Monatshefte für Chemie 117, 879–882 (1986)

Monatshefte für Chemie
Chemical Monthly

Linear Expanded Xanthines [1]

Short Communication

Gary R. Rodgers and **William J. P. Neish**

Department of Pharmacology, University of Sheffield, Western Bank, Sheffield S10 2TN, England

(Received 28 January 1986. Accepted 24 February 1986)

Expansion of the xanthine ring system has been accomplished by linear formation of a benzo, pyrido or pyrazino ring between the pyrimidine and imidazole portions.

[Keywords: Anil; Covalent hydrate; Lin-benzo-xanthines; Lin-pyrido-xanthines; Lin-pyrazino-xanthines]

Linear expandierte Xanthine (*Kurze Mitteilung*)

Durch Einbau eines Benzo-, Pyrido- oder Pyrazino-Ringes zwischen den Pyrimidin- und Imidazoleinheiten wurde die lineare Expansion des Xanthin-Ringsystems erreicht.

In 1975, *Leonard* et al. [2] described the synthesis of linear benzoadenine by insertion of a benzo ring between the pyrimidine and imidazole moieties of the adenine molecule. *Schneller* and *Christ* [3] prepared benzologues of other biologically-active molecules such as theophylline, caffeine and fervenulin. *Cuny* et al. [4] synthesised benzoallopurinol and its derivatives.

Since 1975 we have studied the anti-cancer activity of a variety of xanthines towards the rat RD 3 tumour. Included in these studies were various linear benzo-, pyrido- and pyrazino-xanthines which are the Series I, II and III end-products ($R = Et$ and Z = H, OH, SH, and Cl) as shown in Scheme 1. Most of the corresponding compounds in which $R = Me$ have also been synthesised and reference is made to some of them in the text.

In view of the current interest in "stretched-out" versions of biologically-active materials it seems appropriate to outline briefly the

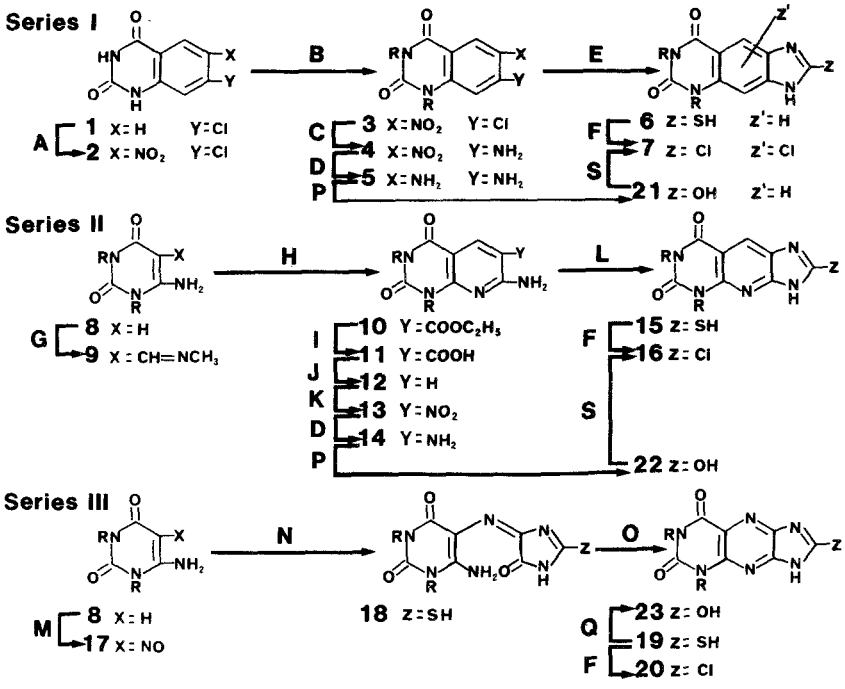
synthesis and properties of some of the new xanthines (see Scheme 1 and key). In the text which follows m.p. (°C, uncorrected) and mass ion (*m/z*) are given in brackets after the named or numbered compounds. Sometimes microanalyses are also included in these brackets.

Series I. Nitration of 7-chloroquinazoline-2,4(1*H*,3*H*)-dione [3] **1** yielded **2** (336°, 241) which on ethylation [5] gave **3** (144°, 297). On amination [3] **3** was converted to **4** (209°, 278) which on reduction gave **5** (235°, 248). By route E [6], **5** yielded 5,7-diethyl-2-mercaptoimidazo[4,5—*g*]quinazoline-6,8(5*H*,7*H*)-dione, **6** (361°, 290; $C_{13}H_{14}N_4O_2S$, calcd. S 11.03, found S 10.75). Chlorination of **6** with SO_2Cl_2 gave a dichloro derivative **7** (160°, 326) in which one Cl has replaced SH and another has displaced a H at either C-4 or C-9 of the benzo ring. The corresponding 5,7-dimethyl derivative (**6**, where $R = Me$, 403°, 262) also yielded a dichloro compound **7** (180°, 298). Attempted chlorination of **21** with $POCl_3/Et_3N$ [16] gave the dichloro derivative **7** but this was always contaminated with unreacted **21** and coloured by-products were often present.

Series II. Anhydrous 1,3-diethyl-6-aminouracil [9] **8** (198°, 183) was reacted with methylamine/$POCl_3$ [10] to give **9** (194°, 224). When **9** was refluxed with ethyl cyanoacetate, 1,3-diethyl-6-carbethoxy-7-aminopyrido[2,3—*d*]pyrimidine-2,4(1*H*,3*H*)-dione **10** (207°, 306) was obtained. Hydrolysis of **10** gave **11** (332°, 278) which, on fusion, lost CO_2 and yielded **12** (201°, 234). Compound **12** (m.p. 204–206°) has been prepared by *Papesch* [11] by another route. On nitration, **12** gave **13** (224°, 279) which was reduced to **14** (240°, 249). On fusion with thiourea **14** yielded **15** viz. 5,7-diethyl-2-mercaptoimidazo[4,5—*g*]pyrido[2,3—*d*]pyrimidine-6,8(5*H*,7*H*)-dione (329°, 291; $C_{12}H_{13}N_5O_2S$, calcd. S 10.87, found S 11.00). With SO_2Cl_2, **15** yielded the 2-chloro derivative **16** (252° dec., 293). This substance contained no 2-hydroxyimidazo derivative nor was any dichloro compound present.

Series III. Nitrosation of 1,3-diethyl-6-aminouracil **8** gave **17** (204°, in NH_3 vapour $[M + H]^+ = 213$) which reacted with 2-thiohydantoin in *Ac*OH to give the anil **18** (276°, 310; $C_{11}H_{14}N_6O_3S$, calcd. S 10.32, found S 10.33) which was ring-closed in boiling 0.1 *N* NaOH [12]. The pyrazino derivative **19** was precipitated by addition of conc. HCl to *pH* 4.5. If after filtration of **19** (in 30% yield), the *pH* 4.5 mother liquor is brought to *pH* 2 another compound (280°, 310), pale pink in colour, is precipitated. This compound is probably a covalent hydrate of **19** having $m/z = 310$. When this material (lg) was dissolved in conc. H_2SO_4 (10 ml), kept at ~ 170° for 30 min and poured into water, a bright yellow precipitate was formed. On crystallisation from 80% dimethylformamide the compound gave bright yellow crystals similar to **19** with m.p. 325° (lower then m.p. of authentic **19**) and $m/z = 292$. The mass spectra of the two compounds, however, were identical in every respect. Compound **19** which is 5,7-diethyl-2-mercaptoimidazo[4,5—*g*]pteridine-6,8(5*H*,7*H*)-dione (350°, 292) crystallised as yellow needles from 80% dimethylformamide. It gave the following analyses: $C_{11}H_{12}N_6O_2S$, calcd. C 45.21 H 4.11 N 28.77 S 10.96. found C 45.24 H 4.43 N 28.92 S 10.48. With SO_2Cl_2 **19** gave the 2-chloro derivative **20** (330°, 294). According to its mass spectrum this compound always contains some 2-hydroxyimidazo compound. No dichloro compound was present. Attempts to purify **20** by chromatography have so far been unsuccessful. Compound **19** gave **23** by method Q [15]. With $POCl_3/Et_3N$ (route S) [16] **23** yielded **20** which contained unreacted 2-hydroxyimidazo compound.

Scheme 1



A fuming HNO_3/H_2SO_4 at —10 °C, then 100 °C for 10 min [3].
B EtI/K_2CO_3/*DMF*, 50 °C, 9 h [5].
C anhydrous NH_3/*n*-butanol, 120 °C, 24 h [3].
D $SnCl_2$/conc. HCl, 80 °C.
E CS_2/pyridine, 45 °C, 7 h [6].
F SO_2Cl_2, r.t., 3 days [7].
G $POCl_3/CHCl_3$/*DMF*, 100 min [8].
H $NCCH_2COOEt/CHCl_3$ reflux 4.5 h.
I 1% $NaHCO_3$ (200 ml/g of **10**) reflux 6 h., conc. HCl to *pH* 5.
J fusion at 340 °C to constant weight.
K KNO_3/H_2SO_4 at —5 °C, then 100 °C for 30 min, neutralise with 40% NaOH.
L thiourea fusion, 200 °C, 15 min.
M $NaNO_2$/*Ac*OH.
N 2-thiohydantoin/*Ac*OH reflux 20 min.
O 0.1 *N* NaOH (40 ml/g of **18**). reflux 10 min, bring to *pH* 4.5 with conc. HCl [12].
P urea fusion, 180 °C; 15 min for **22**; 1 h for **21**.
Q H_2O_2/1 *N* NaOH, r.t. for 1 h then 80 °C for 1 h [15].
S $POCl_3/Et_3N$, 125 °C for 30 min [16].

In Series I only lin-benzotheophylline (m.p. 289–292) has been reported previously [3]. Our product (see Scheme, compound no. **6** in which $R = Me$ and $Z = Z' = H$) had m.p. 338–340° and $m/z = 230$.

Apparently no examples of Series II compounds have been reported hitherto.

Two examples of Series III compounds were found in the literature. A formyl derivative of 2,4-diamino-imidazo[4,5—*g*]pteridine has been described [13] and the synthesis of a natural product russupteridine yellow has been effected in low yield by condensation of 5-amino-6-(*D*-ribitylamino)uracil with parabanic acid [14]. Our efforts to obtain Series III compounds ($Z = OH$) by fusing 1,3-dialkyl-5,6-diaminouracils with parabanic acid were unsuccessful. We attempted to obtain starting materials for Series III products by nitrating the readily accessible 7-amino-1,3-dialkylpteridines but the 7-nitroamines which were obtained failed to rearrange to the required 6-nitro-7-amino-1,3-dialkylpteridines.

References

[1] This work was supported by a grant from the Yorkshire Cancer Research Campaign. We thank Mr. *David Smith* of the Dept. of Chemistry, University of Sheffield for help with amination of the chloroquinazoline diones, Messrs *P. Ashton* and *I. Johnstone* for the mass spectrum determinations and Miss *M. McKinnon* for the microanalyses.
[2] *Leonard NJ, Morrice AG, Sprecker MA* (1975) J Org Chem 40: 356
[3] *Schneller SW, Christ WJ* (1981) J Org Chem 46: 1699
[4] *Cuny E, Lichtenthaler FW, Moser A* (1980) Tetrahedron Lett 21: 3029
[5] Alkylation based on the method of *Albert A* (1978) J Chem Soc Perkin I: 513
[6] *Baker BR, Joseph JP, Schaub RE* (1954) J Org Chem 19: 635
[7] *Moon NS* (1949) U.S.Patent 2,469,697; SO_2Cl_2 was used by *Moon* to convert 2-mercapto- to 2-chloro-benzothiazoles.
[8] *Bamberger E, Lorenzen J* (1893) Liebig's Ann. Chem. 273, 269: 2-methylbenzimidazoles react with hypochlorite to give unstable N-chloroimides which easily transfer Cl to replace one or more H in the benzene ring. A similar reaction may explain the formation of dichloro derivatives in the lin-benzo-xanthine Series I.
[9] *Papesch V, Schroeder EF* (1951) J Org Chem 16: 1879
[10] *Bredereck H, Effenberger F, Simchen G* (1964) Chem Ber 97: 1403; *Bredereck H, Simchen G, Wahl R, Effenberger F* (1968) Chem Ber 101: 512
[11] *Papesch V* (1966) U.S.Patent 3,272,816 (1966); Chem Abstr 65: 20145
[12] *Taylor EC, Cain CK, Loux HM* (1954) J Amer Chem Soc 76: 1874
[13] *Taylor EC, Sherman WR* (1959) J Amer Chem Soc 81: 2464.
[14] *Märki-Danzig H, Eugster CH* (1984) Helv Chim Acta 67: 570
[15] *Cook AH, Thomas GH* (1950) J Chem Soc 1884
[16] *Robins RK, Christensen BE* (1952) J Am Chem Soc 74: 3624