# SYNTHESIS AND OXIDATION OF AROMATIC SUBSTITUTED 6,7-DIHYDROPYRAZOLO[1,5-a]PYRIMIDINES

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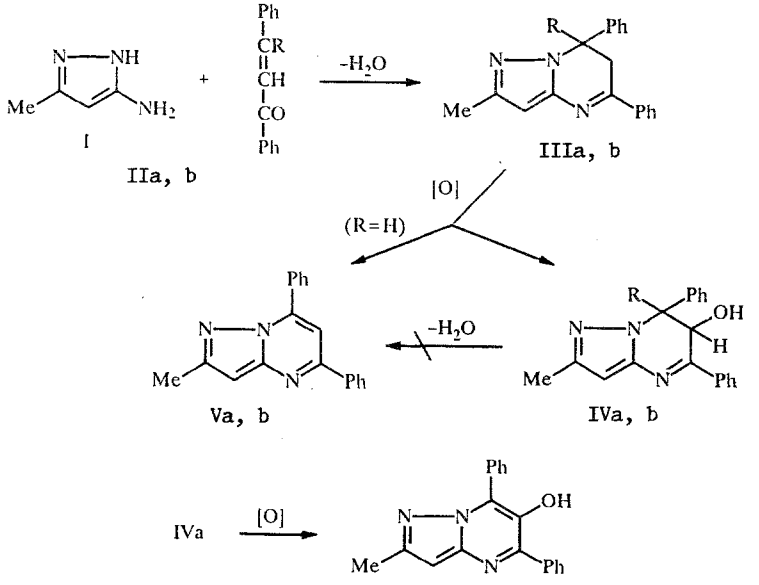
*Condensation of 5-amino-3-methylpyrazole with chalcone or dypnone gives aromatic substituted 6,7-dihydropyrazolo[1,5-a]pyrimidines which undergo air oxidation. An x-ray structure for 2-methyl-6-hydroxy-5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine is reported.*

We have previously shown [1, 2] that cyclocondensation of aminoazoles with $\alpha,\beta$-unsaturated ketones gives dihydroazolopyrimidines which can undergo oxidation to the corresponding heteroaromatic analogs. However, refluxing a solution of 5-amino-3-methylpyrazole (I) and chalcone (IIa) in DMF with free access of air gives the 6-hydroxy substituted IVa, VI together with compounds IIIa, V. Oxidation of IIIa can be avoided by carrying out the synthesis in an inert atmosphere with preliminary deoxygenation of the solvent. The 5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine (IIIa) obtained can be oxidized to form IVa, V, VI by passage of oxygen through an acetone solution for 1 h. Compound IIIb was synthesized by reaction of amine I and dione IIb and is considerably more stable. Appreciable amounts of the hydroxy derivative IVb could only be obtained by increasing the reaction time to 10-12 h. 40% of starting IIIb remained. Further increase in the reaction time did not give an increased yield of IVb due to tarring. The lower sensitivity towards oxidation on going from IIIa to IIIb is probably connected with steric factors.

The structure of IVa predisposes its ready dehydration to the corresponding heteroaromatic species. However, the hydroxy derivative IIIa remains unchanged both in the solid state and in refluxing DMF solution ether with alcohol or




II—IV a R = H, b R = Me

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0009-3122/93/2901-0095$12.50 

TABLE 1. Data for Compounds III-VI

| Compound | Empirical formula | mp, °C | IR spectrum, $cm^{-1}$ | | $\lambda_{max}$, nm ($\varepsilon \cdot 10^3$) | Chemical shift, δ, ppm, (spin-spin coupling, Hz, protons*) | | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $\nu_{C=N}$ (in KBr) | $\nu_{OH}$ (in $CCl_4$) | | 3-H, s | 6-H | 7-H | OH | $CH_3$, s | |
| IIIa | $C_{19}H_{17}N_3$ | 120...121 | 1610 | — | 317 (13,6) | 6,30 | 3,55 (2H, d, 6,0) | 5,64 (t) | — | 2,16 | 90 |
| IIIb | $C_{20}H_{19}N_3$ | 128...130 | 1606 | — | 316 (14,3) | 6,35 | 3,13 (1H, d, 16,9); 4,14 (1H, d) | — | — | 1,97; 2,27 | 72 |
| IVa | $C_{19}H_{17}N_3O$ | 208...210 | 1615 | 3566 | 315 (12,5) | 6,38 | 4,95 (1H, d, d, 6,0, 1,9) | 5,55 (s) | 6,59 (d) | 2,19 | 48 |
| IVb | $C_{20}H_{19}N_3O$ | 165...166 | 1608 | 3569 | 302 (11,7) | 6,37 | 5,13 (1H, d, d, 6,5, 1,9) | — | 6,61 (d) | 1,93; 2,27 | 30 |
| V | $C_{19}H_{15}N_3$ | 110...112 | 1609 | — | 321 (7,7) | 6,64 | 7,68 (s) | — | — | 2,43 | 25 |
| VI | $C_{19}H_{15}N_3O$ | 215...216 | 1604 | 3550 | 330 (6,6) | 6,53 | — | — | 8,93 (s) | 2,33 | 90 |

*Aromatic protons of III-VI occur at 6.5-8.0 ppm.

TABLE 2. Some Valence ($\omega$) and Torsional ($\tau$) Angles (degrees) in IV

| Angle | $\omega$ | Angle | $\tau$ |
|---|---|---|---|
| $N_{(2)}N_{(1)}C_{(1)}$ | 105,7(8) | $C_{(1)}N_{(1)}N_{(2)}C_{(3)}$ | 1,9(9) |
| $N_{(1)}C_{(1)}C_{(2)}$ | 111,3(11) | $N_{(1)}N_{(2)}C_{(3)}C_{(2)}$ | -1,0(10) |
| $C_{(1)}C_{(2)}C_{(3)}$ | 105,6(9) | $N_{(2)}C_{(3)}C_{(2)}C_{(1)}$ | -0,3(8) |
| $C_{(2)}C_{(3)}N_{(2)}$ | 105,5(10) | $C_{(3)}C_{(2)}C_{(1)}N_{(1)}$ | 1,6(11) |
| $C_{(3)}N_{(2)}N_{(1)}$ | 111,8(9) | $C_{(2)}C_{(1)}N_{(1)}N_{(2)}$ | -2,1(7) |
| $C_{(3)}N_{(2)}C_{(6)}$ | 121,6(10) | $N_{(3)}C_{(3)}N_{(2)}C_{(6)}$ | 6,7(9) |
| $N_{(2)}C_{(6)}C_{(5)}$ | 107,3(8) | $C_{(3)}N_{(2)}C_{(6)}C_{(5)}$ | -36,5(10) |
| $C_{(6)}C_{(5)}C_{(4)}$ | 109,6(9) | $N_{(2)}C_{(6)}C_{(5)}C_{(4)}$ | 47,1(8) |
| $C_{(5)}C_{(4)}N_{(3)}$ | 121,9(10) | $C_{(6)}C_{(5)}C_{(4)}N_{(3)}$ | -35,9(9) |
| $C_{(4)}N_{(3)}C_{(3)}$ | 118,7(8) | $C_{(3)}C_{(4)}N_{(3)}C_{(5)}$ | 5,4(8) |
| $N_{(3)}C_{(3)}N_{(2)}$ | 122,2(10) | $C_{(4)}N_{(3)}C_{(3)}N_{(2)}$ | 11,3(10) |
| $N_{(3)}C_{(3)}C_{(2)}$ | 131,9(9) | $N_{(3)}C_{(4)}C_{(7)}C_{(8)}$ | 8,9(11) |
| $N_{(1)}N_{(2)}C_{(6)}$ | 125,0(8) | $C_{(5)}C_{(4)}C_{(7)}C_{(12)}$ | 6,2(12) |
| $C_{(2)}C_{(1)}C_{(19)}$ | 127,8(10) | $C_{(5)}C_{(6)}C_{(13)}C_{(14)}$ | -72,6(10) |
| $N_{(1)}C_{(1)}C_{(19)}$ | 120,9(10) | $N_{(2)}C_{(6)}C_{(13)}C_{(18)}$ | -17,2(9) |
| $N_{(3)}C_{(4)}C_{(7)}$ | 119,2(8) | $N_{(3)}C_{(4)}C_{(5)}O$ | 85,6(9) |
| $C_{(5)}C_{(4)}C_{(7)}$ | 118,8(9) | $N_{(2)}C_{(6)}C_{(5)}O$ | -70,6(12) |
| $C_{(4)}C_{(5)}O$ | 106,1(8) | $C_{(4)}C_{(5)}C_{(6)}C_{(13)}$ | -77,0(10) |
| $C_{(6)}C_{(5)}O$ | 112,3(9) | $C_{(3)}N_{(2)}C_{(6)}C_{(13)}$ | 87,8(9) |
| $N_{(2)}C_{(6)}C_{(13)}$ | 112,4(10) | $C_{(7)}C_{(4)}C_{(5)}H_{(5)}$ | 25,3(10) |
| $C_{(5)}C_{(6)}C_{(13)}$ | 112,5(9) | $H_{(6)}C_{(6)}C_{(5)}O$ | 33,8(9) |
| | | $H_{(5)}C_{(5)}C_{(6)}H_{(6)}$ | -91,7(11) |

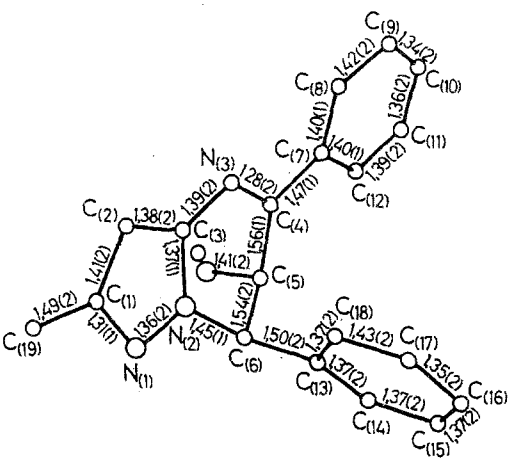


Fig. 1. Structure of IVa (without H atoms) and bond lengths (Å).

addition of HCl, KOH, $ZnCl_2$ or to p-toluenesulfonic acid. Moreover, if heating these solutions is carried out with free access of air, almost quantitative dehydrogenation of IVa to 6-hydroxy-5,7-diphenylpyrazolo[1,5-a]pyrimidine VI results.

The products were identified by elemental analysis and spectroscopic methods.

In their mass spectra, conversion of IIIa to IVa is accompanied by an increase in molecular weight of 16 units (molecular ions m/z 287 and 303 respectively) supporting the extra oxygen atom in IVa. The IR spectra of III, IV as KBr tablets show absorbances for C=N stretching at 1606-1615 $cm^{-1}$ respectively (Table 1). IR of IIIa,b in $CCl_4$ at concentrations of $10^{-3}$ M and above imply formation of intermolecular hydrogen bonds. The free OH stretching bands (3200 $cm^{-1}$) is lowered in intensity and very broad bands at about 3200 $cm^{-1}$ appear (partly obscured by the $\nu_{CH}$ absorption). The electronic spectra of III, IV are quite similar and show long wavelength absorption at 302-317 nm.

The PMR spectra of IIIa, b show signals for the aromatic protons, the pyrazole ring proton, and those of the pyrimidine $C(R)-CH_2$ fragment (see Table 1). In IIIa the methylene protons are virtually equivalent whereas in IIIb they form an AB system with $\delta_{HA}-\delta_{HB}$ of 1.01 ppm and $J_{AB}$ of $-16.9$ Hz). The hydroxy derivatives IVa, b show signals for the

TABLE 3. Atomic Coordinates ($\times 10^4$) for IIIa

| Atom | x | y | z | Atom | x | y | z |
|---|---|---|---|---|---|---|---|
| O | -597(8) | 3933(4) | 426(11) | C(9) | 1762(11) | 438(9) | 1890(17) |
| N(1) | -514(8) | 4010(6) | -3783(12) | C(10) | 2058(12) | 930(12) | 3058(17) |
| N(2) | -143(8) | 3661(5) | -2523(12) | C(11) | 1824(12) | 1936(12) | 3255(16) |
| N(3) | 166(9) | 2077(5) | -1275(12) | C(12) | 1305(11) | 2496(9) | 2207(15) |
| C(1) | -886(9) | 3204(8) | -4446(13) | C(13) | 1635(9) | 4298(6) | -1947(13) |
| C(2) | -730(9) | 2304(7) | -3648(15) | C(14) | 2300(10) | 4992(8) | -1304(14) |
| C(3) | -252(9) | 2620(7) | -2408(13) | C(15) | 3346(10) | 5068(9) | -1566(16) |
| C(4) | 517(9) | 2573(7) | -213(13) | C(16) | 3746(10) | 4404(10) | -2505(16) |
| C(5) | 402(9) | 3756(7) | -102(13) | C(17) | 3117(10) | 3715(9) | -3169(15) |
| C(6) | 513(8) | 4244(6) | -1540(12) | C(18) | 2032(9) | 3638(7) | -2896(14) |
| C(7) | 1019(9) | 2012(7) | 954(12) | C(19) | -1393(10) | 3299(8) | -5859(15) |
| C(8) | 1231(10) | 970(8) | 792(15) | | | | |

C(R)−CH−OH group and also for the 6-H protons (which show an additional splitting due to interaction with one of the aromatic protons (J = 1.9 Hz). By contrast, a spin−spin interaction of the vicinal protons 6-H and 7-H is not seen. The absence of an additional doubling of similar signals in IVa, b implies that only one of the possible diastereoisomers is formed in both cases.

The PMR spectra of V, VI show signals only for aromatic and heteroaromatic protons (Table 1) and, for VI, the hydroxy group proton.

The stability of IVa to dehydration along with the favoring of the reaction IIIa to IVa (when compared with dehydrogenation IIIa to V) are nontrivial results in the chemistry of dihydroheteroatomatic compounds. Hence for IVa we carried out an x-ray structural investigation (Fig. 1, Tables 2 and 3) which showed it to be 2-methyl-5,7-diphenyl-6-hydroxy-6,7-dihydropyrazolo[1,5-a]pyrimidine. As in other pyrazoles [3], the five-membered ring in IV is virtually planar (see torsional angles in Table 3). Corresponding to [4, 5] the calculated conformational parameters for the dihydropyrimidine ring are S = 0.61, $\theta$ = 46.2, and $\varphi$ = 28.9 which (in agreement with [4]) points to a chair conformation for this ring. The trans oriented phenyl substituent at $C_6$ and hydroxy at $C_5$ are in quasi-equatorial positions. The near cis-oid mutual orientation of the hydroxy group and atom $H_6$ ($H_6C_6C_5O$ = 33.8(6)°) is unfavorable for the dehydration reaction [6] which explains the relative stability reported above.

The steric structure of IVa explains its NMR spectral properties. In fact, the torsional angle of 91.7(5)° for $H_5C_5C_6H_6$ agrees with the absence of a marked spin−spin interaction for protons $H_5$ and $H_6$. On the other hand, the near planarity for the fragment $H_5C_5C_4C_7C_{12}H_{12}$ (see torsional angles in Table 2) is favorable for long-range spin interaction of $H_5$ and $H_{12}$. These results point to a similar steric structure for IVa in both the solid state and in solution.

The values of the torsional angles of the strongly flattened benzalaminopyrazole fragment do not exceed 11.3° (see Table 2) and so allow retention of the conjugated $\pi$-electron systems in the $C_7-C_{12}$ aromatic substituent, the azomethine, and the pyrazole ring.

## EXPERIMENTAL

X-ray structural investigation. Crystalline 2-methyl-5,7-diphenyl-6-hydroxy-6,7-dihydropyrazolo[1,5-a]pyrimidine $C_{19}H_{17}N_3O$ were monoclinic. At 20°C, a = 12.770(3), b = 13.068(3), c = 9.658(2) Å, $\beta$ = 92.61(3)°, Z = 4, $d_{calc}$ = 1.247 g/cm$^3$, space group $P2_1/C$. Unit cell parameters and intensities of 809 independent reflections with $|F| \geq 4\sigma(F)$ were measured on an automatic 4 circle Siemens P3/PC diffractometer using MoK$\alpha$ radiation and a graphite monochromator.

The structure was solved by a direct method using the SHELXTL PLUS program. The position of all hydrogen atoms excluding the hydroxyl were realized in difference synthesis and not refined. Refinement of non-hydrogen atoms in the anisotropic approximation (with location of isotropic hydrogen atoms) was carried out to R = 0.048 ($R_W$ = 0.049).

Atomic coordinates are given in Table 3.

IR Spectra for III-V, VIIa-d were recorded for KBr tablets and $CCl_4$ solutions on a Specord IR-75 instrument, UV spectra on a Specord M-40 instrument using 2-4 $\times$ $10^{-5}$ molar solutions in methanol. PMR spectra were recorded on a

Gemini-200 spectrophotometer for $CF_3COOD$ or DMSO-$D_6$ solutions and HMDS internal standard. The reaction course and compound purities were monitored using TLC on Silufol UV-254 plates with benzene–methanol (10:1) eluent.

The nitrogen analysis for the compounds obtained agreed with those calculated.

**2-Methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine (IIIa).** A mixture of IIa (0.4 g, 2 mmole), 5-amino-3-methylpyrazole (0.2 g, 2 mmole), and DMF (0.5 ml) was refluxed in a nitrogen stream for 5 min, cooled, mixed with acetone (10 ml), and filtered to give IIIa (0.5 g, 90%) with mp 120-122°C (from isopropanol).

IIIb was obtained similarly.

**Oxidation of 2-Methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine (IIIa).** Oxygen was passed through a solution of IIIa (0.4 g, 1.4 mmole) in acetone (10 ml) at 50-55°C for 1 h. The solution was evaporated, the residue dissolved in isopropanol (5 ml), and the cooled solution filtered to give IVa (0.15 g, 36%) with mp 208-210°C (from isopropanol). The filtrate was evaporated and the oily residue chromatographed on a grade III activity $Al_2O_3$ column (diameter 1 cm, filling height 10 cm) with benzene as eluent. The products were V (0.1 g, 25%, $R_f$ 0.8, mp 110-112°C from isopropanol), VI (0.11 g, 27%, $R_f$ 0.4, mp 215-216°C from isopropanol) and IVa (0.05 g, 12%).

Under similar conditions (reaction time 10 h), IVb ($R_f$ 0.2) was obtained from IIIb.

**2-Methyl-5,7-diphenyl-6-hydroxypyrazolo[1,5-a]pyrimidine (VI).** IVa (0.3 g, 1 mmole) was dissolved in 10 ml of 2% KOH solution in methanol and refluxed for 1 h in conditions of free access of oxygen. The product was mixed with water (50 ml), neutralized with HCl (1:1), and filtered to give VI (0.28 g, 94%).

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