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A SIMPLE, EFFICIENT ROUTE TO THE SYNTHESIS OF DIBENZOCOUMARANONES AND ARISTOLACTAMS.

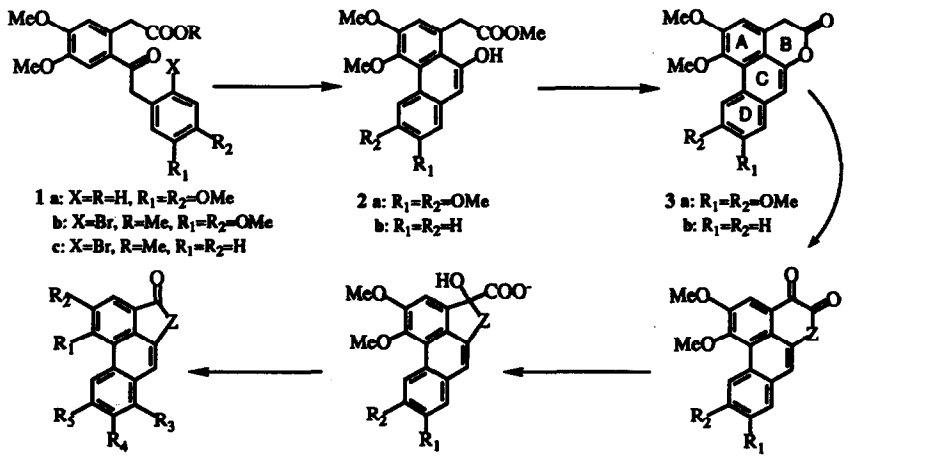
Juan C. Estévez, M. Carmen Villaverde, Ramón J. Estévez and Luis Castedo*.

Departamento de Química Orgánica de la Universidad de Santiago and Sección de Alcaloides (C.S.I.C.).
15706 Santiago de Compostela. SPAIN.

SUMMARY.- We report the first synthesis of dibenzo[cd,f]coumaranones that could be readily transformed into their nitrogen analogues, the aristolactams.

Aristolactams,[1-3] a minor group of natural compounds of pharmacological interest, are biogenetically related to aporphines[1,2] and probably to dibenzocoumaranones, a class of phenanthrene lactones whose only known natural member is aristololide (**6a**).[4]

Previous described methods of preparing aristolactams are usually laborious and low-yielding,[5-7] due perhaps to the presence or the generation of a five-membered ring in the key cyclization step. As a continuation of our investigations in this field we approached the synthesis of aristolactams by a route involving the formation of dibenzochromanones **3** and subsequent contraction of their six-membered ring B followed by lactone-lactam transformation .



1 a: X=R=H, R_1=R_2=OMe
b: X=Br, R=Me, R_1=R_2=OMe
c: X=Br, R=Me, R_1=R_2=H

2 a: R_1=R_2=OMe
b: R_1=R_2=H

3 a: R_1=R_2=OMe
b: R_1=R_2=H

6 a: Z=O, R_1+R_2=OCH_2O, R_3=OMe, R_4=R_5=H
b: Z=O, R_1=R_2=R_4=R_5=OMe, R_3=H
c: Z=O, R_1=R_2=OMe, R_3=R_4=R_5=H
d: Z=NH, R_1=R_2=R_4=R_5=OMe, R_3=H
e: Z=NMe, R_1=R_2=R_4=R_5=OMe, R_3=H
f: Z=NH, R_1=R_2=OMe, R_3=R_4=R_5=H

5 a: Z=O, R_1=R_2=OMe
b: Z=NMe, R_1=R_2=OMe
c: Z=O, R_1=R_2=H

4 a: Z=O, R_1=R_2=OMe
b: Z=NMe, R_1=R_2=OMe
c: Z=O, R_1=R_2=H

After unsuccessfull attempts to form the strategic bi-aryl bond of dibenzochromanone **3a** by electrocyclization[8] of hydroxystilbenic lactone derived from ketoacid **1a**, we found that it was readily achieved by tributyltin hydride-induced radical cyclization.[9] Refluxing the readily prepared bromoketoester **1b**[10] with Bu_3SnH and AIBN in benzene for 18 hours under argon afforded an 80% yield of dibenzochromanone **3a** (mp 180-181 °C, methanol),[11] most probably by lactonization of the initially formed phenanthrenic hydroxy ester **2a**. Subsequent benzylic oxidation of a dioxane solution of **3a** with oxygen in the presence of sodium hydroxide at room temperature for 72 hours afforded a 70% yield of dibenzocoumaranone **6b** (mp 196-197 °C, methanol),[11] probably via the phenanthrenic ketolactone **4a**; it is hypothesized that in the basic conditions used, benzilic-type rearrangement[12] of **4a** is followed by oxidative decarboxylation of the intermediate **5a**, as in the transformation of the 4,5-dioxoaporphine alkaloid pontevedrine (**5b**) into its corresponding aristolactam (**6e**).[13]

Treatment of the dibenzocoumaranone **6b** with aqueous ammonia gave a quantitative yield of aristolactam **6d**, which was easily transformed (by treatment with NaH and MeI in THF) into *N*-methylaristolactam **6e**, identical with a sample of this compound obtained from pontevedrine (**4b**).[13]

Analogous results were achieved from bromoketoacid derivative **1c**,[10] which was subjected to the described radical cyclization procedure to give dibenzochromanone **3b** (mp 160-162 °C, methanol)[11] in a better yield (90%) than that of **3a**. As expected, oxidation of **3b** as above gave dibenzocoumaranone **6c** (mp 176-178 °C, methanol)[11]. Reaction of **6c** with aqueous ammonia afforded cefaranone B (**6f**), identical with an authentical sample of this natural aristolactam.[5]

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11. All new compounds gave satisfactory spectroscopic data. **3a**: IR ($\nu_{máx}$, cm^{-1}, KBr): 1760 (C=O); ^{1}H-NMR (∂, ppm, $CDCl_3$): 3.95 (s, 3H, $-OCH_3$), 4.05 (s, 6H, 2x$-OCH_3$), 4.07 (s, 3H, $-OCH_3$), 4.26 (s, 2H, $-CH_2-$), 7.05 (s, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.18 (s, 1H, Ar-H) and 9.12 (s, 1H, Ar-H). MS (m/z, FAB): 355 [$(M+1)^+$, 24%)], 354 (M^+, 100%). **6b**: IR ($\nu_{máx}$, cm^{-1}, KBr): 1780 (C=O); ^{1}H-NMR (∂, ppm, $CDCl_3$): 4.05 (s, 3H, $-OCH_3$), 4.08 (s, 6H, 2x$-OCH_3$), 4.17 (s, 3H, $-OCH_3$), 7.17 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H) and 8.74 (s, 1H, Ar-H). MS (m/z, %): 340 (M^+, 100). **3b**: IR ($\nu_{máx}$, cm^{-1}, KBr): 1760 (C=O); ^{1}H-NMR (∂, ppm, $CDCl_3$): 3.96 (s, 3H, $-OCH_3$), 4.04 (s, 3H, $-OCH_3$), 4.27 (s, 2H, $-CH_2-$), 7.09 (s, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 7.56-7.60 (m, 2H, 2xAr-H), 7.76-7.80 (m, 1H, Ar-H) and 9.50-9.54 (m, 1H, Ar-H). MS (m/z,%): 294 (M^+, 100). **6c**: IR ($\nu_{máx}$, cm^{-1}, KBr): 1780 (C=O); ^{1}H-NMR (∂, ppm, $CDCl_3$): 4.10 (s, 3H, $-OCH_3$), 4.18 (s, 3H, $-OCH_3$), 7.26 (s, 1H, Ar-H), 7.62-7.66 (m, 2H, 2xAr-H), 7.84 (s, 1H, Ar-H), 8.89-7.93 (m, 1H, Ar-H) and 9.22-9.25 (m, 1H, Ar-H). MS (m/z, %): 280 (M^+, 100).
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