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Reactions with 3-Pyrazolin-5-ones: Synthesis of 3.4-Dihydropyridone and Pyrano [2.3-c] pyrazole Derivatives

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Several antipyrinylpyridones and pyrano [2.3-*c*] pyrazoles were synthesized from 4-(cyanomethylcarbonyl)antipyrine and pyrazolinone derivatives.

Reaktionen mit 3-Pyrazolin-5-onen: Synthese von 3.4-Dihydropyridon- und Pyrano[2.3-c]pyrazol-Derivaten

Einige Antipyrinyl-pyridone und Pyrano [2.3-c] pyrazole wurden u. a. aus 4-(cyanomethylcarbonyl)-antipyrin und Pyrazolinon-Derivaten hergestellt.

The considerable biological activities of antipyrine (1-phenyl-2.3-dimethyl-3-pyrazolin-5-one) has stimulated interest in the synthesis of differently substituted antipyrine derivatives. In the last few years we have been involved in a program[1–4] directed to the development of synthetic approaches to various heterocyclic derivatives with antipyrinyl substituents. Recently[5–8], it has been found that cinnamonitriles react readily with active methylene nitriles to give pyrans in good yields. In this context we report our results synthesizing pyran-6-ylantipyrines utilising Soto's approach[5] to pyrans.

Thus, it has been found that **1** reacts with the ylidene malononitriles **2a–c** to yield 1:1 adducts. The same products were obtained on reacting the ylidene derivatives **3a–c** with malononitrile. Four different possible isomeric structures were thus considered (cf. **4–7**). Structure **4** was readily ruled out by IR spectra of the reaction products

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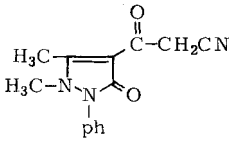
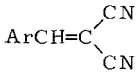
which clearly revealed the absence of amino group absorption. If the reaction products were pyrans, a singlet for the C-4 proton would have appeared at $\delta = 4.5$–5.5 ppm[6, 7]. The band at 3400 cm^{-1} can be coordinated to the hydroxy function in **6** (a tautomer of **5**) or to the NH band in **7**. **5** and **6** were, however, ruled out as ^{1}H-NMR revealed a pattern different than that expected for structures **5** or **6**. Thus, the dihydropyridone structure **7** was established for the reaction products. The formation of **7** from **1** and **2** is assumed to proceed via the intermediate **4** formed from the Michael adducts **5** or possible isomers **6**. Rearrangement of **4** to **7** finds parallism to reported[9] rearrangements of pyrans into pyridines.

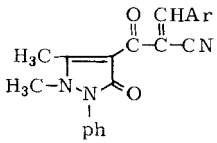


1



2-7

a, Ar = C_6H_5
b, Ar = $C_6H_4 \cdot Cl$ (p)
c, Ar = $C_6H_4 \cdot OCH_3$ (p)
d, Ar = $C_6H_4 \cdot N(CH_3)_2$ (p)



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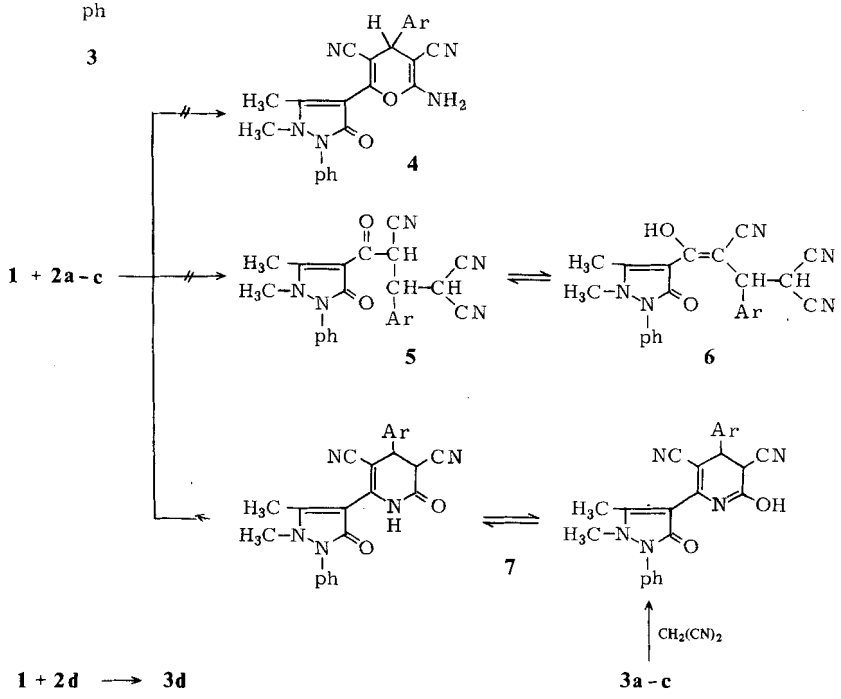
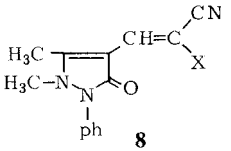
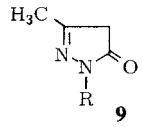




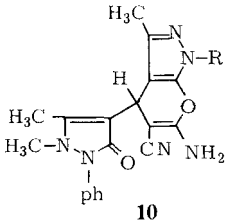
8

a, X = CN
b, X = $COOC_2H_5$
c, X = COC_6H_5



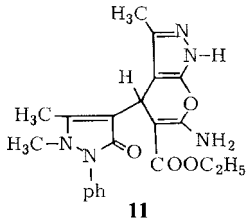
9

a, R = H
b, R = C_6H_5



10

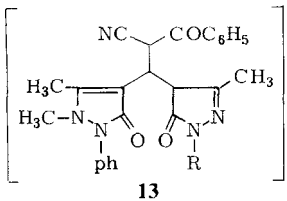
a, R = H
b, R = C_6H_5



11

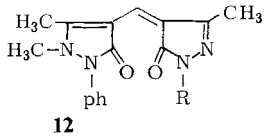
9a + 8b ⟵

8c + 9a, b ⟶



13

⟶



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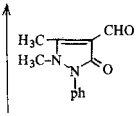

9a, b

However, in contrast to reported ready oxidation[10-12] of dihydropyridine derivatives into pyridines, compounds **7** were found to be fairly stable and could be crystallized and stored in solid state without any noticeable change. Isolation of similarly stable dihydropyridines has been recently observed[13].

In contrast to the behaviour of **2a–c** toward **1**, **2d** reacted with **1** to yield a product that was proved to be the ylidene derivative **3d** as it was also obtained via condensation of p-dimethylaminobenzaldehyde with **1**.

Similar to the previously reported[6, 7] formation of pyranopyrazoles from cinnamonitriles and 3-methylpyrazolones **8**, compound **9a** reacted with **8a** to yield the pyranopyrazole derivative **10a**. Also **9b** reacted with **8a** to yield the pyran derivative **10b**.

Tab. 1: Newly synthesized products

Comp. No.	M. P. (C°)	Yield % (Solvent)	IR; cm^{-1} (Selected bands)	Formula (M. W.)	Found / Calcd.	Analysis (%) C	H	N
3b	208	80 (DMF)	2200 (conjugated CN); 1710 (exocyclic CO); 1660 (antipyrinyl CO) .	$C_{21}H_{16}N_3O_2Cl$ (377.85)	Found	66.7	4.15	11.3
					Calcd.	66.7	4.27	11.1
3c	180	85 (C_2H_5OH)	2205 (conjugated CN); 1700 (exocyclic CO); 1650 (antipyrinyl CO) .	$C_{22}H_{19}N_3O_3$ (373.42)	Found	70.7	5.24	11.1
					Calcd.	70.7	5.13	11.2
3d	205	75 (C_2H_5OH)	2205 (conjugated CN); 1690 (exocyclic CO); 1660 (antipyrinyl CO) .	$C_{23}H_{22}N_4O_2$ (386.46)	Found	71.5	5.64	14.4
					Calcd.	71.4	5.74	14.5
7a	300	70 (Chloroform)	3400 (OH); 3000 (CH_3); 2200 (CN); 1660 (antipyrinyl CO) .	$C_{24}H_{19}N_5O_2$ (409.45)	Found	70.2	4.76	17.2
					Calcd.	70.4	4.68	17.1
7b	318	72 (DMF)	3420 (OH); 3000, 2990 (CH_3); 2210 (CN); 1660 (antipyrinyl CO) .	$C_{24}H_{18}N_5O_2Cl$ (443.89)	Found	65.1	4.21	15.6
					Calcd.	64.9	4.09	15.7
7c	305	75 (DMF)	3480 (OH); 3010, 3000 (CH_3); 2200 (CN); 1660 (antipyrinyl CO) .	$C_{25}H_{21}N_5O_3$ (439.48)	Found	68.2	4.76	15.7
					Calcd.	68.3	4.82	15.9
10a	230	70 (C_2H_5OH)	3480, 3300, 3150 (NH, NH_2); 2200 (CN); 1660 (antipyrinyl CO) .	$C_{19}H_{18}N_6O_2$ (362.40)	Found	62.9	5.13	23.4
					Calcd.	62.9	5.01	23.2
10b	> 300	65 (DMF)	3300, 3100 (NH_2); 2205 (CN); 1660 (antipyrinyl CO) .	$C_{25}H_{22}N_6O_2$ (438.5)	Found	68.3	5.12	19.2
					Calcd.	68.4	5.06	19.1
11	271 (dec.)	68 (aq. DMF)	3500, 3300, 3100 (NH, NH_2); 1720 (ester CO); 1650 (antipyrinyl CO) .	$C_{21}H_{23}N_5O_4$ (409.45)	Found	61.7	5.56	16.9
					Calcd.	61.6	5.66	17.1
12a	242	72 (aq. C_2H_5OH)	3010, 2990 (CH_3); 1660 (antipyrinyl CO); 1610 (C=C) .	$C_{16}H_{16}N_4O_2$ (296.33)	Found	64.7	4.58	18.7
					Calcd.	64.8	4.44	18.9
12b	188	80 (C_2H_5OH)	3010, 2990 (CH_3); 1650 (antipyrinyl CO); 1610 (C=C) .	$C_{22}H_{20}N_4O_2$ (372.43)	Found	70.9	5.60	15.2
					Calcd.	70.9	5.41	15.0

Structure **10** was infered from its ^{1}H-NMR spectrum which reveales a one H singlet at $\delta = 4.7$ ppm for the pyran proton. Compound **8b** reacted with **9a** to give **11**. The IR spectrum of **11** reaveals the absence of a CN absorption and indicates that the ester group was not involved into the reaction. In contrast, reaction of **8c** with **9a** or **9b** afforded the ylidene derivatives **12a** and **12b**, respectively. Compounds **12a** and **12b** could be also obtained from the reaction of **9a** or **9b** with 4-formylantipyrine. **12** is assumed to be formed via addition of **8c** to **9** and elimination of benzoylacetonitrile. A similar mechanism has been previously suggested to account for the formation of ylidene derivatives from α-cyanochalcones and active methylene reagents[6].

Experimental Part

MP: uncorr.-Infrared spectra: (KBr disc) Pye-Unicam SP-1100 spectrophotometer. – ^{1}H-NMR spectra: Varian A-60, Me_4Si as int. stand., chem. shifts in δ (ppm). Analytical data Microanalytical Center at Cairo University. Compound **3a** was prepared following lit. procedure[1].

Reactions of **1** with aromatic aldehydes: A suspension of **1** (0.1 mol) in ethanol (100 ml) and triethylamine (1 ml) was refluxed for 3 h with 0.1 mol of aromatic aldehydes. The solid product was crystallized and identified as **3b–d** (Table 1).

Reaction of **1** and **9** with ylidene malononitrile **2a–c** or **8a, b**: A suspension of equimol. amounts (0.01 mol) of **1** or **9** and **2** or **8** in ethanol and a few drops of triethylamine was refluxed untill precipitation is complets (time ranges from 15 min. for **7a–c** to 4 h for **10a, b** and **11**). The solid product was crystallized and identified (Table 1).

Compounds **7a–c** were also obtained in 85–90 % yield by refluxing equimol. amounts of **3a–c** and malononitrile in ethanol-triethylamine for 15 min.

Compounds **12a, b** were also obtained by refluxing equimol. amounts of **9a, b** and 4-formylantipyrine in ethanol in 90 % yield.

Tab. 2: ^{1}H-NMR data of the newly prepared compounds

Compd. No.	^{1}H-NMR; δ (ppm)
3d	2.6 (s, 3H, CH_3); 3.1 (s, 6H, $N(CH_3)_3$; 3.4 (s, 3H, N-CH_3); 6.7–7.0 (m, 7H, aromatic); 7.5 (m, 2H, o-aromatic); 7.9 (s. 1H, ylidene proton).
7a	2.4 (s, 3H, CH_3); 3.3 (s, 3H, N-CH_3); 4.4 (d, J = 6 Hz,1H, pyridone); 4.9 (d, J = 6 Hz, 1H, pyridone); 7.2–7.5 (m, 11H, aromatic + NH).
7b	2.4 (s, 3H, CH_3); 3.2 (s. 3H, N-CH_3); 4.4 (d, J = 6Hz, 1H, pyridone); 5.0 (d, J = 6 Hz, 1H, pyridone); 7.4–7.6 (m, 10H, aromatic + NH).
7c	2.4 (s, 3H, CH_3); 3.2 (s, 3H, N-CH_3); 3.9 (s, 3H, OCH_3); 4.2 (d, J = 6 Hz,1H, pyridone); 5.0 (d, J = 6 Hz,1H, pyridone); 6.9–7.6 (m, 10H, aromatic + NH).
10a	2.4 (s, 3H, CH_3); 2.55 (s, 3H, CH_3); 3.35 (s, 3H, N-CH_3); 4.7 (s, 1H, pyran); 6.9 (s, 2H, NH_2); 7.3–7.6 (m, 5H, aromatic); 12.3 (s, 1H, NH).
12a	2.4 (s, 3H, CH_3); 2.6 (s,3H, CH_3); 3.5 (s, 3H, N-CH_3); 7.2–7.6 (m, 5H, aromatic); 7.9 (s, 1H, ylidene 1H); 12.1 (s, 1H, NH).

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Oligopeptide der β-Carbolin-3-carbonsäure – Synthese und Affinität zu Benzodiazepinrezeptoren

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Es wurden Oligopeptide der β-Carbolin-3-carbonsäure dargestellt und deren Affinität zum Benzodiazepinrezeptor in Mäusehirn-Membranen bestimmt. Über Struktur-Affinitätsbeziehungen wird berichtet.

Oligopeptides of β-Carboline-3-carboxylic Acid – Synthesis and Benzodiazepine Receptor Affinity

Oligopeptides of β-carboline-3-carboxylic acid were prepared and tested with respect to their affinity for the benzodiazepine receptor in mouse brain membranes. Structure-affinity relationships are reported.

Die Beobachtung, daß Derivate des β-Carbolins wie Harman, Norharman und vor allem Ester der β-Carbolin-3-carbonsäure mit unterschiedlicher Affinität an Benzodiazepinrezeptoren binden[1, 2], hat zu einer intensiven Suche nach Substanzen hoher Affinität[3–6] geführt. Dabei spielte die Frage, ob β-Carboline als endogene Liganden des Benzodiazepinrezeptors in Betracht kommen, eine besondere Rolle[1, 4, 7, 8]. Im Rahmen unserer Suche nach Verbindungen hoher Affinität, die aufgrund ihrer chemischen Struktur

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