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BENZO-SEPARATED PYRAZOLOPYRIMIDINES: EXPEDITIOUS SYNTHESES OF [3,4-g]- and [3,4-h]-LINKED PYRAZOLOQUINAZOLINONES [1)]

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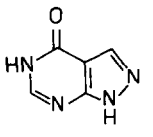
Syntheses for pyrazolo[3,4-*g*]quinazolin-8(7H)-one (8) and its [3,4-*h*]-analog 11 have been developed involving elaboration of aminoindazol-carboxylic acids 15 and 30 from correspondingly substituted methyl-nitroindazols, and subsequent anellation of the pyrimidine ring by v. Niementowski cyclization.

Linear insertion of an aromatic ring between the pyrazol and pyrimidine portions of allopurinol (1), i.e. 1→2, retains the capacity for xanthine oxidase inhibition, the pyrazoloquinazolinones 2 and 3 showing comparable[2-4)], the amino derivative 4[4)] an even higher inhibitory activity. About 30 fold less active proved to be the angled isomer 5[2,5,6)], probably due to hydrogen bonding between the favorably peri-positioned N^1-H and 9 carbonyl, which conceivably disturbs appropriate interactions with the enzymatic binding site.

Of higher biological significance than 5, which defacto is an angularly extended benzolog of the [4,3-d]-linked pyrazolopyrimidinone 6, should be the linear pyrazolo[3,4-g]quinazolinones 8, or ribosides thereof, in particular as 6 constitutes the aglycon of formycin B (7), a nucleoside antibiotic with antifungal, antiviral and cytostatic properties[7)]. We here describe facile and efficient syntheses for 8, its 6-oxo- (9) and 3-oxo-derivative (10), as well as for the [3,4-h]-linked pyrazoloquinazolinone 11[8)].



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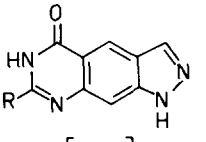
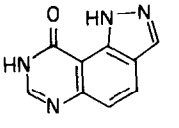


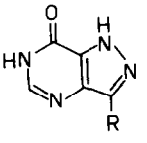
[4,3-g]

2 : R = H
3 : R = OH
4 : R = NH_2



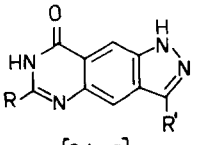
[3,4-f]

5



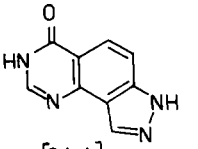
6 : R = H

7 : R = 



[3,4-g]

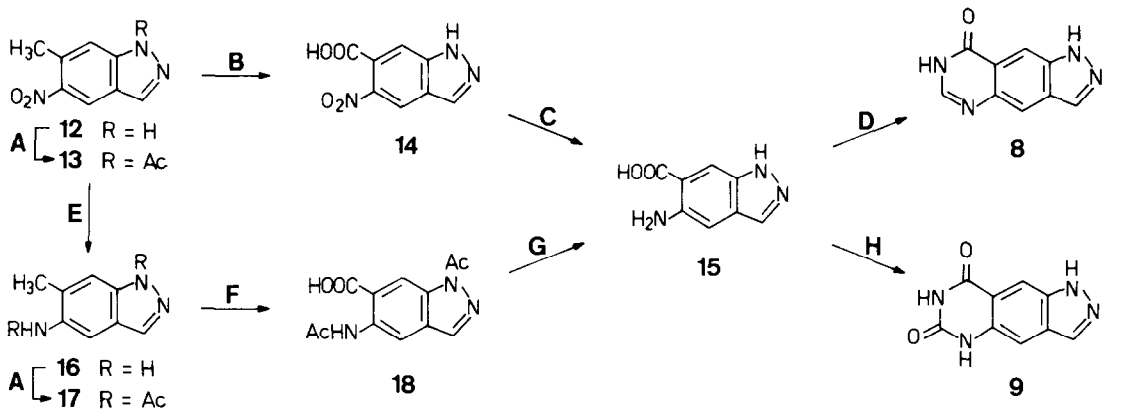
8 : R = R' = H
9 : R = OH; R' = H
10 : R = H ; R' = OH



[3,4-h]

11

Pursuant to the synthesis of 8 and 9, 6-methyl-5-nitroindazol (12)[9] was converted into the respective aminoindazolcarboxylic acid 15 (dec. ~ 280°C, after subl. to needles at 200°C, M^+ (70 eV) at m/e = 177, ^{1}H-NMR cf. ref. 10) by two routes involving 3-step or 4-step sequences. Of these, the shorter one via N-acetylation to 13 (needles of mp 202-204°C after subl. ~140°C, 95 % yield), CrO_3-oxidation to the nitroindazolcarboxylic acid 14 (stapelets, dec. ~190°C, 25 %) and subsequent reduction (31 %) proved to be less efficient due to the pronounced tendency of 14 for decarboxylation. This complication in the conversion 12→15 is avoided by reversing oxidation and reduction steps, resulting in an 38 % overall yield



Key

A : Ac_2O/HOAc, 70°C, 2 h.

B : CrO_3/conc. H_2SO_4, 0-5°C, 3 h.

C : H_2/10 % Pd, C in THF/CH_3OH.

D : formamidine acetate/NaOAc in 2-methoxyethanol, 70°C, 2 d.

E : $FeSO_4$/25 % aqueous NH_3 in ethanol/water, 80°C, 12 h.

F : $KMnO_4$ in tBuOH/H_2O/HOAc, $MgSO_4$, reflux 8 h.

G : aqueous NH_2NH_2 in EtOH, 50°C, 8 h.

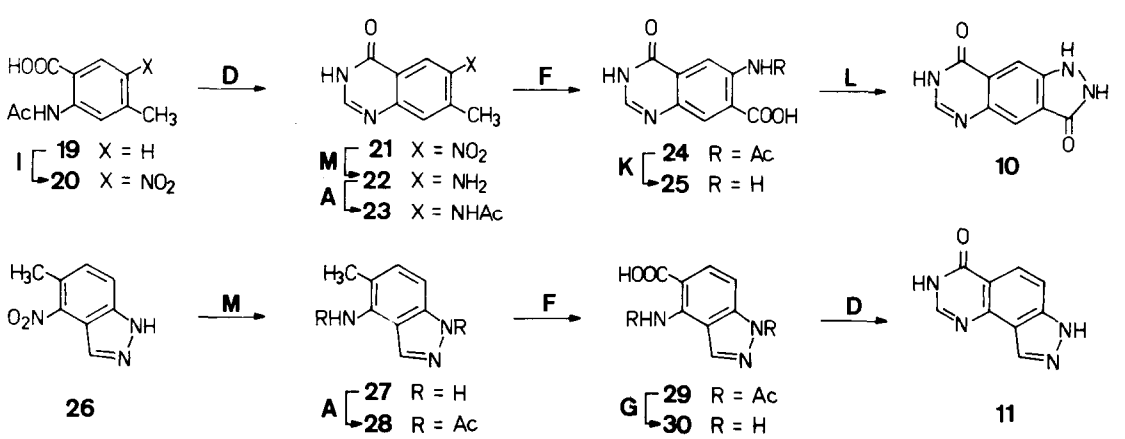
H : fusion with urea, 160°C, 15 min.

I : H_2SO_4/conc. HNO_3 (2:1), 25°C, 1 h.

K : 6 N HCl, 100°C, 1 h.

L : $NaNO_2$/HCl, 0°C, 30 min followed by saturation with SO_2.

M : 10 % Pd, C/hydrazine hydrate in EtOH, 80°C, 3 h.



via 16 (mp 210°C, dec., 75 %), 17 (needles from EtOH, mp 233-234°C after subl. ~170°C, 91 %), subsequent permanganate oxidation to 18 (needles, mp 252°C, 64 %) and deacetylation, which is readily effected by treatment with aqueous hydrazine (88 %).

In 15, the pyrimidine heterocycle is annelated by heating with formamide acetate in methoxyethanol[11] to yield 8 (mp >310°C[10], 91 %), or, alternately, by fusion with urea[12] to afford the pyrazolo-quinazolin-6,8-dione 9[10] (mp > 310°C, 76 %).

For the preparation of 1H-pyrazolo[3,4-g]quinazolin-3,8(2H,7H)-dione (10) a different approach was used, involving the somewhat lengthy yet nonetheless straightforward (35 % yield over 8 steps) elaboration of 6-aminoquinazolinone-7-carboxylic acid (25) from readily accessible[13] 4-methylanthranilic acid (19, H instead of Ac), and ensuing annelation of the pyrazolone portion 25 → 10 according to a procedure worked out for the conversion of anthranilic acid into indazolone[14]. The N-acetate 19 (mp 97°C), obtained by treatment of the parent aminocarboxylic acid with acetic anhydride/acetic acid (1 h, 70°C) in quantitative yield, is nitrated at the 5-position with high regioselectivity (→ 20, plates of mp 206°C after subl. ~ 190°C, 90 %). Subsequent deacetylation (6 N HCl, 80°C) gave the free 4-methyl-5-nitro-anthranilic acid (mp 191-192°C, after subl. into platelets ~ 160°C[15], 86 %) which was readily cyclized to nitroquinazolinone 21 (mp 287°C after subl. into plates ~200°C, 68 %). Ensuing reduction (→ 22, needles, mp >300°C, 90 %), N-acetylation (→ 23, mp > 310°C, 94 %), permangate oxidation (→ 24, mp >300°C, 78 %) and deacetylation gave the pyrimidinone-fused anthranilic acid 25 (mp >300°C after subl. into needles at ~ 220°C, quant.). The final conversion 25 → 10 (dec. ~220°C[10], 69 %) was then effected by a one-pot procedure[14] involving diazotization, sulfite reduction and cyclization of the acryl-hydrazine formed.

Construction of the pyrazolo[3,4-h]quinazolinone system 11 commenced from 5-methyl-4-nitroindazol 26[9] which in a sequence analogous to that used for 12 → 15 was converted into the 4-aminoindazolcarboxylic acid 30 (dec. ~ 185°C, ^{1}H-NMR: ref. 10) in a 33 % overall yield for the four steps 26 → 27 → 28 → 29 → 30[16]. Subsequent closure of the pyrimidine ring by gentle heating with formamidine acetate[11] afforded the desired 11 (mp >330°C after subl. into needles at 280°C, ^{1}H-NMR: ref. 10, 89 %).

The biological evaluation of these heterocycles with regard to their xanthine oxidase inhibitory activities and antiviral and cytostatic properties is underway. These points will be elaborated upon in the near future as well as on the preparation of aminopyrazoloquinazolines, e.g. the 8-amino analogue of 8, which represent benzo-separated analogs of the formycin A nucleobase.

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8. In the terms of the descriptive names proposed by Leonard[5], 8 would be a *lin*-benzo-isoallopurinol, 11 the respective *dist* isomer. We deliberately refrain from using these names, since isoallopurinol — unlike allopurinol for 1 — is not a customary designation for 6, and, in addition, this terminology becomes increasingly labyrinthic when using it for derivatives.
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10. All new compounds gave satisfactory elemental analyses and spectroscopic data in accord with the structures proposed. ^{1}H-NMR characteristics (100 MHz in D_6-DMSO, δ-values) of key and final products:

    8: 8.01 and 8.16 (two 0.7 Hz-d, 1H each, 3- and 4-H), 8.36 (0.7 Hz-dd, 1H, 9-H), 8.38 (s, 1H, 6-H), 12.0 and 13.6 (two broad s, 1H each, exchangeable with D_2O, 1- and 7-NH).

    9: 7.53, 8.18 and 8.23 (three S containing fine structure < 0.7 Hz, 3-, 4-, and 9-H), 11.0, 11.2 and 13.3 (3 broad s, 1H each, 1-, 5- and 7-NH).

    10: 7.78, 8.20 and 8.24, (3s, 1H each, 4-, 6- and 9-H), 8.06, 8.20 and 8.72 (3s, 1H each, exchangeable with D_2O, 1-, 2- and 7-NH).

    11: 7.67 and 8.05 (two 9 Hz-d, 1H each, 4- and 5-H), 8.30 and 8.50 (2s, 1H each, 1- and 8-H), 12.4 and 13.6 (2 broad s, 1H each, 3- and 7-NH).

    15: after D_2O-exchange of OH and NH: 6.99 (0.8 Hz-d, 1H, 4-H), 7.87 and 8.05 (1.0 Hz-d and 0.8/1.0 Hz-dd, 1H each, 3- and 7-H).

    30: after D_2O-exchange of OH and NH: 6.67 and 7.69 (9 Hz-d, 1H each, 6- and 7-H), 8.36 (s, 1H, 3-H).
11. In adaption of the procedure introduced by E.C. Taylor and W.A. Ehrhart, *J. Am. Chem. Soc.* 82, 3138 (1960).
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15. These characteristics are in contrast to those for an alleged monohydrate of 4-methyl-5-nitroanthranilic acid (needles, mp 235-236°C), obtained via pressure ammonolysis (180°C) of 2-bromo-5-nitrotoluic acid by M. Fileti and F. Crosa, *Gazz. Chim. Ital.* 18, 303 (1888).
16. Data for compounds 27: mp 191°C, subl. to rhombs ~130°C, 86 %, based on 26. — 28: mp 264°C, 72 %. — 29: mp 211°C, subl. to needles ~170°C, 63 %.

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