SYNTHESIS OF A [3,4-*f*]-LINKED PYRAZOLOQUINAZOLINONE[1]

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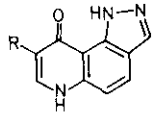
A convenient synthesis is described for pyrazolo[3,4-*f*]quinazolin-9-one (4), an internally expanded benzolog of the biologically relevant pyrazolo[4,3-*d*]pyrimidines (2).

Of Kametani's many outstanding contributions to heterocyclic chemistry, parts 718[2] and 756[3] of his "Studies on the Syntheses of Heterocyclic Compounds" dealt with pyrazolo[3,4-*f*]quinolinones (1), which are of potential antibacterial activity. Similarly, antibacterial and, in particular, cytostatic properties may be expected for 8-aza-analogues of 1, i.e. for pyrazolo[3,4-*f*]quinazolinone 4, as well as for its [3,4-*g*]- (5) and [3,4-*h*]-linked isomers (6), since they are angular and linear expanded benzologs of pyrazolo[4,3-*d*]pyrimidinone 2, the nucleobase of formycin B (3), and benzologously modified purines and pyrazolopyrimidines have been of particular biological relevance[1,4].



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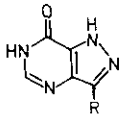

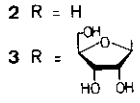

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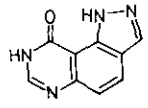

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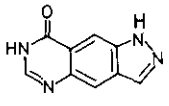
[3,4-f]



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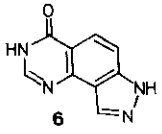

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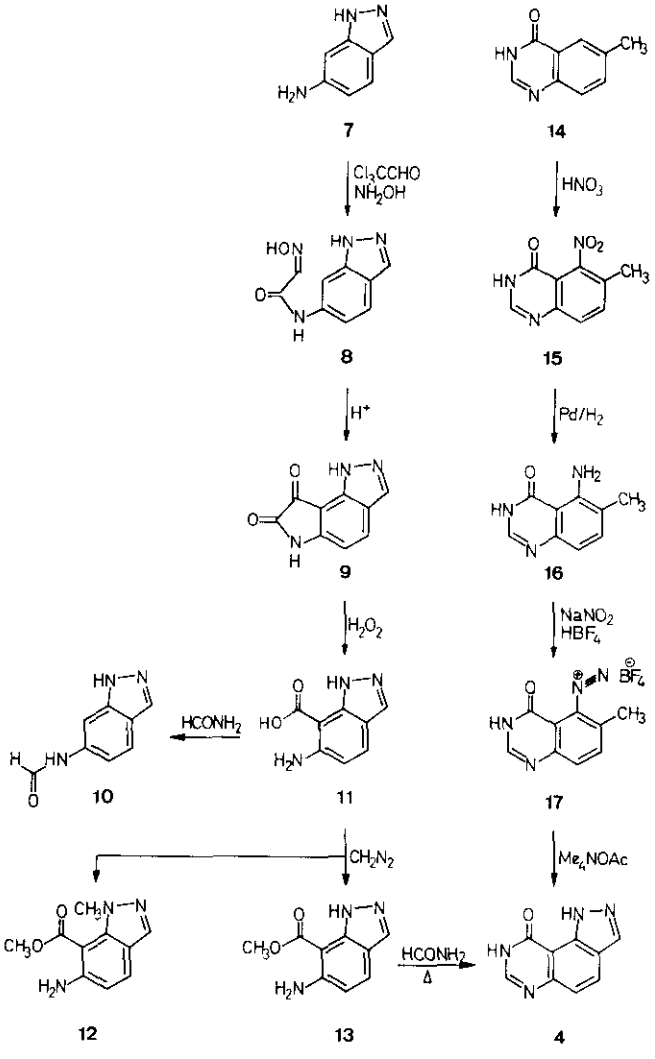
[3,4-h]

In a study directed toward the development of efficient syntheses for these novel heterocycles as well as ribosides thereof[5], we firstly report on an access to 4 by two independent, preparatively comparable routes[6].

Like Kametani's approach to 1[2], the one route to 4 started from readily accessible[7] 6-aminoindazol (7), into which a carboxylic acid function was introduced at C-7 by a procedure previously used by Sandmeyer[8] for the synthesis of isatin , i.e. reaction of 7 with chloral hydrate/hydroxylamine to the N-hydroximinoacetyl derivative 8 and subsequent sulfuric acid-induced cyclization to the

pyrazolo-isatin 9, feasible in 67 % overall yield. Ensuing oxidative ring cleavage afforded the 6-aminoindazol-7-carboxylic acid 11, which in the free form could not be converted into 4 due to extensive decarboxylation on heating with formamide; the N-formyl compound 10 was obtained instead. The corresponding methyl ester 13, however, obtained on treatment of 11 with diazomethane in 64 % yield aside small quantities (6 %) of a higher methylated compound (presumably 12), was readily converted into 4 (74 %) by heating with formamide. Thus, the five-step conversion 7 → 4 is effected in an overall yield of 32 %.



The alternate route to 4 comprised the attachment of a pyrazol ring onto readily available[9] 6-methylquinazolinone 14, which was initiated by a highly regioselective nitration to 15 (67 %). Subsequent reduction gave the 5-amino derivative 16 (82 %) that could be diazotized in the

presence of HBF_4 to the diazonium fluoborate 17 (quant.). Consecutively, 17 was subjected to tetramethylammonium acetate in chloroform which elaborated 4 via an expectedly smooth[10] intramolecular azo coupling. Accordingly, the conversion 14 → 4 can be accomplished in an overall yield of 27 % for the four steps.

Structures of the products were ascertained by analytical, ^{1}H-NMR and MS data (cf. experimental part), their discussion being negligible due to lack of any peculiarity. 4 exhibits a characteristically structured UV spectrum with an intense maximum at 252 nm and a less intense p-band from 300-330 nm; interestingly, no decisive spectral shifts are observed when going from the neutral species (i.e. 4 at pH 7.7) to a deprotonated form (pH 12.6), which may indicate that removal of the amide proton (H-8) has little influence on the electron distribution obviously due to strong hydrogen bonding between H-1 and the C-9 carbonyl oxygen.

Evaluation of the biological properties of 4 has so far been limited to determination of its inhibitor capacity for xanthine oxidase, which proved to be about 30 fold lower than that observed for allopurinol[11]. Assessment of antibacterial and antitumor properties are presently being underway.

EXPERIMENTAL

Melting points are determined on a Bock Monoskop and are uncorrected. Spectral measurements were effected with Varian XL 100 (NMR), Varian MAT 311 A (MS) and Perkin-Elmer 550 instruments (UV). TLC on Kieselgel F_{254} plastic sheets (Merck, Darmstadt) was used to monitor the reactions and to ascertain the purity of the products. Developers employed: A, ethyl acetate/water/n-propanol 4:2:1 (upper phase); B, chloroform/methanol 10:1 and 2:1. The spots were visualized by UV light or by spraying with 80 % aqueous sulfuric acid and charring at 110°C for 5 min. Column chromatography was carried out on Kieselgel 60 (70-230 mesh, Merck).

*6-(Hydroximinoacetyl-)amino-*1H-*indazole Hydrochloride* (8·HCl): To an aqueous solution of 6-amino-1H-indazole (7)[7] (13.3 g, 0.1 mol, in 60 ml) was added conc. HCl (10 ml), a solution of chloral hydrate (16.5 g, 0.1 mol) in water (250 ml), sodium sulfate hydrate (260 g) and an aqueous solution of hydroxylamine hydrochloride (22.0 g, 0.3 mol, in 100 ml). The mixture was refluxed for 1-2 min and the precipitate formed on cooling was collected, washed with water and dried (P_2O_5): 16.1 g (79 %) of 8, m.p. 199-201°C. — *Anal.* Calc. for $C_9H_8N_4O_2$·HCl: C 44.92, H 3.77, N 23.28; Found C 44.72, H 3.69, N 22.99. — *^{1}H-NMR* (D_6-DMSO/D_2O): 7.30 and 7.73 (two 1H-d, J = 9 Hz, H-4 and H-5), 7.78 and 8.07 (two 1H-s, H-3 and H-7). — *MS* (70 eV): m/e = 204 (18 %, M^+), 187 (24 %, M-OH), 159 (100 %, M - H_2O and HCN).

1H-Pyrazolo[3,4-e]isatin (9): A stirred mixture of 8 (37.3 g, 0.18 mol) and conc. sulfuric acid (65 ml) was gradually heated to 80°C, and after solution had taken place was kept at 80°C for 10 min. The cooled mixture was poured onto ice (350 g) and the precipitate formed was collected, followed by purification through dissolution in 10N NaOH (200 ml) and reprecipitation by addition of 2 N HCl to pH 5: 31.5 g (85 %) of 9 as a monohydrate; recrystallization from water followed by drying in vacuo (P_2O_5) at 80-90°C gave wine-red stocky crystals of m.p. > 300°C. — *Anal.* Calc. for $C_9H_5N_3O_2$: C 57.76, H 2.69, N 22.45; Found: C 57.74, H 2.67, N 22.38. — ^{1}*H-NMR* (D_6-DMSO/D_2O): δ = 6.77 and 8.13 (two 1H-d, J = 8.5 Hz, H-4 and H-5), 8.11 (1H-s, H-3), 11.07 (1H-s, NH, not exchangeable by the little D_2O added). — *MS* (70 eV): m/e = 187 (65 %, M^+).

6-Amino-1H-indazole-7-carboxylic acid methyl ester (13): To a solution of 9 (9.4 g, 50 mmol) in 10 % aqueous NaOH (100 ml) was added 10 % aqueous hydrogen peroxide (17 ml, 50 mmol) and the mixture was kept at 100°C for 10 min, whereafter CO_2 formation ceased. After cooling conc. HCl was added until pH 5 was reached and the acid 11, which had precipitated, was collected and washed with cold water: 7.8 g (87 %) of crude 11 as a brown powder of m.p. 177°C (dec) (M^+-peak at m/e = 177, as required), suited for ensuing experiments. — To an ice-cooled, stirred solution of crude 11 (5.3 g, 30 mmol) in 300 ml water/methanol (9:1) was added an ethereal solution of diazomethane and the mixture was kept at ambient temperature for 30 min. Subsequent evaporation to dryness, dissolution of the residue in chloroform (350 ml) and successive washing with 2 N NaOH and water afforded upon removal of the solvent an orange crystalline mixture of 12 and 13 in the approximate ratio of 1:4 (TLC in A). Trituration with ether (100 ml) left 2.8 g (49 %) of pure 13, further quantities being obtained on evaporation of the mother liquor and separation on a silica gel column with ethyl acetate/water/n-propanol (4:2:1); total yield: 4.23 g (74 %), m.p. 178-181°C. — *Anal.* Calc. for $C_9H_9N_3O_2$: C 56.54, H 4.75, N 21.98; Found: C 56.45, H 4.80, N 21.88. — ^{1}*H-NMR* (D_6-DMSO/D_2O): δ = 4.00 (3H-s, OCH_3), 7.36 and 7.69 (two 1H-d, $J_{4,5}$ = 9 Hz, H-4 and H-5), 7.94 (1H-s, H-3). — *MS* (FD): m/e = 191 (M^+, 100 %).

The minor fraction from the above column separation gave, upon evaporation to dryness, 400 mg (6 %) of an N-methyl derivative of 13, of m.p. 218-219°C, which is tentatively assigned structure 12. — *Anal.* Calc. for $C_{10}H_{11}N_3O_2$: C 58.53, H 5.40, N 20.48; Found: C 58.46, H 5.43, N 20.35. — ^{1}*H-NMR* (D_6-DMSO): δ = 3.84 and 4.05 (two 3H-s, O- and N-CH_3), 6.64 and 7.60 (two 1H-d, $J_{4,5}$ = 9 Hz, H-4 and H-5), 7.36 (2H-s, D_2O-exchangeable, NH_2), 8.12 (1H-s, H-3). — *MS* (FD): m/e = 205 (100 %, M^+).

6-Formylamino-1H-indazole (10): A mixture of crude 11 (1.7 g) and formamide (1 ml) was heated to 180°C for 2 h. After cooling the fused mass was triturated with water (10 ml) and filtered through a silica gel column (2 x 20 cm), which was subsequently washed with methanol (200 ml). Evaporation

of the filtrate in vacuo and recrystallization of the residue from water (40 ml) afforded 0.79 g (53 %), m.p. 205-207°C. — *Anal.* Calc. for $C_8H_7N_3O$: C 59.62, H 4.38, N 26.07; Found: C 59.59, H 4.28, N 26.01. — ^{1}*H-NMR* (D_6-DMSO): δ = 7.16 (1H-q, $J_{4,5}$ = 8 and $J_{4,7}$ = 2 Hz, H-4), 7.75 (8 Hz-d, 1H, H-5), 8.05 and 8.22 (two 1H-s, H-3 and CHO), 8.43 (2 Hz-d, 1H, H-7), 10.4 and 13.0 (two broad s, 2 NH). — *MS* (70 eV): m/e = 161 (100 %, M^+).

6-Methyl-5-nitroquinazolin-4(3H)-one (15): 6-Methylquinazolinone 14[9] (40.0 g, 0.3 mol) was gradually added to a stirred mixture of fuming nitric acid (80 ml) and conc. sulfuric acid (80 ml) that was kept at 18°C. Stirring was then continued at room temperature for 30 min, followed by heating on a boiling water bath (1 h). Cooling and stirring into crushed ice (1.2 kg) resulted in a precipitate which was collected, washed with water and recrystallized from acetic acid (900 ml): 35.0 g (67 %); m.p. 304-305°C. — *Anal.* Calc. for $C_9H_7N_3O_3$: C 52.68, H 3.44, N 20.48; Found: C 52.56, H 3.41, N 20.52. — *MS* (70 eV): m/e = 205 (100 %, M^+).

5-Amino-6-methylquinazolin-4(3H)-one (16): To a mixture of 15 (10.0 g), 10 % Pd/C (1.0 g) and ethanol (150 ml) was gradually added an aqueous hydrazine solution (83 %, 10 ml) in ethanol (10 ml) under inert conditions (N_2). Refluxing the mixture for 1 h followed by cooling to room temperature afforded crystals which were dissolved in dimethylformamide (150 ml) and the catalyst was removed by filtration. Solvent evaporation and subsequent recrystallization from ethanol furnished 7.0 g (82 %) of 16 as light yellow crystals of m.p. 260-261°C (dec). — *Anal.*Calc. for $C_9H_9N_3O$: C 61.70, H 5.18, N 23.99; Found: C 61.65, H 5.13, N 23.86. — ^{1}*H-NMR* (D_6-DMSO): δ = 2.13 (3H-s, CH_3), 6.70 and 7.36 (two 1H-d, $J_{7,8}$ = 8.5 Hz, H-7 and H-8), 7.00 (2H-m, NH_2), 7.88 (1H-s, H-2), 11.67 (1H-s, NH). — *MS* (70 eV): m/e = 175 (100 %, M^+).

6-Methylquinazolin-4-(3H)-on-5-diazonium tetrafluoborate (17): Aqueous fluoboric acid (35 %, 5.04 g, 20 mmol) was added to a suspension of 16 (1.75 g, 10 mmol) in ethyl acetate (40 ml), whereupon the yellow tetrafluoborate of 16 precipitated. It was dissolved on gradual addition of sodium nitrite (0.75 g, 10 mmol) at 5°C with stirring. The solution was further stirred for 1 h and the pale green crystals formed at the iodide/starch end point were collected and washed well with ethyl acetate: 2.75 g (100 %) of 17 with m.p. 157° (dec). Further purification of the product was effected by dissolution in acetone followed by addition of ether. A satisfactory elemental analysis could not be obtained due to thermal lability of the product. — *IR* (KBr): 2280 cm^{-1} (-N≡N, sharp). — *MS* (70 eV): m/e = 178 (48 %, M^+ of 5-fluoro-6-methylquinazolin-4-one, formed by a Schiemann reaction during measurement); *MS* (FD): m/e = 186 (100 %, M^+ of 5-diazo-6-methyl-4-oxoquinazolinyl$^+$).

1-Pyrazolo[3,4-f]quinazolin-9-(8H)-one (4):

a) *By cyclization of* 13 *with formamide*: A mixture of 13 (1.35 g, 7 mmol) and formamide (4.3 ml) was heated at 140°C for 4.5 h and again at 180°C for 1.5 h. The product formed on cooling was collected and washed with a little cold water: 555 mg of 4; from the mother liquor a further crop could be obtained, the cumulative yield being 965 mg (74 %); m.p. 325-327°C (dec). — *Anal.* Calc. for $C_9H_6N_4O$: C 58.06, H 3.25, N 30.10; Found: C 57.98, H 3.20, N 30.02. — *UV* (phosphate buffer, pH 7.7): λ_{max} (lgε) = 252 nm (4.31), 304 sh (3.79), 313 (3.89), and 326 (3.89); λ_{min} = 221 (3.72), 277 (3.50), and 321 (3.85). — *UV* (NaOH, pH 12.6): λ_{max} 253 (4.31), 260 (4.26), 284 (3.69), 302 sh (3.78), 312 (3.90), and 325 (3.89); λ_{min} = 228 (3.88), 258 (4.24), 277 (3.67), 291 (3.67), and 319 (3.83). — ^{1}*H-NMR* (D_6-DMSO): δ = 7.45 and 8.22 (two 1H-d, $J_{4,5}$ = 9 Hz, H-4 and H-5), 8.30 and 8.32 (two 1H-s, H-3 and H-7), 13.44 (broad 2H-signal, 1-H and 8-H). — *MS* (70 eV): m/e = 186 (100 %, M^+).

b) *By cyclization of diazonium salt* 17: To a solution of tetramethylammonium acetate (1.0 g) in chloroform (25 ml) was added 660 mg (2.5 mmol) of 17 and the mixture was stirred for 1 h at ambient temperature. Evaporation to dryness, trituration of the residue with ethanol and filtration gave 380 mg of crude 4, m.p. 325°C. Further purification by elution from a silica gel column with chloroform/methanol (20:1) gave 230 mg (49 %), m.p. 330°C.

Acknowledgement. We wish to express appreciation to Siegfried AG, Zofingen, for their support of this investigation.

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11. We are indebted to Dr. U. Jahn, Pharmacology Research Laboratory, Siegfried AG, Zofingen, Switzerland, for performing this experiment.

Received, 10th September, 1980