TRANSFORMATION OF A 6-METHYLTHIOPYRAZOLO[3,4-d]PYRIMIDINE DERIVATIVE BY ACTION OF HYDRAZINE AND SYNTHESIS OF NOVEL PYRAZOLOTRIAZOLOPYRIMIDINES

Jan Světlík

Drug Research Institute, Palárikova 31, 811 04 Bratislava, Czechoslovakia

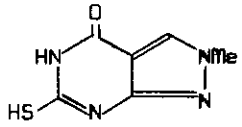
Abstract - Nucleophilic displacement of the methylthio group during hydrazinolysis of 2,5-dihydro-2,5-dimethyl-6-methylthio-4H-pyrazolo-[3,4-d]pyrimidin-4-one led unexpectedly to a 5-amino-6-hydrazino substituted product. A possible course for this reaction has been proposed. On treatment with ortho esters a novel tricyclic heterocycle, pyrazolo[4,3-e]-1,2,4-triazolo[4,3-a]pyrimidine, was formed.

The pyrazolopyrimidine ring system has attracted considerable synthetic interest since a member of this class, allopurinol (1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one), plays a critical role in the treatment of gout and related metabolic disorders[1]. This important drug, as well as its substituted products and some [1,5-a]-isomeric analogues proved to be inhibitors of xanthine oxidase[1]. During the past few years, a number of these substances have been claimed to have antiparasitic activities[2]. The pyrazolo[1,5-a]pyrimidines are reported to act as effective cAMP phosphodiesterase inhibitors[1], too.

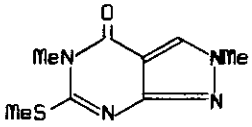
The wide range of pronounced pharmacological properties stimulated us to continue our research on fused polycyclic pyrazoles[3] and to study novel heterocycles in view of their structural resemblance to allopurinol. For this purpose, 2,5,6,7-tetrahydro-2-methyl-6-thioxo-4H-pyrazolo[3,4-d]pyrimidin-4-one (I) appeared to be an attractive substrate readily available by fusion of ethyl 3-amino-1-methyl-1H-pyrazole-4-carboxylate and thiourea[4]. Methylation of I has already been described[4]. Accordingly, the alkylation procedure using dimethyl sulfate in aqueous sodium hydroxide at room temperature gave 2,5-dihydro-2,5-dimethyl-6-methylthio-4H-pyrazolo-[3,4-d]pyrimidin-4-one (II). In the next step, a simple nucleophilic displacement of the methylthio group by hydrazine should provide conveniently a useful precursor for further elaboration.

Initial attempts to perform the substitution under mild conditions (boiling EtOH)

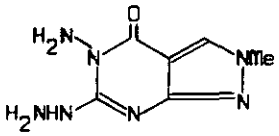
had failed and led only to recovery of the starting material even upon prolonged time. However, when the reaction was carried out in neat hydrazine hydrate (80%) at reflux temperature for 6 h, an unexpected compound III resulted instead.



I



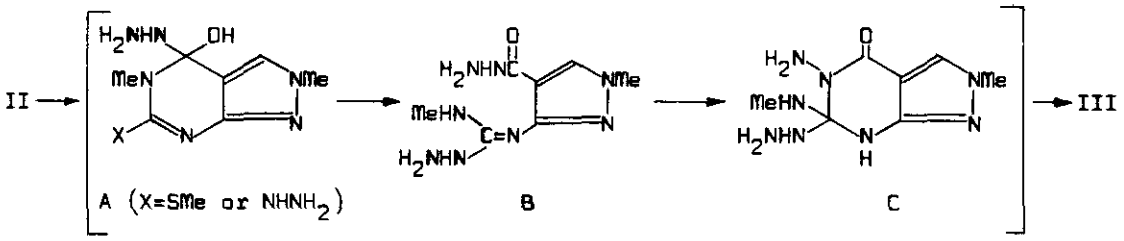
II



III

The formula ($C_6H_9N_7O$ by combustion analysis and high resolution MS) indicates that the substance isolated may be regarded as a 1:2 condensation product of II and hydrazine from which methyl mercaptan along with methylamine were lost. Indeed, the lack of signals of both alkyl groups attached to pyrimidine nucleus in the ^{1}H-NMR spectrum clearly establishes the structural identity of 5-amino-6-hydrazino-2,5-dihydro-2-methyl-4H-pyrazolo[3,4-d]pyrimidin-4-one (III).

The observed transformation can be explained to proceed via the ANRORC mechanism[5] accompanied with an anticipated nucleophilic substitution at 6-position, occurring simultaneously or in tandem. Hence, the initially formed derivative A, arising from the nucleophilic attack of hydrazine, undergoes ring opening to give guanidino-pyrazole B. It could be then postulated that an intramolecular cyclization takes place, followed by final elimination of $MeNH_2$ (C→III).

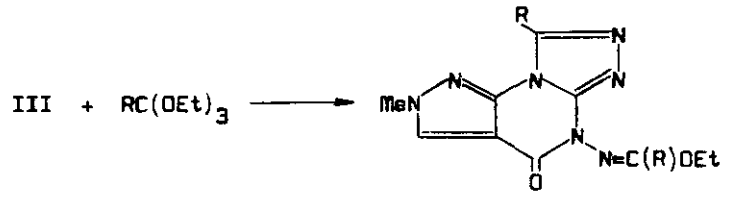


A (X=SMe or $NHNH_2$) B C

Nevertheless, this result is not quite surprising since similar processes account for the aminolysis[6] or hydrazinolysis[7] of quinazolin-4(3H)-ones. The mechanistic aspects have been constructively interpreted by Leonard and Curtin who considered intervention of an acyclic species during the reaction course[6]. In addition, an analogous conclusion for the related action on substituted pteridines has received direct experimental verification[8].

One of the promising routes of using a hydrazine moiety possessing endocyclic C=N bond to build up a 1,2,4-triazole consists in the annelation with ortho esters. Thus, cyclocondensation of III with triethyl orthoformate in refluxing dimethyl-

formamide gave IVa as a single product. 4,7-Dihydro-4-(ethoxymethyleneamino)-7-methyl-5H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-a]pyrimidin-5-one obtained here represents a novel tricyclic bridgehead heterocycle[9]. A similar treatment of triethyl orthoacetate led to its methyl homologue IVb.



IVa: R=H

IVb: R=Me

The ^{1}H NMR spectrum, besides typical ethoxycarbonyl and N-methyl signals, exhibited three singlets at 8.47 (pyrazole, H-6), 8.70 (O-CH=N) and 9.20 ppm (triazole, H-1). The chemical shift value of triazole ring proton is consistent with angular fusion in [4,3-a] mode[3] and clearly excludes the possibility of Dimroth type rearrangement to [5,1-a] linked isomer. Likewise, the side chain proton resonates in the range characteristic of the ethoxymethyleneamino moiety[10]. On the other hand, differentiation of both isolated C-methyl groups (singlets at 1.86 and 2.70 ppm) in IVb follows from the reported data of methyltriazoles[11].

EXPERIMENTAL

Melting points were determined on a Perkin-Elmer DSC-2 (comp. III) and on a Boetius micro hot-stage apparatus. Infrared spectra were obtained on a Perkin-Elmer 377 spectrophotometer. ^{1}H NMR spectra were recorded on Jeol FX-100 and Varian XL-200 spectrometers using tetramethylsilane as internal standard. Mass spectra were taken on a Jeol JMS D-100 spectrometer. Elemental analyses were performed in the Department of Analytical Chemistry, Chemical Technology Institute, Bratislava. Compounds I and II were synthesized as described previously[4].

5-Amino-6-hydrazino-2,5-dihydro-2-methyl-4H-pyrazolo[3,4-d]pyrimidin-4-one (III): A suspension of methylthio derivative II (1.5 g, 7 mmol) in 80% hydrazine hydrate (10 ml) was heated under reflux for 6 h. During a short period the reaction mixture became clear. After cooling the precipitate was filtered off, washed with diethyl ether and recrystallized from 80% ethanol; yield 0.70 g (50%), m.p. 277 °C (Anal. Calcd. for $C_6H_9N_7O$: C, 36.92; H, 4.65; N, 50.23. Found: C, 36.96; H, 4.73; N, 49.98%; M^+, 195). IR (KBr): 3322 (NH), 1685 (C=O), 1624, 1599, 1508 cm^{-1} (C=N, C=C). ^{1}H NMR (DMSO-d_6): 8.26 (s, 1H, H-3), 8.00 (br s, 1H, NH), 5.20 (s, 2H, NH_2), 4.29 (br s, 2H, NH_2) and 3.87 ppm (s, 3H, CH_3).

Preparation of pyrazolo[4,3-e]-1,2,4-triazolo[4,3-a]pyrimidines (IVa and IVb): A solution of III (0.39 g, 2 mmol) in dimethylformamide (10 ml) and triethyl orthoformate (4 ml) was refluxed for 1 h. The solvent was removed in vacuo and the oily residue triturated with a small volume of ethanol. The crystalline material formed was collected and recrystallized from ethanol to give 4,7-dihydro-4-(ethoxymethyleneamino)-7-methyl-5H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-a]pyrimidin-5-one (IVa); yield 0.20 g (38%) of colorless needles, m.p. 238-239 °C (Anal. Calcd. for $C_{10}H_{11}N_7O_2$: C, 45.97; H, 4.24; N, 37.53. Found: C, 45.69; H, 4.20; N, 37.70%). IR (KBr): 1684 (C=O), 1598, 1582, 1498 cm^{-1} (C=N, C=C). ^1H NMR (DMSO-d_6): 9.20 (s, 1H, H-1), 8.70 (s, 1H, O-CH=N), 8.47 (s, 1H, H-6), 4.10 (q, 2H, CH_2), 4.01 (s, 3H, CH_3-N) and 1.40 ppm (t, 3H, CH_3).

The methyl homologue IVb was prepared similarly from III and triethyl orthoacetate in 67% yield. The reaction time was 6 h; m.p. 241-243 °C (Anal. Calcd. for $C_{12}H_{15}N_7O_2$: C, 49.82; H, 5.23; N, 33.89. Found: C, 49.91; H, 5.20; N, 33.75%). IR (KBr): 1695 (C=O), 1627, 1599, 1577, 1489 cm^{-1} (C=N, C=C). ^1H NMR (DMSO-d_6): 8.58 (s, 1H, H-6), 4.40 (q, 2H, CH_2), 4.01 (s, 3H, CH_3-N), 2.70 (s, 3H, CH_3-triazole), 1.86 (s, 3H, CH_3-CON) and 1.39 ppm (t, 3H, CH_3).

REFERENCES

1. R. K. Robins, P. C. Srivastava, G. R. Revankar, T. Novinson and J. P. Miller, Lect. Heterocyclic Chem., 1982, 6, 93.
2. K. Senga, T. Novinson, H. R. Wilson and R. K. Robins, J. Med. Chem., 1981, 24, 610.
3. J. Světlík, Heterocycles, 1984, 22, 2513.
4. P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, Helv. Chim. Acta, 1959, 42, 349.
5. H. C. van der Plas, Acc. Chem. Res., 1978, 11, 462; H. C. van der Plas, Tetrahedron, 1985, 41, 237.
6. N. J. Leonard and D. Y. Curtin, J. Org. Chem., 1946, 11, 341.
7. N. J. Leonard and W. V. Ruyle, J. Org. Chem., 1948, 13, 903.
8. E. C. Taylor, J. Am. Chem. Soc., 1952, 74, 1651.
9. Following systems are known: pyrazolo[3,4-d]-1,2,4-triazolo[2,3-a]pyrimidine, N. Heimbach, U. S. Patent, 2,444,607 (1948) [Chem. Abstr., 1948, 42, 7178]; pyrazolo[1,5-a]-1,2,4-triazolo[4,3-c]pyrimidine, H. Reimlinger and M. A. Peiren, Chem. Ber., 1971, 104, 2237; pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]-

pyrimidine and pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine, A. G. Bhat and L. B. Townsend, J. Chem. Soc. Perkin Trans. 1, 1981, 2387; U. D. Treuner and H. Breuer, U. S. Patent, 4,053,474 (1977) [Chem. Abstr., 1978, 88, 37826s]; pyrazolo[4,3-e]-1,2,3-triazolo[1,5-a]pyrimidine, M. A. Khan and A. C. C. Freitas, J. Heterocyclic Chem., 1980, 17, 1603.

10. H. Wamhoff, M. Ertas and S. M. S. Atta, Liebigs Ann. Chem., 1985, 1910; P. Finlander and E. B. Pedersen, Arch. Pharm., 1985, 318, 452.

11. T. Huynh-Dinh, J. Igolen, J. P. Marquet, E. Bisagni and J. M. Lhoste, J. Org. Chem., 1976, 41, 3124; D. J. Brown and K. Shinozuka, Aust. J. Chem., 1981, 34, 189.

Received, 9th January, 1986