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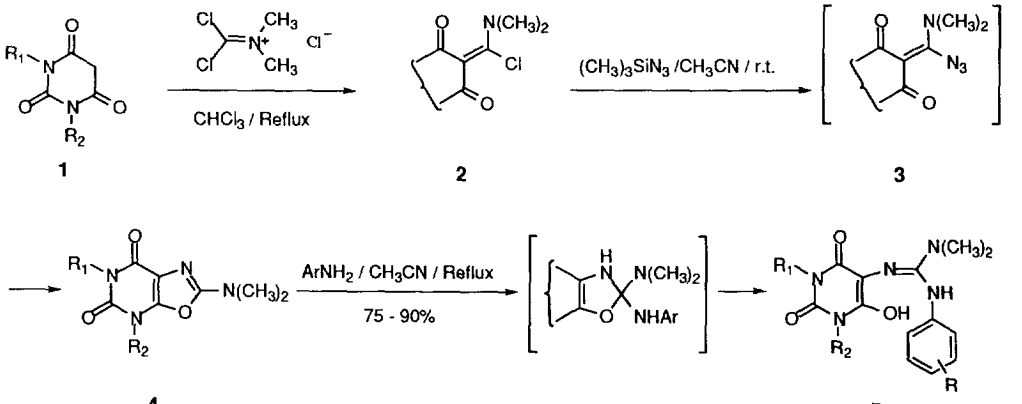
A Facile Entry into a New Heterocyclic System: Synthesis of 4,5-Annulated-2-Dimethylamino-1,3,8,10-tetraaza-spiro[5.5]-1,4-undecadiene-7,9,11(3H,8H,10H)triones.

Bruno Kokel[1]

Laboratoire de Bioorganique et Biotechnologies du C.N.R.S., Ecole Nationale Supérieure de Chimie de Paris, 11, rue Pierre et Marie Curie, 75231 Paris Cedex 05, France.

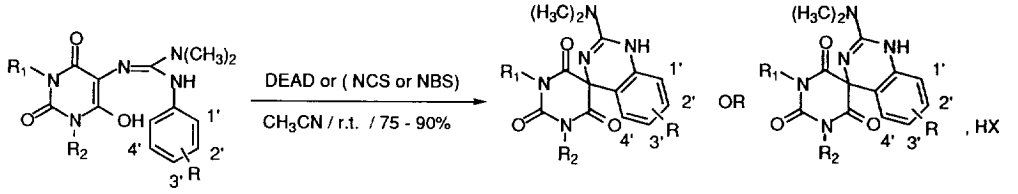
Abstract : 4,5-annulated-2-dimethylamino-1,3,8,10-tetraaza-spiro[5.5]-1,4-undecadiene-7,9,11 (3H,8H,10H) triones, related to barbituric acids and representatives of a new heterocyclic system, were synthesized starting from corresponding 2-dimethylaminooxazolo[5,4-d]pyrimidine-4,6-diones, through reaction with various aromatic amines and subsequent dehydrogenative cyclization using diethyl azodicarboxylate (DEAD) or N-halosuccinimides (NCS or NBS) as dehydrogenating agents.

In the course of our programme devoted to the synthesis of novel heterocyclic systems of biological value, starting from uracils and related fused pyrimidines, we found earlier that the barbituric acids **1** are directly converted into the 2-dimethylaminooxazolo[5,4-d]pyrimidine-4,6-diones **4**, upon condensation with dimethyldichloromethyleniminium chloride[2,3] and subsequent treatment with trimethylsilylazide[4,5]. As outlined below (Scheme 1), that conversion of **1** affords successively, the 5-(dimethylaminochloromethylene)barbituric acids (α-chloroenamines) **2** and the very unstable α-azidoenamines **3**, which rearrange into **4** (Scheme 1)[6-9]. While focusing on their utilization as synthetic intermediates, we recently observed that when heated in refluxing acetonitrile in the presence of an aromatic amine, these oxazolo[5,4-d]pyrimidines **4** undergo, as expected, an oxazole ring cleavage, to form the corresponding 5-[N-(N'-aryl-N"-dimethyl)guanidinyl] barbituric acids **5** in very good yields (Scheme 1)[10-12].



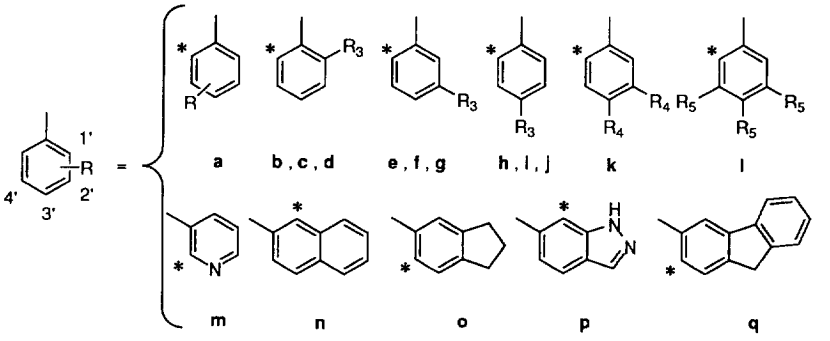
Scheme 1

An interesting feature of guanidines **5** is their facile dehydrogenative cyclization into the previously unknown 4,5-annulated-2-dimethylamino-1,3,8,10-tetraaza-spiro[5.5]-1,4-undecadiene-7,9,11(3H, 8H, 10H) triones **6** (Scheme 2), when treated, under very mild reaction conditions (acetonitrile at room temperature), with diethyl azodicarboxylate (DEAD)[13]. Using N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS) as dehydrogenating agents instead of DEAD, affords hydrohalide salts **7** of the same heterocyclic system[14-17]. In the latter case however, a concomitant halogenation of the aromatic moiety of **7**, was occasionally observed for R = (R_3, R_5) = OCH_3[18].



5A , 5B (a , b , ... p , q) **6A , 6B (a , b , ... p , q)** **7A , 7B (a , b, ... p , q)**

A : $R_1 = R_2 = CH_3$ **B** : $R_1 = CH_3$ / $R_2 = H$ X = Cl , Br



a : R = H; **b , c , d** : R = R_3 = 1' - CH_3 , C_2H_5 , OCH_3; **e , f , g** : R = R_3 = 2' - CH_3 , C_2H_5 , OCH_3;

h , i , j : R = R_3 = 3' - CH_3 , C_2H_5 , OCH_3; **k** : R = R_4 = 2' , 3' - $(CH_3)_2$; **l** : R = R_5 = 2', 3', 4' - $(OCH_3)_3$

The (*) marks pinpoint the *ortho*-carbon atom of the aromatic amines involved in the formation of the spiro derivatives as shown by the spectral data. 5A - 7B : mp > 270 °C.

Scheme 2

The structure of the spiro derivatives **6** and **7** as well as that of the guanidines **5**, was recently established by X-ray analysis of **5Aa** ($R_1 = R_2$ = methyl ; R = H), **5Ad** ($R_1 = R_2$ = methyl ; $R = R_3$ = 1'-methoxy), **6Aa** ($R_1 = R_2$ = methyl ; R = H), **7Ab** ($R_1 = R_2$ = methyl ; $R = R_3$ = 1'-methyl ; X = Cl), **7Ai** ($R_1 = R_2$ = methyl ; $R = R_3$ = 3'-ethyl ; X = Cl) and **7Bh** (R_1 = methyl ; R_2 = H ; $R = R_3$ = 3'-methyl ; X = Cl), (Scheme 2)[19].

EXPERIMENTAL

5-[N-(N'-aryl-N"-dimethyl) guanidinyl]barbituric acids **5** *: general procedure.* A stirred mixture of oxazolo[5,4-d]pyrimidine **4** (0.01 mole) and aromatic amine (0.02 mole)[20] in dry acetonitrile (50 ml), protected from the atmospheric moisture, was heated under reflux for 24 hours. After cooling to room temperature, either a clear homogeneous solution or a suspension of guanidine **5** was obtained[21]. In the latter case, about 60% of the solvent was removed *in vacuo* and the precipitate was collected, washed successively with dry acetonitrile (2 x 10 ml) and ether (2 x 20 ml) and dried *in vacuo* at room temperature. The filtrate was then evaporated *in vacuo* and the oily residue treated with ether (10 ml). The precipitate was worked up as before to collect an additional fraction of the expected guanidine. In the former case, about 90% of the solvent was removed *in vacuo* and the residue was treated with ether (15-20 ml) and worked-up as before to obtain **5**. Yield: 75 to 90%; mp°C > 270.

Spiro derivatives **6** *: general procedure.* Two equivalents of DEAD (0.002 mole) was added to a stirred solution or suspension of guanidine **5** (0.001 mole)[22] in dry acetonitrile (20 ml). The mixture was allowed to stand overnight at room temperature and about 90% of the solvent removed *in vacuo*. Ether (10 ml) was added to the residue and the spiro derivative was filtered off, washed with ether and dried *in vacuo*. Yield: 75 to 90%; mp°C > 270.

Spiro derivatives **7** *: general procedure.* A stirred mixture of guanidine **5** (0.001 mole), NCS (0.002 mole)[18] and dry acetonitrile (20 ml), was allowed to stand overnight at room temperature[22]. The majority of the solvent (about 75%) was then removed *in vacuo* and the residue was worked-up as before. Yield: 75 to 90%; mp°C > 270.

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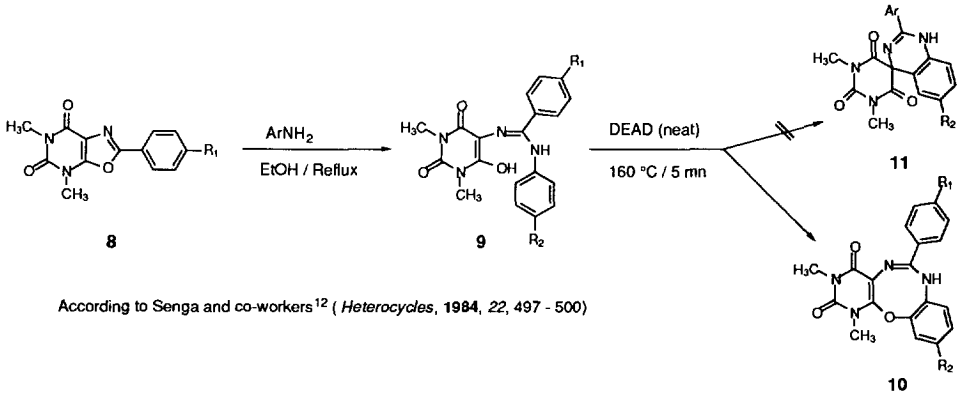
6. The structure of the α-chloroenamines **2** was assigned based on the X-ray analysis of **2A** ($R_1 = R_2$ = methyl) : Kokel, B.; Bachet, B. and Cousson, A. Z. *Kristallogr.*, in press.
7. The structure of the oxazolo[5,4-d]pyrimidines **4** was unambiguously established by X-ray crystallography performed on the representative compound **4A** ($R_1 = R_2$ = methyl)[8,9], mistakenly reported first, in the absence of X-ray analysis, as the isomeric 3-dimethylaminoisoxazolo[5,4-d]pyrimidine[4,5].
8. Kokel, B.; Hubert-Habart, M.; Cousson, A. and Bachet, B. 14th European Colloquium on Heterocyclic Chemistry, Toledo, Spain, October 1-3, 1990. Proceedings, **1990**, 222.
9. Cousson, A.; Bachet, B.; Kokel, B.; Hubert-Habart, M. *Acta Cryst.*, **1992**, *C48*, 74-76.

10. The oxazole ring cleavage of oxazolo[5,4-d]pyrimidines related to uracils, *via* reaction with amines, is a known process used earlier by Senga and co-workers to form 9-substituted-8-phenyltheophyllines[11] and pyrimido[4,5-b]benzoxadiazocines[12].
11. Nishigaki, S.; Sato, J.; Shimizu, K. and Senga, K. *Chem. Pharm. Bull.*, **1980**, *28*, 1905-1908.
12. Senga, K.; Ohwaki, J.; Kanazawa, H.; Ichiba, M. and Nishigaki, S. *Heterocycles*, **1984**, *22*, 497 - 500.
13. It should be mentioned here, an earlier transformation reported by Senga and co-workers[12], occuring under rather more drastic reaction conditions (neat DEAD heated at 160°C for 5 mn) than those we are using (DEAD in acetonitrile at room temperature) and involving the 1,3-dimethyl-2-phenyloxazolo[5,4-d]pyrimidines **8**, the structure of which resembles that of oxazolo[5,4-d]pyrimidines **4**, except for having an aryl group instead of a dimethylamino moiety. Surprisingly, although it affords first, the expected 5-(N-aryl-arylamidino)-1,3-dimethylbarbituric acids **9**, the conversion of **8** gives pyrimido[4,5-b]benzo[g]oxadiazocines **10**, which are fused eight membered ring heterocyclic systems. The formation of spiro derivatives **11** is not observed.



According to Senga and co-workers[12] (*Heterocycles*, **1984**, *22*, 497 - 500)

14. Note that atmospheric oxygen in the presence of a catalytic amount of a 5-deazaflavin, which acts as a turnover catalyst, induces slowly the dehydrogenative cyclisation of the guanidines **5** as well. Auto-recycling oxidation by 5-deazaflavins has been extensively studied over the last two decades, by Yoneda and co-workers[15,16].
15. Yoneda, F. and Tanaka, K. *Med. res. rev.*, **1987**, *7*, 477-506, and references cited therein.
16. Yoneda, F. and Kokel, B. Syntheses and properties of 5-deazaflavins. In *Chemistry and Biochemistry of Flavoenzymes*; Muller, F. Ed.; CRC Press: Boca-Raton, Ann Arbor, Boston. 1991; Vol. 1, pp. 121-169, and references quoted.
17. The conversion of the oxazolo[5,4-d] pyrimidine **4C** ($R_1 = R_2 = H$) into the corresponding spiro derivatives **6C** and **7C**, has proved successful as well.
18. Halogenation of the aromatic moiety of **7** for R = (R_3, R_5) = OCH_3, can be avoided when using corresponding guanidines and N-halogenosuccinimides in stoichiometric proportions.
19. Kokel, B.; Bachet, B. and Cousson, A. To be submitted for publication.
20. 0.012 mole (1.2 equivalents) in the case of aromatic amines insoluble in acetonitrile or ether.
21. The oxazolo[5,4-d]pyrimidine **4A** ($R_1 = R_2 = CH_3$) is soluble in acetonitrile at room temperature while the corresponding guanidines **5A**, usually soluble in refluxing acetonitrile, precipitate slowly at room temperature. Conversely, most of the guanidines **5B** ($R_1 = CH_3$; $R_2 = H$) as well as their precursor, the oxazolo[5,4-d]pyrimidine **4B**, are insoluble even in refluxing acetonitrile and their formation does often occur under heterogeneous conditions.
22. Depending on the nature of the corresponding R_1, R_2 and R groups, the dehydrogenative cyclization process of **5** may take place under heterogeneous reaction conditions.

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