-methoxyphenylalanine methyl ester **3**. Anodic oxidation of this compound gave rise to the

† Even attempted anodic oxidation of *N*-acetyl-3-chlorotyrosine methyl ester proved to be unsuccessful.



3 4α 4β 5α 5β

Scheme 1 *Reagents and conditions:* i, 0.1 mol dm^{-3} $LiClO_4$ in MeOH, 10 V, 25–30 mA, 3 h, room temp.



4α : 4β : 5α : 5β
41 : 10 : 26 : 23

Fig. 1 Lowest-strain-energy conformations of **4α**, **4β**, **5α** and **5β** from MM calculations. Isomers **4β** and **5α** are characterized by W-coupling between 7a-H and 4-H, whereas with both isomers **4α** and **5β** 4-H appears as a singlet.

desired cyclization product in 23% yield, although, as explained below, because of the nature of this compound, equilibration to all possible stereoisomers **4α**, **4β**, **5α** and **5β** (41:10:26:23) occurred (Scheme 1). A more elaborate electrochemical procedure, by carrying out the electrolysis at controlled potential, failed to improve the yields of products; electrochemical studies showed that the primary reaction products suffer further oxidation at the electrode, which is detrimental to the yields.

Equilibration of the four stereoisomers **4α**, **4β**, **5α** and **5β** was particularly rapid in the presence of water, which prevented the use of reversed-phase HPLC for their separation. This problem was satisfactorily solved by the use of a CN-HPLC column which behaves like a reversed-phase HPLC column although operating in anhydrous solvents; this allowed the separation of pure stereoisomers (see Experimental section). However, even in $CDCl_3$ or C_6D_6, equilibration among the above four stereoisomers was not completely prevented, which only allowed us to run NMR spectra on enriched samples for each stereoisomer (see Experimental section).

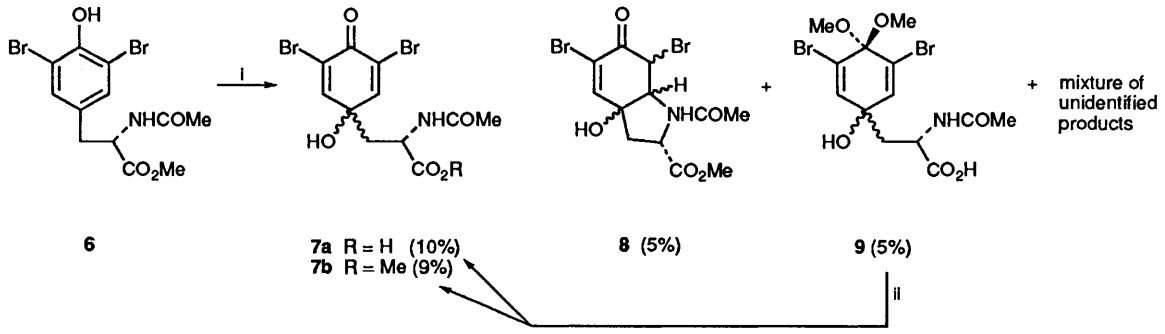
Elucidation of structures **4α**, **4β**, **5α** and **5β** was much aided by molecular mechanics calculations [12] where extensive use was made of the dihedral-angle driver option. It was thus established that the overall strain energy is also dependent on the conformation of the (unnatural) chain at C-2 (see Fig. 1). This is reflected in the NMR parameters, where we observe a generally good agreement between experimental and calculated *J*-values (see Experimental section). The most clear-cut NMR features that allow us to distinguish the four stereoisomers from one another is W-coupling between 7a-H and 4-H for both **4β** and **5α**, whereas with both **4α** and **5β** 4-H appears as a singlet (7a-H is W-coupled with 3-H_α in the case of **4α** or with 3-H_β in the case of **5β**, as indicated in Fig. 1). Overall, the **4**:**5** molar ratio proved to be ~1:1. All this can be rationalized in terms of a reversible Michael-type addition where N–C(7a) bond breaking and five-membered ring reclosure by N attack at C-4 bring about the interconversion of the **4**- and **5**-type stereoisomers. Actually there are many precedents for reversible Michael-type cycloadditions with nitrogen nucleophiles.[13]

Reversible processes of the type observed for the isomeric products **4** and **5** are unlikely to occur, in the absence of enzymes, with the cavernicolins because of their non-nucleophilic nitrogen atom. In any event, since the cavernicolins lack chirality at C-2, the reversible process would pass unnoticed when C-5 and C-7 carry the same halogen atom, such as with dibromide **2**. Formally, this is not the case with cavernicolins that bear different halogen atoms at C-5 and C-7, which have also been isolated from the sponge *A. cavernicola*.[1] However, only a mixture of 7-Br_α/5-Cl and 7-Cl_α/5-Br cavernicolins could be separated by reversed-phase HPLC from a mixture of the C-7 epimers (7-Br_β/5-Cl and 7-Cl_β/5-Br), and this was followed by rapid equilibration to a mixture of the four stereoisomers.[1]

Attempts at Intramolecular Michael-type Cyclization of Esterified N-*Acylhalogenotyrosines* via *Chemically Generated* 3,5-*Dihalogenoquinols*.—When this work was already completed a highly diastereoselective iodobenzene diacetate-mediated cyclization of *N*-acyltyrosines, to give compounds with the dehalogenocavernicolin skeleton, was reported.[14]* This prompted us to investigate if iodobenzene diacetate performs well also with halogenotyrosines. This proved not to be the case: by using the *N*-acylated halogenotyrosine **6** as substrate (Scheme 2) the desired bicyclic product **8** could be obtained, albeit in extremely low yield, in a complex mixture with quinols **7a** and **7b** and the ketal **9** of **7a**.

Conclusions.—We conclude, from present and previous work,[7] that tyrosines bearing halogen atoms at positions *ortho* to the phenolic hydroxy group constitute cases apart from non-halogenated tyrosines with respect to oxidation reactions. Moreover, success in obtaining compounds of types **4**/**5** from anodic oxidation of the carboxy-protected dihalogenotyrosine **3** (Scheme 1) suggests this as a new model for the biogenesis of the cavernicolins from tyrosine precursors. This may replace our previous spirolactone model [1,4] in view of the failure of the

* Lack of reversibility by five-membered ring opening and reclosure in this case [14] can be attributed to deactivation of nitrogen by acyl protection and perhaps also to the absence of an acidifying halogen atom at C-7.



Scheme 2 *Reagents and conditions:* i, PhI $(OAc)_2$ (1 mol equiv.) in MeOH, 15 min; then $NaHCO_3$ (1.2 mol equiv.), 15 min, room temp.; ii, $CDCl_3$, room temp., overnight

N-protected diahalogenotyrosine **6** to undergo oxidative cyclization to a spirolactone.*

Experimental

General.—All evaporations were carried out under reduced pressure. TLC was performed on Merck Kieselgel $60PF_{254}$, 2 mm thick plates; reversed-phase HPLC on a Perkin-Elmer RP18, 10 μm, 8 × 250 mm column; and CN-HPLC on Merck LiChrosorb CN, 7 μm, 10 × 250 mm column (3 cm^3 min^{-1} in all cases). NMR spectra were taken, unless otherwise stated, on a Varian-XL-300 spectrometer (299.94 MHz for ^1H, 75.43 MHz for ^{13}C; both δ- and *J*-values in ^1H NMR spectra were derived from differential double irradiations); for spectra at 200 or 60 MHz (in $CDCl_3$, probe temperature 21 °C, unless otherwise stated) Varian Gemini BB200 or Varian EM360 spectrometers were used. In all cases δ-values are reported with respect to internal $SiMe_4$ (δ 0) and *J*-values in Hz. COSY 120 experiments[15] and ^{13}C–^1H NMR shift-correlation experiments[16] were also carried out. Differential NOE (obtained with 4 s preirradiation) are reported in the form: irradiated proton ⟶ % NOE on the observed proton(s). Mass spectra (EI) were taken with a Kratos MS80 spectrometer with home-built computerized acquisition system.

3,5-*Dibromo*-4-*methoxyphenylalanine Methyl Ester* **3**.—To a suspension of 3,5-dibromotyrosine (0.30 g, 0.88 mmol) in Et_2O (5 cm^3) containing a few drops of MeOH was added an excess of ethereal CH_2N_2 at room temp. In 3 h a homogeneous mixture was obtained; this was evaporated to leave 3,5-dibromo-4-methoxyphenylalanine methyl ester **3** as an oil (0.19 g, 60%); δ_H(200 MHz) 2.75 (dd, *J* 13.8 and 8.0, A of ABX, H_A of CH_2), 2.95 (dd, *J* 13.8 and 5.0, B of ABX, H_B of CH_2), 3.35 (dd, *J* 8.0 and 5.0, X of ABX, CH_2CH), 3.68 (s, 4-OMe), 3.81 (s, CO_2Me) and 7.30 (s, 2- and 6-H).

Anodic Oxidation of 3,5-*Dibromo*-4-*methoxyphenylalanine Methyl Ester* **3**.—A solution of 3,5-dibromo-*O*-methyltyrosine methyl ester (0.103 g, 0.28 mmol) was electolysed in a smaller, modified electrolytic cell with respect to previous work.[7] Thus, electrolysis was carried out at a 4.9 cm^2 Pt electrode, current 25–30 mA for 3 h, on a solution (50 cm^3) in a cell made of two 100 cm^3 compartments divided by a glass frit. The anodic mixture was evaporated and the oily residue was subjected to TLC with $CHCl_3$–MeOH (98:2), with a band at R_F 0.4 being collected, which was extracted ($CHCl_3$) to give oily material (25 mg). This was subjected to CN-HPLC with hexane–propan-2-ol (9:1); four fractions were collected corresponding to stereoisomers **4α** (t_R 14.0 min), **4β** (t_R 16.0 min), **5α** (t_R 12.0 min) and **5β** (t_R 17.0 min) in equilibrium concentration proportions 41:10:26:23. Overall yield was 23%; *m/z* (%) (on equilibrated mixture of the four stereoisomers) 381/383/385 (1,2,1, $M^{\bullet+}$, 322/324/326 (52,100,52, $[M - CO_2Me]^+$), 290/292/294 (9,18,9, $[M - CO_2Me - MeOH]^{\bullet+}$) and 102 (66); *m/z* (HRMS) 293.8771. Calc. for $C_8H_6{}^{81}Br_2NO_2$, *m/z* 293.8775.

Data of compound **4α**: δ_C 40.41 (d, C-2), 30.92 (t, C-3), 84.12 (s, C-3a), 147.59 (d, C-4), 126.96 (s, C-5), 58.50 (d, C-7), 66.57 (d, C-7a), 51.85 (q, OMe) and 52.60 (q, CO_2Me); δ_H 3.95 [dd, $J_{2,3\beta}$ 9.0 (calc. 9.7), $J_{2,3\alpha}$ 2.7 (calc. 3.0), 2-H], 3.76 (s, CO_2Me), 2.36 (dd, J_{gem} 13.8, $J_{3\beta,2}$ 9.0, 3-H_β), 2.57 (ddd, J_{gem} 13.8, $J_{3\alpha,2}$ 2.7, $J_{3\alpha,7a}$ 0.9, 3-H_α), 3.20 (s, OMe), 7.23 (s, 4-H), 4.45 [d, $J_{7,7a}$ 9.3 (calc. 11.1), 7-H] and 4.05 (dd, $J_{7a,7}$ 9.3, $J_{7a,3\alpha}$ 0.9, 7a-H); NOE 4.45 ⟶ on 2.36 and (weak) 2.71.

Data of compound **4β**: δ_H 4.02 [dd, *J*(2, 3α) 9.2 (calc. 11.4), *J*(2, 3β) 5.4 (calc. 5.2), 2-H], 3.76 (s, CO_2Me), 2.55 (dd, J_{gem} 13.3, $J_{3\beta,2}$ 5.4, 3-H_β), 2.42 (dd, J_{gem} 13.3, $J_{3\alpha,2}$ 9.2, 3-H_α), 3.40 (s, OMe), 6.59 (d, $J_{4,7a}$ 1.6, 4-H), 5.06 [d, $J_{7,7a}$ 3.5 (calc. 2.6), 7-H], 4.03 (dd, $J_{7a,7}$ 3.5, $J_{7a,4}$ 1.7, 7a-H). Signals were too weak to measure NOE confidently.

Data of compound **5α**: δ_C 41.05 (d, C-2), 29.69 (t, C-3), 145.39 (d, C-4), 122.97 (s, C-5), 56.42 (d, C-7), 65.40 (d, C-7a), 54.18 (q, OMe) and 52.60 (q, CO_2Me); δ_H 3.83 [dd, $J_{2,3\alpha}$ 8.7 (calc. 11.1), $J_{2,3\beta}$ 7.0 (calc. 5.5), 2-H], 3.76 (s, CO_2Me), 1.91 (m, 3-H_2), 3.36 (s, OMe), 7.16 (d. $J_{4,7a}$ 1.6, 4-H), 4.99 [d, $J_{7,7a}$ 3.3 (calc. 3.0), 7-H] and 4.11 (dd, $J_{7a,7}$ 3.3, $J_{7a,4}$ 1.6, 7a-H); NOE 4.11 ⟶ on 3.83; 3.83 ⟶ on 4.11 and 1.91.

Data of compound **5β**: δ_C 40.31 (d, C-2), 29.69 (t, C-3), 148.11 (d, C-4), 57.03 (d, C-7) and 68.12 (d, C-7a); δ_H 4.19 [dd, $J_{2,3\alpha}$ 8.8 (calc. 8.7), $J_{2,3\beta}$ 8.2 (calc. 7.8), 2-H], 3.74 (s, CO_2Me), 2.53 (ddd, J_{gem} 13.9, $J_{3\beta,2}$ 8.2, $J_{3\beta,7a}$ 1.0, 3-H_β), 2.24 (dd, J_{gem} 13.9, $J_{3\alpha,2}$ 8.8, 3-H_α), 3.29 (s, OMe), 7.30 (s, 4-H), 4.73 [d, $J_{7,7a}$ 10.1 (calc. 11.1), 7-H] and 3.99 [dd, $J_{7a,7}$ 10.1 (calc. 11.1), $J_{7a,3\beta}$ 1.0, 7a-H]; NOE 4.73 ⟶ on 2.24.

Chemical Oxidation of N-*Acetyl*-3,5-*dibromotyrosine Methyl Ester* **6**.—To a solution of compound **6**† (0.107 g, 0.27 mmol) in MeOH (15 cm^3) was added iodobenzene diacetate (Aldrich)

* *Note added in proof:* however, we agree with Dr. M. D'Ambrosio (personal communication) that the possibility that the arene oxide equilibrates with a chiral oxepin-type compound should not be overlooked (D. R. Boyd and M. E. Stubbs, *J. Am. Chem. Soc.*, 1983, **105**, 2554).

† Prepared by electro-oxidation of *N*-acetyl-3,5-dibromotyrosine in MeOH–$LiClO_4$ in the electrolytic cell described above under a potential difference 10 V, current 50 mA, for 4 h; yield 10%.

Data of compound **6**: δ_C 130.60 (s, C-1), 132.71 (d, C-2 and -6), 109.79 (s, C-3 and -5), 148.56 (s, C-4), 36.48 (t, CH_2), 53.15 (d, CH), 171.63 (s, NHCOMe), 23.15 (q, NHCO*Me*), 169.64 (s, CO_2Me) and 52.63 (q, CO_2Me); δ_H 7.18 (s, 2- and 6-H), 2.97 (dd, *J* 14.0 and 5.6. A of ABX, H_A of CH_2), 3.05 (dd, *J* 14.0 and 5.6, B of ABX, H_B of CH_2), 4.80 (dt, *J* 7.5 and 5.6, X of ABX, CH_2CH), 5.97 (d, *J* 7.5, NH), 3.74 (s, CO_2Me) and 2.01 (s, COMe); *m/z* (%) 393/395/397 (1.3, 2.6, 1.3, $M^{\bullet+}$), 334/336/338 (27, 54, 27, $[M - NHCOMe]^+$), 303/305/307 (5, 10, 5), 263/265/267 (7.4, 14.5, 7.7), 88 (81) and 43 (100).

(0.32 mmol) at room temp. After 15 min, solid $NaHCO_3$ (27 mg) was added to the mixture, which was then stirred for a further 15 min, evaporated, and the residue was taken into $CHCl_3$, washed twice with water, and dried. The organic solvent was evaporated off and the residue was subjected to reversed-phase HPLC with MeCN–water (4:6), with collection of four fractions corresponding to compounds **7b** (t_R 4.3 min, 9.8 mg, 9%), **7a** (t_R 6.6 min, 11.4 mg, 10%), **8** (t_R 6.9 min, 5.5 mg, 5%) and **9** (t_R 9.2 min, 5.8 mg, 5%).

Data of compound **7a**: δ_H(200 MHz) 7.23 and 7.40 (2 d, *J* 2.8, 2- and 6-H), 2.46 (dd, *J* 13.5 and 6.3, A of ABX, H_A of CH_2), 2.80 (dd, *J* 13.5 and 5.0, B of ABX, H_B of CH_2), 4.48 (td, *J* 6.3 and 5.0, X of ABX, CH_2CH), 6.20 (d, *J* 6.3, NH) and 2.03 (s, COMe).

Data of compound **7b**: δ_C 72.69 (s, C-1), 150.67 (d, C-2 or -6), 121.41 (s, C-3 and -5), 171.40 (s, C-4), 150.96 (d, C-6 or -2), 44.09 (t, CH_2), 48.56 (d, CH), 169.80 (s, NHCOMe), 23.17 (q, NHCO*Me*), 53.64 (q, CO_2Me) and 171.24 (s, CO_2Me); δ_H 7.26 and 7.45 (2 d, *J* 2.8, 2- and 6-H), 2.12 (dd, *J* 14.8 and 6.6, A of ABX, H_A of CH_2) 2.36 (dd, *J* 14.8 and 4.4, B of ABX, H_B of CH_2), 4.74 (td, *J* 6.6 and 4.4, X of ABX, CH_2CH), 6.54 (d, *J* 6.6, NH), 2.00 (s, COMe) and 3.81 (s, CO_2Me); *m/z* (%) 391/393/395 (0.6, 1.2, 0.6, $[M - H_2O]^{\cdot+}$), 333/335/337 (6, 12, 6, $[M - H_2O - NHCOMe]^+$), 291/293/295 (16, 31, 16) and 43 (100).

Data of compound **8**: δ_H(200 MHz) 6.12 (d, *J* 7.0, NH), 2.05 (s, COMe), 4.60 (ddd, $J_{2,3\beta}$ 11.9, $J_{2,NH}$ 7.0, $J_{2,3\alpha}$ 3.9, 2-H), 3.75 (s, CO_2Me), 2.40 (dd, J_{gem} 13.9, $J_{3\alpha,2}$ 3.9, 3-H_β), 2.96 (dd, J_{gem} 13.9, $J_{3\beta,2}$ 11.9, 3-H_α), 6.98 (s, 4-H), 5.51 (d, $J_{7,7a}$ 5.5, 7-H) and 4.78 (d, $J_{7a,7}$ 5.5, 7a-H). This sample decomposed overnight at room temp. to give a mixture of at least four products that were detected by HPLC though not identified.

Data of compound **9**: δ_H(200 MHz) 7.10 and 7.30 (2 d, *J* 2.8, 2- and 6-H), 3.30 and 3.36 (2 s, 2 × OMe), 2.11 (dd, *J* 13.5 and 8.0, A of ABX, H_A of CH_2), 2.54 (dd, *J* 13.5 and 7.5, B of ABX, H_B of CH_2), 4.62 (td, *J* 8.0 and 7.5, X of ABX, CH_2CH), 5.90 (d, *J* 8.0, NH) and 1.98 (s, COMe). When kept overnight at room temp. this NMR sample gave a ~ 1:1 mixture of ketones **7a** and **7b**.

Acknowledgements

We thank Mr. A. Sterni for recording the mass spectra, and MURST (Progetti 40%) and CNR, Roma, for financial support.

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Paper 3/03646D
Received 25*th June* 1993
Accepted 19*th July* 1993