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A NOVEL PROCEDURE FOR THE PREPARATION OF SOME PYRAZOLO/4,3-d/PYRIMIDINE DERIVATIVES AS AN APPROACH TO FORMYCIN B

M.Sprinzl, J.Farkaš and F.Šorm

Institute of Organic Chemistry and Biochemistry,

Czechoslovak Academy of Sciences, Prague

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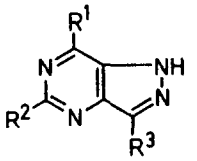
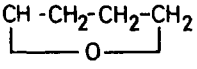
We wish to report herein the synthesis of 3-hydroxymethyl-7-hydroxypyrazolo/4,3-d/pyrimidine (I) and 3-hydroxymethyl-5,7-dihydroxypyrazolo/4,3-d/-pyrimidine (II) by using a novel procedure which might be extended to the synthesis of formycin B (ref. 1) and its analogs.



I $R^1=OH; R^2=H; R^3=CH_2OH$

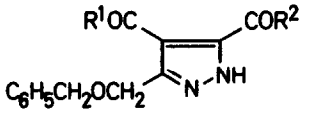
II $R^1=R^2=OH; R^3=CH_2OH$

XV $R^1=R^2=OH; R^3=CH_2OCH_2C_6H_5$

XVIII $R^1=R^2=OH; R^3=$ 

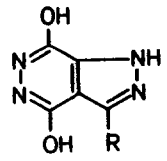
2-Benzyloxyethylurea (III), m.p. 78°, prepared by treatments of 2-hydroxyethylurea with benzyl chloride and sodium hydride in dimethylformamide was converted into N-nitroso-2-benzyloxyethylurea (IV), m.p. 42°, λ max (ethanol) 211 mμ and 235 mμ(logε 4.00 and 3.74), according to the procedure of Kirmse[2]. The ethereal solution of IV was treated with 20% aqueous sodium hydroxide to give a yellow solution of 2-benzyloxydiazoethane (V) which reacted with dimethyl acetylenedicarboxylate (1,3-cycloaddition[3]) yielding the sirupy dimethyl 3-benzyloxymethylpyrazol-4,5-carboxylate (VI), characterized as VII, m.p.205°; max (ethanol) 211 mμ (logε 4.04). After treatment of dimethyl ester VI with

hydrazine hydrate, the very insoluble dihydrazide VIII was obtained. By heating in 0.01M HCl at 80°, VIII was cyclized to 3-benzyloxymethyl-4,7-dihydroxypyrazolo/3,4-d/pyridazine (IX), m.p. 258°, λ max (0.1N NaOH) 277 mμ (log ε 3.78), which by hydrogenolysis over palladium afforded the debenzylated product X, not melting below 300°; λ max (0.1N HCl) 263 mμ (log ε 3.74); λ max (0.05N NaOH) 217 and 274 mμ (log ε 4.34 and 3.79).



VI $R^1=R^2=OCH_3$ *VIII* $R^1=R^2=NHNH_2$ *XII* $R^1=NHNH_2;R^2=NH_2$
VII $R^1=R^2=OH$ *XI* $R^1=OCH_3;R^2=NH_2$ *XIII* $R^1=N_3;R^2=NH_2$

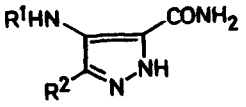
Dimethylester VI was treated with methanolic ammonia at room temperature to give methyl 3-benzyloxymethyl-5-carbamylpyrazol-4-carboxylate (XI), m.p. 153--154°, λ max (ethanol) 213 mμ (log ε 4.16). The structure of XI was assigned in analogy to the reported course of ammonolysis of dimethyl pyrazol-3,4-dicarboxylate[4]. Amide XI was converted into the corresponding azide XIII via 3-benzyloxymethyl-5-carbamyl-4-pyrazolcarboxylic hydrazide (XII), m.p. 163°, λ max (ethanol) 210 mμ (log ε 4.10). Azide XIII was rearranged in refluxing ethanol to give 3-benzyloxymethyl-4-ethoxycarbonylaminopyrazol-5-carboxamide (XIV) as the predominating product (yield 63%) along with 3-benzyloxymethyl-5,7-dihydroxypyrazolo/4,3-d/pyrimidine (XV) in 23% yield. Amide XIV: m.p. 218°, λ max (ethanol) 210 and 251 mμ (log ε 4.36 and 3.53); λ max (0.05N NaOH) 218 and 248 mμ



IX R = $CH_2OCH_2C_6H_5$ *X* R = CH_2OH

(logε 4.19 and 3.94). Compound XV: m.p. 222°, λ max (0.1N HCl) 208 and 284 mμ (logε 4.36 and 3.83); λ max (0.05N NaOH) 222 and 302 mμ (logε 4.39 and 3.65). By hydrogenolytical removal of benzyl group, XV afforded the expected product II, not melting below 300°, λ max (0.1N HCl) 207 and 287 mμ (logε 4.29 and 3.72) λ max (0.05N NaOH) 223 and 307 mμ (logε 4.35 and 3.66).

When the rearrangement of azide XIII was carried out in benzyl alcohol at 100°, benzylurethan XVI was obtained as the sole product, m.p. 182-183°, λ max 210 and 253 mμ (logε 4.37 and 3.49). The hydrogenolysis of both benzylic groups of XVI led to 3-hydroxymethyl-4-amino-5-pyrazolcarboxamide (XVII) which was isolated by means of chromatography on Dowex 50 (H^+) exchange resin as a sirupy product characterized with UV spectra, λ max (0.1N HCl) 210 mμ (logε 3.83); λ max (0.1N NaOH) 220 and 250 mμ (logε 3.94 and 3.85). Cyclisation of amine XVI in formamide at 170° afforded the desired product I, m.p. 267-268°; λ max (0.1N HCl) 222 and 277 mμ (logε 3.72 and 3.44); λ max (0.05N NaOH) 228 and 291 mμ (logε 3.70 and 3.43).



XIV $R^1 = CO_2C_2H_5$; $R^2 = CH_2OCH_2C_6H_5$
XVI $R^1 = CO_2CH_2C_6H_5$; $R^2 = CH_2OCH_2C_6H_5$
XVII $R^1 = H$; $R^2 = CH_2OH$

Whereas the Curtius rearrangement of azide XIII in alcohols gave corresponding urethans (XIV and XVI) as main products, the analogous reaction of 3-(2-tetrahydrofuryl)-5-carbamyl-4-pyrazolcarboxylic azide led exclusively to 3-(2-tetrahydrofuryl)-5,7-dihydroxypyrazolo/4,3-d/pyrimidine (XVIII), m.p. 270-271°; λ max (0.1N HCl) 208 and 288 mμ (logε 4.36 and 3.82); λ max (0.05N NaOH) 222 and 302 mμ (logε 4.46 and 3.65).

All crystalline compounds gave satisfactory elemental analyses.

The attempts to use the described procedure in the synthesis of formycin B are in progress.

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