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REACTIONS OF 3-METHYL-1-(2-PYRIDYL)-4-CHLORO-5-FORMYL-6,7-DIHYDROINDAZOLE

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The reactions of 3-methyl-1-(2-pyridyl)-, 3-methyl-1-phenyl-, and 3-methyl-1,6-diphenyl-4-chloro-5-formyl-6,7-dihydroindazoles with guanidine and benzo- and 3- and 4-pyridinecarbamidines gave the corresponding 8-substituted 1-methyl-3-(2-pyridyl)- and 1-methyl-3-phenyl-4,5-dihydropyrazolo[5,4-h]quinazolines. With acetic anhydride the same indazole derivatives gave the 4-acetoxy-5-formyl derivatives, and with hydroxylamine they gave4-chloro-5-hydroxyiminomethyl-6,7-dihydroindazoles. Thereactionof4-acetoxy-1-(2-pyridyl)-5-formyl-6,7-dihydroindazole with hydroxylamine gave 8-methyl-6-(2-pyridyl)-4,5-dihydroisoxazolo[5,4-e]indazole, while dehydration of 5-hydroxyiminomethyl-3-methyl-4-chloro-6,7-dihydroindazole gave the 4-chloro-5-cyano derivative. The reaction of the latter with nucleophilic reagents was investigated.

Earlier we modified indazoles in the reactions of 3-methyl-1-(2-pyridyl)-5-formyl-4-chloro-6,7-dihydroindazoles (I, II) with hydrazines, *o*-phenylenediamine, and certain C-nucleophiles [1]. In the present paper we discuss the reactions of the β-chloroaldehydes (I-III) with guanidine, amidines, and hydroxylamine, leading to pyrazolo[5,4-*h*]quinazolines (IV-XII) and isoxazolo[5,4-*e*]indazole (XVII) respectively.

When the chloroaldehydes (I, II) were boiled with guanidine carbonate, benzamidine hydrochloride, and 3- and 4-pyridinecarbamidine hydrochlorides in ethanol in the presence of sodium ethoxide, the corresponding 8-substituted 1-methyl-3-(2-pyridyl)-4,5-dihydropyrazolo[5,4-*h*]quinazolines (IV-IX) were obtained. 3-Methyl-1-phenyl-5-formyl-4-chloro-6,7-dihydroindazole (III) also reacts with 3- and 4-pyridinecarbamidines [2].

The structure of the pyrazolo[4,5-*d*]quinazolines (IV-XII) is confirmed by the IR and PMR spectra (Table 1). Thus, the primary amino group of compound (IV) is characterized by the stretching vibrations at 3350 and 3150 cm^{-1}, while the PMR spectrum contains a two-proton signal at δ 5.52 ppm.

The reactions of the chloroaldehydes (I, II) with hydroxylamine hydrochloride in pyridine lead to the oximes (XIII, XIV). When boiled with acetic anhydride the chloroaldehydes (I, III) form the 4-acetoxy derivatives (XV) and (XVI). In the IR spectra of the enol acetates (XV) and (XVI) the carbonyl groups are characterized by absorption at 1774 (XV) and 1764 (XVI) cm^{-1}. The treatment of 4-acetoxy-5-formylindazole (XV) with hydroxylamine leads to the isoxazolo[5,4-*e*]indazole (XVII).

The aldoxime (XIII) is easily dehydrated to 3-methyl-1-(2-pyridyl)-4-chloro-5-cyano-6,7-dihydroindazole (XVIII) by boiling in acetic anhydride. Nucleophilic substitution of the chlorine atom in the latter is realized by the action of sodium alkoxide and also of potassium hydroxide and leads to the formation of the 4-ethoxy derivative (XIX) and 3-methyl-4-oxo-1-(2-pyridyl)-5-cyano-4,5,6,7-tetrahydroindazole (XX) respectively. The strong absorption band of the carbonyl group in the latter is found at 1686 cm^{-1}, while $\nu_{C\equiv N}$ is formed at 2250 cm^{-1}. The cyano ketone (XX) was also obtained by the action of hydroxylamine on 4-acetoxy-5-formylindazole (XV) in pyridine.

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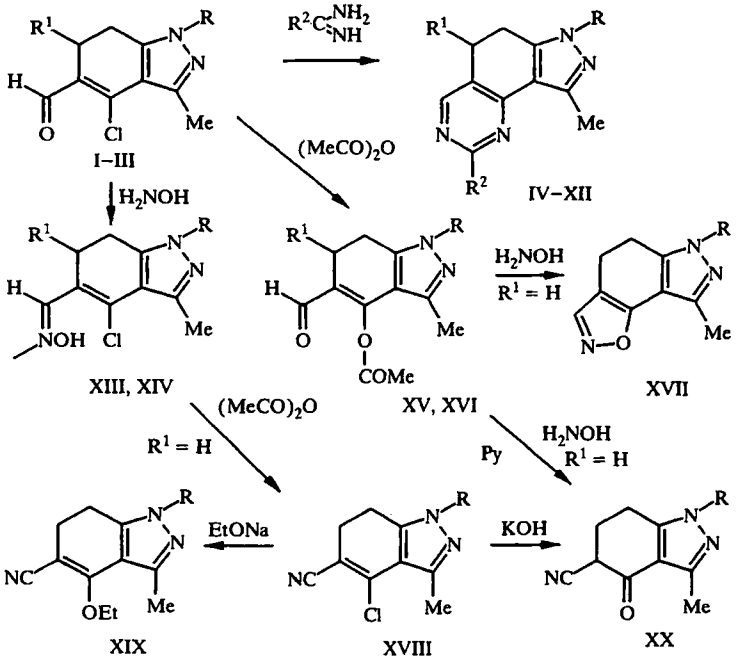

I R = 2-C_5H_4N, R^1 = H; II R = 2-C_5H_4N, R^1 = Ph; III R = Ph, R^1 = H; IV R = 2-C_5H_4N, R^1 = H, R^2 = NH_2; V R = 2-C_5H_4N, R^1 = Ph, R^2 = NH_2; VI R = 2-C_5H_4N, R^1 = H, R^2 = Ph; VII R = 2-C_5H_4N, R^1 = H, R^2 = 3-C_5H_4N; VIII R = 2-C_5H_4N, R^1 = H, R^2 = 4-C_5H_4N; IX R = 2-C_5H_4N, R^1 = H, R^2 = $C_6H_4CONH_2$(4); X R = Ph, R^1 = H, R^2 = 3-C_5H_4N; XI R = Ph, R^1 = H, R^2 = 4-C_5H_4N; XII R = Ph, R^1 = H, R^2 = $C_6H_4CONH_2$ (4); XIII, XV R = 2-C_5H_4N, R^1 = H; XIV, XVI R = 2-C_5H_4N, R^1 = Ph; XVII—XX R = 2-C_5H_4N

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer for suspensions in Vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The frequencies of the C−H vibrations in the region of 3050-2800 cm^{-1} are not indicated. The PMR spectra were obtained in deuterochloroform and DMSO-d_6 on a Bruker WH 90/DS spectrometer at 90 MHz with TMS as internal standard. The yields, melting points, and elemental analyses are given in Table 2. Compound (IX) is poorly soluble even in hexamethylphosphorotriamide, and it was not possible to obtain an accurate PMR spectrum for this compound.

8-Amino-1-methyl-3-(2-pyridyl)- and 1-Methyl-3-(2-pyridyl)-5-phenyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines (IV) and (V). A mixture of 3 mmole of the chloroaldehyde (I) or (II) and 5 mmole of guanidine carbonate was boiled for 6 h in a solution of sodium ethoxide, prepared from 10 mmole of sodium and 30 ml of absolute ethanol. The reaction mixture was evaporated to half on a rotary evaporator, and the residue was diluted with 15 ml of water. The precipitate was filtered off and recrystallized from ethanol.

3,8-Diaryl-1-methyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines (VI-XII). A mixture of 2 mmole of the chloroaldehyde (I) or (III) with an equimolar amount of the respective arylamidine hydrochloride was boiled for 6 h in a solution of sodium ethoxide, prepared from 4 mmole of sodium and 20 ml of absolute ethanol. The reaction mixture was cooled and diluted with 50 ml of water. The precipitate was filtered off and recrystallized from ethanol, except in the case of the pyrimidine (XII), which was crystallized from DMFA.

5-Hydroxyiminomethyl-3-methyl-1-(2-pyridyl)-4-chloro-6,7-dihydroindazole (XIII). A mixture of 2.16 g (8 mmole) of the chloroaldehyde (I) and 0.56 g (8 mmole) of hydroxylamine hydrochloride in 20 ml of pyridine was boiled for 3 h. After cooling the reaction mixture was diluted with 60 ml of water. The precipitated indazole (XIII) was filtered off and recrystallized from ethanol.

5-Hydroxyiminomethyl-3-methyl-1-(2-pyridyl)-4-chloro-6-phenyl-6,7-dihydroindazole (XIV). A solution of 1.75 g (5 mmole) of the aldehyde (II), 0.35 g (5 mmole) of hydroxylamine hydrochloride, and 0.4 g (5 mmole) of anhydrous sodium

TABLE 1. IR Spectra and PMR Spectra of Compounds (IV)-(XX)

Compound	IR spectra, ν, cm^{-1}	PMR spectra, δ, ppm
1	2	3
IV	1654, 1592, 1550; 3350, 3150	($CDCl_3$ + DMSO) 2,61 (3H, s, CH_3); 2,86 (2H, m, ^3J = 7Hz, CH_2); 3,46 (2H, m, ^3J = 7 Hz, CH_2); 5,52 (2H, bs, NH_2); 7,23 (1H, m, Py); 7,87 (2H, m, Py); 8,01 (1H, s, =CH–); 8,43 (1H, m, ^3J = 5 Hz, Py)
V	1660, 1596, 1580, 1538; 3520, 3400	($CDCl_3$) 2,67 (3H, s, CH_3); 3,54...4,37 (3H, m, CH_2CHCH_2); 4,99 (2H, bs, NH_2); 7,21 (6H, m, C_6H_5, Py); 7,62 (1H, s, =CH–); 7,81 (2H, m, Py); 8,30 (1H, m, Py)
VI	1584, 1548	($CDCl_3$) 2,83 (3H, s, CH_3); 3,01 (2H, t, ^3J = 7 Hz, CH_2); 3,57 (2H, ^3J = 7 Hz, CH_2); 7,14 (1H, m, Py); 7,43...8,46 (9H, m, C_6H_5, Py, =CH–)
VII	1584, 1550	($CDCl_3$) 2,83 (3H, s, CH_3); 3,01 (2H, t, ^3J = 7 Hz, CH_2); 3,57 (2H, ^3J = 7 Hz, CH_2); 7,14 (1H, m, Py); 7,43...8,46 (9H, m, C_6H_5, Py, =CH–) VII 1582, 1550 ($CDCl_3$) 2,81 (3H, s, CH_3); 3,08 (2H, t, ^3J = 7 Hz, CH_2); 3,61 (2H, t, ^3J = 7 Hz, CH_2); 7,32 (2H, m, Py); 7,81 (1H, m, Py); 7,99 (1H, m, Py); 8,41 (2H, m, Py, =CH–); 8,72 (2H, m, Py); 9,68 (1H, bs, Py)
VIII	598, 1584, 1548	($CDCl_3$) 2,81 (3H, s, CH_3); 3,08 (2H, t, ^3J = 7 Hz, CH_2); 3,61 (2H, t, ^3J = 7 Hz, CH_2); 7,14 (1H, m, Py); 7,79 (2H, m, Py); 8,30 (2H, m, ^3J = 6 Hz, Py); 8,39 (1H, m, Py); 8,50 (1H, s, =CH–); 8,74 (2H, m, ^3J = 6 Hz, Py)
IX	1654, 1616, 1580, 1538; 3400, 3180	
X	1582, 1550	($CDCl_3$) 2,81 (3H, s, CH_3); 3,08 (2H, t, ^3J = 7 Hz, CH_2); 3,63 (2H, t, ^3J = 7 Hz, CH_2); 7,32 (2H, m, Py, Ph); 7,86 (2H, m, Py, Ph); 8,41 (1H, m, Py, Ph); 8,45 (1H, s, =CH–); 8,68 (2H, m, Py, Ph); 9,68 (1H, bs, Py)
XI	1584, 1546, 1506	($CDCl_3$) 2,86 (3H, s, CH_3); 3,06 (4H, s, $2CH_2$); 7,43 (5H, m, C_6H_5); 8,28 (2H, m, ^3J = 6 Hz, Py); 8,46 (1H, s, =CH–), 8,70 (2H, m, ^3J = 6 Hz, Py)
XII	1666, 1615, 1586, 1540, 1510; 3400, 3200	($CDCl_3$ + DMSO) 2,74 (3H, s, CH_3); 3,08 (4H, s, $2CH_2$); 7,54 (6H, m, C_6H_5 + NH); 8,01 (3H, m, J = 8 Hz, C_6H_4 + NH); 8,48 (2H, ^3J = 8 Hz, C_6H_4); 8,63 (1H, s, =CH–)
XIII	1588, 1578, 1544; 3200...3120	(DMSO) 2,40 (3H, s, CH_3); 2,80 (2H, t, ^3J = 7 Hz, CH_2); 3,33 (2H, t, ^3J = 7 Hz, CH_2); 7,36 (1H, m, Py); 7,91 (2H, m, Py); 8,24 (1H, s, =CH–); 8,44 (1H, m, Py); 11,36 (1H, s, OH)
XIV	1590, 1575, 1544; 3250...3200	(DMSO) 2,50 (3H, s, CH_3); 3,66 (1H, dd, ^2J = 18 Hz, ^3J = 10 Hz, CH_2); 4,03 (1H, dd, ^2J = 18, ^3J = 1 Hz, CH_2); 4,62(1H, dd, ^3J = 10, ^3J = 1 Hz, CH); 7,18 (5H, m, C_6H_5); 7,23 (1H, m, Py); 7,89 (2H, m, Py); 8,28 (1H, s, =CH–); 8,36 (1H, m, Py); 11,42 (1H, s, OH)
XV	1774, 1680, 1620, 1594, 1578, 1554, 1540	($CDCl_3$) 2,27 (3H, s, CH_3); 2,56 (3H, s, CH_3); 2,96 (2H, t, ^3J = 7 Hz, CH_2); 3,51 (2H, t, ^3J = 7 Hz, CH_2); 7,22 (1H, m, Py); 7,84 (2H, m, Py); 8,20 (1H, dd, ^4J = 1 Hz, CHO); 8,40 (1H, m, Py)
XVI	1764, 1680, 1660, 1620, 1594, 1582, 1538	($CDCl_3$) 2,30 (3H, s, CH_3); 2,56 (3H, s, CH_3); 3,69...4,80 (3H, m, CH—CH_2); 7,17...8,42 (9H, m, C_6H_5, Py); 10,12 (1H, s, CHO)
XVII	1628, 1590, 1575, 1556, 1545, 1512	($CDCl_3$) 2,57 (3H, s, CH_3); 2,95 (2H, t, ^3J = 7 Hz, CH_2); 3,63 (2H, t, ^3J = 7 Hz, CH_2); 7,26 (1H, m, Py); 7,90 (2H, m, Py); 8,10 (1H, s, =CH–); 8,43 (1H, m, Py)
XVIII	1594, 1578, 1536; 2200	$CDCl_3$) 2,49 (3H, s, CH_3); 2,76 (2H, t, ^3J = 7 Hz, CH_2); 3,49 (2H, t, ^3J = 7 Hz, CH_2); 7,20 (1H, m, Py); 7,82 (1H, m, Py); 7,90 (1H, m, Py); 8,37 (1H, m, Py)
XIX	1604, 1580, 1566; 2190	($CDCl_3$) 1,43 (3H, t, ^3J = 7 Hz, CH_3); 2,41 (3H, s, CH_3); 2,66 (2H, t, ^3J = 7 Hz, CH_2); 3,39 (2H, t, ^3J = 7 Hz, CH_2); 4,59 (2H, q, ^3J = 7 Hz, OCH_2); 7,21 (1H, m, Py); 7,88 (2H, m, Py); 8,44 (1H, m, Py)
XX	1686, 1596, 1575, 1550; 2250	($CDCl_3$) 2,52 (3H, s, CH_3); 2,52 (2H, m, CH_2); 3,59 (2H, m, CH_2) 7,26 (1H, m, Py); 7,90 (2H, m, Py); 8,39 (1H, m, Py)

acetate in 40 ml of ethanol was boiled for 3 h. The reaction mixture was diluted with 100 ml of water, and the precipitated oxime (XIV) was filtered off and recrystallized from ethanol.

TABLE 2. Characteristics of the Synthesized Compounds (IV)-(XX)

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl		
IV	$C_{15}H_{14}N_6$	64.50 64,73	5.00 5,07	29.96 30,20		186...188	71
V	$C_{21}H_{18}N_6$	70.93 71,17	4.98 5,12	23.49 23,71		232...235	58
VI	$C_{21}H_{17}N_5$	74.04 74,31	5.01 5,05	20.43 20,64		179...180	41
VII	$C_{20}H_{16}N_6$	70.78 70,57	4.70 4,74	24.50 24,69		211...212	40
VIII	$C_{20}H_{16}N_6$	70.66 70,57	4.63 4,74	24.60 24,69		210...212	38
IX	$C_{22}H_{18}N_6O$	69.32 69,10	4.61 4,74	21.69 21.98		> 330	33
X	$C_{21}H_{17}N_5$	74.18 74,31	5.00 5,05	20.38 20,64		214	39
XI	$C_{21}H_{17}N_5$	74.05 74,31	4.92 5,05	20.35 20,64		198...200	29
XII	$C_{23}H_{19}N_5O$	72.19 72,42	4.87 5,02	18.30 18,36		> 330	40
XIII	$C_{14}H_{13}ClN_4O$	58.01 58,24	4.50 4,54	19.22 19,41	12.50 12,28	215...217	86
XIV	$C_{20}H_{17}ClN_4O$	65.60 65,84	4.72 4,70	15.44 15,36	9.50 9,72	234...235	60
XV	$C_{16}H_{15}N_3O_3$	64.37 64,64	5.02 5,09	14.00 14,13		172...173	63
XVI	$C_{22}H_{19}N_3O_3$	70.49 70,76	5.20 5,13	11.11 11,25		133...135	45
XVII	$C_{14}H_{12}N_4O$	66.41 66,65	4.65 4,80	21.97 22,21		139...141	60
XVIII	$C_{14}H_{11}ClN_4$	61.90 62,11	4.14 4,10	20.52 20,70	13.00 13,10	160...161	65
XIX	$C_{16}H_{16}N_4O$	68.38 68,55	5.70 5,75	19.90 19,99		109...111	53
XX	$C_{14}H_{12}N_4O$	66.49 66,65	4.70 4,80	22.02 22,21		172...174	50

4-Acetoxy-3-methyl-1-(2-pyridyl)-5-formyl- and 4-Acetoxy-3-methyl-1-(2-pyridyl)-6-phenyl-6,7-dihydroindazoles (XV) and (XVI). A solution of 8 mmole of the β-chloroaldehyde (I) [or compound (II)] in 40 ml of acetic anhydride was boiled for 4 h. The reaction mixture was cooled and poured into 60 ml of water. After 24 h the precipitate was filtered off and recrystallized from ethanol.

8-Methyl-6-(2-pyridyl)-4,5-dihydroisoxazolo[5,4-*e*]indazole (XVII). A mixture of 0.60 g (2 mmole) of the acetoxy derivative (XV), 0.21 g (3 mmole) of hydroxylamine hydrochloride, and 0.25 g (3 mmole) of anhydrous sodium acetate in 30 ml of absolute ethanol was boiled for 6 h. The solution was diluted with 50 ml of water and left at 0-5°C for 24 h. The precipitate was filtered off and recrystallized from 50% ethanol.

3-Methyl-1-(2-pyridyl)-4-chloro-5-cyano-6,7-dihydroindazole (XVIII). A mixture of 0.58 g (2 mmole) of the oxime (XIII) and 0.82 g (10 mmole) of anhydrous sodium acetate in 40 ml of acetic anhydride was boiled for 3 h. The reaction mixture was cooled and poured into 30 ml of water, and the precipitate was filtered off and recrystallized from ethanol.

3-Methyl-1-(2-pyridyl)-5-cyano-4-ethoxy-6,7-dihydroindazole (XIX). A 0.54-g sample (2 mmole) of the chlorovinylnitrile (XVIII) was boiled in an ethanol solution of sodium ethoxide, prepared from 0.10 g (4 mmole) of sodium and 30 ml of absolute ethanol, and the reaction mixture was diluted with 60 ml of water. The precipitated ethoxy derivative (XIX) was filtered off and recrystallized from ethanol.

3-Methyl-1-(2-pyridyl)-4-oxo-5-cyano-4,5,6,7-tetrahydroindazole (XX). A mixture of 0.60 g (2 mmole) of compound (XV) and 0.21 g (3 mmole) of hydroxylamine hydrochloride in 6 ml of dry pyridine was boiled for 5 h. The mixture was cooled and diluted with 50 ml of water. After 24 h the precipitate was filtered off and dissolved in 5 ml of ethyl acetate, and 10 ml of petroleum ether was added to the solution. The mixture was quickly filtered, and the filtrate was left in the refrigerator for 24 h. The precipitated oxonitrile (XX) was recrystallized from a 1:2 mixture of ethyl acetate and petroleum ether.

The same oxonitrile was obtained by boiling compound (XVIII) with potassium hydroxide in absolute ethanol for 14 h.

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