

Linear Expanded Xanthines [1]

Short Communication

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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.

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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 ferverulin. 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

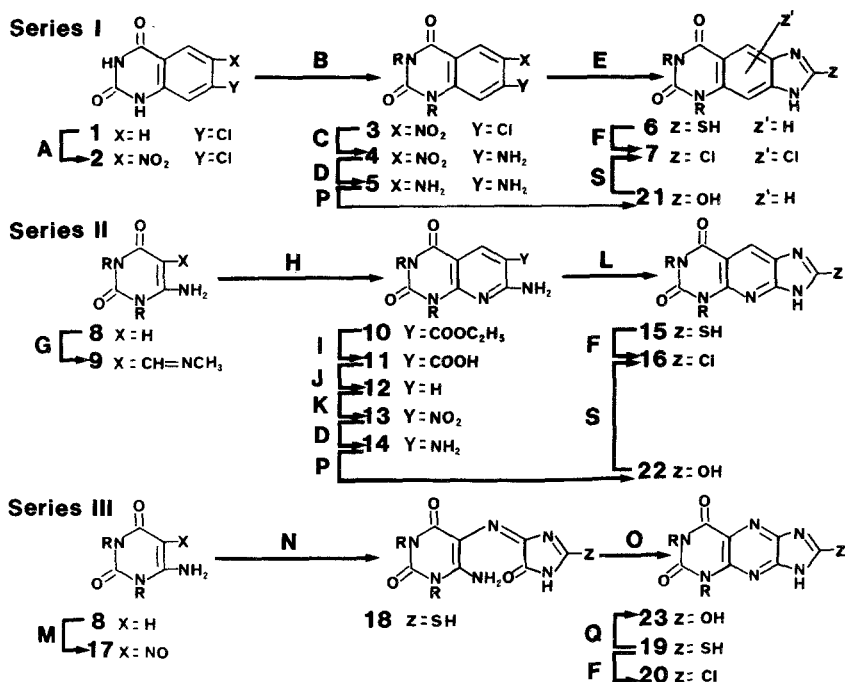
synthesis and properties of some of the new xanthenes (see Scheme 1 and key). In the text which follows m.p. ($^{\circ}\text{C}$, uncorrected) and mass ion (m/z) are given in brackets after the named or numbered compounds. Sometimes microanalyses are also included in these brackets.

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; $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$, 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 $R = \text{Me}$, 403° , 262) also yielded a dichloro compound **7** (180° , 298). Attempted chlorination of **21** with $\text{POCl}_3/\text{Et}_3\text{N}$ [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. $204\text{--}206^{\circ}$) 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; $\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}_2\text{S}$, 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 [$M + \text{H}$] $^+ = 213$) which reacted with 2-thiohydantoin in AcOH to give the anil **18** (276° , 310; $\text{C}_{11}\text{H}_{14}\text{N}_6\text{O}_3\text{S}$, 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 $\sim 170^{\circ}$ 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 than 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: $\text{C}_{11}\text{H}_{12}\text{N}_6\text{O}_2\text{S}$, 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 $\text{POCl}_3/\text{Et}_3\text{N}$ (route S) [16] **23** yielded **20** which contained unreacted 2-hydroxyimidazo compound.

Scheme 1



A fuming HNO₃/H₂SO₄ at -10 °C, then 100 °C for 10 min [3].

B EtI/K₂CO₃/DMF, 50 °C, 9 h [5].

C anhydrous NH₃/*n*-butanol, 120 °C, 24 h [3].

D SnCl₂/conc. HCl, 80 °C.

E CS₂/pyridine, 45 °C, 7 h [6].

F SO₂Cl₂, r.t., 3 days [7].

G POCl₃/CHCl₃/DMF, 100 min [8].

H NCCH₂COOEt/CHCl₃ reflux 4.5 h.

I 1% NaHCO₃ (200 ml/g of 10) reflux 6 h., conc. HCl to pH 5.

J fusion at 340 °C to constant weight.

K KNO₃/H₂SO₄ at -5 °C, then 100 °C for 30 min, neutralise with 40% NaOH.

L thiourea fusion, 200 °C, 15 min.

M NaNO₂/AcOH.

N 2-thiohydantoin/AcOH 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 H₂O₂/1 N NaOH, r.t. for 1 h then 80 °C for 1 h [15].

S POCl₃/Et₃N, 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 russuapteridine 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

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