SYNTHESIS AND TRANSFORMATIONS OF CHLOROPYRAZOLEALDEHYDES

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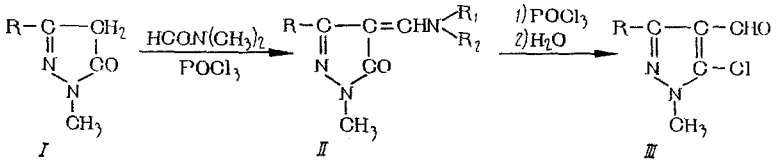
With the object of expanding the possibilities of synthesizing new physiologically active compounds in the pyrazole series, we have prepared 1-methyl-5-chloropyrazolealdehydes (III) and have studied some of their properties.

These compounds were synthesized by the reaction of appropriate pyrazolones (I) with dimethylformamide in the presence of excess phosphorus oxychloride. It is known that such a type of synthesis may be accomplished either by direct treatment of the pyrazolone with dimethylformamide and an excess of phosphorus oxychloride or from the dimethylaminomethylene derivative of the pyrazolone (II) by the action of phosphorus oxychloride on it, with subsequent treatment with water [1]:



I: a) R = CH_3; b) R = C_6H_5

II: a) R = R_1 = R_2 = CH_3; b) R = C_6H_5; R_1 = R_2 = CH_3; c) R = CH_3; R_1, R_2 = $-(CH_2)_5-$; d) R = CH_3, R_1 = H, R_2 = C_6H_5

III: a) R = CH_3; b) R = C_6H_5

In the case where 1,3-dimethyl-5-pyrazolone (Ia) was used for this reaction, the intermediate product (IIa) was so reactive that it was not possible to isolate it; even when phosphorus oxychloride was used in an amount somewhat less than the stoichiometric, all the same there was formed a certain amount of the chloropyrazolealdehyde (IIIa) plus, besides this, depending on the work-up conditions of the reaction mixture, either 1,3-dimethyl-5-pyrazolonealdehyde (IVa), or an oxanole dye (V). (See scheme on page following.)

We succeeded in preparing compounds of type II by the reaction of the pyrazolone aldehyde IV with dimethylamine or other amines. They display high reactivity in the reaction with phosphorus oxychloride, upon acid or alkaline hydrolysis being converted respectively into compounds IIIa, IV, or V.

The chloropyrazolealdehyde IIIa was characterized in the form of derivatives: the oxime, the phenylhydrazone, and the thiosemicarbazone (VI-VIII). A carboxylic acid (IX, R_3 = OH) is formed upon oxidation of it; from this a number of derivatives were prepared (Table 1). Oxidation of the aldehyde group to a carboxyl was performed with chromic anhydride in acetic acid or with potassium permanganate in aqueous-dioxane solution. It turned out that the oxidation proceeds better by the second method, and the yield is appreciably higher.

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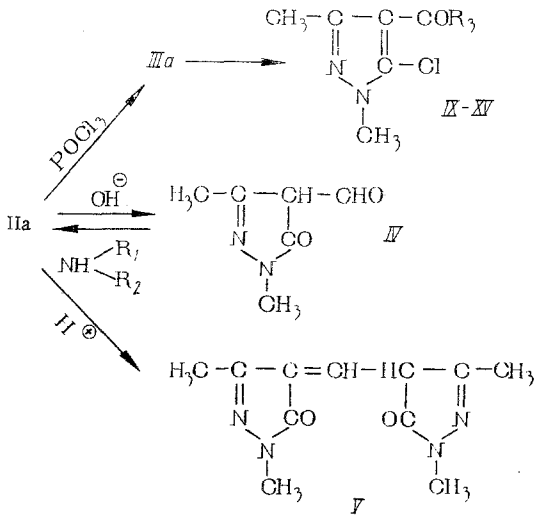
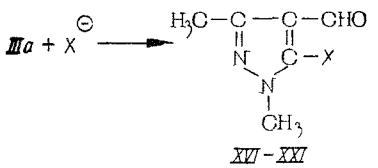


It was of interest to study the ease of substitution of the chlorine action byvarious nucleophilic agents in compound IIIa. As a rule, 5-chloropyrazoles enter into nucleophilic substitution reactions with great difficulty [2-5]; however, the presence of an aldehyde group in position 4 activates the chlorine atom to some degree, and compound IIIa readily enters into nucleophilic substitution reactions with amines or with hydroxyl, methoxide, or thiolate ions:



As was to be expected, this reaction takes place most easily of all with thiolate anions, and most difficultly with amines. With dimethylamine, piperidine or morpholine, reaction takes place only at 130-140° and under pressure (compounds XVI-XVIII; Table 2). Replacement of the chlorine by an alkoxy or alkylthio group takes place upon treatment of a methanol solution of the chloroaldehyde with an equimolecular amount of sodium alcoholate or sodium thiolate at room temperature or upon brief heating (compounds XIX-XXI). Upon reaction with sodium methoxide, along with the main reaction product (XIX), there is obtained a small amount of pyrazolonealdehyde (IV). The latter compound is formed as the main reaction product upon heating with aqueous-alcoholic alkali.

From the amino- and alkoxypyrazolealdehydes we prepared oximes, methiodides, and hydrochlorides by the usual methods; and from compound XIX we prepared a thiosemicarbazone. An oxime could not be prepared from compound XX, just as it was not possible to obtain a thiosemicarbazone from XX or XXI.

Interesting results were obtained upon reaction of chloropyrazolealdehydes (IIIa or IIIb) with thioglycolic acid. Together with replacement of the chlorine atom by the thioglycolic acid residue, in the presence of an excess of alkali an intramolecular condensation took place, with closure of a thiophene ring and formation of the condensed thieno [2, 3 c] pyrazole system.

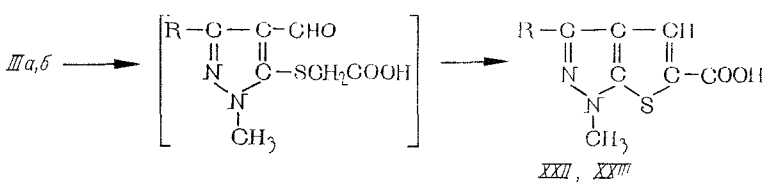


TABLE 1. Derivatives of 1,3-Dimethyl-5-chloropyrazole-4-aldehyde (VI-VIII) and of the 4-Carboxylic Acid

Compound	Mp (in deg)	Recrystallization solvent	Yield (in %)	Found (in %)			Empirical formula	Calcd (in %)	
VI, Oxime	164—5	Ethanol-water	80,5	N	24,50	Cl	$C_6H_8ClN_3O$	N24,32	Cl 20,46
					24,41	20,40			
VII, Phenylhydrazone	135,5—136	Benzene	87,5	N	22,57	Cl	$C_{12}H_{13}ClN_4$	N22,52	Cl 14,28
					22,42	14,33			
						14,40			
VIII, Thiosemicarbazone	235—7	Ethanol-water	81,9	N	30,13	—	$C_7H_{10}ClN_5S$	N30,24	—
					30,34		$C_7H_9ClN_2O_2$	N4,85	—
XI, R_3=OCH_3	39	Petroleum ether	75,2	N	14,72				
					14,80	6,82	$C_{12}H_{20}ClN_3O_2 \cdot HCl$	C46,45	H 7,0
XII, R_3=$O(CH_2)_2N(C_2H_5)_2 \cdot HCl$	148—50	Absolute ethanol-ether	55	N	46,22	H 7,19			
					46,39	—	$C_{12}H_{20}ClN_3OS \cdot HCl$	N12,88	—
XIII, R_3=$S(CH_2)_2N(C_2H_5)_2 \cdot HCl$	183—5	Dioxane	52,1	N	12,95				
					12,98	7,44	$C_{13}H_{23}ClJN_3OS$	N9,73	S 7,41
XIV, R_3=$S(CH_2)_2\overset{\oplus}{N}(C_2H_5)_2 \cdot CH_3I$	165—6	Acetone-ether	71,5	N	9,49	S 7,68			
					9,68	Cl 18,96	$C_6H_9ClN_4O$	N29,71	Cl18,83
XV, R_3=$NHNH_2$	154—5 (разл.)	Benzene	80	N	30,04	18,75			
					29,80				

The pharmacological action of some of the compounds was studied in the pharmacology laboratory of the I. M. Sechenov Institute of Evolutionary Physiology (laboratory director, M. Ya. Mikhel'son). Compounds XII-XIV possess a weak cholinolytic action; the anticholinesterase activity of the aldoximes (XVIb, XVIIb, XXIb, etc.) was also small.

EXPERIMENTAL

1,3-Dimethyl-5-chloropyrazole-4-aldehyde (IIIa). To 17.5 g of dimethylformamide, with stirring at 0-5°, was added 71.2 g of phosphorus oxychloride. To the mixture so obtained, at the same temperature, was added 22.4 g of 1,3-dimethyl-5-pyrazolone. The reaction mixture was slowly heated to 80°, and was kept at 80-85° for 8 h. After cooling, the reaction mixture was dissolved in the minimum amount of water and was neutralized at 0-5° with a 20% sodium hydroxide solution to pH 4.0-5.0. The yield of product was 22.2 g (70%), mp 78-79° (from water or petroleum ether). Found, %: N 18.03, 17.87; Cl 22.03, 22.25. $C_6H_7ClN_2O$. Calculated, %; N 17.73; Cl 22.39.

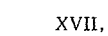
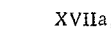
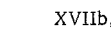
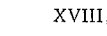
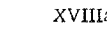
1-Methyl-3-phenyl-5-chloropyrazole-4-aldehyde (IIIb). This compound was prepared by a method like that used in the preceeding synthesis. From 8.7 g of 1-methyl-3-phenyl-5-pyrazolone the yield was 8.7 g of product (60%), mp 63° (from alcohol) [6].

1,3-Dimethyl-5-pyrazolone-4-aldehyde (IV). To 1.75 g of dimethylformamide, with stirring and cooling to 0°, was added 3.3 g of phosphorus oxychloride. Then, at this same temperature, there was added 2.24 g of 1,3-dimethyl-5-pyrazolone. The reaction mixture was slowly warmed to 45-50° and was kept at this temperature for 3 h. After cooling, the reaction mixture was poured over ice and was then neutralized at 0° with a 10% sodium hydroxide solution to pH 4.0-5.0. The precipitate of 1,3-dimethyl-5-chloropyrazole-4-aldehyde was filtered off, washed with water, and dried. The yield was 0.86 g (27%), mp 76-77°. The filtrate was made alkaline, to pH 10.0 approximately, and was warmed at 40° for 1 h. Then the solution was evaporated under vacuum and was acidified at 0° with concentrated hydrochloric acid. The precipitate of IV which fell was filtered off, washed with water, and dried. The yield was 1 g (35.7%), mp 174-175° (dec., from a mixture of benzene and petroleum ether). Found, %: C 51.85, 51.63; H 5.87, 5.81; N 20.09, 19.97. $C_6H_8N_2O_2$. Calculated, %: C 51.43; H 5.71; N 20.0.

1,3-Dimethyl-4-(1',3'-dimethyl-4'-methylidene-5'-pyrazolone (V). This compound separates upon prolonged standing of the aqueous solution, after the 1,3-dimethyl-5-chloropyrazole-4-aldehyde in the preceding experiment. Mp 214° (from alcohol). Compound V is also obtained upon heating an acidified alcoholic solution of compounds Ia and IV. Found, %: N 24.22, 24.04. $C_{11}H_{14}N_4O_2$. Calculated, %: N 23.93.

1,3-Dimethyl-4-dimethylaminomethylene-5-pyrazolone (IIa). To a benzene solution of 0.5 g of compound IV was added a benzene solution of 0.65 g of dimethylamine. The solution was allowed to stand overnight at room temperature, then it was heated to boiling. After this, two-thirds of the solvent was

TABLE 2. 5-Amino-Substituted 1,3-Dimethylpyrazole-4-aldehydes and Their Derivatives

Compound	Mp (in deg)	Recrystallization solvent	Yield (in %)	Found (in %)		Empirical formula	Calcd. (in %)	
				N	Halogen		N	Halogen
XVI, Aldehyde, $N(CH_3)_2$	Bp 100°(1 mm) $n_D^{20}=1,5303$		57,1	25,30 25,18	—	$C_8H_{13}N_3O$	25,15	—
XVIa, Oxime, $N(CH_3)_2$	116	Ethanol-water	60,5	30,67 30,90	—	$C_8H_{14}N_4O$	30,77	—
XVIb, Oxime, $[\overset{+}{N}(CH_3)_3]I^-$	169—70	Methanol-ether	54,2	—	39,50 39,35	$C_9H_{17}JN_4O$		39,20
XVII, Aldehyde, 	Oily product		60,5	20,22 20,15	—	$C_{11}H_{17}N_3O$	20,03	—
XVIIa, Oxime, 	144—6	Ethanol-water	82,0	24,97 24,76	—	$C_{11}H_{18}N_4O$	25,02	—
XVIIb, Oxime, 	173—4	Ethanol-ether	60,8		34,71 34,53	$C_{12}H_{21}JN_4O$	—	34,89
XVIII, Aldehyde, 	73—5	Petroleum ether	20,0	20,13 20,10	— —	$C_{10}H_{15}N_3O_2$	20,09	
XVIIIa, Oxime, 	197—8	Ethanol-water	80,2	24,81 24,87	— —	$C_{10}H_{16}N_4O_2$	25,0	—
XIX, Aldehyde, OCH_3	55—6	Petroleum ether	60,1	18,23 18,04	—	$C_7H_{10}N_2O_2$	18,18	—
XIXa, Thiosemicarbazone, OCH_3	204 (dec.)		7,20	30,67 30,58	—	$C_8H_{13}N_5OS$	30,83	—
XX, Aldehyde $O(CH_2)_2N(C_2H_5)_2$	Oily product	Reprecipitated from benzene with petroleum ether	90,1	17,26 17,39	—	$C_{12}H_{21}N_3O_2$	17,57	
XXI, Aldehyde, $S(CH_2)_2N(C_2H_5)_2 \cdot HCl$	190—2	Absolute ethanol-ether	68,5	14,38 14,48	—	$C_{12}H_{21}N_3OS \cdot HCl$	14,40	—
XXIa, Oxime, $S(CH_2)_2N(C_2H_5)_2$	79—80	Petroleum ether	52,5	20,91 20,86	—	$C_{12}H_{22}N_4OS$	20,76	—
XXIb, Oxime, $[S(CH_2)_2\overset{\oplus}{N}(C_2H_5)_2CH_3]\overset{\ominus}{I}$	127—8	Acetone	80,1	13,38	30,74 30,68	$C_{13}H_{25}JN_4OS$	13,59	30,84

removed under vacuum, and petroleum ether was added to the residue. The precipitated slightly-yellowish crystalline solid was filtered off, and was washed with petroleum ether. There was obtained 0.5 g (83.3%). Mp 126-128° (from benzene-petroleum ether mixture). Found, %: C 57.37, 57.19; H 7.81, 7.97; N 25.09, 25.26. $C_8H_{13}N_3O$. Calculated, %: C 57.48; H 7.78; N 25.15.

1,3-Dimethyl-4-piperidinomethylene-5-pyrazolone (IIc). This was prepared analogously to the foregoing compound. Yield, 85%; mp 156-158° (from mixture of benzene and petroleum ether). Found, %: C 63.77, 63.52; H 8.28, 8.35; N 20.42, 20.27. $C_{11}H_{17}N_3O$. Calculated, %: C 63.77; H 8.21; N 20.29.

1,3-Dimethyl-4-phenylaminomethylene-5-pyrazolone (IId). This compound was prepared analogously to compound IIa. Yield, 90%, mp 156-157° (from mixture of benzene and petroleum ether). Found, %: N 19.69, 19.63. $C_{12}H_{13}N_3O$. Calculated, %: N 19.53.

1,3-Dimethyl-5-chloropyrazole-4-carboxaldehyde (IX, R_3 = OH). To a solution of 1.58 g of compound IIIa in 25 ml of water was added a solution of 1.55 g of potassium permanganate and 0.05 g of potassium hydroxide in 20 ml of water. The solution was heated on a water bath for 1 h with stirring, was filtered hot from the precipitate, cooled to 0°, and acidified with concentrated hydrochloric acid. The precipitate which fell was filtered off, washed with water, and dried. There was obtained 1.4 g (80%) of product, mp 197-198° (from dilute acetic acid). Found, %: C 41.35, 41.45; H 4.12, 4.10; N 15.80, 15.81. $C_6H_7ClN_2O_2$. Calculated, %: C 41.15; H 4.01; N 15.95.

1,3-Dimethyl-5-chloropyrazole-4-carbonyl Chloride (X, R_3 = Cl). A mixture of 1.75 g of the acid and 3.57 g of thionyl chloride in 20 ml of dry chloroform was boiled for 2 h. Then the excess thionyl chloride and solvent were distilled off. The yield of product was 1.3 g (67%), mp 49° (from petroleum ether). Found, %: Cl 36.44, 36.52. $C_6H_6Cl_2N_2O$. Calculated, %: Cl 36.78.

Synthesis of Esters (XI-XVI). A mixture of 0.01 mole of acid chloride (X) and 0.1 mole of the appropriate alcohol was heated on a boiling water bath for about 10 h. After the solvent had been stripped off, the residue was washed with water, extracted into ether, the ether extract dried, and then the compound prepared was isolated from it in the form of the hydrochloride by addition of an ether solution of hydrogen chloride, or in the form of the base after distilling off the ether.

Synthesis of 5-Amino-Substituted 1,3-Dimethylpyrazole-4-aldehydes (XVI-XVIII). 1,3-Dimethyl-5-chloropyrazole-4-aldehyde (0.02 mole) was placed in a thick-walled tube, 0.06 mole of the appropriate amine was added as such or in the form of a toluene solution, plus 5 ml of dry toluene, the tube was sealed, and it was heated for 15-18 h at 140-150°. After opening, the contents of the tube was filtered from the amine salt, the toluene solution was washed with water, it was dried, and the solvent was distilled off. The residue was distilled or crystallized from a suitable solvent (see Table 2).

Methiodides of XIV, XVIb, XVIIb, and XXIb. These were prepared by treatment of an acetone solution of the appropriate base with a five-fold excess of methyl iodide at room temperature. After standing for 24-48 h, the precipitate which separated was filtered off. Sometimes the quaternary salts were isolated by precipitation with ether from the acetone solutions.

1,3-Dimethylthieno(2,3c)pyrazole-5-carboxylic Acid (XXII, R = CH_3). To a solution of 0.94 g of potassium hydroxide in 30 ml of methanol was added 0.78 g of thioglycolic acid plus 0.8 g of 1,3-dimethyl-5-chloropyrazole-4-aldehyde. The reaction mixture was boiled for 3 h, after which the solvent was distilled off; the residue was dissolved in water, the solution was filtered, and it was acidified with 10% hydrochloric acid. An oil precipitated, which then crystallized. The finely-crystalline light-yellow solid was filtered, washed with water, and dried. There was obtained 0.8 g (81.6%), mp 126-127° (from benzene). Found, %: S 16.05, 15.98. $C_8H_8N_2O_2S$. Calculated, %: S 16.38.

1-Methyl-3-phenylthieno(2,3c)pyrazole-5-carboxylic Acid (XXIII, R = C_6H_5). This was prepared analogously to compound XXII, from 6.8 g of potassium hydroxide in 35 ml of methanol, 4.56 g of thioglycolic acid, and 7.3 g of 1-methyl-3-phenyl-5-chloropyrazole-4-aldehyde. The yield was 56.3%, mp 249-250° (from acetic acid). Found, %: S 12.56, 12.44. $C_{13}H_{10}N_2O_2S$. Calculated, %: S 12.40.

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