SYNTHESIS OF DI- AND TRISUBSTITUTED 1,2,4-TRIAZOLES CONTAINING INDOLE FRAGMENTS

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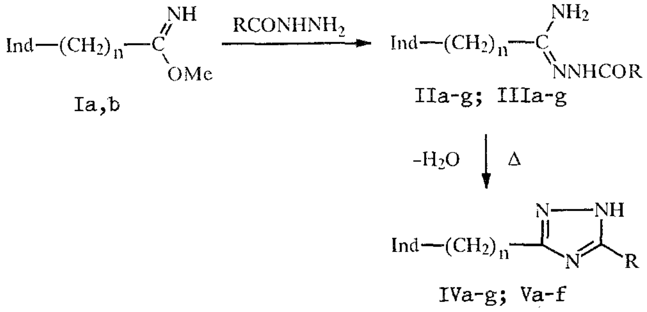
The reaction of imino esters of indole-series acids with acid hydrazides gave $N_{(1)}$-acylamidrazones, which, during heating, were converted to 3,5-disubstituted 1H-1,2,4-triazoles containing indole fragments. Compounds of this type were also synthesized by the reaction of indolyl-containing 2,5-disubstituted 1,3,4-oxadiazoles with formamide. Condensation of 2,5-disubstituted 1,3,4-oxadiazoles with aniline gave 3,4,5-trisubstituted 4H-1,2,4-triazoles containing indolyl radicals. Cyclocondensation of $N_{(1)}$-phenylamidrazones of indole-series acids with benzoyl chloride gave 1,3,5-trisubstituted 1H-1,2,4-triazoles.

The increased interest in bisheterocyclic systems containing simultaneously indole and 1,2,4-triazole fragments is explained by the fact that some indolyl-containing 1,2,4-triazoles have diverse biological activity [1-4]. Therefore, it seemed appropriate to develop convenient methods for synthesis of bisheterocyclic compounds of such a type.

It is known [5, 6] that $N_{(1)}$-acylamidrazones of carboxylic acids can be starting substances for synthesis of 3,5-disubstituted 1H-1,2,4-triazoles. In the present paper, the starting compounds were $N_{(1)}$-acylamidrazones of indole-3-carboxylic (IIa-g) and 3-indolylacetic acids (IIIa-g), which were formed in 85-95% yields (see Table 1) during condensation of equimolecular amounts of methyl imino esters of indole-3-carboxylic (Ia) or 3-indolylacetic (Ib) acid with acid hydrazides. It should be noted that $N_{(1)}$-acylamidrazones IIIa-g were obtained during boiling of the components in methanol for several minutes, whereas longer-term heating (1-1.5 h) was required for preparation of $N_{(1)}$-acylamidrazones IIa-g.



Ind = 3-indolyl; Ia, IIa-g, IVa-g n = 0; Ib, IIIa-g, Va-f n = 1; IIa, IIIa, IVa, Va R = Me; IIb, IIIb, IVb, Vb R = Ph; IIc, IIIc, IVc, Vc R = 4-$NO_2C_6H_4$; IId, IIId, IVd, Vd R = 4-ClC_6H_4; IIe, IIIe, IVe, Ve R = 5-nitro-2-furyl; IIf, IIIf, IVf R = 3-indolyl; IIg, IIIg, IVg, Vf R = 3-indolylmethyl

The IR spectra of $N_{(1)}$-acylamidrazones IIa-g and IIIa-g contained intense absorption maximums in the regions of 3350-3340 and 3150-3100 cm^{-1}, characteristic of stretching vibrations of the NH group of indole [7] and NH_2 and NH groups of the

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TABLE 1. Characteristics of $N_{(1)}$-Acylamidrazones II, III, VI, and VII

Compound	Empirical formula	mp, °C (decomp.)	Yield, %	Compound	Empirical formula	mp, °C (decomp)	Yield, %
IIa	$C_{11}H_{12}N_4O$	131...132	84	IIIc	$C_{17}H_{15}N_5O_3$	158...159	94
IIb	$C_{16}N_{14}N_4O$	183...184	92	IIId	$C_{17}H_{15}ClN_4O$	164...164,5	87
IIc	$C_{16}H_{13}N_5O_3$	254...256	95	IIIe	$C_{15}H_{13}N_5O_4$	200...201	84
IId	$C_{16}H_{13}ClN_4O$	172...173	90	IIIf	$C_{19}H_{17}N_5O$	180...181,5	87
IIe	$C_{14}H_{11}N_5O_4$	212...214	83	IIIg	$C_{20}H_{19}N_5O$	134...135	89
IIf	$C_{18}H_{15}N_5O$	118...120	91	VIa	$C_{16}H_{14}N_4O$	158...159,5	78
IIg	$C_{19}H_{17}N_5O$	228...229	86	VIb	$C_{14}H_{11}N_5O_4$	184...185	71
IIIa	$C_{12}H_{14}N_4O$	98...99	85	VIIa	$C_{17}H_{16}N_4O$	140...141	66
IIIb	$C_{17}H_{16}N_4O$	115...117	90	VIIb	$C_{15}H_{13}N_5O_4$	118...119	60

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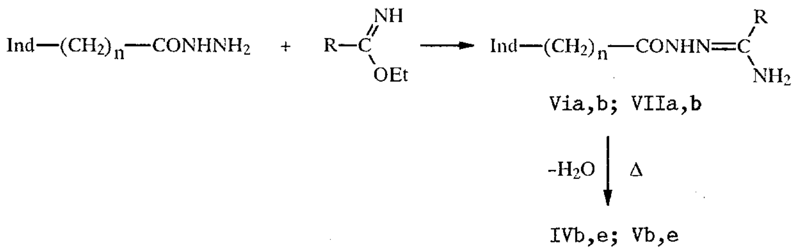
*Compounds IIa, IIb, IIf, IIg, and IIId were recrystallized from aqueous ethanol; IIc-e, IIIc, IIIe, and VIb were recrystallized from aqueous DMFA; IIIb, IIIf, and VIa were recrystallized from ethanol; IIIg and VIIb were recrystallized from aqueous dioxane; and VIIa was recrystallized from aqueous acetone.

amidrazone fragment [8]. The absorption bands in the region of 1675-1655 and 1635-1620 cm^{-1} should be assigned to stretching vibrations of the C=O and C=N groups in the acylamidrazones, respectively.

Cyclodehydration of $N_{(1)}$-acylamidrazones IIa-g and IIIa-g occurred facilely during heating 5-10°C above their melting point for 5-10 min. As a result, 3-(3-indolyl)- (IVa-g) and 3-(3-indolylmethyl)-5-substituted 1H-1,2,4-triazoles (Va-f) were formed in high yield (80-90%) (method A). Ring closure occurred most facilely in the case of 3-indolylacetic $N_{(1)}$-acylamidrazone (IIIa): Partial formation of the corresponding 1H-1,2,4-triazole Va was observed even during recrystallization of acylamidrazone IIIa from ethanol. During cyclization of $N_{(1)}$-acylamidrazones IIg and IIIf, the same compound 3-(3-indolyl)-5-(3-indolylmethyl)-1H-1,2,4-triazole (IVg) was obtained.

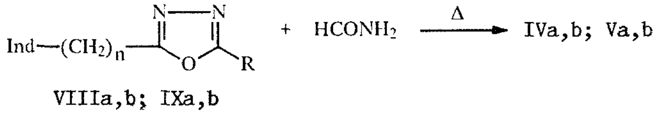
Some of the indolyl-containing 1H-1,2,4-triazoles (compounds IVb, IVe, Vb, and Ve) were also obtained by reverse synthesis (method B), i.e., cyclodehydration of carboxylic $N_{(1)}$-(3-indolylcarbonyl)- (VIa and VIb) and $N_{(1)}$-(3-indolylacetyl)-amidrazones (VIIa and VIIb) synthesized from indole-3-carboxylic and 3-indolylacetic hydrazides and the corresponding ethyl imino esters (Table 1).



Ind = 3-indolyl; VIa, VIb n = 0; VIIIa, VIIIb n = 1; a R = Ph; b R = 5-nitro-2-furyl

It should be noted that the yield of 1H-1,2,4-triazoles IVe and Ve obtained by method B was significantly lower than in their preparation from 5-nitrofuran-2-carboxylic hydrazide (method A).

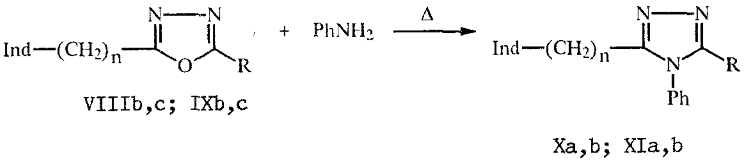
The literature contains data [9] that, during heating with formamide, 2,5-disubstituted 1,3,4-oxadiazoles are converted to 3,5-disubstituted 1H-1,2,4-triazoles. It seemed of interest and promising to use this method for synthesis of indolyl-containing 1H-1,2,4-triazoles. For this purpose, the reaction of some 1,3,4-oxadiazoles VIIIa, VIIIb, IXa, and IXb, containing indole substituents with formamide, was investigated (method C)



Ind = 3-indolyl; VIIIa, VIIIb n = 0; IXa, IXb n = 1; a R = Me, b R = Ph

It was determined that the reaction occurs smoothly during heating of 1,3,4-oxadiazoles VIIIa, VIIIb, IXa, and IXb with a large excess of formamide at 170-180°C for several hours. 2-Methyl-5-(3-indolylmethyl)-1,3,4-oxadiazole (IXa) underwent such conversion facilely, and 2-phenyl-5-(3-indolyl)-1,3,4-oxadiazole (VIIIb) underwent it with greatest difficulty. At the same time, 2-(4-nitrophenyl)- and 2-(5-nitro-2-furyl)-5-(3-indolyl)-1,3,4-oxadiazoles did not react with formamide under these conditions: The starting compounds were recovered for the reaction mixture unchanged, even after heating with formamide at 175°C for 20 h.

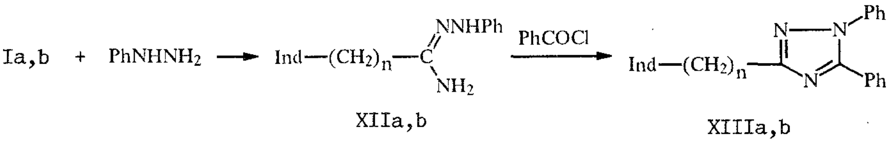
It is known [10, 11] that 3,4,5-trisubstituted 4H-1,2,4-triazoles are formed during heating of 2,5-disubstituted 1,3,4-oxadiazoles with aromatic amines. We decided to extend this method to the preparation of indolyl-containing 4H-1,2,4-triazoles, and, for this purpose, we studied the reaction of the corresponding 1,3,4-oxadiazoles with aniline (method D). The reaction of 1,3,4-oxadiazoles VIIIb, VIIIc, IXb, and IXc with aniline was carried out with heating of equimolecular amounts of the reagents under pressure in an inert-gas atmosphere at temperatures from 260 to 320°C for 16-20 h.



Ind = 3-indolyl; VIIIb, VIIIc, Xa, Xb n = 0; IXb, IXc, XIa, XIb n = 1; VIIIb, IXb,
Xa, XIa R = Ph; VIIIc, IXc, Xb, XIb R = 3-indolyl

Only 4-phenyl-3,5-disubstituted 4H-1,2,4-triazoles Xa, Xb, XIa, and XIb were recovered from the reaction mixture, and in all cases some amount of the starting 1,3,4-oxadiazole was returned from the reaction. Carrying out the reaction of 1,3,4-oxadiazoles VIIIb and IXb with aniline for 48 h at 310°C or the use of excess aniline did not affect the yield of 4H-1,2,4-triazoles Xa, Xb, XIa, and XIb.

For preparation of trisubstituted 1H-1,2,4-triazoles containing indole fragments, indole-3-carboxylic $N_{(1)}$-acylamidrazone (XIIa) and 3-indolylacetic $N_{(1)}$-phenylamidrazone (XIIb), which are formed in the reaction of imino esters Ia and Ib with phenylhydrazine, were also used as starting compounds.



a $n = 0$,b $n = 1$

The literature contains data [12, 13] that $N_{(1)}$-substituted amidrazones undergo cyclization to 1,3,5-trisubstituted 1H-1,2,4-triazoles during treatment with acid halides or acid anhydrides. We studied the condensation of $N_{(1)}$-phenylamidrazones XIIa and XIIb with benzoyl chloride and obtained the corresponding 1,5-diphenyl-2-substituted 1H-1,2,4-triazoles XIIIa and XIIIb in good yield (65-70%) (method E).

The IR spectra of all the di- and trisubstituted 1,2,4-triazoles IVa-g, Va-f, Xa, Xb, XIa, XIb, XIIIa, and XIIIb contain not only adsorption frequencies characteristic of indole fragments (1615, 1520-1490, 1250, 1010, and 920 cm^{-1} [7, 14]), but also a series of adsorption bands caused by vibrations of the 1,2,4-triazole ring. Stretching vibrations of C=N and C=C fragments of heteroaromatic rings are characterized by absorption bands of variable intensity at 1630-1615, 1600-1575, 1565-1560, and 1475-1460 cm^{-1}. The latter group of bands is characteristic of the 1,2,4-triazole ring [7]. The presence of this ring is also confirmed by adsorption bands of stretching (1505-1500 and 1120 and 1110) and bending (1050-950) vibrations of the 1,2,4-triazole ring [15, 16] and also by a group of intense absorption bands at 1290-1275 cm^{-1} that are characteristic of

TABLE 2. Characteristics of Indolyl-Containing 1,2,4-Triazoles IV, V, X, XI, and XIII

Compound	Empirical formula	Mp, ° C	R_f**	PMR spectrum, δ, ppm***	Yield, % (method)
1	2	3	4	5	6
IVa	$C_{11}H_{10}N_4$	110...111.5	0.38 (A)	2.52 (3H, s, CH_3), 7.05...7.56 (4H, m, H_{arom}), 7.76 (1H, d, indole 2...H, J_{12} = 2.6 Hz), 8.02 (1H, bs, NH), 8.20 (1H, bs, NH)	90 (A) 58(B)
IVb	$C_{16}H_{12}N_4$	235...236	0.41 (A)	6.82...7.46 (9H, m, H_{arom}), 7.69 (1H, d, indole 2...H, J_{12} = 2.8 Hz), 8.10 (1H, ws, NH), 8.22 (1H, bs, NH)	94 (A) 90 (B) 66 (B)
IVc	$C_{16}H_{11}N_5O_2$	291...292	0.50 (A)	6.71...7.54 (8H, m, H_{arom}), 7.80 (1H, d, indole 2...H, J_{12} = 3.5 Hz), 8.08 (1H, s, NH), 8.24 (1H, ws, NH)	91 (A)
IVd	$C_{16}H_{11}ClN_4$	178...179	0.39 (A)		88 (A)
IVe	$C_{14}H_9N_5O_3$	200...201	0.40 (A)	6.60...7.04 (4H, m, H_{arom}), 7.18 (1H, d, 3...H furan, J_{34} = 3.5 Hz), 7.52 (1H, d, 4...H Furan), 7.82 (1H, d, 2...H indole, J_{12} = 2.5 Hz), 7.98 (1H, bs, NH), 8.16 (1H, s NH)	82 (A) 55 (B)
IVf	$C_{18}H_{13}N_5$	145...145.5	0.26 (A)		80 (A)
IVg	$C_{19}H_{15}N_5$	184...185	0.34 (A)	3.94 (2H, s, CH_2), 6.93...7.32 (8H, m, H_{arom}), 7.40 (1H, d, indole 2...H, J_{12} = 2.7 Hz), 7.82 (1H, d, indole 2...H, J_{12} = 4.0 Hz), 8.06 (1H, s, NH), 8.18 (1H, ws, NH)	85 (A)
Va	$C_{12}H_{12}N_4$	88...90	0.56 (A)	2.50 (3H, s, CH_3), 4.02 (2H, s, CH_2), 6.98...7.18 (4H, m, H_{arom}), 7.34 (1H, d, indole 2...H, J_{12} = 3.3 Hz), 8.12 (1H, s,NH), 8.23 (1H, ws, NH)	87 (A) 62 (B)
Vb	$C_{17}H_{14}N_4$	123...124	0.42 (A)	3.90 (2H, s, CH_2), 6.80...7.24 (9H, m, H_{arom}), 7.38 (1H, d, indole 2...H, J_{12} = 3.0 Hz), 8.10 (1H, s, NH), 8.22 (1H, bs, NH)	80 (A) 86 (B) 68 (C)

Vc	$C_{17}H_{13}N_5O_2$	256...257.5	0.31 (A)		95 (A)
Vd	$C_{17}H_{13}ClN_4$	186...187	0.48 (A)	4.16 (2H, s, CH_2), 6.76...7.18 (8H, m, H_{arom}), 7.30 (1H, d, indole 2...H, J_{12} = 2.7 Hz), 8.02 (1H, bs, NH), 8.24 (1H,s, NH)	92 (A)
Ve	$C_{15}H_{11}N_5O_3$	166...167	0.22 (A)	4.04 (2H, s, CH_2), 6.72 (1H, d, furan 3...H, J_{34} = 4.0 Hz), 6.88...7.20 (4H, m, H_{arom}), 7.38 (1H, d, indole 2...H, J_{12} = 2.9 Hz), 7.54 (1H, d, furan 4...H), 8.10 (1H, s, NH), 8.21 (1H, bs, NH)	85 (A) 42 (B)
Vf	$C_{20}H_{17}N_5$	133...134	0.40 (A)	4.12 (4H, bs, CH_2), 6.90...7.27 (8H, m, H_{arom}), 7.40 (2H, d, indole 2...H, J_{12} = 3.4 Hz), 8.12 (2H, ws, NH), 8.25 (1H, s, NH)	82 (A)
Xa	$C_{22}H_{11}N_4$	129...130.5	0.58 (B)		62
Xb	$C_{24}H_{17}N_5$	151...153	0.32 (B)	6.80...7.35 (13H, m, H_{arom}), 7.70 (1H, d, indole 2...H, J_{12} = 3.2 Hz), 8.08...8.14 (2H, ws, NH)	48
XIa	$C_{23}H_{13}N_4$	104...105	0.67 (B)	3.92 (2H, s, CH_2), 6.78...7.62 (15H, m, H_{arom}), 8.18 (1H, s, NH)	58
XIb	$C_{25}H_{19}N_5$	94...95	0.38 (B)		67
XIIIa	$C_{22}H_{11}N_4$	102...103.5	0.74 (C)	6.80...7.58 (14H, m, H_{arom}), 7.72 (1H, d, indole 2...H, J_{12} = 3.6 Hz), 8.08 (1H, s, NH)	65
XIIIb	$C_{23}H_{13}N_4$	87...88	0.69 (C)	3.98 (2H, s, CH_2), 6.96...7.80 (15H, m, H_{arom}), 8.10 (1H, bs, NH)	61

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*Compounds IVa, IVd, IVg, Va, Vd, Xb, XIa, and XIIIa were recrystallized from aqueous ethanol; IVb, Vf, and XIIIb were recrystallized from aqueous dioxane; IVc, IVe, IVf, Vb, Vc, and Ve were recrystallized from aqueous DMFA; and Xa and XIb were recrystallized from 1-butanol.

**The solvent system is indicated in parentheses.

***The spectra of compounds IVa-c, IVg, Vb, Ve, Xb, and XIa were recorded in DMSO-D_6, and the spectra of IVe, Va, Vd, Vf, XIIIa, and XIIIb were recorded in acetone-D_6.

stretching vibrations of C–N bonds in substituted 1,2,4-triazoles [16]. The spectra of all the synthesized 1,2,4-triazoles contain several intense absorption bands in the region of 810-785 and 755-745 cm^{-1}, which are characteristic of 3-substituted indoles [14, 17].

In the high-frequency region, the IR spectra of 3,5-disubstituted 1H-1,2,4-triazoles IVa-g and Va-f contained two groups of absorption bands, at 3410-3380 and 3270-3150 cm^{-1}. The first group of bands should be assigned to NH stretching vibrations of the 1,2,4-triazole ring on the basis that absorption in this region is absent in spectra of 3-substituted 1,2,4-triazoles Xa, Xb, XIa, XIb, XIIIa, and XIIIb.

In the PMR spectra of 3-(3-indolyl)-5-R-1H-1,2,4-triazoles (IVa-g) and also 4-phenyl-3-(3-indolyl)-5-R- (Xa and Xb) and 1,5-diphenyl-3-(3-indolyl)-1H-1,2,4-triazole (XIIIa), the 2-H peak of the pyrrole ring was manifested as a doublet at 7.68-7.82 ppm and spin–spin coupling constant 2.5-4.0 Hz, and, in comparison with unsubstituted indole and 3-phenylindole (6.68 and 7.03 ppm, respectively [17]), it was shifted to a weak field. In the spectra of compounds in which the rings were separated by a methylene group Va-f, Xa, Xb, and XIIIb, the peak of this proton was observed at 7.30-7.40 ppm, and we assigned a singlet with intensity of two proton units at 3.90-4.16 ppm to protons of the methylene group.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 instrument in tablets with KBr or in white mineral oil. The PMR spectra were obtained with a Bruker WP-100 SY spectrometer, and the internal standard was TMS. The course of the reactions and the purity of the obtained compounds were monitored by thin-layer chromatography on Al_2O_3 of Brockmann activity grade III in solvent systems benzene–methanol, 10:1 (A), benzene–methanol, 20:1 (B), and benzene–methanol, 5:1 (C), with development by iodine vapor.

The data of elemental analyses of the compounds for C, H, and N corresponded to calculated data.

Methyl imino esters of indole-3-carboxylic (Ia) and 3-indolylacetic (Ib) acids [18] and also 2,5-disubstituted 1,3,4-oxadiazoles VIIIa-c and IXa-c were synthesized by known methods [19].

General Method for Preparation of $N_{(1)}$-Acylamidrazones of Indole-3-carboxylic (IIa-g) and 3-Indolylacetic (IIIa-g) Acids (Table 1). A mixture of 20 mmoles of methyl imino ester Ia or Ib and 20 mmoles of the hydrazide of the corresponding acid was boiled with stirring in 50 ml of absolute methanol (for 5-7 min in the preparation of IIIa-g or 1.5 h in the preparation of IIa-g). The reaction mixture was cooled to 20°C and poured into 200 ml of cold water. The precipitate was filtered, dried, and crystallized from suitable solvents [$N_{(1)}$-acylamidrazone IIIa was subsequently used without preliminary purification].

$N_{(1)}$-(3-Indolylcarbonyl)- (VIa and VIb) and $N_{(1)}$-(3-Indolylacetyl)amidrazones of Carboxylic Acids (VIIa and VIIb). These compounds were similarly obtained from indole-3-carboxylic or 3-indolylacetic hydrazide and ethyl imino esters of the corresponding acids (Table 1).

3,5-Disubstituted 1H-1,2,4-Triazoles (IVa-g and Va-f) (Table 2). **A.** A mixture of 0.15 mmole of the corresponding $N_{(1)}$-acylamidrazone IIa-g and IIIa-g was heated for 10-15 min at a temperature 5-10°C higher than their melting points. The reaction products were crystallized from suitable solvents with activated carbon. 1H-1,2,4-Triazoles Va and Vf were purified chromatographically on columns with Al_2O_3 (50 × 4.5 cm^{-1}) and eluted with a 5:1 benzene–methanol mixture.

B. Compounds IVb, IVe, Vb, and Ve were similarly obtained from $N_{(1)}$-acylamidrazones VIa, VIb, VIIa, and VIIb.

C. At 170-180°C, 20 mmoles of 1,3,4-oxadiazole VIIIa,VIIIb, IXa, and IXb in 50 ml of formamide was stirred for 8-10 h at 170-180°C. The reaction mixture was cooled to 20°C and poured into 300 ml of cold water. The resulting precipitate was filtered, washed on a filter with water, and boiled for 1 h with 40 ml of 10% hydrochloric acid. The precipitate was filtered, washed on a filter with water, and dried in vacuo over P_2O_5.

Combined samples of the 1H-1,2,4-triazoles obtained by different methods did not give a melting-point depression, and their IR and PMR spectra were identical.

4-Phenyl-3,5-disubstituted 4H-1,2,4-Triazoles (Xa, Xb, XIa, and XIb) (Table 2). A mixture of 20 mmoles of 1,3,4-oxadiazole XVIIIb, XVIIIc, IXb, or IXc and 1.86 g (20 mmoles) of aniline was heated in a sealed ampul in a nitrogen atmosphere for 16-18 h at 300-320°C. The reaction mixture was cooled to 20°C and worked up with 50 ml of 5% hydrochloric acid, and the resulting precipitate was filtered, washed with water, dried, and extracted with a suitable solvent at 20°C: acetone in the preparation of Xa, ether in the preparation of XIa, and dioxane in the preparation of Xb and XIb. 4H-1,2,4-Triazoles Xa, Xb, XIa, and XIb were recovered from the extract.

Indole-3-carboxylic $N_{(1)}$-Phenylamidrazone (XIIa; $C_{15}H_{14}N_4$). A solution of 1.74 g (10 mmoles) of methyl imino ester Ia and 1.08 g (10 mmoles) of freshly distilled phenylhydrazine in 20 ml of absolute ethanol was stirred for 2 h at 20°C and poured into water. The recovered precipitate was filtered, dried, and crystallized from aqueous ethanol. We obtained 1.8 g (73%) of amidrazone XIIa, mp 98-98.5°C; R_f 0.29 (B). IR spectrum: 3385-3180 (NH), 1650 (C=N), 1615, 1590, 1575 (rings), 950, 805, 770 cm^{-1} (CH).

3-Indolylacetic $N_{(1)}$-Phenylamidrazone (XIIb, $C_{16}H_{16}N_4$). This compound was similarly obtained from methyl imino ester Ib in 72% yield, with mp 84-85°C (from aqueous ethanol) and R_f 0.33 (B).

1,5-Diphenyl-3-(3-indolyl)-1H-1,2,4-triazole (XIIIa) (Table 2). A mixture of 2.5 g (10 mmoles) of $N_{(1)}$-phenylamidrazone XIIa and 7.0 ml of benzoyl chloride was heated for 12 h at 120°C. The reaction mixture was cooled to 20°C and worked up with 30 ml of a 10% aqueous ammonia solution. The resulting precipitate was filtered, washed with water, and dried.

1,5-Diphenyl-3-(3-indolylmethyl)-1H-1,2,4-triazole (XIIIb). This compound was similarly prepared from $N_{(1)}$-phenylamidrazone XIIb.

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