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5-DIAZO-6,6-DIMETHYL-4-OXO-4,5,6,7-TETRAHYDROINDAZOLES IN [3+2] CYCLOADDITION REACTIONS

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The [3+2] cycloaddition reactions of a series of 1,3-substituted 5-diazo-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles with maleic anhydride and dimethyl acetylenedicarboxylate gave 1',3'-substituted 3-spiro[4,6-dioxo-4,6,3a,6a-tetrahydro-3H-furo[3,4-c]pyrazole]-5'-[6',6'-dimethyl-4'-oxo-4',5',6',7'-tetrahydroindazoles] and 1',3'-substituted 3-spiro[4,5-di(methoxycarbonyl)-3H-pyrazole]-5'-[6',6'-dimethyl-4'-oxo-4',5',6',7'-tetrahydroindazoles] respectively. When heated the former eliminate nitrogen and are transformed into 1',3'-substituted 6-spiro[2,4-dioxo-3-oxabicyclo[3.1.0]hexane]-5'-[6',6'-dimethyl-4'-oxo-4',5',6',7'-tetrahydroindazoles].

Keywords: dimethyl acetylenedicarboxylate, 1,3- and 2,3-substituted 5-diazo-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles, maleic anhydride, [3+2] cycloaddition.

In the last ten years the range of indazole derivatives with valuable biological activity has increased substantially. Among them agonists of estrogen receptors [1] and dopamine D3 receptors [2], HIV protease inhibitors [3], and new anti-inflammatory substances [4] have been discovered. In this connection in a continuation of researches on the synthesis of 4,5-bifunctional 6,7-dihydro- and 4,5,6,7-tetrahydroindazoles [5-10] we realized [3+2] cycloaddition reactions between 5-diazo-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles **1a-d** and maleic anhydride.

The diazoindazoles **1a**,**b**,**d** were obtained by the decomposition of the corresponding tosylhydrazones **2a**,**b**,**d** in a water–ethanol solution of sodium hydroxide according to the procedure in [11, 12] that we used earlier for the preparation of the diazoindazoles **1c** and **3**.

In the reaction of the diazoindazoles **1a-d** with maleic anhydride by the classical methods [13, 14] the corresponding 1',3'-substituted 6',6'-dimethyl-4,6,4'-trioxo-4,6,3a,6a,4',5',6',7'-octahydro-3H-spirofuro[3,4-*c*]-pyrazole-3,5'-indazoles **4a-d** are formed. The reactions were carried out by keeping equimolar amounts of the reagents in methylene chloride for 15 days. The precipitated spiro compound **4** was filtered off and recrystallized from ethyl acetate with minimal boiling.

Heating of the pyrazolines **4b**,**c** for 1-2 min at the melting point or boiling in toluene led to the release of nitrogen and transformation into the corresponding 1',3'-substituted 6',6'-dimethyl-2,4,4'-trioxo-4',5',6',7'-tetrahydrospiro-3-oxabicyclo[3.1.0]hexane-6,5'-indazoles **5b**,**c**.

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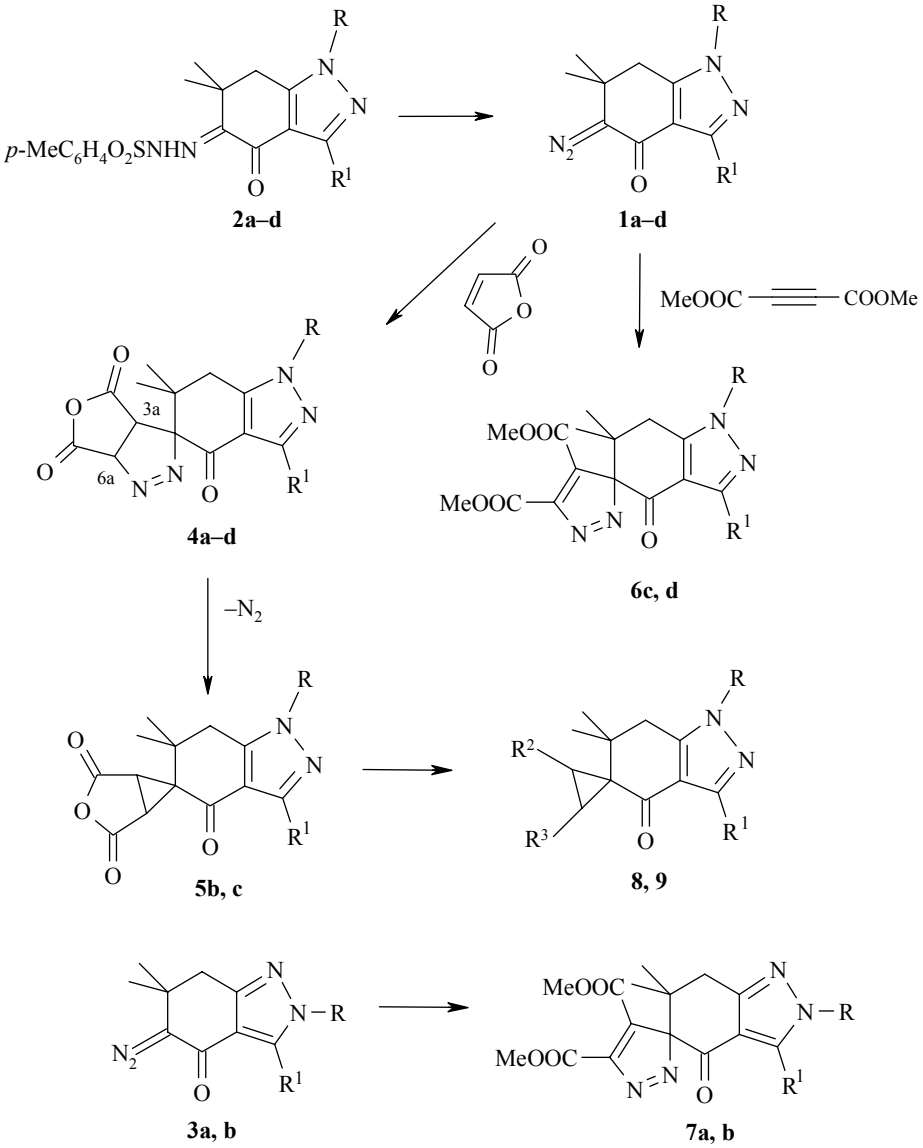

1, 2, 4 a R = Ph, R^1 = H; **b** R = Ph, R^1 = Me; **c** R = Py-2, R^1 = Me; **d** R = $C_6H_3(CF_3)_2$-3,5, R^1 = Me; **3, 7 a** R = 2- pyridyl, R^1 = Ph; **b** R = Ph, R^1 = C_6H_4OMe-4; **5 b** R = Ph, R^1 = Me; **c** R = Py-2, R^1 = Me; **6 c** R = Py-2, R^1 = Me; **d** R = $C_6H_3(CF_3)_2$-3,5, R^1 = Me; **8** R = Ph, R^1 = Me, R^2 = R^3 = COOH; **9** R = 2- pyridyl, R^1 = Me, R^2 = COOH, R^3 = $CONHCH_2Ph$

Heating of the solution of the anhydride **5b** in 5% aqueous sodium hydroxide solution to boiling followed by acidification leads to the dicarboxylic acid **8**. The benzylamide **9** is formed when a benzene solution of equimolar amounts of the anhydride **5c** and benzylamine is heated to boiling.

The reaction of the diazoindazoles **1b**,**c** and **3a**,**b** [12] with dimethyl acetylenedicarboxylate is carried out by keeping equimolar amounts of the reagents in methylene chloride at 20°C for 4-5 days. In all cases the corresponding 1',3'- or 2',3'-substituted 4,5-di(methoxycarbonyl)-6,6'-dimethyl-4'-oxo-4',5',6',7'-tetrahydro-3H-spiropyrazole-3,5'-indazoles **6c**,**d** and **7a**,**b** were obtained.

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{15}H_{14}N_4O$	67.51 / 67.65	5.35 / 5.30	20.88 / 21.04	174-175	73
1b	$C_{16}H_{16}N_4O$	68.37 / 68.55	5.55 / 5.75	20.08 / 19.99	145-147	63
1d	$C_{18}H_{14}F_6N_4O$	51.70 / 51.93	3.30 / 3.39	13.25 / 13.46	185-187	69
2a	$C_{22}H_{22}N_4O_3S$	62.63 / 62.55	5.11 / 5.25	13.12 / 13.26	118-119	88
2b	$C_{23}H_{24}N_4O_3S$	63.11 / 63.28	5.40 / 5.54	12.75 / 12.84	149-151	70
2d	$C_{25}H_{22}F_6N_4O_3S$	52.27 / 52.44	3.90 / 3.87	9.66 / 9.79	160-162	41
4a	$C_{19}H_{16}N_4O_4$	62.45 / 62.63	4.30 / 4.43	15.31 / 15.38	167-169 (dec.)	51
4b	$C_{20}H_{18}N_4O_4$	63.26 / 63.48	4.59 / 4.79	14.70 / 14.81	179–181 (dec.)	50
4c	$C_{19}H_{17}N_5O_4$	60.01 / 60.15	4.58 / 4.52	18.35 / 18.46	154-156 (dec.)	68
4d	$C_{22}H_{16}F_6N_4O_4$	51.19 / 51.37	3.03 / 3.14	10.93 / 10.89	162-164 (dec.)	40
5b	$C_{20}H_{18}N_2O_4$	68.44 / 68.56	5.02 / 5.18	7.85 / 7.99	202-204	43
5c	$C_{19}H_{17}N_3O_4$	64.70 / 64.95	4.68 / 4.88	11.80 / 11.96	257-258	56
6c	$C_{21}H_{21}N_5O_5$	59.39 / 59.56	4.92 / 5.00	16.36 / 16.54	159-160	95
6d	$C_{24}H_{20}F_6N_4O_5$	51.49 / 51.62	3.50 / 3.61	9.88 / 10.03	230-231	56
7a	$C_{26}H_{23}N_5O_5$	64.11 / 64.32	4.60 / 4.77	14.21 / 14.43	185-186	50
7b	$C_{28}H_{26}N_4O_6$	65.27 / 65.36	5.11 / 5.09	11.03 / 10.89	195-197	45
8	$C_{20}H_{20}N_2O_5$	65.00 / 65.21	5.33 / 5.47	7.49 / 7.60	252-253	94
9	$C_{26}H_{26}N_4O_4$	67.93 / 68.10	5.55 / 5.72	12.30 / 12.22	285-287	64

The structure of the synthesized compounds was confirmed by the data from the IR and ^{1}H NMR spectra (Table 2) and in the case of the spiro compound **4c** also by X-ray crystallographic experiments (Table 1).

In the indazole derivatives **4** the methyl groups at $C_{(6)}$ and also each of the hydrogens of the $C_{(7)}$ methylene group appear as separate signals. In compounds **5** there are six-proton singlets for the two $C_{(6)}$ methyl groups and also singlets for the $C_{(7)}$ methylene groups. The signals of the methyl groups in compounds **5** were assigned according to their ^{13}C satellite signals in the ^{1}H NMR spectra, which make it possible to record $^3J_{HH}$ between the magnetically equivalent protons (4-5 Hz).

The signals for the protons of the furopyrazole structural fragments at the $C_{(3a)}$ and $C_{(6a)}$ atoms of compounds **4** are found at δ 3.21-3.76 (3a) and 6.29-6.78 ppm (6a) and for the symmetrical spiro-substituting groups of compounds **5** at δ 3.62-3.67 ppm.

For an objective assessment of the structure of compound **4c** an X-ray crystallographic analysis of the crystals of this compound was undertaken (Fig. 1, Tables 3-5).

TABLE 2. The Spectra of the Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1} (C=O, NH, OH)	^{1}H NMR spectrum, δ, ppm. (SSCS, *J*, Hz)*
1a	1630, 2095	1.35 (6H, s, $2CH_3$); 2.96 (2H, s, CH_2); 7.22-7.70 (5H, m, C_6H_5); 8.06 (1H, s, H-3)
1b	1630, 2090	1.26 (6H, s, $2CH_3$); 2.56 (3H, s, CH_3); 3.40 (2H, s, CH_2); 7.50-7.80 (5H, m, C_6H_5)
1c	1640, 2095	1.44 (6H, s, $2CH_3$); 2.53 (3H, s, CH_3); 3.06 (2H, s, CH_2); 7.42 (3H, br. s, C_6H_3)
2a	1642, 3230	1.21 (6H, s, $2CH_3$); 2.55 (3H, s, CH_3); 3.35 (2H, s, CH_2); 7.28-8.00 (10H, m, C_6H_5, C_6H_4, H-3); 12.50 (1H, br. s, NH)
2b	1650, 3260	1.30 (6H, s, $2CH_3$); 2.42 (3H, s, CH_3); 2.60 (3H, s, CH_3); 3.45 (2H, s, CH_2); 7.25-7.80 (9H, m, C_6H_5, C_6H_4); 12.65 (1H, br. s, NH)
2d	1645, 3250	1.40 (6H, s, $2CH_3$); 2.45 (3H, s, CH_3); 2.60 (3H, s, CH_3); 3.50 (2H, s, CH_2); 7.30-7.95 (7H, m, C_6H_4, C_6H_3); 12.65 (1H, br. s, NH)
4a	1864, 1782, 1684	0.98 (3H, s, CH_3); 1.04 (3H, s, CH_3); 3.18 and 3.28 (2H, two d, ^2J = 12.4, H-7); (1H, d, *J* = 12.4, H-7); 3.74 (1H, d, *J* = 9.6, H-3a); 6.77 (1H, d, *J* = 9.6, H-6a); 7.53–7.78 (5H, m, Ar); 8.27 (1H, s, H-3a)
4b	1860, 1775, 1670	0.96 (3H, s, CH_3); 1.27 (3H, s, CH_3); 2.51 (3H, s, CH_3); 2.95 (1H, d, ^2J = 16.8, H-7); 3.28 (1H, d, *J* = 10.0, H-3a); 3.76 (1H, d, ^2J = 16.8, H-3a); 6.29 (1H, d, *J* = 10.0, H-6a); 7.54 (5H, m, Ar)
4c	1867, 1779, 1671	1.03 (3H, s, CH_3); 1.09 (3H, s, CH_3); 2.39 (3H, s, CH_3); 3.21 (3H, m, CH_2, CH); 6.75 (1H, d, *J* = 10.0, H-6a); 7.48 (1H, m, Py); 7.95-8.13 (2H, m, Py); 8.58 (1H, m, *J* = 5.0, Py)
4d	1862, 1775, 1670	0.98 (3H, s, CH_3); 1.04 (3H, s, CH_3); 2.41 (3H, s, CH_3); 3.28 (2H, br. s, CH_2); 3.74 (1H, d, *J* = 10.0, H-3a); 6.78 (1H, d, *J* = 10.0, H-6a); 8.29 (1H, br. s, Ar); 8.42 (1H, br. s, Ar)
5b	1850, 1772, 1658	0.98 (6H, s, $2CH_3$); 2.37 (3H, s, CH_3); 3.11 (2H, br. s, H-7); 3.62 (2H, s, H-3a, H-6a); 7.48-7.62 (5H, m, Ar)
5c	1845, 1776, 1658	1.03 (6H, s, $2CH_3$); 2.38 (3H, s, CH_3); 3.47 (2H, s, H-7); 3.67 (2H, s, H-3a, H-6a); 7.45 (1H, dd, *J* = 5.0, *J* = 8.0, Ar); 7.92 (1H, d, *J* = 8.0, Ar); 8.05 (1H, dt, *J* = 8.0, *J* = 2.0, Ar); 8.56 (1H, d, *J* = 5.0, Ar)
6c	1740, 1720, 1660	1.48 (6H, s, $2CH_3$); 2.66 (3H, s, CH_3); 3.65 (2H, s, CH_2); 3.92 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 7.33 (1H, m, Ar); 7.89-7.92 (2H, m, Ar); 8.47 (1H, m, Ar)
6d	1745, 1730, 1662	1.44 (6H, s, $2CH_3$); 2.65 (3H, s, CH_3); 3.10 (2H, s, CH_2); 3.92 (6H, s, $2OCH_3$); 7.91 (2H, br. s, Ar); 7.99 (1H, s, Ar)
7a	1740, 1730, 1660	1.53 (6H, s, $2CH_3$); 3.26 (2H, s, CH_2); 3.89 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 7.23-7.35 (7H, m, Ar); 7.67 (1H, dt, *J* = 8.0, *J* = 2.5, Ar); 8.46 (1H, m, Ar)
7b	1732, 1726, 1701	1.51 (6H, s, $2CH_3$); 3.20 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 6.82 (2H, m, Ar); 7.22-7.32 (7H, m, Ar)
8	1865, 1711, 1677; 2640-2580	0.92 (6H, s, $2CH_3$); 2.36 (5H, s, CH_2, CH_3); 2.98 (2H, s, H-3a, H-6a); 7.38-7.62 (5H, m, Ar); 12.25 (1H, br. s, COOH); 13.12 (1H, br. s, COOH)
9	1760, 1715, 1661; 3180, 2660-2600	0.99 (3H, s, CH_3); 1.06 (3H, s, CH_3); 2.37 (3H, s, CH_3); 2.47 (1H, d, *J* = 9.0, CH); 2.58 (1H, d, *J* = 9.0, CH); 3.43 (1H, d, *J* = 18.0, CH); 3.58 (1H, d, *J* = 18.0, CH); 4.12 (1H, dd, *J* = 15.0, *J* = 5.0, CH); 4.37 (1H, dd, *J* = 15.0, *J* = 5.0, CH); 7.01-7.21 (5H, m, Ar); 7.41 (1H, m, Ar); 8.02 (1H, d, *J* = 8.0, Ar); 8.04 (1H, dt, *J* = 8.0, *J* = 2.0, Ar); 8.51 (1H, m, Ar); 9.15 (1H, t, *J* = 5.0, NH); 13.94 (1H, br. s, COOH).

* The ^{1}H NMR spectra were recorded in $CDCl_3$ (compounds **1a-c**, **2a**,**b**,**d**, **4b**, **6c**,**d**, **7a**,**b**) and DMSO-d_6 (compounds **4a**,**c**,**d**, **5b**,**c**, **8**, **9**).

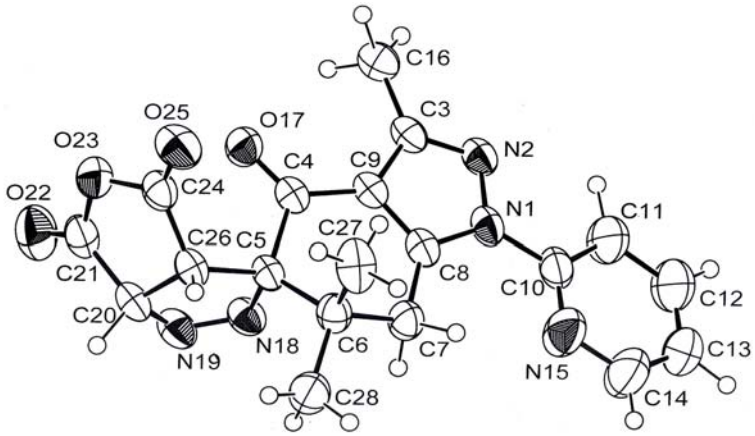

Fig. 1. Three-dimensional model of the molecule **4c** with the numbers of the atoms and the thermal vibration ellipsoids.

TABLE 3. The Crystallographic Data of Compound **4c**

Empirical formula	$C_{19}H_{17}N_5O_4$
M_r	379.38
Crystal system	Monoclinic
Space group	*C* 2/*c*
Unit cell parameters:	
a, Å	23.1182(5)
b, Å	9.8210(3)
c, Å	19.2573(4)
β, deg.	114.909(2)
V, Å^3	3965.4(2)
Molecular multiplicity, *Z*	8
Density of crystals, *d*, g/cm^3	1.271
Absorption coefficient, μ, mm^{-1}	0.092
Number	
of independent reflections	5031
reflections with $I > 2\sigma(I)$	3411
refined parameters	265
Final *R* factor	0.0874
Employed programs	SIR97 [1], SHELXL97 [2]

TABLE 4. The Principal Bond Lengths (*l*) in the Molecule of Compound **4c**

Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}$–$N_{(2)}$	1.375(4)	$C_{(7)}$–$C_{(8)}$	1.489(4)
$N_{(1)}$–$C_{(8)}$	1.352(4)	$C_{(8)}$–$C_{(9)}$	1.379(5)
$N_{(1)}$–$C_{(10)}$	1.432(4)	$N_{(18)}$–$N_{(19)}$	1.234(4)
$N_{(2)}$–$C_{(3)}$	1.320(4)	$N_{(19)}$–$C_{(20)}$	1.491(4)
$C_{(4)}$–$C_{(5)}$	1.556(4)	$C_{(20)}$–$C_{(21)}$	1.502(5)
$C_{(4)}$–$C_{(9)}$	1.434(4)	$C_{(21)}$–$O_{(22)}$	1.196(4)
$C_{(4)}$–$O_{(17)}$	1.217(4)	$C_{(20)}$–$C_{(26)}$	1.514(4)
$C_{(5)}$–$C_{(6)}$	1.539(4)	$C_{(21)}$–$O_{(23)}$	1.360(5)
$C_{(5)}$–$N_{(18)}$	1.515(4)	$O_{(23)}$–$C_{(24)}$	1.405(4)
$C_{(5)}$–$C_{(26)}$	1.555(4)	$C_{(24)}$–$O_{(25)}$	1.181(4)
$C_{(6)}$–$C_{(7)}$	1.554(4)	$C_{(24)}$–$C_{(26)}$	1.508(5)

TABLE 5. The Principal Valence (ω) and Torsion (τ) Angles in the Molecule of compound **4c**

Angle	ω, deg	Angle	τ, deg
$N_{(2)}$–$N_{(1)}$–$C_{(8)}$	111.6(3)	$C_{(9)}$–$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	32.3(3)
$N_{(1)}$–$N_{(2)}$–$C_{(3)}$	106.2(2)	$C_{(5)}$–$C_{(26)}$–$C_{(20)}$–$C_{(21)}$	113.5(3)
$C_{(5)}$–$N_{(18)}$–$N_{(19)}$	113.8(2)	$N_{(19)}$–$C_{(20)}$–$C_{(26)}$–$C_{(24)}$	128.2(3)
$N_{(18)}$–$N_{(19)}$–$C_{(20)}$	111.7(3)		
$C_{(21)}$–$O_{(23)}$–$C_{(24)}$	110.8(3)		

EXPERIMENTAL

The IR spectra were obtained on a Specord IR-75 instrument for suspensions in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The frequencies of the stretching vibrations of the C–H bonds in the region of 3050-2800 cm^{-1} are not given. The ^1H NMR spectra were recorded on a Varian Mercury BB spectrometer (200 MHz) with TMS as internal standard.

5-Diazo-6,6-dimethyl-1-phenyl (1a), 5-Diazo-3,6,6-trimethyl-1-phenyl- (1b), and 1-[(3,5-Bistrifluoromethyl)phenyl]-5-diazo-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles (1d). The corresponding tosylhydrazone **2a**,**b**,**d** (2 mmol) was suspended in aqueous solution (40 ml) sodium hydroxide (0.4 g). The mixture was heated at 80-90°C with stirring for 1 h, and ethanol (15 ml) was added. The precipitate was filtered off, compounds **1a**,**b** were recrystallized from benzene–hexane and **1d** from ethyl acetate–hexane.

6,6-Dimethyl-4-oxo-1-phenyl-5-tosylhydrazono- (2a), 3,6,6-Trimethyl-4-oxo-1-phenyl-5-tosylhydrazono- (2b), and 1-[(3,5-Bistrifluoromethyl)phenyl]-3,6,6-trimethyl-4-oxo-5-tosylhydrazono-4,5,6,7-tetrahydroindazoles (2d). A solution of the corresponding 4,5-dioxo derivative (5 mmol) [10, 15] and tosylhydrazone (5 mmol) in ethanol (30 ml) was boiled for 2 h, cooled, and in the case of **2d** diluted with an equal quantity of water. The tosylhydrazone was filtered off and recrystallized from ethanol.

1',3'-Substituted 6',6'-Dimethyl-4,6,4'-trioxo-4,6,3a,6a,4',5',6',7'-octahydrospiro[3H-furo[3,4-*c*]-pyrazole-3,5′-indazoles] 4a-d. A solution of the corresponding diazoindazole **1a-d** (3 mmol) and maleic anhydride (3 mmol) in methylene chloride (30 ml) was left at 20°C for 15 days. The precipitate was filtered off, washed on the filter with methylene chloride, and recrystallized from ethyl acetate by briefly boiling.

1',3'-Substituted 6',6'-Dimethyl-2,4,4'-trioxo-4',5',6',7'-tetrahydrospiro[3-oxabicyclo[3.1.0]hexane-6,5'-indazoles] 5b,c. The pyrazolines **4b**,**c** in a wide test tube were immersed in an oil bath at 150°C for 2-3 min. Bubbles of nitrogen were released. The residue was recrystallized from ethanol.

The same compounds **5b**,**c** were obtained by boiling of the pyrazolines **4b**,**c** (5 mmol) in toluene (30 ml) for 2 h. The mixture was cooled, and the product was filtered off and recrystallized from ethanol.

2,3-Dicarboxy-5',3',6',6'-trimethyl-4'-oxo-1'-phenyl-4',5',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole] (8). The indazole spiro derivative **5b** (3 mmol) in 2% aqueous sodium hydroxide (3 ml) solution was heated to boiling, cooled, and acidified to pH 3-4 with hydrochloric acid. The precipitated dicarboxylic acid was filtered off and recrystallized from a solution of 1:1 ethanol–water.

3-Benzylaminocarbonyl-2-carboxy-5',3',6',6'-tetramethyl-4'-oxo-1'-(2-pyridyl)-4',5',6',7'-tetrahydrospiro[cyclopropane-1,5′-indazole] (9). To a solution of the anhydride **5c** (3 mmol) in dry benzene (30 ml) we added benzylamine (3.5 mmol). The mixture was boiled for 2-3 min and cooled. After 24 h the precipitated compound **9** was filtered off and recrystallized from acetic acid.

4,5-Dimethoxycarbonyl-3'-(4-methoxyphenyl)-3′,6′,6′-trimethyl-4'-oxo-1'-(2-pyridyl)- (6c) and 1'-[(3,5-Bistrifluoromethyl)phenyl]-4,5-dimethoxycarbonyl-3'-(4-methoxyphenyl)-3',6',6'-trimethyl-4'-oxo- (6d), 4,5-Dimethoxycarbonyl-3'-(4-methoxyphenyl)-6',6'-dimethyl-4'-oxo-3-phenyl-2'-(2-pyridyl)- (7a)

and 4,5-Dimethoxycarbonyl-3'-(4-methoxyphenyl)-6′,6′-dimethyl-4′-oxo-2'-phenyl-4',5',6',7'-tetrahydro-spiro[3H-pyrazole-3,5'-indazole] (7b). A solution of the corresponding diazoindazole **1c**,**d** or **3a**,**b** (3 mmol) and dimethyl acetylenedicarboxylate (3 mmol) in methylene chloride (30 ml) was left at 20°C for four days. Hexane (60 ml) was added, and the precipitated pyrazoles **6c**,**d** and **7a**,**b** were recrystallized from ethanol.

X-ray Crystallographic Investigations (Tables 3-5). For X-ray crystallographic analysis the diffraction pattern of a single crystal of compound **4c**, measuring 0.05×0.26×0.33 mm, was recorded on an automatic Nonius KappaCCD diffractometer up to $2\theta_{max} = 57°$ (λMo = 0.71073 Å).

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