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Potential Antidiabetics: Syntheses of Some N^1-Substituted 3,5-Dimethylpyrazoles, N^1-Substituted 3-Methyl-2-pyrazolin-5-ones and Related Compounds

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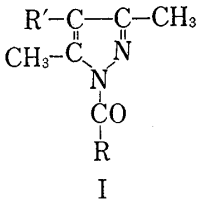
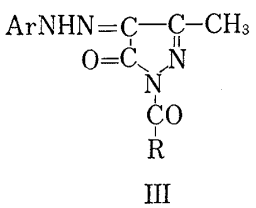
Some new N^1-substituted 3,5-dimethyl (I), 4-arylazo (II) pyrazoles, N^1-substituted 4-arylhydrazono-2-pyrazoline-5-ones (III) and N^1-substituted 2-pyrazoline-5-ones (IV) have been synthesised by the condensation of aroyl/aryloxyacetylhydrazine with 2,4-pentanedione or arylhydrazones of 2,3,4-pentanetrione and ethyl 3-oxobutyrate respectively. Some oxalyl/adipyl-1,1′-bis-3,5-dimethylpyrazoles (V) and oxalyl/adipyl-1,1′-bis-3-methyl-2-pyrazolin-5-ones (VI) have also been prepared by the reaction of oxalyl/adipylhydrazine with 2,4-pentanedione and ethyl 3-oxobutyrate respectively.

The hypoglycemic properties of pyrazoles,[2,3] isoxazoles and antidiuretic effects of 2-pyrazolin-5-ones[4,5] have been well studied by previous workers.[6,7] Working on this hypothesis that introduction of carbonyl group in nitrogen heterocycles enhances the blood sugar lowering properties of the compound,[2] attempts were made to incorporate carbonyl group at position N^1- in pyrazoles, and pyrazolin-5-ones, in the anticipation that the resulting carbamoyl[8] derivatives might be highly active.

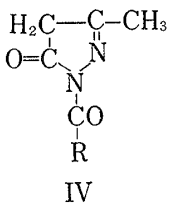


I

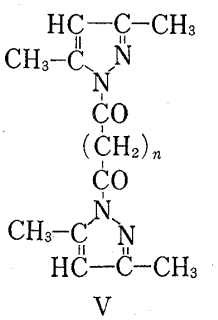
I	R′	R
a	H	2,4-dichlorophenoxymethyl
b	H	2,4,5-trichlorophenoxymethyl
c	H	2-hydroxyphenyl
d	H	$CONHNH_2$
e	H	$(CH_2)_4CONHNH_2$
II		
a	phenylazo	2,4-dichlorphenoxymethyl
b	*p*-chlorphenylazo	2,4-dichlorphenoxymethyl



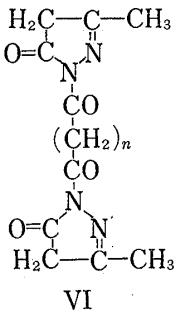
III



IV



V



VI

a : $n=0$
b : $n=4$

1) Location: *Ballia (U.P.) India.*
2) J.B. Wright, W.E. Dulin, and J.H. Markillie, *J. Med. Chem.*, **7**, 102 (1964).
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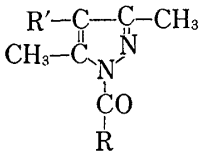
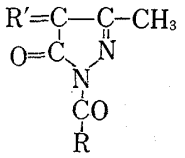
Based on these facts, compounds of the type (I to VI) with different structural units were prepared under different reaction conditions with a view to evaluate their bioligical activities. Compounds of the types I to IV were prepared from 2,4-pentanedione and ethyl 3-oxobutyrate and subsequent cyclisation with aroyl/aryloxyacetylhydrazine to yield the corresponding pyrazoles (I, II) and pyrazolin-5-ones (III, IV). Bispyrazoles (V) and bis-pyrazolin-5-ones (VI) were also prepared by the condensation of oxalyl/adipylhydrazine with 2,4-pentanedione and ethyl 3-oxobutyrate respectively. Some bispyrazoles (V) and bis-pyrazolin-5-ones (VI) along with N^1-substituted 3,5-dimethylpyrazoles (Id, e) were also isolated and characterised by spectral studies and elemental analyses.

Infrared (IR) spectrum of the compound (III) shows sharp bands at 3180 (strong) and 1750 cm^{-1} (medium) which are attributed for -NH stretching vibrations and carbonyl (C=O) group. Peaks at 2950, 2880 cm^{-1} of medium intensity are arised due to C–H stretching vibrations while bands at 1490, 1450 and 1390 cm^{-1} are due to C–H bending vibrations in plane. A strong peak at 1640 cm^{-1} is expected due to NH- deformation coupled with C=C stretching vibrations. Peaks in lower region of the spectrum *i.e.* at 805,880 cm^{-1} are believed due to C–H bending vibrations in out of plane. Spectrum of Ie shows two intense and sharp peaks at 1720 and 1740 cm^{-1} in carbonyl region are expected due to presence of two carbonyl groups situated in different environments. The -NH stretching frequency is greatly affected by the vicinal presence of two carbonyl groups and thus a weak peak appears at 3140 cm^{-1}. A strong and sharp peak appears at 1600 cm^{-1} which is attributed for -NH deformation coupled with C=C stretching vibrations. Peaks at 3230 cm^{-1} in the spectrum of N^1-adipylhydrazino-3-methyl-2-pyrazolin-5-one, reveals the presence of free $-NH_2$ group and strong bands at 2880, 2940 cm^{-1} are attributed for C–H stretching vibrations. A medium band at 1740 cm^{-1} shows the presence of carbonyl (C=O) group while peaks at 1675 and 1610 cm^{-1} are expected due to -NH deformation coupled with C=C stretching vibrations.

TABLE I.



Compound No. I



Compound No. II

No.	R′	R	mp °C	Formula	Calcd.	Found
		Compound No. I				
a	H	2,4,5-trichloro-phenoxymethyl	118	$C_{13}H_{11}O_2N_2Cl_3$	8.39	8.5
b	H	2-hydroxyphenyl	300	$C_{12}H_{12}O_2N_2$	12.96	13.4
c	*p*-chlorophenylazo	2,4-dichlorophenoxy-methyl	210	$C_{19}H_{15}O_2N_4Cl_3$	12.80	13.1
		Compound No. II				
d	H_2	2,4,5-trichloro-phenoxymethyl	220	$C_{12}H_9O_3N_2Cl_3$	8.34	8.5
e	H_2	2-hydroxyphenyl	125	$C_{11}H_{10}O_3N_2$	12.84	13.2
f	phenylhydrazono	2,4,5-trichloro-phenoxymethyl	220	$C_{18}H_{13}O_3N_4Cl_3$	12.74	12.9
g	*p*-chlorophenylazo	2,4-dichlor-phenoxymethyl	198	$C_{18}H_{13}O_3N_4Cl_3$	12.74	12.5

Experimental[9]

N¹-(2,4-Dichlorophenoxy)acetyl-3,5-dimethylpyrazole (Ia)——2,4-Dichlorophenoxyacetylhydrazine (0.002 mole) and 2,4-pentanedione were dissolved in EtOH (20 ml) and refluxed for 2 hr. After this period AcOH (5 ml) was added and futher refluxed for 1 hr. Excess of solvent was evaporated and cooled. A white solid was obtained which was filtered and washed several times with cold EtOH and finally crystallised with EtOH, yield 65%, mp 230°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2Cl_2$: N, 9.36. Found: N, 9.6.

The characteristics of other similar compounds are summarized in Table I.

N¹-(2,4-Dichlorophenoxy)acetyl-3,5-dimethyl-4-phenylazopyrazole (IIa)——It was prepared by the reaction of 2,3,4-pentanetrione-3-phenylhydrazone (0.002 mole) and 2,4-dichlorophenoxyacetylhydrazine (0.002 mole) as described above, mp 200°, yield, 45%. *Anal.* Calcd. for $C_{19}H_{16}O_2N_4Cl_2$: N, 13.9. Found: N, 14.1.

Other compounds in this series are listed in Table I along with their relevant data.

N¹-(2,4-Dichlorophenoxy)acetyl-3-methyl-4-phenylhydrazono-2-pyrazolin-5-one (III)——To a hot solution of 2,4-dichlorophenoxyacetylhydrazine (0.002 mole) in EtOH (20 ml) was added ethyl 3-oxobutyrate-2-phenylhydrazone (0.002 mole) in EtOH (5 ml) the mixture was refluxed on a water bath for 2 hr followed by the addition of AcOH (5 ml). The mixture was further refluxed for 2 hr. Excess of solvent was removed and the contents were cooled in ice when an yellow precipitate was obtained. Crystallization of the crude product with DMF–EtOH mixture gave the pure sample, mp 160°. *Anal.* Calcd. for $C_{18}H_{14}O_3N_4Cl_2$: N, 13.86. Found: N, 14.1.

Other similar compounds, along with relevant data are presented in Table I.

N¹-(2,4-Dichlorophenoxy)acetyl-3-methyl-2-pyrazoline-5-one (IV)——The title compound was prepared by the reaction of ethyl 3-oxobutyrate (0.001 mole) and 2,4-dichlorophenoxyacetylhydrazine as described above, isolated as usual and crystallized from ether, mp 120°, yield 60%. *Anal.* Calcd. for $C_{12}H_{10}O_3N_2Cl_2$: N, 9.3. Found: N, 9.6.

Similar other compounds in this series are recorded in Table I.

Oxalyl-1,1′-bis-3,5-dimethylpyrazole (Va)——A mixture of oxalylhydrazine (0.001 mole) and 2,4-pentanedione (0.002 mole) in EtOH (30 ml) was refluxed for 2 hr followed by the addition of AcOH (5 ml). The mixture was again refluxed for 2 hr more and concentrated to a small volume. On cooling, a white solid separated, was extracted with ether, which on evaporation afforded Va and was crystallized with ether, mp 110°. *Anal.* Calcd for $C_{12}H_{14}O_2N_4$: N, 22.76. Found: N, 23.1.

The ether insoluble portion was recrystallized with EtOH, mp 160° and characterized as Id. *Anal.* Calcd. for $C_7H_{10}O_2N_4$: N, 30.76. Found: N, 30.4.

Adipyl-1,1′-bis-3,5-dimethylpyrazole (Vb)——It was prepared by the procedure described above from adipylhydrazine (0.001 mole) and 2,4-pentanedione (0.002 mole). In this also two fractions were obtained. The ether soluble fraction on evaporation gave white crystalline solid which was characterized as bis pyrazole mp 115°. *Anal.* Calcd. for $C_{16}H_{22}O_2N_4$: N, 18.54. Found: N, 18.7.

The ether insoluble portion was crystallized with EtOH whose microanalysis corresponds to Ie, mp 200°. *Anal.* Calcd for $C_{11}H_{18}O_2N_4$: N, 23.5. Found: N, 24.0.

Oxalyl-1,1′-bis-(3-methyl-2-pyrazoline-5-one) (VIa)——Oxalylhydrazine (0.001 mole) and ethyl 3-oxobutyrate (0.002 mole) in EtOH (30 ml) were refluxed for 2 hr, followed by addition of AcOH (5 ml). The mixture was further refluxed for 1 hr. Excess of solvent was removed and the residue was extracted with ether. Evaporation of the extract afforded crystalline solid mp 120°. *Anal.* Calcd. for $C_{10}H_{10}O_4N_4$: N, 22.4. Found: N, 22.6.

In this case no ether insoluble residue was obtained.

N¹-Adipylhydrazino-3-methyl-2-pyrazolin-5-one——Adipylhydrazine (0.001 mole) and ethyl 3-oxobutyrate (0.002 mole) in EtOH (40 ml) were refluxed as described above. The ethereal extract gave traces of crystalline leaflet which could not be characterized while the ether insoluble portion on crystallization with EtOH afforded a white solid which was characterized as N¹-monoadipylhydrazino-3-methyl-2-pyrazoline-5-one, mp 300°. *Anal.* Calcd. for $C_{10}H_{16}O_3N_4$: N, 23.32. Found: N, 22.9.

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9) All the melting points are not corrected.