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PYRAZOLES DERIVED FROM DIHYDRALAZINE

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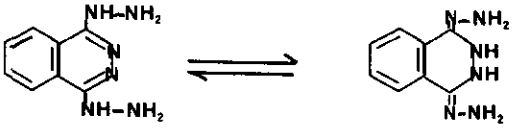
Abstract —— The syntheses of some bis-(3,5-disubstituted pyrazolyl)phthalazines derived from dihydralazine (1) are described. Their structure assignments are based on ^{1}H-, and ^{13}C-nmr-spectroscopic data as well as results of elemental analyses.

During our studies directed towards the synthesis of novel heterocycles of potential biological application, we noticed that there exist only a few reports involving dihydralazine (1,4-bis-hydrazinophthalazine) (1), as building block for heterocycles.[3] Since 1 possesses antihypertensive properties,[4] and recent investigations demonstrated significant biological activities in derivatives of 3,5-disubstituted pyrazoles,[5] we undertook the synthesis of the bis-(3,5-disubstituted pyrazolyl)phthalazine system to exploit the availability of the versatile compound 1 to provide compounds of potential interest for biological testing. Earlier Amer and Zimmer[6] showed that the reaction of hydralazine with di- or tricarbonyl compounds, depending on the reaction conditions, led to formation of different products. In this report the influence of variations of reaction conditions on the formation of products from reactions of 1 with different carbonyl compounds will be discussed.



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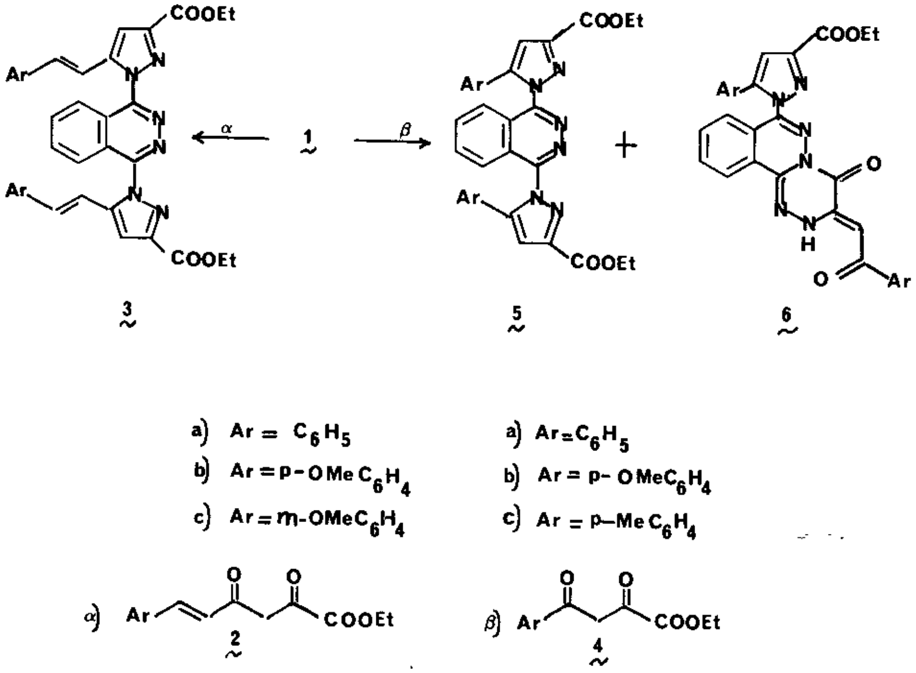
1. Reaction of 1 with 1,2,4-Tricarbonyl Compounds:

Refluxing 1-HCl with ethyl 6-aryl-2,4-dioxo-5-hexenoates[7], (2a-2c) in ethanol afforded the bis-pyrazoles (3a-3c) as colorless crystals (Scheme I).

Scheme I



a) Ar = C_6H_5
b) Ar = p-OMeC_6H_4
c) Ar = m-OMeC_6H_4

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c) Ar = p-MeC_6H_4

The structural assignments for these compounds were based on their elemental analyses, ^{1}H-, and ^{13}C-nmr spectroscopic data. The elemental analyses of these compounds revealed that during the condensation reaction four molecules of water were lost. Because of the symmetry in type 3 compounds their ^{1}H-nmr spectra are rather simple. They are summarized in Table I. The ^{13}C-nmr spectrum of 3b exhibited the characteristic pyrazole C-4 signal at δ105.790 ppm (^1J=180.474 Hz).

When 1-HCl was reacted under the above stated conditions with 2,4-dioxo-4-arylbutanoates, (4a-4c) the expected bis-pyrazoles, (5a-5c) did not form. However, they conveniently could be prepared in good yields along with traces of orange solids by treating 1 as free base with type 4 compounds in polyphosphoric acid (Scheme I). The structures of compounds 5a-5c are based on their elemental analyses and interpretation of their ir- and ^{1}H-nmr spectroscopic data (Table I). The reaction of 1 with 4b yielded an amount sufficient for the identification of the orange solid. Its ir spectrum showed a band at 1640 cm^{-1} (C=O) and a band in the region of the stretching vibration of the N-H bond, at 3300 cm^{-1}. The ^{1}H-nmr spectrum of this compound exhibited a triplet/quartet pattern at δ 1.40 (t, 3H) and 4.40 (q, 2H) indicating the presence of an ethyl ester group; the presence of two methoxy groups is indicated by two singlets at δ3.77 and 3.87 respectively; the aromatic moieties and the vinyl proton give rise to a multiplet at δ6.80-8.43 (14H, 13H Ar, 1H=CH); finally the singlet at δ 14.03 is assigned to the NH-group. Based on these data and its elemental analysis which agreed with the molecular formula of $C_{32}H_{26}N_6O_6$, its structure was assigned as 7-[3'-carboethoxy-5'-(p-methoxyphenyl)pyrazolyl]-3-[2-oxo-2-(p-methoxyphenyl)ethyl]-4H-as-triazino[3,4-a]phthalazin-4-one (6b), mp 250-252°C ($CHCl_3$-EtOH).

Table I

Elemental Analyses and Spectral Data of Compounds 3a-3c, 5a-5c, and 6b

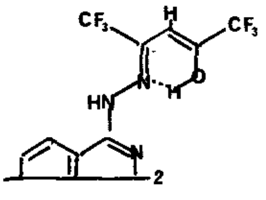
Compound	Molecular Formula	MP °C	Yield %	ir(KBr) C=O(CM^{-1})	^{1}H-nmr(CDCl$_3$) ppm	Analysis*		
						C	H	N
3a	$C_{36}H_{30}N_6O_4$	274-276	54	1727	1.45(t,6H); 4.50(q,4H), 7.30,8.13(2m,2OH)	70.80 70.76	4.95 4.92	13.76 13.85
3b[a]	$C_{38}H_{34}N_6O_6$	288	50	1715 1725 1740	1.454(t,6H,J=7.2Hz); 3.781(s,6H) 4.49(q,4H,J=7.2Hz); 6.814 (d,4H,J=8.7Hz); 6.906 (d,2H,J=16.2Hz); 7.209 (d,2H,J=16.2Hz); 7.186(s,2H); 7.330(d, 4H,J=8.7Hz); 8.036, 8.183 (2m,4H)	68.05 68.19	5.11 5.27	12.53 12.68
3c	$C_{38}H_{34}N_6O_6$	252	60	1710	1.47(t,6H);3.77(s,6H0; 4.48 (q,4H); 7.10,8.10 (2m,18H)	68.05 67.97	5.11 5.22	12.53 12.69
5a	$C_{32}H_{26}N_6O_4$	224	92	1735	1.43(t,6H);4.47(q,4H); 7.17,8.07(2m,16H)	68.80 68.71	4.69 4.89	15.05 15.06
5b	$C_{34}H_{30}N_6O_6$	238-240	77	1735	1.43(t,6H); 3.70(s,6H); 4.47 (q,4H); 6.70(d,4H), 7.13 (m,8H); 8.03(s,4H)	66.01 66.07	4.89 5.12	13.59 13.68
5c	$C_{34}H_{30}N_6O_4$	245	85	1740	1.43(t,6H); 2.27(s,6H); 4.48(q,4H); 7.10(m,12H); 8.03(s,4H)	69.61 69.86	5.15 5.20	14.33 13.97

*Calculated Values
Found Values

[a] ^{13}C-nmr data are in good agreement with proposed structure; it showed sixteen signals at δ 161.944, 160.214, 152.706, 146.435, 146,255, 134.549, 134.470, 128.380, 126.070, 125.478, 114.157, 111.517, 105.790, 61.436, 55.264 and 14.398.

2. Reaction of 1 with 1,3-Dicarbonyl Compounds:

Reaction of 1 with acetylacetone[7] (7) gave mainly the bis-(3',5'-dimethylpyrazolyl)phthalazine, (8), as colorless crystals. In the ^{1}H-nmr spectrum of 8 in CDCl$_3$, the signals for the protons of the methyl groups at C-3' and C-5' appeared at δ2.40 (s) and 2.50 (s) respectively, and the signal for the proton at C-4' showed up at 6.02 (s). The protons of the phthalazine ring cause two multiplets at δ 8.00 and 8.40 of four protons intensity. Its ^{13}C-nmr off-resonance decoupled spectrum exhibited signals at δ 12.391, 13.708, 108.102, 125.725, 126.142, 133.188, 142.970, 151.091 and 152.065. They were assigned to the methyl groups at C-5' and at C-3' and to the C-atoms at positions C-4', C-9, C-8, C-7, C-5', C-3', and C-1, respectively. In contrast, the reaction of 1 with hexafluoroacetylacetone[7] (9) afforded a yellow product, (10), instead of a colorless one. The ir spectrum of this product showed a band at 1640 cm^{-1} (C=N) and a band in the region of the stretching vibration of the O-H bond at 3240 cm^{-1}. Its exact mass spectrum showed the molecular ion peak at m/z 570.0711 ($C_{18}H_{10}F_{12}N_6O_2$)$^{+\cdot}$ indicating loss of two molecules of water. This suggested 10 to be bis-[5-hydroxy-3,5-di(trifluoromethyl)-pyrazolinyl]phthalazine (Scheme II). According to the ^{1}H-nmr data this compound may exist in more than one form depending on the solvent. In $CDCl_3$ solution there were only signals corresponding to the 5-hydroxypyrazoline form 10. The spectrum did not change with time, thereby confirming the absence of tautomeric equilibria. The protons of the methylene group formed a typical AB system of two doublets at δ 3.352 and 3.577 with spin-spin coupling constant of 19.2 Hz. Its ^1H-nmr spectrum in DMSO-d_6 solution, however, showed the presence of a mixture of 10 and its enol-imine tautomer (11).



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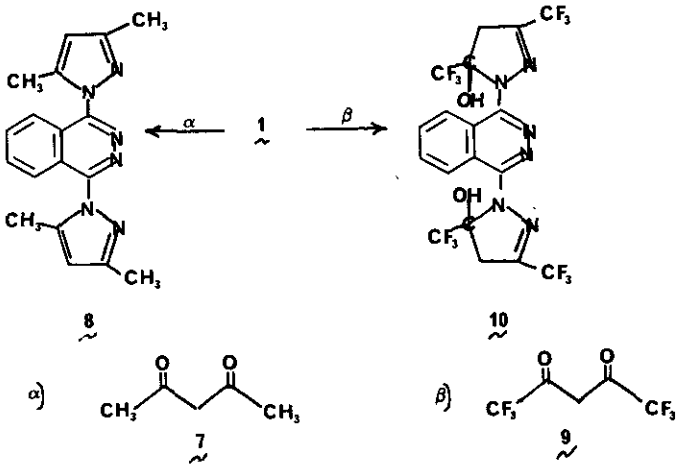
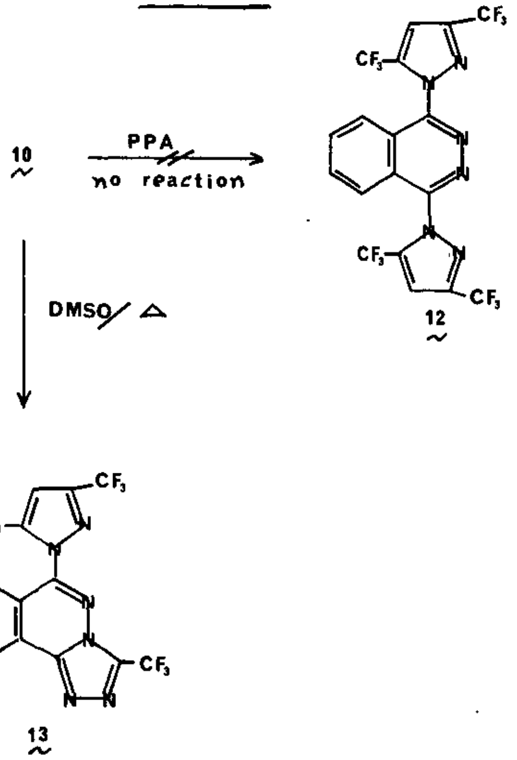
This structure proposal is based on the observation of a singlet at δ5.433 due to the olefinic proton. The ^{13}C-nmr spectrum of 10 in $CDCl_3$ solution showed signals at δ42.190 (s, C-4'), 95.782 (q, $^2J_{C-F}$ = 34.03 Hz, C-5'), 119.624, 123.045 (2q, $^1J_{C-F}$ = 270.668 Hz, $^1J_{C-F}$ = 285.683 Hz, $2CF_3$ at C-3' and C-5'), 124.948 (s, C-9), 126.200 (s, C-8), 133.548 (s, C-7), 142.642 (q, $^2J_{C-F}$ = 39.540 Hz, C-3'), and 154.695 (s, C-1).

Scheme II



An attempt to synthesize the bis-pyrazole (12) from 10 through dehydrative cyclization by using PPA was unsuccessful. However, when compound 10 was refluxed in DMSO for 30 min and then quenched with water, a colorless compound having ^1H-nmr signals at δ7.319 (1H), 7.969 (2H), 8.119 (1H) and 8.919 (1H) was obtained. On the basis of these data, its structure is assigned as 6-[3',5'-di(trifluoromethyl)pyrazolyl]-3-trifluoromethyl-s-triazolo[3,4-a]phthalazine (13). This assignment was confirmed by its exact mass spectrum which showed the molecular ion at m/z 440.0473 (calc. for $(C_{15}H_5F_9N_6)^+$; m/z 440.04335) (Scheme III).

Scheme III



EXPERIMENTAL

Melting points were determined with a Fisher-Johns and/or Melt-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 599 spectrometer and/or Unicam SP 1025. NMR spectra were recorded on a Varian T-60, EM-390 90, and/or Nicolet NT300 narrow-bore spectrometers. Mass spectral data were obtained on a Kratos MS80 instrument (NSF grant PCM-8219912). Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona and/or Alexandria University, Faculty of Science Central Laboratory.

Bis-[3-carboethoxy-5-(substituted-styryl)pyrazolyl]phthalazine (3a-3c); General Procedure

A mixture of the appropriate 1,2,4-tricarbonyl compound (2) (0.002 mole) and 1-HCl (0.001 mole) in ethanol (5 ml) was refluxed for 2 h. After cooling, the product was filtered off and recrystallized from chloroform-methanol.

Bis-(5-aryl-3-carboxyethyl pyrazolyl)phthalazine (5a-5c); General Procedure

The appropriate 1,2,4-tricarbonyl compound, (4), (0.02 mole) and 1 (0.01 mole) in polyphosphoric acid (15 g) were heated on a water-bath for 30 min. The resultant mixture was poured onto saturated sodium bicarbonate solution followed by filteration and washing with water. Pure compounds were obtained by recrystallization from a mixture of chloroform and methanol.

Bis-(3,5-dimethylpyrazolyl)phthalazine (8)

A mixture of 1 (0.01 mole) and acetylacetone (0.02 mole) was heated on a water-bath for 1 h and cooled. The residue was triturated with cold ethyl acetate and filtered off (yield = 80%). Pure compound was obtained by recrystallization from ethyl acetate; mp 225°C.

Anal. Calcd. for $C_{18}H_{18}N_6$: C, 67.90; H, 5.70. Found: C, 67.76; H, 5.83.

Bis[5-hydroxy-3,5-di(trifluoromethyl)pyrazolinyl]phthalazine (10)[8]

A mixture of 1 (0.01 mole) and hexafluoroacetylacetone (0.02 mole) was heated on a water-bath for 1 h. The residue was recrystallized from methanol-water; yield 92%; mp 143-144°C.

Anal. Calcd. for $C_{18}H_{10}F_{12}N_6O_2$: C, 37.91; H, 1.77; N, 14.74. Found: C, 38.22; H, 1.87; N, 14.86.

REFERENCES

1. Part I: "Synthetic Reactions and Structural Studies of Heterocycles Containing Nitrogen."
2. To whom correspondence should be addressed.
3. (a) R. Ruggieri, Boll. Chim. Farm., 1964, 103, 196; Chem. Abs., 1964, 61, 4344.
   (b) British Pat. 1954, 707, 337; Chem. Abs., 1955, 49, 7606.
   (c) G. A. Reynolds, J. A. Van Allan, and J. F. Tinker, J. Org. Chem., 1959, 24, 1205.
   (d) K. T. Potts and C. Lovelette, ibid., 1969, 34, 3221.
4. P. A. Reece, Med. Res. Rev., 1981, 1, 73.
5. R. Soliman, J. Med. Chem., 1979, 22, 321.
6. (a) A. Amer and H. Zimmer, J. Heterocyclic Chem., 1981, 18, 1625.
   (b) A. Amer and H. Zimmer, ibid., 1983, 20, 1231.
   (c) H. Zimmer, K. Weisz, and A. Amer, Abstracts of papers ORGN 190, ACS National Meeting, New York, N.Y., April 16, 1986.
7. These type of compounds are well known to exist in several tautomeric forms, namely keto-enol tautomers.
8. Compound 10 was found to be the only reaction product when the reaction took place in alcoholic medium or in PPA or when 1 was used as hydrochloride salt.

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