NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CLI.*
THE PREPARATION OF 1H-PYRAZOLO [4,3-*d*] PYRIMIDINE AS AN APPROACH TO THE SYNTHESIS OF FORMYCIN B**

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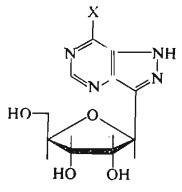
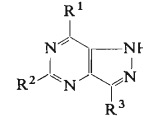
Addition of 2-benzyloxydiazoethane to dimethyl acetylenedicarboxylate afforded the pyrazole derivative *IXa* which was subjected to ammonolysis and then hydrazinolysis. The resulting hydrazide *XIIIa* was converted to the azide *XIVa*. Treatment of the latter with ethanol led to a 3 : 1 mixture of the urethane *XVIII* and the cyclic compound *V*. Reaction of the azide *XIVa* and benzyl alcohol afforded the benzyl urethane *XIX*, the hydrogenolysis of which led to the amino derivative *XXI*. This on treatment with formamide afforded the 1*H*-pyrazolo[4,3-*d*]pyrimidine derivative *III*. An analogous addition of tetrahydrofuryldiazomethane to dimethyl acetylenedicarboxylate led to the pyrazole derivative *IXb* which was converted to the 1*H*-pyrazolo[4,3-*d*]pyrimidine derivative *VI* by a similar sequence of reactions. On reaction with hydrazine hydrate, the esters *IXa* and *IXb* were converted to dihydrazides *XIa* and *XIb* which were cyclized in acidic media to the corresponding 1*H*-pyrazolo[3,4-*d*]pyridazine derivatives *XV* and *XVII*.

Formycin[1,2] (*I*) and the structurally related formycin B (*II*) are attractive objects for the total synthesis in view of their unusual nucleosidic structure. Syntheses of the heterocyclic moiety of formycins[3,4] as well as some other 1*H*-pyrazolo[4,3-*d*]pyrimidine derivatives[5–7] have been reported prior to the elucidation of the structure of the aforementioned antiobiotics but none of the reported procedures appears suitable for a total synthesis.



I, X = NH_2
II, X = OH



III, R^1 = OH, R^2 = H, R^3 = CH_2OH
IV, R^1 = R^2 = OH, R^3 = CH_2OH
V, R^1 = R^2 = OH, R^3 = $CH_2OCH_2C_6H_5$
VI, R^1 = R^2 = OH, R^3 = CH(O)—CH_2—CH_2—CH_2

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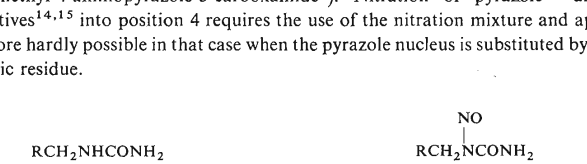
** Preliminary communication: Tetrahedron Letters *1969*, 289.

In the present paper, we wish to illustrate a novel and general procedure for the synthesis of 1*H*-pyrazolo[4,3-*d*]pyrimidine derivatives on preparations of some model compounds, namely, 3-hydroxymethyl-7-hydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*III*), 3-hydroxymethyl-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*IV*), 3-benzyloxymethyl-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*V*), and 3-(2-tetrahydrofuryl)-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*VI*). The substituents at position 3 of model compounds are of such a nature to mimic the sugar moiety of formycins in respect to the susceptibility to chemical reactions.

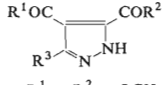
Our proposal of the synthesis of 1*H*-pyrazolo[4,3-*d*]pyrimidine derivatives contains two keysteps. One of them is the synthesis of 3-substituted pyrazole-4,5-dicarboxylic acids consisting in an 1,3-cycloaddition of appropriately substituted diazomethane derivatives to dimethyl acetylenedicarboxylate. As components in the 1,3-cycloaddition, the diazoethers have been used so far only by Reimlinger[8] in the synthesis of 3-methoxymethylpyrazole-4,5-dicarboxylic acid and by Goodman[9] in the synthesis of 3-(2,3-O-isopropylidene-β-DL-*erythro*-furanosyl)pyrazole-4,5-dicarboxylic acid. The other keystep consists in the Curtius degradation (for the pyrazole series see refs[10–12]) of 3-substituted pyrazole-4,5-dicarboxylic acids under the formation of 3-substituted 4-aminopyrazole-5-carboxylic acid derivatives. This procedure permits to introduce the amino group on the pyrazole nucleus under very mild conditions and appears therefore more suitable than that of Robins[3] consisting in nitration of the pyrazole ring and the subsequent reduction of the nitro group (*cf.* the synthesis of 3-methyl-4-aminopyrazole-5-carboxamide[3]). Nitration of pyrazole[13] and its derivatives[14,15] into position 4 requires the use of the nitration mixture and appears therefore hardly possible in that case when the pyrazole nucleus is substituted by a saccharidic residue.



The synthesis of compounds *III* – *V* started from N-(2-hydroxyethyl)urea which was converted by the action of benzyl chloride and sodium hydride in dimethylformamide into N-(2-benzyloxyethyl)urea (*VIIa*). Compound *VIIa* was also prepared from 2-benzyloxyethylamine by reaction with nitrourea[16,17]. The former method, however, was preferred in a large scale preparation of compound *VIIa* since the attempted preparation of the starting 2-benzyloxyethylamine according to the reported procedure[18] (by reaction of sodium 2-aminoethoxide and benzyl chloride in toluene)

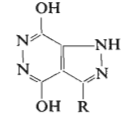
failed to give satisfactory yields. (In addition to the required 2-benzyloxyethylamine, a considerable amount of N-(2-benzyloxyethyl)benzylamine is formed by the reaction mentioned). Nitrosation of compound *VIIa* with nitrogen dioxide in ether[19] led to N-nitroso-N-(2-benzyloxyethyl)urea (*VIIIa*). Treatment of the ethereal solution of compound *VIIIa* with aqueous sodium hydroxide afforded a yellow, coloured solution of 2-benzyloxydiazoethane the reaction of which with dimethyl acetylenedicarboxylate led to dimethyl 3-benzyloxymethylpyrazole-4,5-dicarboxylate (*IXa*). The sirupous ester *IXa* was characterised by conversion (alkaline hydrolysis) into 3-benzyloxymethylpyrazole-4,5-dicarboxylic acid (*Xa*) and the dihydrazide *XIa* which was cyclized* by the action of 0·05M-HCl under the formation of 3-benzyloxymethyl-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*XV*). Hydrogenolysis of the benzyl group of compound *XV* over a palladium catalyst afforded 3-hydroxymethyl-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*XVI*).

Replacement of the 4-methoxycarbonyl group in compound *IXa* by the amino group requires a suitable method for the differentiation of both methoxycarbonyl groups. The different reactivity of the methoxycarbonyl groups in compound *IXa* may be suspected on the basis of the paper of Jones and Whitehead[22]. Thus, ammonolysis of ethyl pyrazole-3-carboxylate was found to proceed considerably faster than that of ethyl pyrazole-4-carboxylate. Furthermore, the ammonolysis of diethyl pyrazole-3,4-dicarboxylate afforded exclusively the 3-carbamoyl derivative even at elevated temperatures. In accordance with these results, the ammonolysis of ester *IXa* afforded a single monoamide which was ascribed by analogy to the mentioned paper[22] the structure of methyl 3-benzyloxymethyl-5-carbamoylpyrazole-4-carboxylate (*XIIa*). On treatment with hydrazine hydrate, compound *XIIa* was converted to the hydrazide of 3-benzyloxymethyl-5-carbamoylpyrazole-4-carboxylic acid (*XIIIa*). The



IXa, IXb, $R^1 = R^2 = OCH_3$
Xa, Xb, $R^1 = R^2 = OH$
XIa, XIb $R^1 = R^2 = NHNH_2$
XIIa, XIIb, $R^1 = OCH_3$, $R^2 = NH_2$
XIIIa, XIIIb, $R^1 = NHNH_2$, $R^2 = NH_2$
XIVa, XIVb, $R^1 = N_3$, $R^2 = NH_2$

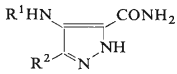
For *a* $R^3 = C_6H_5CH_2OCH_2$, *b* $R^3 =$ 



XV, $R = CH_2OCH_2C_6H_5$
XVI, $R = CH_2OH$
XVII, $R = CH{-}CH_2{-}CH_2{-}CH_2$ (O)

* For the reaction conditions leading to the formation of pyrazolo[3,4-*d*]pyridazine derivatives from the corresponding dicarboxylic acids see ref.[20,21].

hydrazide *XIIIa* was then treated with nitrous acid to afford the azide of 3-benzyloxymethyl-5-carbamoylpyrazole-4-carboxylic acid (*XIVa*). In view of the low stability, the azide *XIVa* was characterised by infrared spectra only.



XVIII, $R^1 = CO_2C_2H_5$, $R^2 = CH_2OCH_2C_6H_5$
XIX, $R^1 = CO_2CH_2C_6H_5$, $R^2 = CH_2OCH_2C_6H_5$
XX, $R^1 = H$, $R^2 = CH_2OCH_2C_6H_5$
XXI, $R^1 = H$, $R^2 = CH_2OH$

Decomposition of the azide *XIVa* in boiling ethanol afforded a mixture of 3-benzyloxymethyl-4-ethoxycarbonylaminopyrazole-5-carboxamide (*XVIII*) and compound *V* in the ratio 3 : 1. The urethane *XVIII* is cyclized by the action of 0·1M-NaOH to give compound *V* (an analogous cyclization has been reported by Lees and Shaw[23]). The ultraviolet spectrum of compound *V* is in accordance with those of related 1*H*-pyrazole[4,3-*d*]pyrimidine derivatives reported by Robins[3,4] and strongly different from those of isomeric 5,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyrimidines[24]. These findings simultaneously confirm the structure of the amide *XIIa* as proposed above. Hydrogenolysis of the benzyl group in compound *V* led to a reasonable yield of compound *IV*. Decomposition of the azide *XIVa* in benzyl alcohol at 100°C leads exclusively to 3-benzyloxymethyl-4-benzyloxycarbonylaminopyrazole-5-carboxamide (*XIX*). The urethane *XIX* was selectively converted into 3-benzyloxymethyl-4-aminopyrazole-5-carboxamide (*XX*) by hydrogenation over palladized charcoal in the ethanol–acetic acid solvent mixture. Both the benzyl groups of compound *XIX* are removed by hydrogenolysis in acetic acid over a palladium on barium sulfate catalyst, 3-hydroxymethyl-4-amino-5-carboxamide (*XXI*) being formed. The amino derivative *XXI* was characterised by ultraviolet spectrum only and then cyclized directly by reaction with formamide[3] at 170°C to the 1*H*-pyrazolo[4,3-*d*]pyrimidine derivative *III*.

The synthesis of compound *VI* was started from N-tetrahydrofurfurylurea (*VIIb*). The above mentioned reaction sequence led then to the analogous compounds *VIIIb*–*XIVb*. The ester *IXb* was also characterised in the form of the 1*H*-pyrazolo-[3,4-*d*]pyridazine derivative *XVII*. Decomposition of the azide *XIVb* in boiling ethanol afforded compound *VI* as the single product. The steric effect of the tetrahydrofuryl group probably prevents the addition of ethanol to the N=C bond of the primarily formed isocyanate and favours the competitive intramolecular cyclisation. The reported synthesis of 1*H*-pyrazolo[4,3-*d*]pyrimidine derivatives using mild reaction conditions in all steps opens to our opinion a promising route to the total synthesis of formycins and their analogues.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are uncorrected. Analytical samples were dried at 25-C/0·05 Torr. UV spectra were recorded on an Optica Milano Model CF-4 apparatus. IR spectra were measured on a Zeiss Model UR-10 apparatus. The 2-tetrahydrofuryl derivatives are racemates.

2-Benzyloxyethylamine

With the use of the procedure of Lappas and Jenkins[18], 61 g of ethanolamine afforded 27 g of the crude 2-benzyloxyethylamine, b.p. 65—70°C/0·7 Torr, and 27 g of a fraction, b.p. 130—135°C / : 0·2 Torr. The lower-boiling product (2·0 g) was dissolved in concentrated hydrochloric acid (5 ml). On cooling down, the solution deposited a solid (1·8 g) which was recrystallised from n-butyl alcohol to yield the hydrochloride, m.p. 143—145°C. For $C_9H_{14}ClNO$ (187·7) calculated: 57·59% C, 7·5:0% H, 7·47% N, 18·90% Cl; found: 57·75% C, 7·44% H, 6·49% N, 18·74% Cl. The aqueous solution of the hydrochloride was made alkaline with 20% aqueous NaOH to liberate 2-benzyloxyethylamine as an oil, b.p. 70°C (bath temperature)/0·1 Torr, n_D^{25} 1·5196. For C_9H_{13}. . NO (151·2) calculated: 71·47% C, 8·75% H, 9·30% N; found: 71·49% C, 8·67% H, 9·26% N.

N-(2-Benzyloxyethyl)benzylamine

The higher-boiling fraction from the preceding experiment (2·0 g) was dissolved in concentrated hydrochloric acid (10 ml). On cooling down, the solution deposited 1·9 g of the hydrochloride which was recrystallised from n-butyl alcohol. M.p. 152—153°C (n-butyl alcohol). For $C_{16}H_{20}$. ClNO (277·8) calculated: 69·18% C, 7·26% H, 5·04% N, 12·79% Cl; found: 69·37% C, 7·19% H, 4·71% N, 12·76% Cl. The aqueous solution of the hydrochloride was made alkaline with 20% aqueous NaOH to liberate the base. The analytical sample was obtained by distillation at 150 to 155°C (bath temperature)/0·1 Tor; n_D^{25} 1·5569. For $C_{16}H_{19}NO$ (241·3) calculated: 79·63% C, 7·94% H, 5·80% N; found: 79·66% C, 8·10% H, 5·60% N. The free base (100 mg) was converted into N-benzyl-N-(2-benzyloxyethyl)acetamide by dissolving in 2 ml of a mixture of pyridine and acetic anhydride (3 : 1). After 12 hours, the mixture was treated with ethanol (5 ml), kept for additional 2 h, evaporated, and the residue coevaporated with two portions of toluene. The final residue was distilled at 150—155°C (bath temperature)/0·07 Torr to afford N-benzyl-N-(2-benzyloxyethyl)acetamide as a viscous oil. IR spectrum (in chloroform): 1636 cm^{-1} (CO amide). For $C_{18}H_{21}NO_2$ (283·4) calculated: 76·29% C, 7·47% H, 4·49% N; found: 76·17% C, 7·43% H, 5·08% N.

Tetrahydrofurfurylamine (ref.[25])

Freshly distilled furfural (24 g) was dissolved in 125 ml of 80% aqueous ethanol presaturated at 0°C with ammonia gas and the solution was hydrogenated in the presence of Raney nickel (1·2 g) at 120°C (initial pressure, 150 atm). After 2 hours, the temperature was raised to 160°C and the hydrogenation was continued for additional 4 h. After cooling down to room temperature, the catalyst was filtered off and washed with ethanol (50 ml). The filtrates were combined and the ethanol was removed by distillation under ordinary pressure with the use of a short column (5 TP). The residue was distilled at 80—90°C (bath temperature)/12 Torr. The fraction boiling at 40—50°C/12 Torr was rectified on a column with a rotating metal spiral (20 TP). Yield, 15 g (60%); b.p. 88°C/80 Torr; n_D^{25} 1·4527.

N-(2-Hydroxyethyl)urea

A solution of ethanolamine hydrochloride (72·5 g; 0·75 mol) in water (100 ml) was treated with a solution of potassium cyanate (61·5 g; 0·75 mol) in water (100 ml), the mixture was kept at room

temperature for 5 days, and evaporated at 45°C/15 Torr. The residual sirup was diluted with ethanol (250 ml) and the mixture was kept at 5°C for 12 h. The precipitate of potassium chloride was filtered off, the filtrate evaporated under diminished pressure, and the residue coevaporated twice with ethanol. The residual sirup was dissolved in hot ethanol (50 ml) and the solution allowed to stand overnight to deposit crystals which were collected with suction and washed with ethanol. Yield, 32·9 g (42·5%) of the title compound, m.p. 91—92° (reported[26], m.p. 95°C and[27] 94—95°C. The mother liquor was concentrated and the concentrate allowed to stand at 5°C for several days. Recrystallisation of the solid from ethanol afforded additional 9·8 g of the title compound, m.p. 91—92°C (overall yield, 55%).

N-(2-Benzyloxyethyl)urea (*VIIa*)

A. Benzyl chloride (127 g; 1 mol) was added dropwise to a suspension of sodium hydride (38·0 g; 1·6 mol) in dimethylformamide (480 ml) at the temperature below 30°C. The resulting mixture was then treated dropwise over 2 hours at 30—50°C with a solution of N-(2-hydroxyethyl)urea (104 g; 1 mol) in dimethylformamide (240 ml) and then stirred at room temperature for additional 12 h. The mixture was then poured into 4 l of water and extracted with six 400 ml portions of chloroform. The extract was dried over sodium sulfate and evaporated under diminished pressure at bath temperature of 30°C and then (to remove dimethylformamide) 80°C. The residue was triturated with ether, the solid collected with suction, and recrystallised from ethyl acetate. Yield, 110 g (57%) of compound *VIIa*, m.p. 78°C (ethyl acetate). For $C_{10}H_{14}N_2O_2$ (194·2) calculated: 61·83% C, 7·27% H, 14·42% N; found: 61·77% C, 7·42% H, 14·53% N. *B*. Nitrourea[28] (0·23 g; 2·2 mmol) was added portionwise over 5 min to a refluxing solution of 2-benzyloxyethylamine (0·30 g; 0·2 mmol) in methanol (10 ml). The mixture was then refluxed for additional 5 min and evaporated under diminished pressure. Crystallisation of the residue from ethyl acetate afforded 0·36 g (93%) of compound *VIIa*, m.p. 78°C, undepressed on admixture with a specimen obtained by procedure *A*.

N-Tetrahydrofurfurylurea (*VIIb*)

Nitrourea[28] (11·5 g; 0·11 mol) was added portionwise to a solution of tetrahydrofurfurylamine (10·1 g; 0·1 mol) in methanol (50 ml) at such a rate to keep the mixture boiling (over about 20 min). The mixture was then refluxed for additional 5 min and evaporated under diminished pressure. The sirupous residue was diluted with ethyl acetate and the mixture kept for several hours to deposit a solid which was recrystallised from ethyl acetate. Yield, 13·4 g (93%) of compound *VIIb*, m.p. 92—93°C (ethyl acetate). For $C_6H_{12}N_2O_2$ (144·2) calculated: 49·98% C, 8·39% H, 19·43% N; found: 50·09% C, 8·50% H, 19·11% N.

N-Nitroso-N-(2-benzyloxyethyl)urea (*VIIIa*)

A solution of nitrogen dioxide (26·0 g; 0·28 mol) in ether (100 ml) was added dropwise over 1 h at −15°C to −20°C under stirring to a solution of compound *VIIa* (38·8 g; 0·2 mol) in ether (400 ml). The temperature was then allowed to raise to 0°C and the mixture was treated at this temperature under vigorous stirring with a suspension of sodium hydrogen carbonate (30 g) in water (50 ml). The vigorous stirring at 0°C was continued for additional 2 h. The ethereal layer was separated and the aqueous layer was extracted with two 100 ml portions of ether. The ethereal solutions were combined, dried over sodium sulfate, and concentrated under diminished pressure at 25°C to about 100 ml. The concentrate was diluted with cyclohexane (20 ml) to depos-

it 32·7 g (70%) of compound *VIIIa*, m.p. 42°C (ether–cyclohexane). UV spectrum (in ethanol): λ_{max} 211 and 235 nm (log ε 4·00 and 3·74, resp.). IR spectrum (in chloroform): 1 742 cm^{-1} (C=O); 1 573 cm^{-1} (NH_2); 1 505 cm^{-1} (N=O). For $C_{10}H_{13}N_3O_3$ (233·3) calculated: 53·80% C, 5·87% H, 18·83% N; found: 53·91% C, 5·96% H, 18·89% N.

N-Nitroso-N-tetrahydrofurfurylurea (*VIIIb*)

N-Tetrahydrofurfurylurea (35·5 g; 0·25 mol) and nitrogen dioxide (27·6 g; 0·3 mol) were processed analogously to the preparation of compound *VIIIa*. Yield, 25·8 g (59%) compound *VIIIb*, m.p. 54°C (cyclohexane). Analytical sample, m.p. 54°C (diisopropyl ether). UV spectrum (in ethanol): λ_{max} 237 nm (log ε 3·60). IR spectrum (in chloroform): 1 740 cm^{-1} (C=O); 1 572 cm^{-1} (NH_2); 1 505 cm^{-1} (N=O). For $C_6H_{11}N_3O_3$ (173·1) calculated: 41·61% C, 6·40% H, 24·27% N; found: 41·85% C, 6·42% H, 24·09% N.

Dimethyl 3-Benzyloxymethylpyrazole-4,5-dicarboxylate (*IXa*)

Under stirring and external cooling with ice, compound *VIIIa* (11·6 g; 0·05 mol) was added portionwise over 5 min to a mixture of 20% aqueous potassium hydroxide (75 ml) and ether (100 ml). The stirring was then continued at 0°C for additional 30 min. The yellow ethereal solution of 2-benzyloxydiazoethane was separated from the aqueous layer and dried 20 min at 0°C over KOH. The dry ethereal solution was filtered and the filtrate treated dropwise under stirring and external ice-cooling with 10% ethereal dimethyl acetylenedicarboxylate[29] (uptake, 6·8 g *i.e* 0·048 mol) until the yellow color of the diazo compound solution disappeared. The ether was evaporated and the residual sirup (13·0 g) chromatographed on a column of silica gel in the solvent system benzene–ethyl acetate (3 : 1). Yield, 8·4 g (55%) of compound *IXa*, chromatographically homogeneous. UV spectrum (in ethanol): λ_{max} 214 nm (log ε 4·50). For $C_{15}H_{16}N_2O_5$ (304·3) calculated: 59·20% C, 5·30% H, 9·21% N; found: 59·52% C, 5·49% H, 9·00% N.

3-Benzyloxymethylpyrazole-4,5-dicarboxylic Acid (*Xa*)

A mixture of the ester *IXa* (1·0 g) and 10 ml of 4M-KOH in 50% aqueous ethanol was refluxed for 2 h, allowed to cool, and applied to a column of Dowex 50 (H^+) ion exchange resin. The column was washed with water, the effluent evaporated under diminished pressure, and the residue recrystallised from water. Yield, 0·71 g of compound *Xa*, m.p. 205°C (water). UV spectrum, (in water): λ_{max} 211 nm (log ε 4·03). For $C_{13}H_{12}N_2O_5$ (276·2) calculated: 56·32% C, 4·38% H, 10·14% N; found: 56·49% C, 4·46% H, 10·37% N.

3-Benzyloxymethyl-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*XV*)

A solution of the ester *IXa* (3·04 g; 0·01 mol) in ethanol (10 ml) was treated with 80% hydrazine hydrate (1·0 ml) and the whole mixture refluxed for 2 h, the sparingly soluble dihydrazide *XIa* being deposited during the heating. The mixture was cooled down, the precipitate collected with suction, and washed with water and ethanol. A suspension of the precipitate in 20 ml of water was treated dropwise under stirring at 80°C with 1M-HCl until the dihydrazide *XIa* dissolved (pH ~ 3). The heating at 80°C was continued for 1 hour and the mixture was then cooled down to deposit a solid which was collected with suction and recrystallised from methanol. Yield 1·66 g (61%) of compound *XV*, m.p. 258°C (methanol). UV spectrum (in 0·1M-NaOH): λ_{max} 277 nm (log ε 3·78). IR spectrum (in nujol): 1 658 cm^{-1} (C=O). For $C_{13}H_{12}N_4O_3$ (272·3) calculated: 57·35% C, 4·44% H, 20·58% N; found: 57·66% C, 4·57% H, 20·42% N.

3-Hydroxymethyl-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*XVI*)

Compound *XV* (0·27 g; 1 mmol) was hydrogenated under atmospheric pressure at room temperature in glacial acetic acid (5 ml) over a 5% palladium on barium sulfate catalyst. The catalyst was filtered off, the filtrate evaporated, and the residue crystallised from water. Yield, 0·14 g (80%) of compound *XVI* which decomposes at 300°C without melting. UV spectrum, in 0·1M-NaOH: λ_{max} 226 and 274 nm ($\log \varepsilon$ 4·16 and 3·81, resp.); in 0·1M-HCl in 50% aqueous ethanol: λ_{max} 264 nm ($\log \varepsilon$ 3·76). IR spectrum (in nujol): 1648 cm^{-1} (C=O). For $C_6H_6N_4O_3$ (181·1) calculated: 39·56% C, 3·32% H, 30·76% N; found: 39·38% C, 3·48% 30·48% N.

Dimethyl 3-(2-Tetrahydrofuryl)pyrazole-4,5-dicarboxylate (*IXb*)

The N-nitroso derivative *VIIIb* (17·3 g; 0·01 mol) was processed analogously to the preparation of compound *IXa*. Yield, 22·5 g (89%) of the sirupous compound *IXb* homogeneous on thin-layer chromatography (silica gel) in the solvent system benzene-ethyl acetate (1:1). The analytical sample was obtained by distillation of the crude product at 120—130°C (bath temperature) / / 0·07 Torr. UV spectrum (in ethanol): λ_{max} 215 nm ($\log \varepsilon$ 4·05). For $C_{11}H_{14}N_2O_5$ (254·2) calculated: 51·96% C, 5·55% H, 11·02% N; found: 52·10% C, 5·62% H, 11·17% N.

3-(2-Tetrahydrofuryl)pyrazole-4,5-dicarboxylic Acid (*Xb*)

The ester *IXb* (1 g) was processed analogously to the alkaline hydrolysis of the ester *IXa*. Yield, 0·60 g (68%) of the acid *Xb*, m.p. 217°C (water). UV spectrum (in ethanol): λ_{max} 210 nm ($\log \varepsilon$ 3·78). For $C_9H_{10}N_2O_5$ (226·2) calculated: 47·79% C, 4·46% H, 12·39% N; found: 47·57% C, 4·47% H, 12·64% N.

Dihydrazide of 3-(2-Tetrahydrofuryl)pyrazole-4,5-dicarboxylic Acid (*XIb*)

The ester *IXb* was processed analogously to preparation of the dihydrazide *XIa*. Yield, 57% of the dihydrazide *XIb*, m.p. 199—200°C (ethanol). For $C_9H_{14}N_6O_3$ (254·3) calculated: 42·51% C, 5·55% H, 33·06% N; found: 42·27% C, 5·70% H, 33·29% N.

3-(2-Tetrahydrofuryl)-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*XVII*)

The dihydrazide *XIb* was processed analogously to the preparation of compound *XV*. Yield, 75% of compound *XVII*, m.p. 243—250°C (decomp.) (water). Ultraviolet spectrum, in 0·1M-NaOH: λ_{max} 275 nm ($\log \varepsilon$ 3·83); in 0·1M-HCl: λ_{max} 263 nm ($\log \varepsilon$ 3·73). IR spectrum (in nujol): 1659 cm^{-1}. (C=O). For $C_9H_{10}N_4O_3$ (222·2) calculated: 48·65% C, 4·54% H, 25·22% N; found: 48·59% C, 4·84% H, 24·93% N.

Methyl 3-Benzyloxymethyl-5-carbamoylpyrazole-4-carboxylate (*XIIa*)

The dimethyl ester *IXa* (15·2 g; 0·05 mol) was dissolved in 120 ml of ethanol previously saturated at 20°C with ammonia. The solution was kept at room temperature overnight, evaporated under diminished pressure, and the residue crystallised from ethanol. Yield, 8·7 g (60%) of compound *XIIa*, m.p. 152—153°C (ethanol). UV spectrum (in ethanol): λ_{max} 213 nm ($\log \varepsilon$ 4·16). For $C_{14}H_{15}N_3O_4$ (289·3) calculated: 58·12% C, 5·23% H, 14·53% N; found: 58·23% C, 5·37% H, 14·47% N.

Methyl 3-(2-Tetrahydrofuryl)-5-carbamoylpyrazole-4-carboxylate (*XIIb*)

The dimethylester *IXb* (25·4 g; 0·1 mol) and ethanol (120 ml) saturated at 20°C with ammonia were processed analogously to the preparation of compound *XIIa*. Yield, 14·4 g (60%) of compound *XIIb*, m.p. 171—172°C (ethanol). UV spectrum (in ethanol): λ_{max} 209 nm (log ε 4·02). For $C_{10}H_{13}N_3O_4$ (239·2) calculated: 50·20% C, 4·48% H, 17·57% N; found: 50·40% C, 4·77% H, 17·35% N.

Hydrazide of 3-Benzyloxymethyl-5-carbamoylpyrazole-4-carboxylic Acid (*XIIIa*)

A suspension of the amide *XIIa* (14·5 g; 0·05 mol), 80% hydrazine hydrate (15 ml), and ethanol (30 ml) was shaken at room temperature for 12 h and then kept at 0°C for 5 h. The precipitate was collected with suction, washed with ethanol and crystallised from ethanol. Yield, 13·0 g (90%) of compound *XIIIa*, m.p. 162—164°C (ethanol). UV spectrum (in ethanol): λ_{max} 210 nm (log ε 4·10). For $C_{13}H_{15}N_5O_3$ (289·3) calculated: 53·97% C, 5·23% H, 24·21% N; found: 54·23% C, 5·43% H, 24·41% N.

Hydrazide of 3-(2-Tetrahydrofuryl)-5-carbamoylpyrazole-4-carboxylic Acid (*XIIIb*)

A suspension of the amide *XIIb* (4·80 g; 0·02 mol), 80% hydrazine hydrate (5 ml), and ethanol (10 ml) was shaken at room temperature for 2 h and then allowed to stand for 10 hours. The precipitate was collected with suction and crystallised from ethanol. Yield, 3·9 g (81%) of compound *XIIIb*, m.p. 192—194°C (ethanol). UV spectrum (in ethanol): λ_{max} 210 nm (log ε 4·10). For $C_9H_{13}N_5O_3$ (239·2) calculated: 45·18% C, 5·48% H, 29·28% N; found: 45·33% V, 5·58% H, 29·05% N.

Azide of 3-Benzyloxymethyl-5-carbamoylpyrazole-4-carboxylic Acid (*XIVa*)

A solution of sodium nitrite (1·38 g; 0·02 mol) in water (10 ml) was added dropwise over 5 min at 15°C under vigorous stirring to a solution containing the hydrazide *XIIIa* (5·80 g; 0·02 mol), dimethylformamide (100 ml), and 2M-HCl (100 ml). The resulting mixture was then stirred at 15°C for additional 30 min, the precipitate of the azide *XIVa* collected with suction, washed with water until neutral, and dried at 25°C in an evacuated desiccator over KOH overnight. The azide *XIVa* decomposes at about 130°C. IR spectrum (in nujol): 2 140 cm^{-1}, 2185 cm^{-1}, 1 298 cm^{-1} (N_3); 1 675 cm^{-1} (CO amide); 1 659 cm^{-1} (CO azide). For $C_{13}H_{12}N_6O_3$ (300·3) calculated: 27·99% N; found: 28·17% N.

3-Benzyloxymethyl-4-ethoxycarbonylaminopyrazole-5-carboxamide (*XVIII*) and 3-Benzyloxymethyl-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*V*)

The azide *XIVa* (dried overnight over potassium hydroxide; 3·0 g; 0·01 mol) was refluxed in ethanol (30 ml) for 6 h and the mixture cooled down. The urethane *XVIII* was collected with suction and crystallised from ethanol. Yield 2·0 g (63%) of compound *XVIII*, m.p. 218°C (ethanol). UV spectrum (in ethanol): λ_{max} 210 nm and 251 nm (log ε 4·36 and 3·53, resp.). IR spectrum (in nujol): 1 708 cm^{-1} and 1 652 cm^{-1} (C=O). For $C_{15}H_{18}N_4O_4$ (318·3) calculated: 56·59% C, 5·70% H, 17·60% N; found: 56·69% C, 5·81% H, 17·47% N. The mother liquor remaining after isolation of the urethane *XVIII* was evaporated under diminished pressure and the residual sirup chromatographed on a column of silica gel in the solvent system ethyl acetate–methanol (1 : 1). The ultraviolet-absorbing fraction was evaporated to afford 0·60 g (22%) of compound *V*, m.p. 222°C (methanol). UV spectrum, in 0·1M-HCl: λ_{max} 208 and 284 nm (log ε 4·36 and 3·83, resp.);

in 0·05M-NaOH: λ_{max} 222 and 302 nm (log ε 4·39 and 3·65, resp.). For $C_{13}H_{12}N_4O_3$ (272·3) calculated: 57·35% C, 4·44% H, 20·58% N; found: 57·56% C, 4·54% H, 20·50% N.

Cyclisation of the urethane XVIII. A suspension of compound *XVIII* (0·32 g; 0·01 mol) in 0·1M-NaOH (5·0 ml) was stirred at room temperature for 48 h and then at 70°C for 5 min. The resulting solution was allowed to cool and precipitated with concentrated hydrochloric acid (2 ml). The precipitate was collected with suction, washed with water, and crystallised from ethanol to afford 2·1 g (77%) of compound *V*, m.p. 222°C, undepressed on admixture with the specimen obtained in the preceding paragraph. The UV and IR spectra were also identical.

3-Benzyloxymethyl-4-benzyloxycarbonylaminopyrazole-5-carboxamide (*XIX*)

A mixture of the azide *XIVa* (3·0 g; 0·01 mol) and benzyl alcohol (30 ml) was heated at 100°C for 3 h. The azide passed into solution under evolution of nitrogen. The mixture was kept at 0°C overnight, the precipitate collected with suction, washed with ethanol, and air-dried. Yield, 2·7 g (72%) of compound *XIX*, m.p. 182—183°C (benzyl alcohol). UV spectrum (in ethanol): λ_{max} 210 and 253 nm (log ε 4·37 and 3·49). IR spectrum (in nujol): 1706 cm^{-1} and 1655 cm^{-1} (C=O). For $C_{20}H_{20}N_4O_4$ (380·4) calculated: 63·15% C, 5·30% H, 14·73% N; found: 63·24% C, 5·35% H, 15·02% N.

3-Benzyloxymethyl-4-aminopyrazole-5-carboxamide (*XX*)

A gentle stream of hydrogen was introduced through a sintered glass inlet tube into a suspension of the urethane *XIX* (0·50 g), ethanol (50 ml), acetic acid (50 ml), and 5% palladium on active charcoal catalyst (0·20 g) over the period of 3 hours until the evolution of carbon dioxide ceased. The catalyst was then filtered off, the filtrate evaporated under diminished pressure, and the residue dissolved in water (5 ml). The aqueous solution was applied to a 1 × 15 cm column of Dowex 50 (H^+) ion exchange resin. The column was washed with water (150 ml) and then 5% aqueous ammonia. The ultraviolet-absorbing ammonia solution (50 ml) was evaporated under diminished pressure and the residue recrystallised from water to afford 0·17 g (52%) of compound *XX*, m.p. 158—160°C (water). UV spectrum, in 0·1M-NaOH: λ_{max} 249 and 284 nm (log ε 3·75 and 3·48); in 0·1M-HCl: a flat curve without maxima. For $C_{12}H_{14}N_4O_2$ (246·3) calculated: 58·52% C, 5·73% H, 22·75% N; found: 58·62% C, 5·77% H, 22·56% N.

3-Hydroxymethyl-4-aminopyrazole-5-carboxamide (*XXI*)

A gentle stream of hydrogen was introduced through a sintered glass inlet tube into a mixture of the urethane *XIX* (3·8 g; 0·01 mol), acetic acid (20 ml), and 5% palladium oxide on barium sulfate catalyst (0·30 g). When the evolution of carbon dioxide ceased (after 3 h), the catalyst was filtered off through a layer of diatomaceous earth, the filtrate concentrated under diminished pressure to the volume of 10 ml, and the concentrate applied to a column of Dowex 50 (H^+) ion exchange resin. The column was washed first with water and then eluted with 5% aqueous ammonia. The ammonia eluate was evaporated to afford 0·86 g (55%) of the sirupous compound *XXI* which darkened on air. UV spectrum, in 0·1M-NaOH: λ_{max} 220 and 250 nm (log ε 3·94 and 3·85); in 0·1M-HCl: λ_{max} 210 nm (log ε 2·83). The product was used without isolation in the next step.

3-Hydroxymethyl-7-hydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*III*)

A mixture of the amine *XXI* (0·86 g) and formamide (8 ml) was heated at 170°C for 30 min, allowed to cool, and dissolved in water (30 ml). After a brief heating with active charcoal, the

mixture was filtered, and the filtrate applied to a column (1·5 × 20 cm) of Dowex 1 (acetate) ion exchange resin. The column was washed with water (500 ml) and then eluted with 5% aqueous acetic acid. Crystallisation from water afforded 0·41 g (45%) of compound *III*, m.p. 267—268°C (decomp.). UV spectrum, in 0·1M-HCl: λ_{max} 222 and 277 nm (log ε 3·72 and 3·44, resp.); in 0·05M-NaOH: λ_{max} 228 and 291 nm (log ε 3·70 and 3·43, resp.). For $C_6H_6N_4O_2$ (166·1) calculated: 43·37% C, 3·64% H, 33·73% N; found: 43·15% C, 3·92% H, 33·63% N.

3-Hydroxymethyl-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*IV*)

Compound *V* (0·27 g; 0·01 mol) was hydrogenated in acetic acid (30 ml) for 6 h over 100 mg of a palladium catalyst (5% palladium oxide on barium sulfate). The catalyst was filtered off through a layer of diatomaceous earth, the filtrate evaporated under diminished pressure, and the residue crystallised from water. Yield, 0·16 g (88%) of compound *IV* (does not melt up to 300°C). UV spectrum, in 0·1M-HCl: λ_{max} 207 and 287 nm (log ε 4·29 and 3·72, resp.); in 0·05M-NaOH: λ_{max} 223 and 307 nm (log ε 4·35 and 3·66). For $C_6H_6N_4O_3$ (182·1) calculated: 39·56% C, 3·32% H, 30·76% N; found: 39·25% C, 3·38% H, 30·66% N.

3-(2-Tetrahydrofuryl)-5,7-dihydroxy-1*H*-pyrazolo[4,3-*d*]pyrimidine (*VI*)

A solution of sodium nitrite (0·7 g; 0·01 mol) in water (10 ml) was added over 5 min at 0°C to a solution of the hydrazide *XIIIb* (2·4 g; 0·01 mol) in 2M-HCl (50 ml) under stirring. The mixture was stirred at 0°C for additional 30 min and then extracted with eight 10 ml portions of ethyl acetate. The extracts were combined, dried over sodium sulfate, and evaporated under diminished pressure (bath temperature 25°C). The residue was dissolved in hot ethanol (25 ml) and the solution refluxed for 6 h. The ethanol was evaporated, the residue triturated with 90% aqueous ethanol (5 ml), the mixture allowed to stand for 12 h, the solid (2·0 g) collected with suction, dissolved in 10% aqueous NaOH (14 ml), and the solution precipitated with 10% aqueous HCl to afford 1·3 g (59%) of compound *VI*. The analytical sample (m.p. 270—271°C from water) was obtained by chromatography on Dowex 1 (acetate) ion exchange resin and elution with 2% aqueous formic acid. UV spectrum, in 0·1M-HCl: λ_{max} 208 and 288 nm (log ε 4·36 and 3·82); in 0·05M-NaOH: λ_{max} 222 nm and 302 nm (log ε 4·46 and 3·65). For $C_9H_{10}N_4O_3$ (222·2) calculated: 48·65% C, 4·54% H, 25·22% N; found: 48·48% C, 4·55% H, 25·46% N.

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