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Reactions with 3-Pyrazolin-5-ones: Synthesis of some 4-Substituted 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-ones

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4-Acetylantipyrine **(1)** was condensed with aromatic or heterocyclic aldehydes to yield the cinnamoylidene derivatives **4a–d**. Compound **4b** was converted into the pyrazolinylantipyrine derivative **9** by hydrazine hydrate. 4-(Chloroacetyl)antipyrine **(2)** reacted with aldehydes to yield the furan-2-one derivatives **11** or the dihydroxy derivative **12**. The behaviour of 4-formylantipyrine toward methylenenitriles was investigated.

Reaktionen mit 3-Pyrazolin-5-onen: Synthese einiger 4-substituierter 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one

4-Acetylantipyrin **(1)** wurde mit aromatischen sowie mit heterocyclischen Aldehyden zu den Cinnamoyliden-Derivaten **4a–d** kondensiert. Das Pyrazolinylantipyrin-Derivat **9** wird durch Reaktion zwischen dem Cinnamoyliden-Derivat **4b** und Hydrazinhydrat hergestellt. 4-Chloracetyl-antipyrin **(2)** reagiert mit Aldehyden zu den Furan-2-on-Derivaten **11** oder den Dihydroxy-Derivaten **12**. Die Reaktionen des 4-Formylantipyrins mit aktiven Methylennitrilen werden untersucht.

Diverse pharmacological properties have been associated with 3-pyrazolin-5-one derivatives[1–6]. These include anti-inflammatory, analgesic, sedative and antipyretic properties. As a part of a medicinal chemistry program in our laboratories[7] we became interested in the synthesis of certain 4-substituted 3-pyrazolin-5-one derivatives.

The readily accessible 4-acetyl-**(1)**[1], 4-chloroacetyl-**(2)**[8] and 4-formylantipyrine **(3)**[9] were utilised as starting materials. Thus, for preparation of the 4-cinnamoylantipyrine derivatives **4**, condensation of 4-acetyl-antipyrine with aromatic aldehydes was attempted. Under a variety of reaction conditions reported to effect condensation of acetylheterocyclic derivatives with aromatic aldehydes, compound **1** failed to condense with aldehydes. However, when **1** was kept with aromatic aldehydes in ethanolic potassium hydroxide solution, condensation products were obtained. Structure **4** or isomeric **5** seemed possible for the reaction products. Structure **4** could be established for the condensation products based on identity of products obtained from the reaction of **6** and cinnamoyl chloride and that obtained from **1** and benzaldehyde.

Similar to aromatic aldehydes, the heterocyclic aldehydes **7a, b** afforded the arylidene derivatives **8a, b** when treated with **1** under the same experimental conditions.

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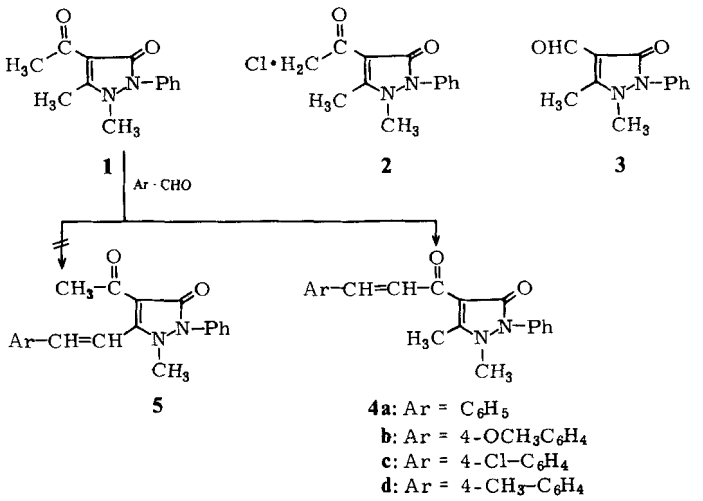


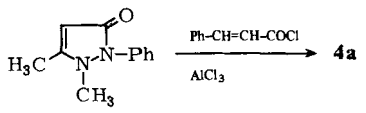
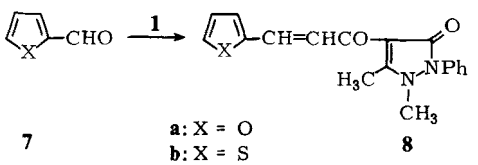
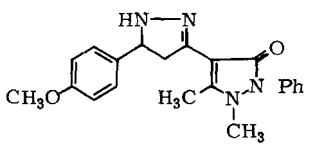


Chart 1



The arylidene derivative **4b** reacted with hydrazine hydrate to yield the 4-(pyrazolin-3-yl)-antipyrine derivative **9**.



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Compound **2** reacted with p-chlorobenzaldehyde, p-nitro-benzaldehyde and thiophen-2-aldehyde to yield products for which structure **10** was suggested based on analytical and spectral data. The formation of **10** in these reactions is assumed to proceed via initial formation of chlorohydrin intermediates which react with another molecule of **2** to yield the final isolable products. In contrast to this p-methoxy- and p-methylbenzaldehyde afforded the hydroxyfuranyl-bipyrazole derivatives **11** under the same conditions. The formation of **11** in this reaction is easily interpreted in terms of tautomerisation of intermediate **10** into **12** which then loses water to yield the final isolable product **11.**

In an attempt to effect condensation of **2** with amines, compound **2** was boiled with equivalent amounts of the amine in pyridine solution. Unexpectedly one and the same reaction product was isolated from reaction of **2** with different amines. The same product was readily obtained on boiling **2** in pyridine solution. Structure **13** could be established for this product based on its analytical and IR data. The formation of **13** is assumed to proceed via the sequence demonstrated in chart 2.

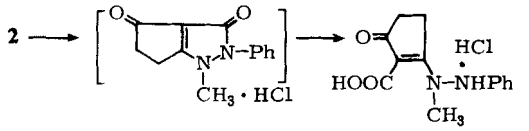
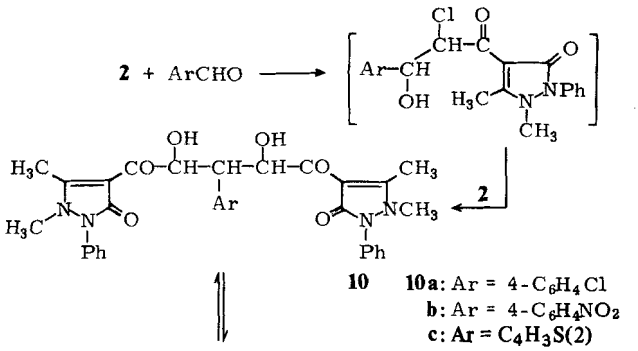
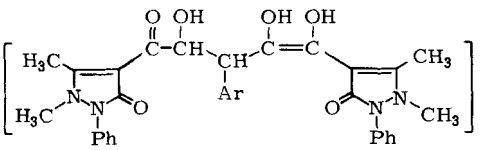
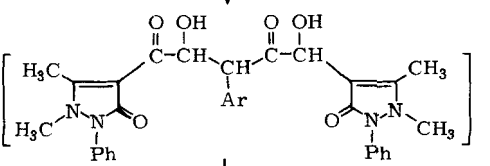


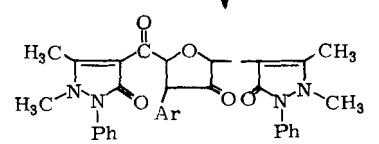
Chart 2 **13**



10 **10a**: Ar = 4-C_6H_4Cl
b: Ar = 4-$C_6H_4NO_2$
c: Ar = $C_4H_3S(2)$

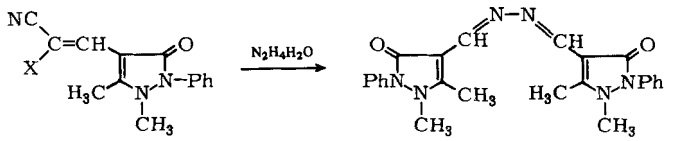






11a: Ar = 4-OCH_3-C_6H_4
b: Ar = 4-CH_3-C_6H_4

Although compound **3** has been reported to condense readily with active methylene derivatives to yield the corresponding ylidene derivatives, the reaction of **3** with ethyl cyanoacetate and with malononitrile has not yet been reported. Now, it has been found that **3** condenses with both reagents to yield the ylidene derivatives **14a, b.** Attempts to convert **14a, b** into amino-pyrazole derivatives by treatment with hydrazines in a manner similar to that reported for the arylcounter analogues has resulted in the formation of the azine **15** and the hydrazone **16.** Compounds **15** and **16** could be directly formed from reaction of **3** with hydrazines.



14a: X = CN
b: X = COOEt

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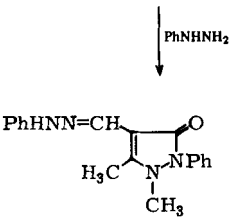

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Biological activity

Compounds **4a–d, 8a, b, 10a–c** and **11a, b** were tested for biological activity. Pronounced analgesic activity was observed for all of the tested compounds.

The authors are deeply indepted to Prof. *M. H. Elnagdi,* Chemistry Department, Faculty of Science, Cairo University, for valuable criticism and discussions.

Experimental Part

Melting points: uncorr. *IR spectra:* (KBr) Pya Unicam SP-1100-Spectrophotometer. *Elemental microanalyses:* Micro-analytical Unit at Cairo University.

4-Cinnamoyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones **4a–d**

General procedure: To a solution of 0.01 mole **1** in 20 ml ethanol a solution of 0.01 mole of the appropriate aldehyde in 10 ml ethanol and 5 ml of 10 % NaOH were added. The reaction mixture was stirred for 1 h then left overnight at room temp. The solid product was crystallised from the proper solvent. The reaction products are listed in table 1. The IR spectrum of a selected typical example is listed in table 2.

Table 1: *4-Substituted 2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones* **4a–d; 8a, b; 10a–c; 11a, b; 15** *and* **16.**

Compound	Cryst. solvent	m.p.	yield	Molec. formula (Molec. Wt.)	Calcd. Found	C	H	N
4a	MeOH	230	85	$C_{20}H_{18}N_2O_2$ (318.4)		75.4 74.7	5.66 5.81	8.8 8.5
4b	EtOH	231	67	$C_{21}H_{20}N_2O_3$ (348.4)		72.4 72.6	5.75 5.80	8.0 7.7
4c	EtOH	216	73	$C_{20}H_{17}ClN_2O_2$ (352.8)		68.1 68.6	4.82 5.03	7.9 7.6
4d	EtOH	241	86	$C_{21}H_{20}N_2O_2$ (332.4)		75.9 75.3	6.02 6.36	8.4 7.9
8a	MeOH	205	82	$C_{18}H_{16}N_2O_2$ (308.3)		70.1 70.6	5.19 5.28	9.0 8.3
8b	AcOH	238	93	$C_{18}H_{16}N_2O_2S$ (324.4)		66.6 66.4	4.94 4.89	8.6 8.2
10a	Dioxan	215	98	$C_{33}H_{31}ClN_4O_6$ (615.1)		64.4 64.8	5.04 4.60	
10b	Benzene	195	80	$C_{33}H_{31}N_5O_8$ (625.6)		63.4 63.4	4.96 4.90	
10c	Benzene	1953	93	$C_{31}H_{30}N_4O_6S$ (586.7)		63.4 63.6	5.11 4.85	
11a	Dioxan	193	93	$C_{34}H_{32}N_4O_5$ (576.7)		70.8 70.9	5.56 5.80	9.7 9.7
11b	Benzene	173	82	$C_{34}H_{32}N_4O_6$ (592.7)		68.1 68.6	5.41 5.64	
15	DMF	290	93	$C_{24}H_{24}N_6O_2$ (428.5)		67.3 67.5	5.61 5.70	
16	DMF	260	97	$C_{18}H_{18}N_4O$ (306.4)		70.6 70.7	5.89 5.90	

Reaction of antipyrine with cinnamoyl chloride

A suspension of 9.4 g antipyrine in 15 ml nitrobenzene and 50 ml carbon disulphide was treated with 10.0 g anhydrous aluminium chloride and 8.4 g cinnamoyl chloride. The reaction mixture was left overnight at room temp. then pourred onto cold dilute hydrochloric acid. The solid product was

Table 2: *IR spectral data of 4-substituted 2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones* **4b, 10a, 10c, 11a, 15, 16.** (KBr)

Compound	IR ; cm^{-1}
4b	3050, 2980–2940 (CH, CH_3); 1660 and 1640 (ring and cinnamoyl C=O) and 1610 (C=C).
10a	3500–3300 (OH); 3000, 2950 (CH, CH_3); 1660–1645 (ring and exocyclic C=O).
10c	3550–3300 (OH); 1690, 1660–1640 (ring and exocyclic C=O).
11a	3010, 3000–2950 (CH and CH_3); 1650–1630 (ring and exocyclic C=O).
15	3090 (NH); 2950 (CH_3); 1660 (ring C=O) and 1630 (C=N).
16	3280 (NH); 3020, 2990 (CH and CH_3); 1660 (ring C=O) and 1610 (C=N).

proved (m. p. and mixed m. p.) to be identical with the product obtained via reaction of **1** with benzaldehyde.

Reaction of **4b** *with hydrazine hydrate*

A mixture of 1.0 g **4b** and 1.0 ml hydrazine hydrate was heated at 100°C (bath temp.) for 2 h. The reaction mixture was triturated with ethanol and the resulting solid product was crystallised. Compound **9** formed yellow crystals from ethanol; m. p. 217; yield 0.5 g. $C_{21}H_{22}N_4O_2$ (362.5) Calcd. C 69.6 H 6.01 Found C 69.8 H 5.48.

Reaction of **2** *with aldehydes*

The experimental procedure described for condensation of **1** with aromatic aldehydes in presence of sodium hydroxide was adopted and the reaction product was crystallised from the proper solvent (cf. table 1). IR spectra of compounds **10a, c** and **11a** are listed in table 2.

Reaction of **2** *with pyridine*

A solution of 2.0 g **2** in 20 ml pyridine was refluxed for 15 min. The solid product was crystallised. Compound **13** formed colourless crystals from ethanol, m. p. 232°C; yield 86 %. IR: 3420, 3390 (OH and NH), 3010, 2970 (CH and CH_3); 1660–1640 cm^{-1} (exocyclic and ring C=O). $C_{13}H_{13}ClN_2O_2$ (264,7) Calcd. C 58.9 H 4.92 N 10.5 Found C 58.2 H 5.79 N 10.2.

Condensation of **3** *with malononitrile and with ethyl cyanoacetate*

To a solution of 2.16 g **3** in 20 ml ethanol 0.01 mole of each of malononitrile or ethyl cyanoacetate was added. The reaction mixture was refluxed for 30 min, then evaporated under vac. to one third of its original vol. The resulting solid product was crystallised from the proper solvent. Compound **14a** formed yellow crystals from DMF; m. p. 225°C; yield 85 %. IR: 2990 (CH and CH_3); 2210 (CN); 1690 cm^{-1} (ring C=O). $C_{15}H_{12}N_4O$ (264.2) Calcd. C 68.2 H 4.55 N 21.2 Found C 68.6 H 4.54 N 20.5.

Compound **14b** formed yellow crystals from methanol; m. p. 148°C, yield 66 %. IR: 3000-2950 (CH and CH_3); 2220 (CN); 1725–1690 cm^{-1} (ester and ring C=O). $C_{17}H_{17}N_3O_3$ (311.3) Calcd. C 65.6 H 5.46 N 13.5 Found C 65.6 H 5.60 N 13.2.

Reaction of **14a, b** *with hydrazines*

A solution of 0.01 mole of **14a** or **14b** in 20 ml ethanol was treated with 0.012 mole hydrazine hydrate or phenyl-hydrazine. The reaction mixture was refluxed for 30 min, then evaporated. The remaining product was triturated with water and acidified with concentrated hydrochloric acid. The solid product was crystallised. Compounds **15** and **16** are listed in table 1. The IR spectral data are listed in table 2.

References

1 K. Stach, Arch. Pharm. (Weinheim) *295,* 853 (1962).
2 W. Krohs, Ber. Dtsch. Chem. Ges. *88,* 866 (1955).
3 W. Ogemann, T. Lauria and V. Zambon, Ber. Dtsch. Chem. Ges. *88,* 1353 (1955).
4 R. K. Robbins, J. Heterocycl. Chem. *14,* 1107 (1977).
5 J. M. Uszler, L. R. Bannett and I. Mena, Radiology *115,* 197 (1975).
6 C. Heidelberger, Nucleic Acid Res. Mol. Biol. *4,* 1 (1965).
7 M. R. H. Elmoghayer, M. K. A. Ibraheim, M. H. Elnagdi and A. H. El-Ghandour, Synthesis *1981,* 635.
8 H. P. Kaufmann and L. S. Huang, Ber. Dtsch. Chem. Ges. *75,* 1214 (1942).
9 I. Ito, J. Pharm. Soc. Jpn. *76,* 167 (1956).

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H_2-Antihistaminika, 11. Mitt.[1)]

Zyklische Guanidine mit H_2-antihistaminischer Wirkung

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Eingegangen am 11. Januar 1982

Es wurden zyklische Guanidine dargestellt und auf ihre H_2-antihistaminische Wirksamkeit untersucht.

H_2-Antihistaminics, XI: Cyclic Guanidines with H_2-Antihistaminic Activity

Cyclic guanidines were prepared and tested for their H_2-antihistaminic activity.

In der vorliegenden Arbeit soll die Frage untersucht werden, in welchem Umfang die polare Thioharnstoff- bzw. Cyanoguanidin-Gruppierung der H_2-Antihistaminika durch einen zyklischen Guanidinrest ersetzt werden kann.

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