Arch. Pharm. Res. Vol. 17, No. 4, pp. 278-280, 1994

Synthesis of Some New 4H-(Pyrano and/or Piperidino)[3,2-d] Pyrazoles and Pyrazolo[5,4-d] Thiopyrans

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(Received July 20, 1993)

1,5-Diketones (**3**) underwent cyclization to 4H-pyrano[3,2-d]pyrazoles (**4a-d**), 4H-piperidino[3, 2-d]pyrazole (**5**) and pyrazolo[5,4-d]thiopyran (**6**) upon treatment with P_2O_5, CH_3COONH_4 and/or P_2S_5. Moreover, treatment of (**4**) with CH_3COONH_4 and/or P_2S_5 afforded (**5**) and (**6**). The structures of the hitherto unknown ring systems have been confirmed by analytical and spectral data.

Key words: Synthesis, pyranopyrazoles, piperidino-pyrazoles, pyrazolothiopyrans

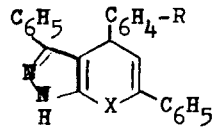
RESULTS AND DISCUSSION

Chemical Synthesis

Some derivatives of pyranopyrazoles were shown to be good vasodialators, hypotensive and hypoglycemic agents (Sato *et al.*, 1975, 1976).

In recent years, some 1,4-dihydropyridine derivatives have been synthesized and developed as calcium antagonists which inhibit smooth and cardiac muscle contractions by blocking the influx of Ca^{+2} through calcium channels (Safak *et al.*, 1990). Some of the thiapyrano derivatires have been reported as anti-inflammatory agents (Khan and Cosenza, 1982).

We wish to communicate the preparation of novel bicyclic 4H-(pyrano and/or piperidino)[3,2-d]pyrazoles and pyrazolo[5,4-d]thiopyrans of general formula (**1**) (Sato *et al.*, 1975, 1976).



1

X= O; NH; S;

R= H; m-NO_2; p-CH_3; p-Cl

Our interest in these heterocycles derives from the diverse biological activities reported for pyrazoles (Wiley *et al.*, 1964; Metwally *et al.*, 1989; Metwally *et al.*, 1992).

Derivatives of 1 were prepared from 1,5-diketones 3 and polyphosphoric acid, ammonium acetate and/or phosphorous pentasulphide.

The 1,5-diketones (**3a-c**) were obtained through michael condensation between 3-phenyl-2-pyrazolin-5-one (**2**) and chalcones in butanol-piperidine. The structure of 1,5-diketones (**3a-d**) was confirmed by their correct analytical and spectral data. The ^{1}H-NMR spectra displayed signals at δ 2.2-2.3 (S, 3H, CH_3), 3.55-3.65 (d, 2H, CH_2), 4.1-4.3 (m, 1H, -CH-Ar), 4.6-4.7 (m, 1H, CO-CH), 7.1-7.9 (m, ArH) and 8.2 ppm (S, 1H, NH). The IR spectra show the expected absorption bands at 1595-1605 (C=N), 1680-1695 (CO-pyrazolone), 3200-3300 (NH-pyrazolone) and 3450-3510 cm^{-1} (enolized exocyclic CO).

The 1,5-diketone (**3c**) underwent heterocyclization with polyphosphoric acid to give the pyranopyrzole derivative 4A rather than 4B. Assignment of the product as 4A rather than 4B was partly based on the appearance in the ^{1}H-NMR spectrum of a signals at δ 10.3, characteristic of (NH) proton and 5.55 (olefinic proton). The IR spectrum showed absorption bands at 1600 (C=N, C=C) and 3200 cm^{-1} (NH).

In connection with the above successful reactions it was the intension to examine the reaction of 3 with ammonium acetate.

Thus, condensation of **3**, (R=CH_3-p) with ammonium aceate in presence of acetic acid resulted in the formation of piperidinopyrazole derivative **5**. Its structure was assigned from its analytical and spectral data. The ^{1}H-NMR spectrum displayed signals at δ 4.6 (-CH-

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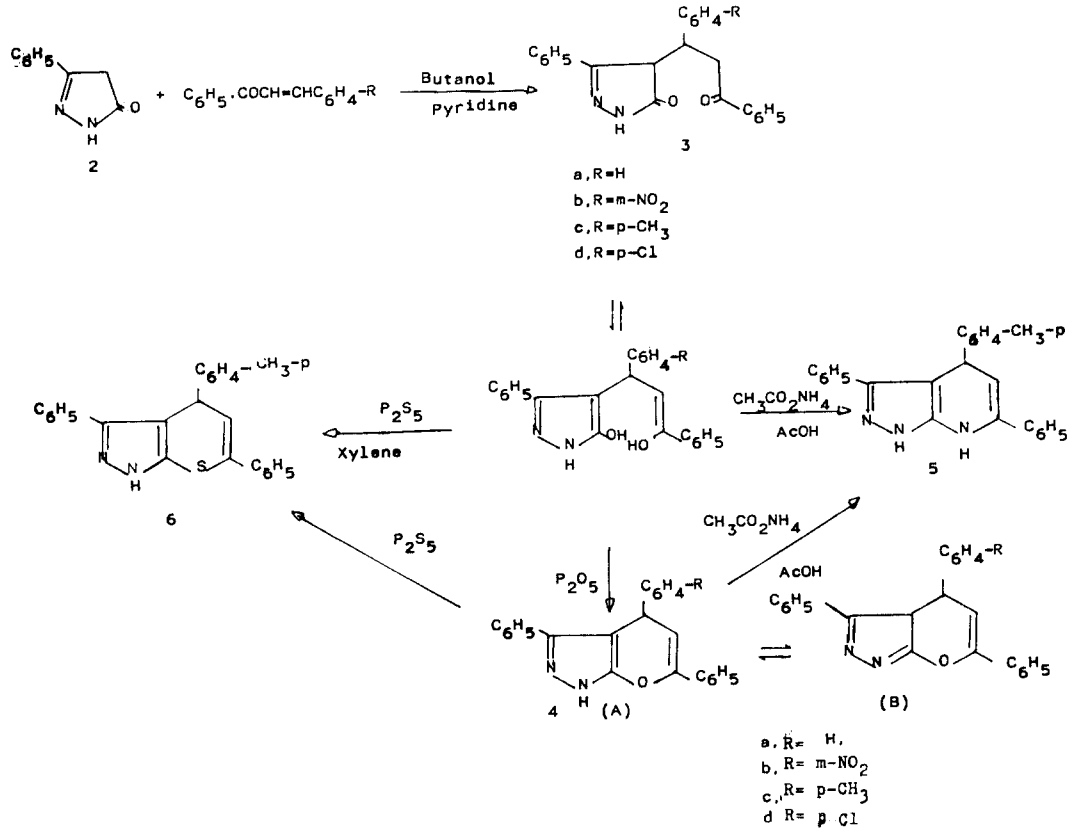

Ar), 5.2 (C=C), 8.3 and 11.9 (2NH).

A proposed synthetic pathway to the structure **5** was proceeded via the interaction of 4 (R=CH_3-p) with the same reagents. The structure of the product **5** fulfils the spectral measurements of that obtained from **3** and the molecular weight is in accordance with the elemental analysis, they have the same melting point and the mixed melting point was unchanged.

Since 1,5-diketones are versatile synthetic intermediates. The condensation of the 1,5-diketones with phosphorous pentasulphide provides a route for a synthesis of thiapyrans. Following the above findings and due to the importance of these compounds as anti-inflammatory agents (Khan and Cosenza, 1982), it was investigated that condensation of **3** with phosphorous pentasulphide would give compounds with potential biological activity. Thus, the reaction of **3** with phosphorous pentasulphide gave the corresponding pyrazolo[5,4-d]thiopyran derivative **6**. Beside the correct analytical data, compound **6** exhibit in its IR spectrum characteristic band at 3210 cm^{-1} (corresponding to one NH). The ^{1}H-NMR spectrum displayed signals at δ 4.3 (-CH-Ar), 5.5 (C=CH) and 9.5 (NH).

Further confirmation for structure **6** was gained from independent synthesis, through the reaction of (**4**) with phosphorous pentasulphide, to give compound (**6**).

Table I. Characterization data of compounds **3a-d**, **4a-d**, **5** and **6**

Compd. No.	m.p. °C	Yield %	Molecular Formula*
3a	95	70	$C_{24}H_{20}N_2O_2$
3b	215	80	$C_{24}H_{19}N_3O_4$
3c	122	83	$C_{25}H_{22}N_2O_2$
3d	90	85	$C_{24}H_{19}N_2O_2Cl$
4a	150	68	$C_{25}H_{17}N_2O$
4b	130	78	$C_{26}H_{20}NO$
4c	115	73	$C_{25}H_{18}NO$
4d	107	80	$C_{25}H_{17}NOCl$
5	230	61	$C_{25}H_{21}N_3$
6	180	70	$C_{25}H_{20}N_2S$

*Satisfactory elemental analysis for C, H and N within ± 0.4% was obtained for all compounds.

EXPERIMENTAL

All melting points are uncorrected. Elemental analysis was performed in the Microanalytical Unit, Faculty of Science, Mansoura University. IR spectra (cm^{-1}) were recorded by means of pressed KBr on Pye-Unicam SP 2000 Infrared Spectrophotometer. ^{1}H-NMR spectra are obtained at 200 MHz using TMS as an internal

standard.

The 1,5-Diketones (3a-d)

General procedure: To a mixture of 3-phenyl-2-pyrazolin-5-one (0.005 mole), α,β-unsaturated ketone (0.005 mole) in n-butanol (30 ml) was added **5** drops of pyridine. The reaction mixture was refluxed for 5 hrs., left to stand at room temperature over night, filtered and crystallized from acetic acid to give compounds (**3a-d**) (see Table I).

Pyrano[3,2-d]pyrazoles (4a-d)

General pracedure: To (0.5 g) of the 1,5-diketones (**3a-d**) was added (10 g PPA). The reaction mixture was heated at 80-100° for 1/2-1 hr., cooled, and poured on to ice-cold water. The solid products that separated were filtered off and treated with sod bicarbonate. solution, washed with cold water, dried and crystallized from ethanol to give compounds (**4a-d**) (see Table I).

Piperidino[3,2-d]pyrazole derivative (5)

Method A: A mixture of **3** (R=CH_3-p) (0.005 mole) and ammonium acetate (0.02 mole) in acetic acid (30 ml) was refluxed for 6 hrs. The solid product that separated was filtered off, dried and crystallized from acetic acid to give compound (**5**) (see Table I).

Method B: To **4** (R=CH_3-p) (0.005 mole) in acetic acid (30 ml) was added (0.02 mole) ammonium acetate. The reaction mixture was refluxed for 6 hrs., left to cool. The solid product that separated was filtered off dried and crystallized from acetic acid to give compound (**5**) (see Table I).

Pyrazolo[5,4-d]thiopyran derivative (6)

Method A: A mixture of 3 (R=CH_3-p) (0.005 mole) and phosphorous pentasulphide (0.005 mole) in dry xylene (40 ml) was refluxed for 5 hrs., left to cool. The solid product that separated was filtered off and crystallized from acetic acid to give compound (**6**) (see Table I).

Method B: To 4 (R=CH_3-p) (0.005 mole) in dry xylene (40 ml) was added phosphorous pentasulphide (0.005 mole). The reaction mixture was refluxed for 6 hrs., left to stand at room temperature for over-night. The solid product that separated was filtered off dried and crystallized from acetic acid to give compound (**6**) (see Table I).

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