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Synthesis of Certain Uracil-6-yl or Tetrazol-5-ylpyrazolin-5-one and Pyrazole Derivatives as Potential Anti-inflammatory Agents

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Abstract□Certain pyrazolin-5-one and pyrazole derivatives bearing uracil-6-yl or tetrazol-5-yl moiety in position 1 have been synthesized. The anti-inflammatory activity of six representative compounds have been tested and the results are reported.

Keywords□Synthesis, anti-inflammatory activity, uracil, tetrazole, pyrazolin-5-ones, pyrazoles.

Molecular hybridization, *i.e.*, association of two different moieties through a covalent bond, is one of the used methods in the development of new drugs[1], as in case of formation of Benorylate from acetyl salicylic acid and acetaminophen. The anti-inflammatory activity of pyrazolone[2, 3] and pyrazole[4] derivatives, in one hand, and those of uracil[5-8] and tetrazole[9, 10] derivatives, on the other hand, are well established. Based on thse observations and making use of the molecular hybridization assumption, we report herein, the synthesis of several pyrazolin-5-one and pyrazole derivatives carrying uracil-6-yl or tetrazol-5-yl moiety in position 1 as potential anti-inflammatory agents.

RESULTS AND DISCUSSION

Chemical synthesis

1,3-Dimethyluracil-6-ylhydrazine[11] **(A)** and 1-phenyl-1H-tetrazol-5-ylhydrazine[12] **(B)** were prepared by the action of hydrazine on 6-chloro-1,3-dimethyluracil[11] and 5-chloro-1-phenyl-1H-tetrazole, respectively. Ethyl α-arylhydrazono-β-oxobutyrates **(1-3)**, ethyl α-arylhydrazono-β-phenyl-β-oxopropionates **(4-6)** and β-arylhydrazonoacetylacetones **(7-9)**, have been prepared by coupling the appropriate aryldiazonium chlorides with the corresponding β-diketones[13]. Condensation of prepared hydrazines **(A, B)** with compounds **(1-6)** afforded 1-(1,3-dimethyluracil-6-yl)-3-methyl or phenyl-4-arylhydrazono-2-pyrazolin-5-ones **10-15** (Table I), and 1-(1-phenyl-1H-tetrazol-5-yl)-3-methyl or phenyl-4-arylhydrazono-2-pyrazolin-5-ones **16-20** (Table I), (Scheme 1).

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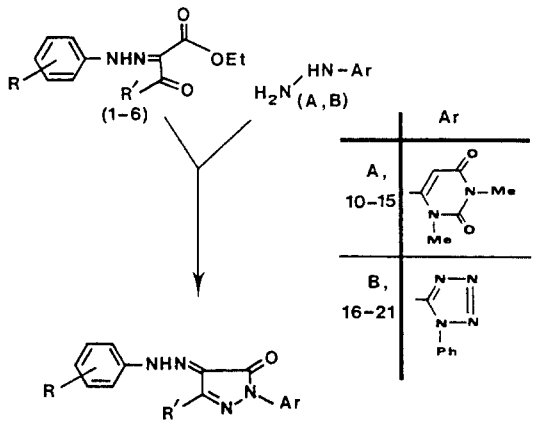
Table I. 1-(1,3-Dimethyluracil-6-yl)-3-methyl or phenyl-4-arylhydrazono-2-pyrazolin-5-ones (10-15) and 1-(1-phenyl-1H-tetrazol-5-yl)-3-methyl or phenyl-4-arylhydrazono-2-pyrazolin-5-ones (16-21).

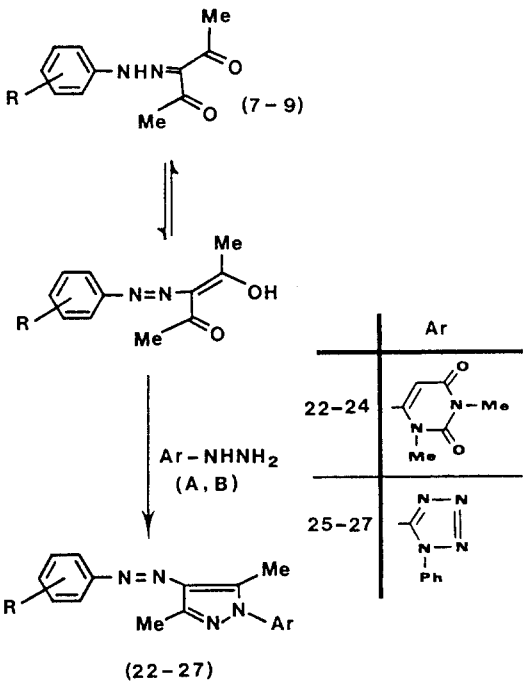
Comp. No.	R	R'	m.p. °C	Yield %	Molecular Formulae*
10	*o*-Cl	CH_3	208-10	69	$C_{16}H_{15}ClN_6O_3$
11	*p*-Cl	CH_3	217-9	65	$C_{16}H_{15}ClN_6O_3$
12	*p*-CH_3O	CH_3	132-4	65	$C_{17}H_{18}N_6O_4$
13	*o*-CH_3	C_6H_5	152-4	55	$C_{22}H_{20}N_6O_3$
14	*m*-CH_3	C_6H_5	194-6	58	$C_{22}H_{20}N_6O_3$
15	*o*-NO_2, *p*-CH_3O	C_6H_5	184-6	50	$C_{22}H_{19}N_7O_6$
16	*o*-Cl	CH_3	200-1	60	$C_{17}H_{13}ClN_8O$
17	*p*-Cl	CH_3	202-4	70	$C_{17}H_{13}ClN_8O$
18	*p*-CH_3O	CH_3	185-7	60	$C_{18}H_{16}N_8O_2$
19	*o*-CH_3	C_6H_5	147-9	66	$C_{23}H_{18}N_8O$
20	*m*-CH_3	C_6H_5	161-3	65	$C_{23}H_{18}N_8O$
21	*o*-NO_2, *p*-CH_3O	C_6H_5	188-90	54	$C_{23}H_{17}N_9O_4$

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

Similarly, 1-(1,3-dimethyluracil-6-yl or 1-phenyl-1H-tetrazol-5-yl)-3,5-dimethyl-4-arylazopyrazoles **22-27** (Table II), were obtained by condensation of the prepared hydrazine derivatives **(A, B)** with β-arylhydrazonoacetylacetones **7-9** (Scheme 2). Longer reaction time was necessary for the formation of compounds **15, 21, 24** and **27** which contain electron withdrawing groups on the arylhydrazono moiety. The



Scheme 1



Scheme 2

structures of the synthesized compounds have been confirmed by microanalytical data, IR and ^{1}H-NMR spectra.

Anti-inflammatory testing

The anti-inflammatory activity of compounds **12, 14, 16, 21, 22** and **27** was determined by the carrageenin-induced paw edema in rats[14]. Groups of five male albino rats each, were dosed with the test compound orally as a uniform suspension in 0.05% aqueous Methocel solution in a dose of 100 mg/kg, one hour before injection of 0.05 m*l* of 1% carrageenin solution subcutaneously into the plantar tissue of left hind paw. The right paw was injected with 0.05 m*l* normal saline solution. Four hours after carrageenin injection, rats were killed by cervical dislocation, the right and left paws were cut at the tibiotarasal articulation and weighed. The percentage increase in the weight of carrangeenin-injected paw over the other paw for each rat was determined and compared with the results obtained in a group of rats received 4 mg/kg indomethacin (as a reference anti-inflammatory drug) orally and treated in the same manner. The results obtained revealed that compounds **12** and **22** displayed a moderate anti-inflammatory activity (Table III), compared to indomethacin, whereas the other tested compounds were devoid of significant

Table II. 1-(1,3-Dimethyluracil-6-yl or 1-phenyl-1H-tetrazol-5-yl)-3,5-dimethyl-4-arylazopyrazoles (22-27)

Comp. No.	R	m.p. °C	Yield %	Molecular Formulae*
22	*p*-Br	222-4	50	$C_{17}H_{17}BrN_6O_2$
23	*p*-CH_3	164-6	55	$C_{18}H_{20}N_6O_2$
24	*p*-COOH	275-7	50	$C_{18}H_{18}N_6O_4$
25	*p*-Br	226-8	50	$C_{18}H_{15}BrN_8$
26	*p*-CH_3	171-3	58	$C_{19}H_{18}N_8$
27	*p*-COOH	262-4	50	$C_{19}H_{16}N_8O_2$

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

Table III. Effect of compounds 12, 14, 16, 21, 22 and 27 (100 mg/kg) and indomethacin (4 mg/kg) on carrageenin-induced paw edema in rats

Treatment	Mean % Increase in* Carrageenin-Injected Paw Weight	% Reduction in Edema from Control
Control	75.2 ± 3.1	–
12	56.9 ± 3.7#	24.3
14	71.3 ± 5.6	5.2
16	73.4 ± 4.2	2.4
21	69.7 ± 4.5	7.3
22	58.7 ± 3.8#	21.9
27	69.8 ± 5.7	7.1
Indomethacin	32.7 ± 1.95	56.5

*Values are expressed as a mean of five measurements ± SEM.
#Significant difference from control at $p < 0.05$

anti-inflammatory activity.

EXPERIMENTAL

Melting points were determined on a Heine melting point apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP 1000 spectrophotometer in KBr discs (ν, in cm^{-1}). ^{1}H-NMR spectra were performed on a Varian EM 390 90 MHz instrument using TMS as an internal standard and $CDCl_3$ as a solvent (chemical shift in δ, ppm).

1-(1,3-Dimethyluracil-6-yl or 1-phenyl-1H-tetrazol-5-yl)-3-methyl or phenyl-4-arylhydrazono-2-pyrazolin-5-ones (10-21), and 1-(1,3-dimethyluracil or 1-phenyl-1H-tetrazol-5-yl)-3,5-dimethyl-4-arylazopyrazoles (22-27)

A mixture of the appropriate β-diketone **1-9** (0.01 mole) and 1,3-dimethyluracil-6-ylhydrazine **A** or 1-phenyl-1H-tetrazol-5-ylhydrazine **B** (0.01 mole), in ethanol (50 m*l*), was heated under reflux for 7 hours (20 hours reflux time was necessary for formation of compounds **15, 21, 24,** and **27**). On cooling, the separated solid was filtered, dried and crystallized from ethanol. Melting points, yield percentages and molecular formulae are listed in Table I (**10-21**) and Table II (**22-27**). IR: **10;** 1550 (C=N), 1755 (C=O) and 3320 (NH). **17:** 1650 (C=N), 1740 (C=O) and 3250 (NH). **22:** 1580 (N=N) and 1660 (C=N). ^{1}H-NMR: **12;** 2.35 (s, 3H, Pyrazolone-CH_3), 2.55 (s, 3H, Uracil-1-CH_3), 3.80 (s, 6H, Uracil-3-CH_3 & OCH_3), 6.90-7.40 (m, 5H, Ar-H) and 13.20 (s, 1H, NH). **17:** 2.35 (S, 3H, CH_3), 7.30-7.65 (m, 9H, Ar-H) and 13.0 (s, 1H, NH). **26:** 2.35 (s, 6H, Pyrazole-CH_3), 2.75 (s, 3H, Ar-CH_3) and 7.25-7.70 (m, 9H, Ar-H).

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