SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

37.* SYNTHESIS OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES CONTAINING INDOLE RADICALS

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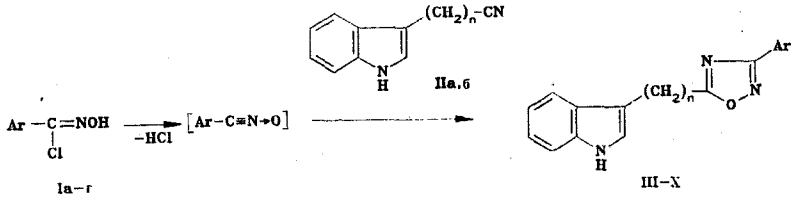
The 1,3-dipolar cycloaddition of nitrile N-oxides to indole nitriles yields 3,5-disubstituted 1,2,4-oxadiazoles containing an indole radical at the 5 position. Condensation of amidoximes with indole iminoester hydrochlorides yields 1,2,4-oxadiazoles having an indole segment at the 3 and/or 5 position of the oxadiazole ring. Pyrolysis of O-acyl derivatives of indole amidoximes yields 1,2,4-oxadiazoles with an indole residue at the 3 position.

In connection with the discovery of the high pharmacological activity of certain indolyl 1,2.4-oxadiazoles [2], it became advisable to elucidate the effect of substituents in the 1,2,4-oxadiazole ring on chemotherapeutic properties, and to develop convenient syntheses of that type of bis-heterocyclic compound. For this purpose we have studied the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from indolecarboxylic acid derivatives, viz., nitriles, iminoesters, and amidoximes. In the present work these derivatives of the simplest indole acids, 3-indolecarboxylic and 3-indoleacetic, have been used.

1,2,4-Oxadiazoles can be synthesized by the 1,3-dipolar cycloaddition of aromatic nitrile N-oxides to nitriles [3]. In spite of the wide use of various nitriles as dipolarophiles, cycloaddition at the C≡N bond of indole nitriles has not previously been described.

1,3-Dipoles, aromatic nitrile N-oxides, are obtained *in situ* from the acid chlorides of the respective arylhydroxamic acids Ia-d by the action of triethylamine in the presence of a dipolarophile, the nitrile of 3-indolecarboxylic (IIa) or 3-indole-acetic (IIb) acids. For the generation of nitrile N-oxides from hydroxamic acid chlorides, two methods are usually used, the action of a solution of base [4] or heating in an aromatic hydrocarbon [5]. Accordingly in the present work 1,2,4-oxadiazoles were synthesized by 1,3-dipolar cycloaddition by two methods: Method A, to a mixture of acid chloride Ia-d and nitrile IIa, b in ether at room temperature was added an ether solution of triethylamine; or Method B, equimolar amounts of Ia-d and IIa, b were kept in boiling benzene until HCl evolution ended.



I a Ar=C_6H_5, b Ar=4-$O_2NC_6H_4$, c Ar=4-ClC_6H_4, d Ar=3-$CH_3C_6H_4$; n=0, 1 (for compounds III-X, see Table 1)

When nitrile IIa was reacted with 4-nitrobenzonitrile N-oxide by method A, the yield of adduct IV did not exceed 30%, and it took 96 h to complete the reaction. This may be explained by the low reactivity of the cyano group in IIa; as a result the furoxane byproduct from the cyclopolymerization of IIa forms in large amounts [6]. It is known [7, 8] that the dipolarophile activity of the nitrile group increases appreciably by complexation with boron fluoride. We found that the use of $(C_2H_5)_2O{\cdot}BF_3$ in 2:1 molar ratio to IIa shortened the reaction time to 32 h and increased the yield of adduct IV to 45%. It was also established that changing the molar ratio of Ia-d to IIa, b does not significantly affect the yield of desired product

*For Communication 36, see [1].

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or the duration of the reaction; therefore all condensations by method A were carried out at equimolar proportions of reagents.

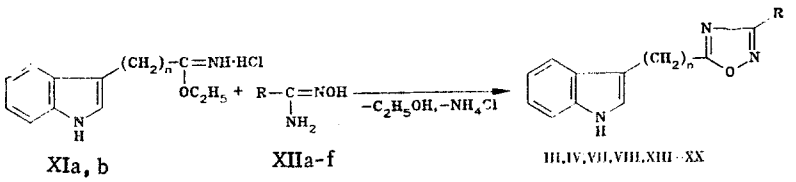
In the reaction of 4-nitrobenzhydroxamic acid chloride (Ib) with IIa in boiling benzene (method B), the reaction is complete after 48 h and the yield of IV is 80%. Use of boiling toluene as solvent forms a significant amount of tar and reduces the yield of IV to 60%.

The yields of the 1,2,4-oxadiazoles VII-X from 3-indole-acetonitrile IIb are significantly lower than the yields of III-VI from 3-indolylcyanide (3-indolecarboxylic acid nitrile), IIa. This is evidence that IIa is more reactive than IIb in 1,3-dipolar cycloaddition reactions.

R. Huisgen [4, 9] has shown that the reactivity of aromatic nitriles toward nitrile N-oxides is significantly greater than that of aliphatic nitriles. Accordingly the introduction of the methylene group between the indole nucleus and the cyano group changes the reactivity of the latter toward nitrile N-oxides; this is expressed by the sharp decrease in the yields of the 3-aryl-5-(indolyl-3-methyl)-1,2,4-oxadiazoles (VII-X).

According to [10], the amidoximes of carboxylic acids are often used as starting materials, for the synthesis of 1,2,4-oxadiazoles. In our work, for the synthesis of indolyl 1,2,4-oxadiazoles we chose a method involving the condensation of iminoester hydrochlorides with amidoximes [11, 12].

We established that the condensation of ethyl iminoesters of 3-indolcarboxylic (XIa) and 3-indolylacetic (XIb) acids with the amidoximes XIIa-f forms 3-substituted 5-(indolyl-3)-(III, IV, XIII-XVI) and 5-(indolyl-3-methyl)-1,2,4-oxadiazoles (VII, VIII, XVII-XX) in good yield (method C).



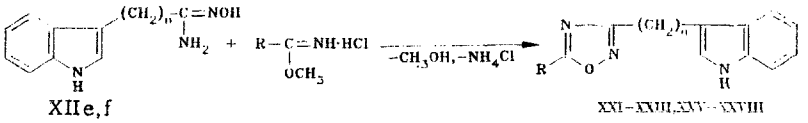
XIa, b XIIa-f III, IV, VII, VIII, XIII-XX

XIIa, R = C_6H_5; b, R = 4-$O_2NC_6H_4$; c, R = 5-nitrofuryl-2; d, R = CH_2Cl; e, R = indolyl-3; f, R = indolyl-3-methyl; n = 0,1

We have previously shown [13] that iminoester hydrochloride XIb is more reactive than XIa toward nucleophilic reagents. XIa condenses with amidoximes XIIa-f when an equimolar mixture of the reagents is boiled in methanol for 10-12 h; under the same conditions the reaction of XIIb with the amidoximes is complete in 2-3 h.

It should be noted that the yields of 1,2,4-oxadiazoles that contain two indole segments (XV, XVI, XIX, and XX) do not exceed 38-50%. The reason for the low yield is the considerable resinification of the reaction mixture and the formation of a number of byproducts, among which the amides and nitriles of the indole acids were found by TLC. The formation of these compounds can be explained by the thermal instability of the starting amidoximes XIIe,f, which decompose even when heated in methanol. Carrying out the reaction at a lower temperature (35-40°) was unsuccessful; after 14 h only the starting reagents could be detected in the reaction mixture.

To synthesize 3,5-disubstituted 1,2,4-oxadiazoles that contain indole segments only at the 3 position of the oxadiazole ring (XXI-XXIII, XXV-XXVIII), the amidoximes XIIe,f were condensed with the methyl iminoester hydrochlorides of some carboxylic acids (method D).



XIIe,f XXI-XXIII, XXV-XXVIII

n=0,1; R=C_6H_5, 4-$O_2NC_6H_4$, 5-nitrofuryl-2, CH_2Cl

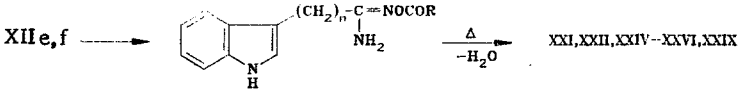
The reaction was carried out by boiling equimolar amounts of the reagents for 2-3 h in methanol. But the yield of 1,2,4-oxadiazole even in these cases did not exceed 40-56%, and the considerable resinification of the reaction mixture hindered the separation of the desired products.

TABLE 1. Properties of 5-(Indolyl-3-)- and 5-(Indolyl-3-methyl)-3-R-1,2,4-oxadiazoles

Compound	3-R[a]	mp, °C	R_f[c]	Found, %			Empirical formula	Calculated, %			Yield, % (method of synthesis)
				C	H	N		C	H	N	
III	C_6H_5	172,5—174	0,56	73,1	4,1	16,3	$C_{16}H_{11}N_3O$	73,5	4,2	16,1	41 (A), 72 (B), 84 (C)
IV	4-$O_2NC_6H_4$	242—244	0,46	62,6	3,6	18,0	$C_{16}H_{10}N_4O_3$	62,7	3,3	18,3	47 (A), 80 (B), 92 (C)
V	4-ClC_6H_4	154—155	0,62	64,5	3,1	14,4	$C_{16}H_{10}ClN_3O$	65,0	3,4	14,2	46 (A), 73 (B)
VI	3-$CH_3C_6H_4$	177—178	0,52	74,4	4,4	15,4	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	40 (A), 67 (B)
VII	C_6H_5	154—155	0,48	74,3	4,6	15,1	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	22 (A), 61 (B), 68 (C)
VIII	4-$O_2NC_6H_4$	192—193	0,40	63,7	3,8	17,1	$C_{17}H_{12}N_4O_3$	63,7	3,8	17,5	27 (A), 66 (B), 85 (C)
IX	4-ClC_6H_4	164—165	0,72	65,8	4,0	13,1	$C_{17}H_{12}ClN_3O$	65,9	3,9	13,6	26 (A), 60 (B)
X	3-$CH_3C_6H_4$	181—183	0,65	74,3	5,5	14,4	$C_{18}H_{15}N_3O$	74,7	5,2	14,5	24 (A), 57 (B)
XIII	5-Nitrofuryl-2	155—156	0,50	55,1	2,5	18,7	$C_{14}H_8N_4O_4$	55,3	2,6	18,4	64 (C)
XIV	CH_2Cl	140—141	0,68	56,7	3,5	18,3	$C_{11}H_8ClN_3O$	56,5	3,4	18,0	56 (C)
XV	Indolyl-3	184—185	0,32	71,8	4,0	18,5	$C_{18}H_{12}N_4O$	72,0	4,0	18,6	50 (C)
XVI	Indolyl-3-methyl	150—151	0,39	72,4	4,5	17,5	$C_{19}H_{14}N_4O$	72,6	4,4	17,8	40 (C)
XVII	5-Nitrofuryl-2	172—174	0,34	58,1	3,2	18,4	$C_{15}H_{10}N_4O_4$	58,0	3,2	18,1	71 (C)
XVIII	CH_2Cl	106—108	0,71	58,1	4,1	17,1	$C_{12}H_{10}ClN_3O$	58,2	4,0	17,0	51 (C)
XIX	Indolyl-3	141—142	0,30	72,5	4,3	17,6	$C_{19}H_{14}N_4O$	72,6	4,4	17,8	53 (C)
XX	Indolyl-3-methyl	108—110	0,41	73,4	5,0	17,2	$C_{20}H_{16}N_4O$	73,2	4,9	17,1	38 (C)

[a]For III-VI and XIII-XVI, n = 0; for VII-X and XVII and XX, n = 1. [b]Recrystallization: III, V, VI, and VIII, from toluene; IV from butanol-1; VII from benzene; IX from chloroform; X and XX from 1:1 DMFA—alcohol; XIII from aqueous alcohol; XIV and XVIII from abs. alcohol—hexane; XV-XVII and XIX from aqueous DMFA. [c]In 5:1 benzene—methanol.

1,2,4-Oxadiazoles of this type were also synthesized by method E, which consists of pyrolysis of O-acyl derivatives of amidoximes [14]. The respective O-acyl derivatives of the indole amidoximes (XXXa-f) were synthesized by acylation of XIIe,f under mild conditions by acetic anhydride or acid chlorides.



XXX a-f

XXX R=CH_3, C_6H_5, 4-$O_2NC_6H_4$; n=0,1

The acylation takes place at the hydroxy group of the amidoxime, and not at the amino group, as confirmed by the IR spectra of the acylation products. The spectra of XXXa-f show absorption bands in the 3480-3470 and 3370-3355 cm^{-1} regions, which are due to the valence vibrations of the amino group in the amidoximes [10], whereas the broad hydroxy bands at 3150-3000 cm^{-1} are absent. The intense maxima in the 1740-1715 cm^{-1} region are due to carbonyl valence vibrations, while those in the 1260-1240 cm^{-1} region are due to the C—O—CO ester bond vibrations [15].

When the O-acylamidoximes XXXa-f are heated for several minutes at 5-7° above their melting points, violent decomposition occurs with evolution of water vapor and the formation of a dark resinous residue; 1,2,4-oxadiazoles XXI, XXII, XXIV-XXVI, and XXIX could be separated from the latter in 35-45% yield (see Table 2). Cyclodehydration of the O-acylamidoximes XXXa-f can also be carried out by brief heating in acetic anhydride, but in that case the 1,2,4-oxadiazole yield does not exceed 40-45%.

In the IR sepctra of all the 3,5-disubstituted 1,2,4-oxadiazoles the C=N bands appear at 1635-1620 cm^{-1}; this is typical of the C=N bond in oxadiazoles [16]. The medium intensity

TABLE 2. Properties of 3-(Indolyl-3)- and 3-(Indolyl-3-methyl)-5-R-1,2,4-oxadiazoles

Compound	5-R[a]	mp, °C	R_f[c]	Found, %			Empirical formula	Calculated, %			Yield, % (method of synthesis)
				C	H	N		C	H	N	
XXI	C_6H_5	159—161	0,55	73,5	4,2	16,0	$C_{16}H_{11}N_3O$	73,6	4,2	16,1	51 (D), 39 (E)
XXII	4-$O_2NC_6H_4$	225—226	0,60	62,3	3,0	18,5	$C_{16}H_{10}N_4O_3$	62,7	3,3	18,3	56 (D), 44 (E)
XXIII	5-Nitrofuryl-2	138—140	0,57	55,5	2,5	18,2	$C_{14}H_8N_4O_4$	55,3	2,6	18,4	56 (D)
XXIV	CH_3	88—89,5	0,72	66,1	4,5	21,3	$C_{11}H_9N_3O$	66,3	4,5	21,1	36 (E)
XXV	C_6H_5	Oil[e]	0,63	74,3	4,6	15,6	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	43 (D), 33 (E)
XXVI	4-$O_2NC_6H_4$	205—206	0,51	63,3	3,5	17,9	$C_{17}H_{12}N_4O_3$	63,7	3,8	17,5	47 (D), 30 (E)
XXVII	5-Nitrofuryl-2	112—114	0,42	58,2	3,1	17,8	$C_{15}H_{10}N_4O_4$	58,0	3,2	18,1	53 (D)
XXVIII	CH_2Cl	64—65	0,86	58,3	4,2	16,9	$C_{12}H_{10}ClN_3O$	58,2	4,0	17,0	58 (D)
XXIX	CH_3	Oil[e]	0,81			19,5	$C_{12}H_{11}N_3O$			19,7	32 (E)

[a]For XXI-XXIV, n = 0; for XXV-XXIX, n = 1. [b]Recrystallization: XXI and XXIII from aqueous alcohol; XXII from butanol-1; XXIV from aqueous dioxane; XXVI from aqueous DMFA; XXVIII from abs. alcohol—hexane mixture; XXVII purified by precipitation from acetone by hexane. [c]In 5:1 benzene—methanol. [d]XXV purified chromatographically on silica gel column. [e]XXIX picrate: mp 200-201.5° (from aqueous acetone). Found: C 49.0; H 3.0; N 19.2%. $C_{12}H_{11}N_3O \cdot C_6H_3N_3O_7$. Calculated: C 48.8; H 3.1; N 19.0%.

TABLE 3. O-Acylamidoximes of Indole Acids

Compound	mp, °C	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
XXXa	138—139	3470, 3395 (NH_2), 3210 (NH), 1730 (C=O), 1650 (C=N), 1605—1580 (indole ring), 1260 (C—O), 755 (CH)	61,0	5,0	19,5	$C_{11}H_{11}N_3O_2$	60,8	5,1	19,3	91
XXXb	170—171	3450, 3380 (NH_2), 3180 (NH), 1740 (C=O), 1655 (C=N), 1600—1585 (indole ring), 1250 (C—O), 750 (CH)	62,4	5,5	17,9	$C_{12}H_{13}N_3O_2$	62,3	5,6	18,1	82
XXXc	184—185	3458, 3390 (NH_2), 3190 (NH), 1715 (C=O), 1640 (C=N), 1610—1595 (indole ring), 1250 (C—O), 755 (CH)	68,6	4,7	15,3	$C_{16}H_{13}N_3O_2$	68,8	4,6	15,0	75
XXXd	130—132	3470, 3350 (NH_2), 3190 (NH), 1720 (C=O), 1665 (C=N), 1605—1595 (indole ring), 1250 (C—O), 750 (CH)	69,5	5,0	14,5	$C_{17}H_{15}N_3O_2$	69,6	5,1	14,3	68
XXXe	201—202	3440, 3385 (NH_2), 3150 (NH), 1715 (C=O), 1635 (C=N), 1600—1585 (indole ring), 1545, 1360 (NO_2), 1250 (C—O), 750 (CH)	59,0	3,7	17,1	$C_{16}H_{12}N_4O_4$	59,2	3,7	17,3	84
XXXf	181—182	3450, 3390 (NH_2), 3180 (NH), 1730 (C=O), 1640 (C=N), 1612—1595 (indole ring), 1550, 1360 (NO_2), 1255 (C—O), 755 (CH)	60,1	4,0	16,8	$C_{17}H_{14}N_4O_4$	60,3	4,1	16,6	73

[a]For XXXa, c, e: n = 0; XXXb, d, f: n = 1; XXXa: R = CH_3; b-d, n = 1; XXXa: R = CH_3; b-d, R = C_6H_5; e, f, R = 4-$O_2NH_6H_4$. [b]Recrystallization; XXXa from butanol-1; XXXb from aqueous methanol; XXXc from propanol-2; XXXd from aqueous acetone; XXXe, f from aqueous DMFA.

bands in the 1590-1570, 1465-1445, and 1400-1365 cm^{-1} regions are due to valence vibrations; those in the 910-890 cm^{-1} region, to planar deformational vibrations of the 1,2,4-oxadiazole ring [16]. For the =N-O bond valence vibrations, the absorption maxima at 1420-1415, 1385-1360, and 1085-1050 cm^{-1} are typical. There are also quite intense bands in the high frequency region at 3400-3300 cm^{-1} that can be assigned to indole NH valence vibrations. It should also be noted that the nature of the substituent at the 3 position of the oxadiazole ring has practically no effect on the vibration frequencies of either the oxadiazole ring as a whole or of individual segments of the ring.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in mineral oil suspension or in KBr tablets. PMR spectra were obtained on a Tesla BS-487C instruments with 80 MHz working frequency in deuteroacetone or DMSO-d_6, with HMDS internal stantard. The reaction and product purity were monitored by TOC on Al_2O_3·II of standard activity in 5:1 benzene–methanol (development with iodine vapors), or Silufol UV-254 sheets in 95:5 chloroform–methanol (development in UV light).

Arylhydroxamic acid chlorides (Ia-d) were prepared by chlorination of the respective arylaldoximes by a known method [17]. Ethyl iminoester hydrochlorides of 3-indolecarboxylic (XIa) and 3-indolylacetic (XIb) acids were previously synthesized [13].

Aminoxime of 3-Indolecarboxylic Acid, XIIe. To a solution of 5.22 g (30 mmole) of the ethyliminoester of 3-indolecarboxylic acid and 5.21 g (75 mmole) of hydroxylamine hydrochloride in 100 ml of 5:1 dioxane–water was added a solution of 3.97 g (37.5 mmole) of Na_2CO_3 in 25 ml of water with stirring. The reaction mixture was stirred for 20 h at 100° and evaporated to dryness at reduced pressure, and the residue was extracted with acetone (3 × 30 ml). The extract was concentrated and chromatographed on an Al_2O_3 column (3.0 × 80 cm). First 1:1 benzene–ether elution washed out 0.35 g of nitrile IIa; then 5:1 benzene–methanol washed out amidoxime XIIe. Removal of solvent yielded 4.2 g (80%) of amidoxime XIIa, mp 149-151° (from aqueous alcohol), R_f 0.24. IR spectrum: 3435-3425 (νNH_2), 3250 (indone NH), 3100 (νOH), 1670 ($\nu C{=}N$, 1610, 1580 (indole ring), 1180 (N–O), 750 cm^{-1} (CH). Found: C 61.6; H 5.0; N 24.3%. $C_9H_9N_3O$. Calculated: C 61.7; H 5.1; N 24.0%.

Amidoxine of 3-Indolylacetic Acid, XIIf. To a solution of hydroxylamine base (from 3.47 g (50 mmole) of the hydrochloride and 4.2 g (50 mmole) of $NaHCO_3$) in 30 ml of water was added a solution of 3.87 g (25 mmole) of nitrile IIb in 50 ml of alcohol with stirring. The reaction mixture was boiled with stirring for 40 h and evaporated to dryness at reduced pressure. The residue was washed with ether (2 × 25 ml), chromatographed on an Al_2O_3 column (3.0 × 40 cm), and eluted with 5:1 benzene–methanol. Removal of solvent yielded 2.55 g (54%) of amidoxime XIIf, mp 147-148° (from aqueous alcohol), R_f 0.32. According to [18], mp 146-148°.

O-Acetylamidoxime of 3-Indolecarboxylic Acid, XXXa. A solution of 2.0 g (11 mmole) of XIIe in 5.0 ml of acetic anhydride was heated for 5 min in a water bath. The solution was cooled to 20° and unreacted anhydride was decomposed with 10% ammonia solution. The precipitate was filtered off, washed with water, and dried.

O-Acetylamidoxime of 3-Indolylacetic Acid, XXXb (Table 3) was obtained similarly.

O-Aroylamidoximes of Indole Acids, XXXc-f (Table 3). A mixture of 13 mmole of XIIe,f and 13 mmole of acid chloride in 25 ml of dry dioxane was stirred for 5 h at 30-35°. The reaction mixture was treated with 30 ml of 5% $NaHCO_3$ solution, heated for 10 min at 45°, and cooled to 10°. The precipitate was filtered off, washed with water, and dried.

3-Substituted 5-(Indolyl-3)- and 5-(Indolyl-3-methyl)-1,2,4-oxadiazoles, III-X, XIII-XX (Table 1). Method A: To a stirred suspension of 0.1 mole of acid chloride Ia-d and 0.1 mole of nitrile IIa,b in 100 ml of dry ether at 0° was added dropwise 20 ml of BF_3 etherate at a rate such that the reaction temperature did not exceed 8-10°. The reaction mixture was stirred for 30 h at 20°, then boiled for 1 h, and cooled, and poured into 500 ml of cold water. The 1,2,4-oxadiazoles III-X were extracted with ether, and the ether extract was washed with water and dried over $MgSO_4$. The solvent was removed in vacuum and the residue was crystallized from a suitable solvent.

Method B: A mixture of 0.1 mole of acid chloride Ia-d and 0.1 mole of nitrile IIa,b in 100 ml of dry benzene was boiled with stirring for 48 h. The reaction mixture was cooled to 10°, the precipitate was filtered off, and the filtrate was evaporated at reduced pressure. The precipitate was combined with the residue from the reaction solution and crystallized. The oxadiazoles III-X were obtained.

Method C: A mixture of 15 mmole of ethyl iminoester hydrochloride XIa,b and 15 mmole of amidoxime XIIa-f in 40 ml of absolute methanol was boiled with stirring for 10-12 h (with XIb, 2-3 h). The reaction mixture was cooled to 0°, the precipitated NH_4Cl was filtered off, the filtrate was evaporated to dryness at reduced pressure, and the residue was extracted with acetone (2 × 15 ml). The extract was evaporated in vacuum, and the 1,2,4-oxadiazoles were purified either by recrystallization (III, IV, VII, VIII, XIII-XV, XVII, XVIII) or by chromatography on an Al_2O_3 column (XVI, XIX) with elution by 4:1 benzene–methanol; XX was purified by preparative thin layer chromatography on Al_2O_3 (40 × 100 cm) with elution by 5:1 benzene–methanol.

3-(Indolyl-3-)- and 3-(Indolyl-3-methyl)-5-substituted 1,2,4-Oxadiazole, XXI-XXIX (Table 2). Method D: A mixutureof 12 mmole of amidoxime XIIe,f and 12 mmole of the methyl iminoester hydrochloride of the appropriate acid in 30 ml of absolute methanol was boiled with stirring for 2-3 h. The reaction mixture was evaporated to dryness at reduced pressure. The oily residue was extracted with acetone (2 × 15 ml), and worked up by one of the following procedures:

1. For the synthesis of XXI, XXII, and XXVI, the extract was evaporated and the residue was chromatographed in an Al_2O_3 column (3.0 × 35 cm). The column was eluted with 10:1 benzene–acetone to remove byproduct amides and nitriles, then with 4:1 benzene–methanol.

2. For the synthesis of XXIII and XXVII, the extract was poured with stirring into 250 ml of cold water and stored for several days in a refrigerator. The amorphous precipitate was collected, dried, and extracted with ether in a Soxhlet apparatus. The solvent was removed; the residue was crystallized (XXIII) or purified by reprecipitation from acetone with hexane (XXVII).

3. For the synthesis of XXV and XXVIII, the extract was concentrated and placed on a sheet for preparative thin layer chromatography on Al_2O_3 (40 × 100 cm), with elution by 5:1 benzene–methanol.

Method E: O-Acylamidoxime XXXa-f, 10 mmole, was heated for 3-5 min at a temperature 5-7° above the melting point. The resulting dark residue was extracted with acetone. The extract was concentrated and chromatographed on an Al_2O_3 column (3.0 × 30 cm) and eluted with 4:1 benzene–methanol. The solvent was removed at reduced pressure and the compounds were purified by recrystallization from suitable solvents (XXI, XXII, XXIV, and XXVI) or were repeatedly chromatographed on silica gel column with elution by 9:1 chloroform–methanol (XXV and XXIX).

PMR spectra of 1,2,4-oxadiazoles: XII (1:1 DMSO-d_6–CCl_4): 7.02-7.80 (5H, m, indole), 7.15 (1H, d, J = 2.5 Hz, furane 3-H), 7.72 (1H, d, J = 3.2 Hz, furane 4-h), 8.12 m.d (1H, s, NH). XIV: (DMSO-d_6): 4.42 (2H, s, CH_2), 7.10-7.84 (5H, m, indole), 8.14 m.d (1H, s, NH). XVIII (2:1 DMSO-d_6–CCl_4): 3.86 (2H, s, CH_2), 4.48 (2H, s, CH_2Cl), 7.08-7.80 (5H, m, indole), 8.20 m.d (1H, s, NH). XXIV (DMSO-d_6): 2.62 (3H, s, CH_3), 7.10-7.78 (5H, m, indole), 8.14 m.d (1H, s, NH). XXIX (CCl_4): 2.52 (3H, s, CH_3), 4.10 (2H, s, CH_2), 7.12-7.90 (5H, m, indole), 8.21 (1H, s, NH).

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