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BENZOLOGS OF ALLOPURINOL: SYNTHESIS OF PYRAZOLO [4,3-*g*] AND [3,4-*f*] QUINAZOLINONES[1)]

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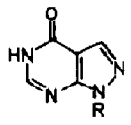
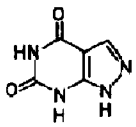
Convenient syntheses of pyrazolo [4,3-*g*] quinazolin-5(6*H*)-one (3), its xanthine oxidase metabolite 4 and the [3,4-*f*] analog 5 have been developed, involving anellation of the pyrimidine ring onto aminoindazolcarboxylic acids 9 and 18, or attachment of the pyrazol portion onto quinazolinone 22 via intramolecular azo coupling.

Allopurinol (1a), both a substrate for and, together with its chief metabolite oxipurinol (2), a potent inhibitor of xanthine oxidase, is the most widely used drug for the treatment of gout[2)]. This primary effect is augmented by secondary effects on pyrimidine and purine biosynthesis, most notably the specific inhibition of orotidylate decarboxylase by minor metabolites such as allopurinol 1-ribonucleotide (1b)[2)], whilst the respective 1-ribonucleoside is a detoxication product in mammalian systems[3)] yet a potent growth inhibitor for leishmanial parasites[4)].



1a R=H
1b R=RibP



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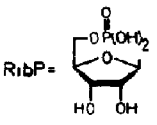

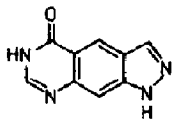

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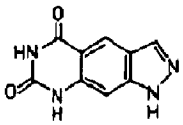

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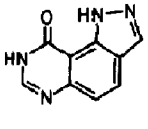

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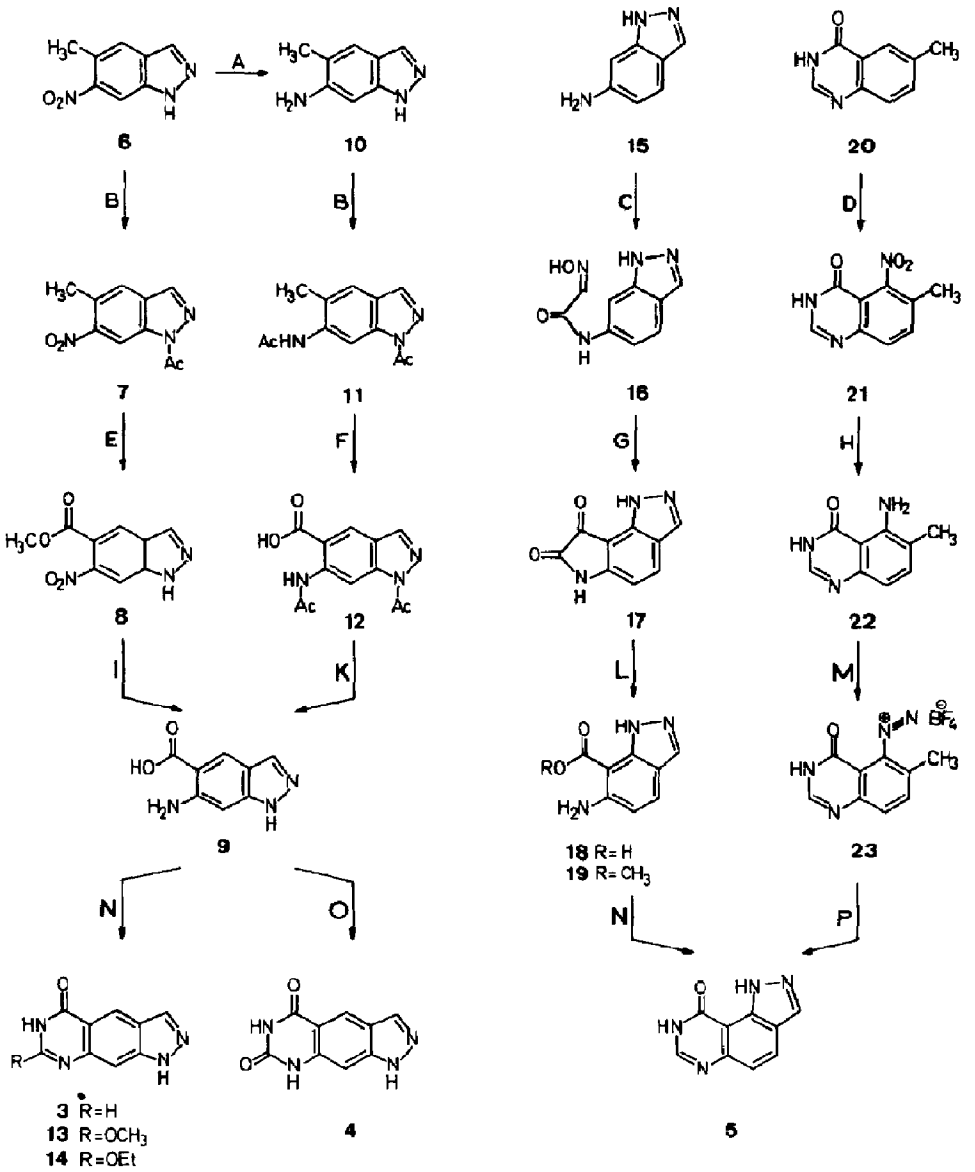
This high chemotherapeutic potential of allopurinol (1a) and our previous studies on its ribosylation[5)] has led us to suspect a similar biological relevance for such base-modified analogs in which the heterocyclic skeleton of 1 or 2 is extended from within by insertion of a benzene ring between the pyrazol and pyrimidine portions — an approach to bioactive analogs that has been particularly successful in the purine series[6)]. We have, by consequence, initiated work towards the synthesis of such benzo-inserted allo- and oxi-purinols, six structural isomers being possible for each. Prompted by a recent report on the preparation of the [4,3-*g*] isomer 3 from 4-bromo-2-methylaniline[7)] we here disclose our results on an efficient, alternate access to 3 and its oxipurinol benzolog 4 from 5-methyl-6-nitroindazol (6) as well as the synthesis of the [3,4-*f*] isomer 5 from either indazol or quinazoline precursors.



Key: A, $FeSO_4$/25 % aqueous NH_3, in ethanol/water, 80°C, 18 h[13]. — B, Ac_2O/HOAc, 25°C, 2 - 8 h. — C, chloral hydrate/$NH_2OH \cdot HCl/Na_2SO_4$ in dil. HCl, 100°C, 2 min. — D, conc. HNO_3/conc. H_2SO_4, 100°C, 2 h. — E, CrO_3/conc. H_2SO_4, 5°C, 20 min, followed by CH_2N_2, 0°C, 30 min. — F, $KMnO_4$ in tBuOH/H_2O, 80°C, 6 h. — G, conc. H_2SO_4, 80°C, 10 min. — H, 10 % Pd/C, H_2 in water. — I, 10 % Pd/C, 85 % aqueous NH_2NH_2 in ethanol, 80°C, 4 h. — K, 6 N HCl, 100°C, 1 d. — L, 10 % H_2O_2 in dil. NaOH, 100°C, 10 min, followed by acidification (pH 5) and CH_2N_2 treatment. — M, 35 % aqueous HBF_4 in EtOAc, $NaNO_2$, 5°C, 90 min. — N, $HCONH_2$, 140°C, 4.5 h, then 1.5 h at 180°C for 3 and 5; cyanogen in methanol or ethanol, 0°C, 5 h for 13 and 14. — O, urea, 140°C, 1 h. — P, pyridine, 20°C, 12 h or $Et_4NOAc/CHCl_3$, 20°C, 1 h.

Of the two conceivable approaches for constructing the pyrazolo[4,3-*g*]quinazoline ring system, the anellation of the pyrimidine ring onto a suitably substituted indazol was considered more promising[8] and was materialized with readily accessible[10] 5-methyl-6-nitroindazol (6) as the educt and 6-amino-indazol-5-carboxylic acid (9) as the key compound.

Two reaction sequences[11] were elaborated for the conversion 6 → 9, of which the CrO_3-oxidation of N^1-acetylated 6 (i.e. 7, m.p. 185°C, 90 %) to the nitroindazol-carboxylic acid[12] and ensuing in situ esterification with diazomethane to 8 (m.p. 162°C, 37 %) proved to be less efficient, affording 9 (m.p. 283°C after sublimation to needles at 260°C, 69 % for 8 → 9) in 23 % overall yield. In the alternate pathway, oxidation and reduction steps were reversed to give 9 in 49 % overall yield via 10 (m.p. 241-242°C, 76 %[13]), 11 (m.p. 243-245°C, 93 %) and permanganate oxidation to 12 (dec. ~ 300°C after sublimation to needles at 215°C, 69 %) with ensuing removal of the acetyl groups by acid (12 → 9, quant.).

Niementowski type reactions[14] readily converted 9 into pyrazolo[4,3-*g*]quinazolinones, formamide yielding 3 (m.p. > 330°C, 72 %[15]), urea correspondingly affording the respective 7-oxo analog 4 (m.p. > 330°C, 55 %). Similarly, action of cyanogen on methanolic or ethanolic solutions of 9 gave the respective 2-methoxy-(13, dec. at 280°C after subl. to needles at 230°C, 60 %) and 2-ethoxy-pyrazolo-quinazolinones (14, m.p. > 330°C after subl. ~ 170°C).

Construction of the pyrazolo[3,4-*f*]quinazolinone system 5 was effected via two independent preparative routes, the first involving the anellation of a pyrimidine ring onto readily available[13] 6-amino-indazol 15 (28 % yield over five steps), the other comprising attachment of the pyrazol portion onto the equally well accessible[16] 6-methylquinazolinone 20 in four steps and an overall yield of 25 %.

The five-step conversion 15 → 5 involved the introduction of the carboxylic acid function at C-7 by a procedure previously used by Sandmeyer[17] for the synthesis of isatin, i.e. reaction of 15 with chloral hydrate/hydroxylamine to the N-oximinoacetyl derivative (16, m.p. 199-201°C, 79 %) and ensuing sulfuric acid-induced cyclization to the pyrazolo-isatin 17 (m.p. > 300°C, 85 %). Subsequent oxidative ring cleavage afforded 6-aminoindazol-carboxylic acid (18, m.p. 177°C dec., 87 %), which via its ester 19 (m.p. 179-181°C, 74 %[18]) was readily converted into 5 (m.p. 325-327°C, 74 %) by heating with formamide[19]. The alternate route 20 → 5 was initiated by nitration to 21 (m.p. 304-305°C, 67 %[20]), followed by reduction to the 5-amino derivative 22 (m.p. 260-261°C dec., 82 %) and diazotization in the presence of HBF_4 to the stable diazonium fluoborate 23 (pale green crystals, m.p. 157°C dec., quant.), and was concluded by pyridine- or tetraethylammonium acetate-induced intramolecular azo coupling (23 → 5, 49 %).

Evaluation of the biological properties of 3 - 5 have so far been limited to determine their substrate and inhibitor capacity for xanthine oxidase[21]. In fact, 3 is readily oxidized by xanthine oxidase to the 7-oxo-derivative 4, as evidenced by TLC and, most characteristically, by UV data[11], resulting in an overall inhibitory effect ($ID_{50} = 7.3 \times 10^{-6}$ M) about four times lower as allopurinol ($ID_{50} = 1.7 \times 10^{-6}$ M). The [3,4-*f*] isomer 5, however, has lower activity (5×10^{-5}) clearly indicating that angular arrangement of the pyrimidine and pyrazol portions of allopurinol are less propitious, either geometrically or due to hydrogen bonding between N^1-H and O^9. As suggested by models, more favorable results may be expected for angular [4,3-*f*] and [3,4-*h*] analogs, their synthesis being presently underway, as well as the conversion of these heterocycles into nucleosides and nucleotides.

REFERENCES AND NOTES

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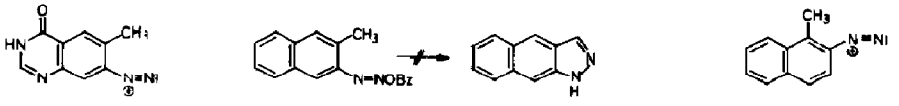
8. The alternate pyrazol anellation onto the quinazoline ring system via diazotization of a 7-amino-6-methylquinazolinone and subsequent intramolecular azo coupling (I → 3) was deemed difficult if at all feasible, since diazo ester intermediate II, like I lacking a "normal *ortho*-relation" of methyl and diazo groups, does not even give traces of 1H-benz[*f*]indazol (III)[9]. This anticipation proved to be correct as evidenced by the resistance of I towards ring closure[7] and by the smooth formation of the respective indazols from diazonium salts IV (pyridine, 25°C, 91 % 1H-benz[*e*]indazol[9] and 22 (→ 5), both having the electron-withdrawing effect of the diazonium moiety in direct mesomeric linkage to the methyl group.



I II III IV

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11. All the new compounds gave satisfactory elemental analysis and IR, ^{1}H-NMR, MS and UV spectra in accord with the structures proposed; the yields have not been optimized. Spectral characteristics (^{1}H-NMR in $(CD_3)_2SO$, MS at 70 eV) of:

    3: ^{1}H-NMR: δ = 7.78, 8.10, 8.44 and 8.76 (four 1H-s, H-3, H-4, H-7 and H-9), 11.92 and 13.36 (two br. 1H-s, 2 NH, exchangeable with D_2O). — MS: m/e = 186 (100 %).

    4: ^{1}H-NMR: δ = 7.22 (1H-s, H-3), 8.50 and 8.27 (two 1H-s, H-4 and H-9), 13.00 and 11.14 (two br. s, 1H and 2H, 3 NH). —MS: M/e = 202 (M^+), 159 (M - CONH). — UV (pH 7.5): λ_{max} = 203 nm (ε x 10^{-3} = 17.98), 239 (sh, 45.82), 245 (52.83), 307 (6.12).

    5: ^{1}H-NMR: δ = 7.45, 8.22 (two 9 Hz-d, 1H-d, 1H each, H-4 and H-5), 8.30, 8.32 (two 1H-s, H-3 and H-7), 13.44 (br. 2H-m, 2 NH). — MS: m/e = 186 (100 %). — UV (pH 7.5): λ_{max} = 255 nm (ε x 10^{-3} = 20.4), 315 (7.15), 327 (7.25).

    9: ^{1}H-NMR (DMSO+D_2O): δ = 6.68 (0.8 Hz-t, 1H, H-4), 7.95 and 8.32 (two 0.8 Hz-d, 1H each, H-3 and H-7). — MS: m/e = 177 (81 %), 159 (100 %), 132 (97 %).

    19: ^{1}H-NMR: δ = 4.00 (3H-s, OCH_3), 7.36 and 7.69 (two 9 Hz-d, 1H each, H-4 and H-5), 7.40 (br. 2H-m, NH_2), 7.94 (1H-s, H-3), 12.55 (br. 1H-s, N^{1}H). — MS: m/e = 191 (100 %), 159 (98 %), 131 (32 %).

    22: ^{1}H-NMR: δ = 2.13 (3H-s, CH_3), 6.70 and 7.36 (two 8.5 Hz-d, 1H each, H-7 and H-8), 7.0 (2H-m, NH_2), 7.88 (1H-s, H-2), 11.67 (br. 1H-s, NH). — MS: m/e = 175 (100 %).

12. The 6-nitroindazolcarboxylic acid (8, H instead of CH_3) may be isolated (yellow crystals of m.p. 143°C, dec.), yet in low yield due to its high tendency for decarboxylation.
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15. This amounts to an overall yield of 35 % for the five step, large scale adaptable conversion 6 → 10 → 11 → 9 → 3, comparing favorably with the 29 % obtained for the synthesis of 3 in five steps from 4-bromo-2-methylaniline[7].
16. V. Oakes, H.N. Rydon, and K. Undheim, *J. Chem. Soc.* 1962, 4678.
17. T. Sandmeyer (I.R. Geigy), *German Pat.* 113 848 (1899); *Helv. Chim. Acta* 2, 234 (1919).
18. Methylation of 18 with diazomethane produced, aside 19, small amounts of 6-amino-7-methoxycarbonyl-1-methylindazol (m.p. 218-219°C, 6 %), readily separable from the mother liquor of 19 by chromatography.
19. Attempts for direct cyclization of 18 with formamide resulted in the formation of 6-formamido-indazol (m.p. 205-207°C, 53 %) due to loss of the carboxylic acid function.
20. Even under drastic conditions (nitrating acid, 100°C) 20 exclusively yielded 21 (TLC), indicating that amino and carboxamide functions have a high directive effect. This finding is complemented by the equally regioselective nitrations of 7-methyl- and 8-methyl-quinazolin-4(3*H*)-ones, which preferentially yield the 6-nitro derivatives of m.p. 303°C (51 %) and 269-271°C (88 %), respectively; 5-methyl-quinazolin-4(3*H*)-one, however, preferentially afforded the 6,8-dinitro compound of m.p. 234-236°C (A. Moser and E. Cuny, unpublished results).
21. We are indebted to Drs. Johanna Fischer and U. Jahn, Pharmacology Research Laboratory, Siegfried AG, Zofingen, Switzerland, for kindly performing these experiments.

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