NEW CONDENSED TRI- AND TETRACYCLIC PYRAZOLE RING SYSTEMS

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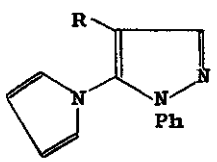
Abstract - 1-Phenylpyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine and its 5-aza analogue were synthesized from ethyl 5-amino-1-phenylpyrazole-4-carboxylate. Additional azolo ring annelations on the pyrazine part of the first heterocycle afforded new tetracyclic systems with two common nitrogen atoms.

Recently, antiviral and neoplasm inhibiting properties of 1-phenylpyrazolo[3,4-b]-pyrazine derivatives have been reported in the patent literature.[1] Other work has been directed to the preparation of related compounds for pharmacological evaluation.[2] In view of these findings we have focused our attention on the synthesis of new condensed heterocycles containing pyrazolo[3,4-b]pyrazine unit.

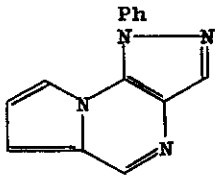
The precursor, ethyl 5-amino-1-phenylpyrazole-4-carboxylate, (I), was readily obtained from ethyl 2-cyano-3-ethoxyacrylate and phenylhydrazine.[3] Condensation of amino ester I with 2,5-dimethoxytetrahydrofuran in hot glacial acetic acid according to a known procedure[4] afforded 5-(pyrrol-1-yl) substituted pyrazole II,[5] which was, in turn, converted to the corresponding hydrazide III upon heating in ethanolic solution of 80% hydrazine hydrate for 5 hours. Subsequent reaction of III with sodium azide in acetic acid at 5 °C proceeded rapidly to form the expected acylazide IV in quantitative yield. Decomposition of the above compound in boiling ethanol followed by hydrolysis of the resulting carbamate V with aqueous ethanolic NaOH produced the requisite 4-amino-1-phenyl-5-(pyrrol-1-yl)pyrazole (VI).

The crucial point in the synthetic pathway involved the construction of a pyrazine skeleton fused to both 5-membered heterocycles. First, VI was smoothly formylated with 99% formic acid under reflux for 2 hours. Final ring closure was carried out conventionally by short heating (45 min) of VII in phosphoryl chloride. Usual work-up and recrystallization from 60% ethanol provided 1-phenylpyrazolo[4,3-e]-pyrrolo[1,2-a]pyrazine (VIII[6]) as colorless needles, m.p. 168-170 °C (86%). Its ^{1}H-NMR spectrum consists of two-well separated singlets at 8.71 (broad, pyrazine, H-5) and 8.31 ppm (pyrazole, H-3). A third strong peak at 7.67 ppm is indicative

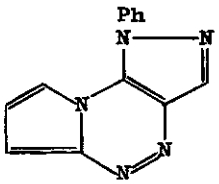
of a non-coplanar phenyl group.[7] Pyrrole ring protons constituting an ABC splitting pattern appear at 7.07 (dd, H-6, $J_{6,7}$=4.1, $J_{6,8}$=1.2 Hz), 6.91 (m, H-8, $J_{8,7}$= 2.9, $J_{8,6}$=1.2, $J_{8,5}$ about 0.5 Hz as estimated from decoupling experiment) and 6.83 ppm (dd, H-7, $J_{7,8}$=2.9, $J_{7,6}$=4.1 Hz).



II: R=CO_2Et
III: R=$CONHNH_2$
IV: R=CON_3
V: R=$NHCO_2Et$
VI: R=NH_2
VII: R=NHCHO

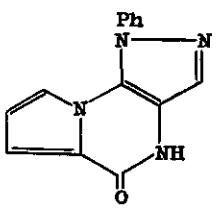


VIII

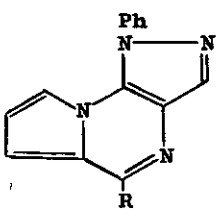


IX

A further possibility to get another new tricyclic bridgehead system implicates a coupling reaction of the diazotized amine function with the adjacent pyrrole ring. The direct formation of 1-phenylpyrazolo[3,4-e]pyrrolo[2,1-c][1,2,4]triazine (IX) was achieved by treating sodium nitrite with VI in the HCl/EtOH/H_2O medium or in aqueous acetic acid at room temperature. After stirring for 1 hour, dilution with cold water and neutralization, the precipitated product was passed through silica gel ($CHCl_3$ eluent). The pure compound IX[8] (51%) was recrystallized from isopropyl alcohol to give pale orange plates, m.p. 226-227 °C.
Attempts to cyclize acylazide IV into X by heating in various high-boiling solvents failed, although the presence of an isocyanate intermediate was observed (IR in xylene: CON_3, 2145 cm^{-1}; NCO, 2265 cm^{-1}). On the other hand, the use of diglyme as a reaction medium led to N,N'-bis[1-phenyl-5-(pyrrol-1-yl)pyrazol-4-yl]urea (XI) which on fusion at 275 °C yielded X[9] (53%, m.p. 297-298 °C from ethanol) and amine VI (40%, isolated from ethanolic mother liquor) following Robba's method.[10] In addition, X is directly available by thermal decomposition of the solid acylazide at the same temperature.

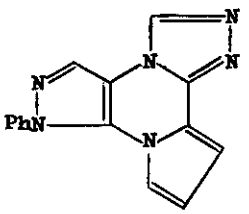


X

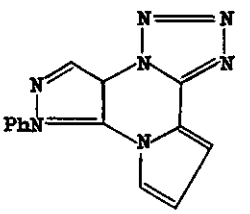


XII: R=Cl
XIII: R=$NHNH_2$

The next two new tetracyclic systems are realized from pyrazinone X possessing a lactam function suitable for further transformation. Thus, heating X for 6 hours in phosphoryl chloride containing a small amount of pyridine gave the key intermediate XII after extraction of the crude product with ethyl ether. As expected, the chlorinated compound XII undergoes a facile displacement of the halogen by hydrazine, yielding XIII. When the 5-hydrazino derivative was refluxed with ethyl orthoformate, the anticipated cyclocondensation occurred surprisingly within few minutes to furnish 8-phenylpyrazolo[4,3-e]pyrrolo[1,2-a][1,2,4]triazolo[3,4-c]pyrazine (XIV[11]), m.p. 294-295 °C from acetone (90%). The fact that the fusion took place in [3,4-c] manner was easily confirmed by the significant low-field position of the triazole proton (9.43 ppm, H-1), similar to those reported for analogous condensed systems.[12] Moreover, a fine splitting of the latter signal was observed as a result of remarkable coupling with the pyrazole proton. Treatment of XIII with sodium azide in aqueous acetic acid at room temperature provided immediately the annelated tetrazole XV,[13] m.p. 228-230 °C from isopropyl alcohol (53%).



XIV



XV

The IR and NMR spectra exhibited no evidence for azido-tetrazole isomerization,[14] i.e. XV exists entirely as the tetrazole in the solid state and in dimethylsulfoxide solution.

Further experiments with the chloro compound XII have revealed that its reduction with zinc dust and acetic acid resulted in the mentioned tricycle VIII. Hence, the hydrodehalogenation method employed also proves the postulated structure.

REFERENCES AND NOTES

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3. P. Schmidt and J. Druey, Helv. Chim. Acta, 1956, 39, 986.
4. N. Clausen-Kaas and Z. Tyle, Acta Chem. Scand., 1972, 6, 667.
5. All new compounds gave satisfactory analytical and spectral data. Melting points and yields of individual intermediates were: II (117-118 °C from diethyl ether, 87%), III (188-190 °C from ethanol/ethyl acetate, 97%), IV (109-111 °C without purification, 92%), V (134-135 °C from n-heptane, 85%), VI (144-145 °C from ethanol, 87%), VII (209-210 °C from ethanol, 96%), XI (264-266 °C from ethanol, 63%), XII (121-124 °C without purification, 67%), XIII (164-166 °C from ethanol, 85%).
6. IR (KBr): 1593, 1570, 1497 cm^{-1} (C=N, C=C).
7. T. J. Batterham, NMR Spectra of Simple Heterocycles, p. 191. Wiley, New York, 1973.
8. IR (KBr): 1609, 1544, 1502 cm^{-1} (C=N, C=C). ^{1}H-NMR (DMSO-d_6): 8.86 (s, 1H, H-3), 7.71 (br s, 5H, C_6H_5), 7.46 (m, 1H, H-6), 7.18 (m, 1H, H-8) and 7.07 ppm (m, 1H, H-7).
9. IR (KBr): 3200-2500 (NH), 1660 (C=O). ^{1}H-NMR (DMSO-d_6): 11.16 (br s, 1H, NH), 7.72 (s, 1H, H-3), 7.66 (s, 5H, C_6H_5), 7.08 (dd, 1H, H-6), 6.68 (dd, 1H, H-8) and 6.54 ppm (dd, 1H, H-7).
10. S. Rault, Y. Effi, M. Cugnon de Sevricourt, J. C. Lancelot and M. Robba, J. Heterocyclic Chem., 1983, 20, 17.
11. IR (KBr): 1635, 1599, 1561, 1508 cm^{-1} (C=N, C=C). ^{1}H-NMR (DMSO-d_6): 9.43 (d, J=1.0 Hz, 1H, H-1), 8.43 (d, J=1.0 Hz, 1H, H-10), 7.70 (s, 5H, C_6H_5), 7.15 (t, 1H, H-4) and 6.62 ppm (d, 2H, H-5 + H-6).
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13. IR (KBr): 1662, 1582, 1566, 1504 cm^{-1} (C=N, C=C). ^{1}H-NMR (DMSO-d_6): 8.68 (s, 1H, H-10), 7.74 (s, 5H, C_6H_5), 7.40 (dd, 1H, H-4) and 6.80 ppm (m, 2H, H-5 + H-6).
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