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Behavior of 4,5-Dihydropyridazinone Derivatives and 3-Chloropyridazine toward Alkylating Agents, Acylhydrazines, and Azides

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The pyridazinones 2 have been synthesized from the interaction of acid 1 with hydrazines. Reactions of 2 with electrophilic reagents gave O-alkylated derivatives, with $POCl_3/PCl_5$ gave chloro derivatives, and with bromine gave the oxidation product. Reaction of the chloro derivative with acylhydrazine, sodium azide, primary amines, and phenylhydrazine gave triazole derivative, tetrazole derivative, (arylamino)pyridazine, and phenylhydrazinopyridazine, respectively.

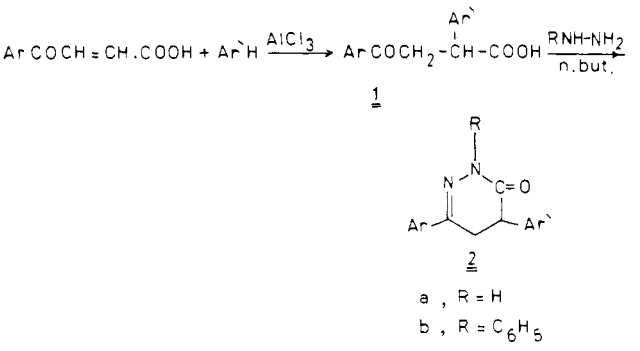
There have been reports of 4,5-dihydropyridazinones that have antihypertensive activity, although they have no classical hypotensive pharmacophor (*1*). In addition, Nannini (*2*) has recently reported that pyridazinones have analgesic and anti-inflammatory activity. We report here on the synthesis of some 4,5-dihydropyridazine derivatives via alkylation of 6-(4-chloro-3-methylphenyl)-4-(2,5-dimethylphenyl)-3-oxo-2,3,4,5-tetrahydropyridazine (**2a**), whose synthetic route was reported by El-Hashash et al. (*3*) (Scheme I). The pyridazinone **2a** could be alkylated with a variety of electrophilic reagents, namely, dialkyl sulfate and ethyl chloroacetate in dry acetone, by using anhydrous K_2CO_3 as catalyst (*4*). The products were identified as 3-O-alkylated 4,5-dihydropyridazine derivatives **3a–c**.

The compound **3c** reacts with benzylamine and/or *p*-anisidine to give the *N*-arylamide derivatives **3d** and **3e**, respectively.

Interaction of **2a** with a mixture of $POCl_3/PCl_5$ (*5*) gives 3-chloro-4,5-dihydropyridazine derivative **4**.

Recently (*6*), it was reported that 6-(substituted phenyl)-1,2,4-tetrazolo[4,3-*b*]pyridazines show activity in tests predictive of anxiolytic activity. Thus, reaction of **4** with acylhydrazines, namely, acetylhydrazine, benzoylhydrazine, and salicyloylhydrazine in refluxing butanol, gave triazolopyridazines **5a–c**. On the other hand, **4** reacts with NaN_3 in boiling DMF (*7*) to give 1,2,3,4-tetrazolopyridazine **6**.

Scheme I



Compound **4** submitted to react with *p*-toluidine, *p*-anisidine, and phenylhydrazine gave 3-(arylamino) and 3-(phenylhydrazino) derivatives **7**.

Oxidation of the dihydropyridazinone **2a** with Br_2/AcOH gave the pyridazinone derivative **8**.

Experimental Section

Melting points reported are uncorrected; the IR spectra were determined with a Pye Unicam Ltd. (Cambridge, England) part No. 641751 spectrophotometer by using the KBr wafer technique (Scheme II). (For the structural assignments cf. Table I.)

***Reaction of the Acid* 1 *with Hydrazines. Formation of Pyridazinones* (2a *and* 2b).** A solution of the acid **1** (0.01 mol) in 1-butanol (50 mL) was treated with hydrazine hydrate or phenylhydrazine (0.01 mol) and the mixture refluxed for 5 h. The solid that separated after concentration and cooling was crystallized from a proper solvent to give the desired pyridazinones **2a** and **2b**. The results are given in Table I.

***Action of Dialkyl Sulfate or Ethyl Chloroacetate on* 2a. *Formation of* 3a–c.** A mixture of **2a** (0.01 mol), anhydrous

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Scheme II

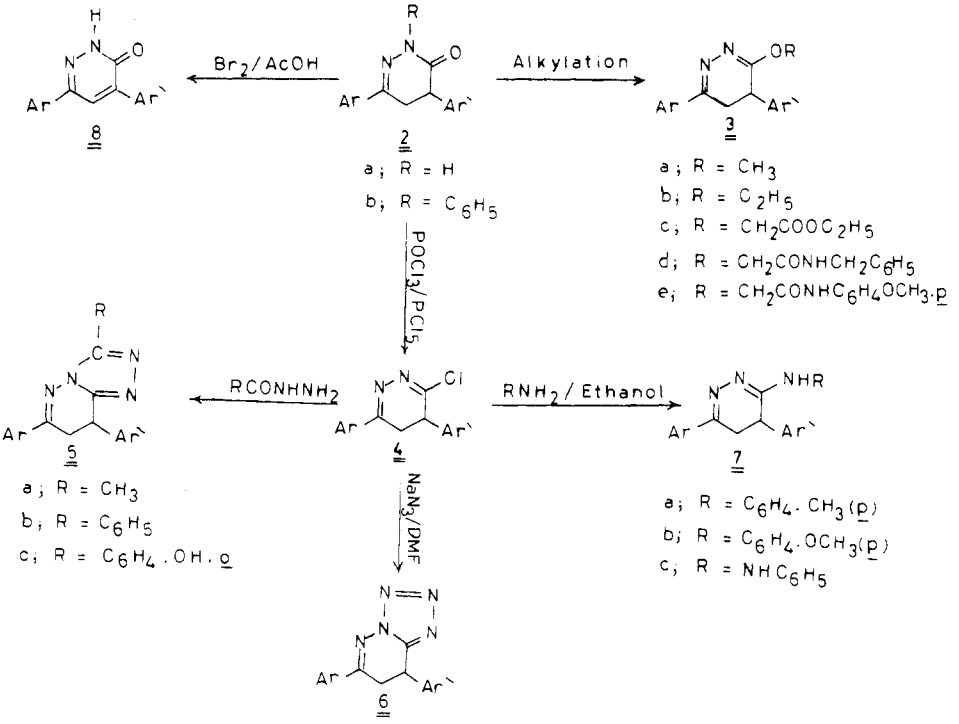

Table I. Physical Data and IR Spectra of Prepared Compounds[a]

				IR (KBr) ν, cm^{-1}					
compd	mp, °C	solv of cryst[b]	yield, %	C=O	C=N or C=C	O—C	NH, OH, or C—Cl	C—H	ref
2a	169	100–120 °C PE	86	1660	1630		3200	2962	*8*
2b	165	benzene	72	1650	1635			2955	*8*
3a	99	60–80 °C PE	80		1635	1230		2965, 2860	*9*
3b	95	60–80 °C PE	78		1630	1245		2950, 2865	*9*
3c	89	60–80 °C PE	82	1750	1635	1240		2950, 2860	*10*
3d	179	ethanol	72	1665	1635	1242	3150	2935, 2855	*11*
3e	194	ethanol	72	1670	1635	1260	3200	2945, 2860	*11*
4	162	benzene (60–80 °C PE)	80		1630		650	2955, 2860	*12*
5a	171	ethanol	55		1650, 1630			2955, 2860	*13*
5b	230	1-butanol	51		1650, 1635			2950, 2855	*13*
5c	296	1-butanol	55		1655, 1630		3250	2950, 2846	*13*
6	132	60–80 °C PE	47		1630	1100[c]		2960	*4*
7a	194	ethanol	57		1630		3200	2950	*9*
7b	243	ethanol	53		1625		3250	2955	*9*
7c	138	ethanol	27		1630		3200	2960	*9*
8	206	ethanol	77	1660	1635, 1610		3200		*9*

[a] The elemental analyses were submitted for review. [b] PE = petroleum ether. [c] Tetrazole ring mode.

potassium carbonate (0.04 mol), and dialkyl sulfate, namely, dimethyl sulfate diethyl suflate, or ethyl chloroacetate (0.04 mol) in dry acetone (60 mL), was refluxed for 15 h. The product was obtained after removing the excess solvent and crystallized from a suitable solvent to give **3a–c** (cf. Table I).

***Reaction of* 3c *with Primary Amines. Formation of* 3d *and* 3e.** A solution of **3c** (0.01 mol) in ethanol (50 mL) was treated with benzylamine or *p*-anisidine (0.01 mol) and then refluxed for 3 h. The solids that separated after cooling were crystallized from a proper solvent to give **3d** and **3e**, respectively. The results are listed in Table I.

***Action of $PCl_5/POCl_3$ on* 2a. *Formation of* 4.** A suspension of **2a** (1 g), PCl_5 (0.5 g), and $POCl_3$ (4 mL) was heated on a water bath for 2 h. The reaction mixture was poured gradually into crushed ice and the solid that separated was filtered and crystallized from a proper solvent (cf. Table I).

***Reaction of Chloropyridazine* 4 *with Acylhydrazine. Formation of Triazole Derivative* 5.** A mixture of **4** (0.01 mol) and the acylhydrazine, namely, acetylhydrazine, benzoylhydrazine, and salicyloylhydrazine (0.02 mol), in 50 mL of 1-butanol was refluxed for 48 h. The solid that separated after concentrating and cooling was filtered off and washed with *n*-hexane and then recrystallized from a proper solvent. The results are listed in Table I.

***Reaction of Chloropyridazine* 4 *with Sodium Azide. Formation of Tetrazole* 6.** A solution of **4** (0.003 mol), sodium azide (0.5 g), H_2O (5 mL), and dimethylformamide (30 mL) was boiled under reflux for 3 h and cooled, and then 100 mL of H_2O was added. The solid that separated was filtered off and crystallized from a suitable solvent to give the tetrazole **6** (cf. Table I).

***Reaction of Chloropyridazine* 4 *with Amines and Phenylhydrazine. Formation of Arylamino and Phenylhydrazino Derivative* 7.** A mixture of **4** (0.01 mol) and primary amines, namely, *p*-toluidine and *p*-anisidine, or phenylhydrazine (0.01 mol) in ethanol (50 mL), was refluxed for 6 h. The solid that separated after concentrating was crystallized from a suitable solvent (cf. Table I).

***Oxidation of* 2a *with Bromine/Acetic Acid. Formation of* 8.** A vigorously stirred solution of **2a** (0.01 mol) in glacial acetic

acid was heated to ~60–70 °C and then treated portionwise with bromine (0.01 mol) for 15 min. The mixture was stirred further for 3 h and poured into ice water. The solid separated was filtered and crystallized from a proper solvent to give **8**.

Registry No. **1**, 84587-35-9; **2a**, 89936-35-6; **2b**, 89936-36-7; **3a**, 89936-37-8; **3b**, 89936-38-9; **3c**, 89936-39-0; **3d**, 89936-40-3; **3e**, 89958-42-9; **4**, 89936-41-4; **5a**, 89936-42-5; **5b**, 89936-43-6; **5c**, 89958-43-0; **6**, 89936-44-7; **7a**, 89936-45-8; **7b**, 89936-46-9; **7c**, 89936-47-0; **8**, 89936-48-1; NH_2NH_2, 302-01-2; $C_6H_5NHNH_2$, 100-63-0; $C_6H_5CH_2NH_2$, 100-46-9; p-$CH_3OC_6H_4NH_2$, 104-94-9; $CH_3CONHNH_2$, 1068-57-1; $C_6H_5CONHNH_2$, 613-94-5; o-$HOC_6H_4CONHNH_2$, 936-02-7; NaN_3, 26628-22-8; p-$CH_3C_6H_4NH_2$, 106-49-0.

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Electron Spin Resonance and Mass Spectra of Substituted Azo Cresol Complexes

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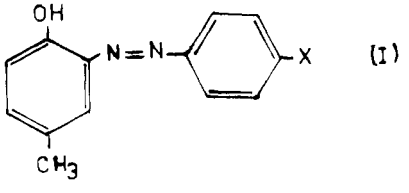
Transition-metal complexes of substituted azo cresol compounds were prepared. The structures and the mode of bonding were investigated on the basis of mass spectra for all systems and electron spin resonance for the copper complexes. The electronic characters of substituents on the data are discussed. The copper complexes give anisotropic ESR spectra with axial symmetry in tetragonal geometry for orbitally nondegenerate ground states.

The interesting azo family compounds continue to find applications in analytical chemistry (*1*). This type of compound is of biological importance from antifungal and antibacterial activities (*2*). The azo group is involved in a number of important biological reactions such as inhibition of DNA, RNA, and protein syntheses, carcinogenesis, and nitrogen fixation (*3*). In our laboratory (*4–16*), we studied the azo ligands with different functional groups from the point of view of their ability to be complexed with many metals. As part of a continuing study of the interesting behavior of such compounds, we have undertaken the title investigation of this manuscript.

Experimental Section

The ligands (I) were prepared by the usual method of diazotization of p-cresol (*17*).



(I)

Table I. Electron Spin Resonance Data for p-Cresol Azo Complexes

substituent	$g_\parallel$	$g_\perp$	$\langle g \rangle$	G
OCH_3	2.300	2.058	2.139	5.17
CH_3	2.330	2.065	2.153	5.89
NO_2	2.260	2.070	2.133	3.71
COOH	2.322	2.074	2.156	4.35
Br		2.135		
Cl	2.28	2.076	2.147	3.68

A general method was applied for the synthesis of cobalt, nickel, and copper complexes. An ammoniacal alcoholic solution of the metal salt (10 mmol) was mixed with the corresponding ligand (20 mmol) dissolved in ethanol. The mixture was refluxed for about 20 min and then allowed to cool, giving a precipitate of the required complex. The complexes were filtered and washed several times with ethanol and dried in a desiccator over P_2O_5. The elemental analysis typified the presence of 1:2 complexes, with cobalt(II), nickel(II), and copper(II) salts and 1:3 iron(III) complexes (*6*, *10*).

The ESR spectra of the copper complexes were recorded with E12 (X band) and E15 (Q band) instruments from varian Associates. 2,2-Diphenyl-1-picrylhydrazide (DPPH, $g = 2.003$) was used as an external standard. The mass-spectral measurements were measured with CH4 and CH7 instruments from MAT-Bremen Co., West Germany. The physical measurements were done at the Chemistry Department, Marburg University, West Germany.

Results and Discussion

Electron Spin Resonance of Copper Complexes. The X-band spectra of the polycrystalline copper complexes (Figure 1) at room temperature are typical of those for axial symmetry

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