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HETEROCYCLIZATIONS OF 1,3,3-TRIMETHYL-ω-FORMYL-2-METHYLENE-INDOLINE HYDRAZONES

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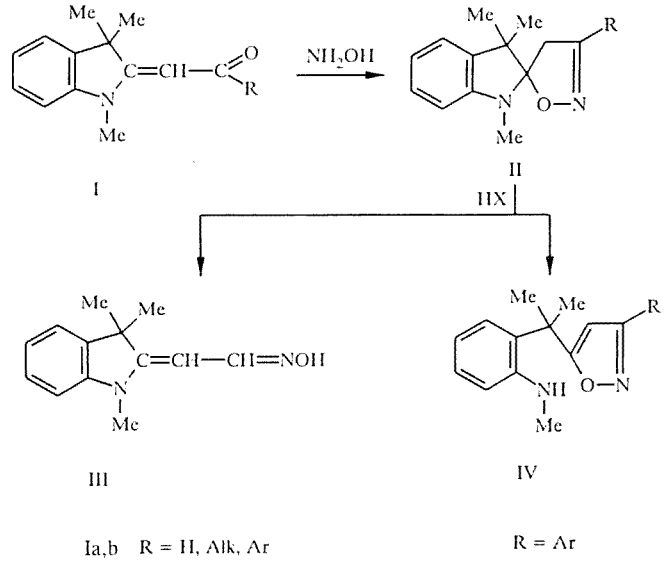
Reaction of 1,3,3-trimethyl-ω-formyl-2-methyleneindoline with hydrazines can occur to form both linear hydrazones and substituted pyrazoles. The availability of the enamine fragment and the N–H protons in these hydrazones is used in their heterocyclizations with dihalo electrophiles.

We have previously shown that reaction of ω-formyl-(acetyl, benzoyl)-1,3,3-trimethyl-2-methyleneindolines (I) with hydroxylamine can produce spiro compounds containing a dihydroisoxazole fragment (II) [1]. Their solution upon treatment with mineral acids can occur with both opening of the dihydroisoxazole ring giving oxime III and with fission of the indoline fragment to give the isoxazole IV [1, 2].



It might be expected that indolines containing hydrazones or semicarbazones groups in place of the oxime would tend to show similar chemical reactions. Hence we have carried out synthesis of 1,3,3-trimethyl-ω-formyl-2-methyleneindoline hydrazones and studied their chemical properties. It is known that heterocyclic hydrazones show a wide spectrum of physiological activity, most particularly those derivatives of 3-formylindole [3].

Although ω-formyl-2-methyleneindoline (Ia) is available, its hydrazones have not been reported [4]. We have found that treatment of aldehyde I with aryl hydrazines and semicarbazide gives only the acyclic hydrazones V and semicarbazone VI. Formation of spiro analogs of the dihydroisoxazoles was not observed. Moreover, reaction of aldehyde I with hydrazine hydrate occurs with fission of the indoline ring and formation of pyrazole VII. A similar reaction has been reported for ω-benzoyl 2-methyleneindoline with various hydrazines [5].

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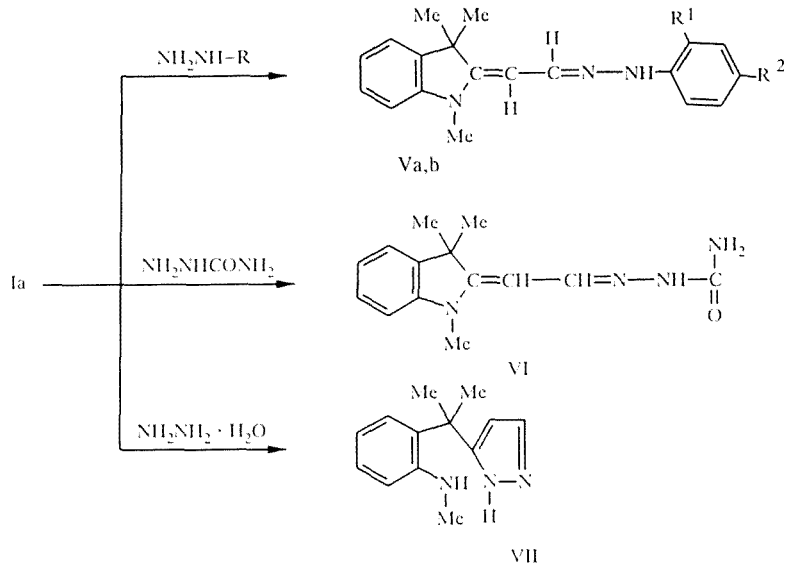
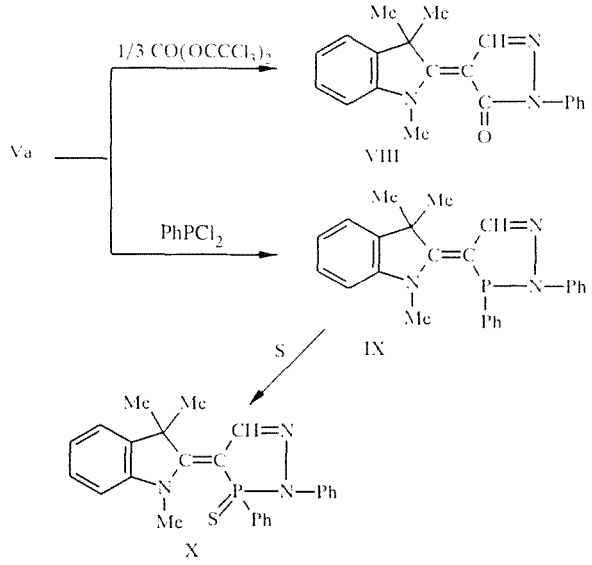


Va,b a $R^1 = R^2 = H$; b $R^1 = H$; $R^2 = NO_2$; c $R^1 = R^2 = NO_2$

The structures of the synthesized compounds is confirmed by PMR spectroscopy (see Table 1). For V, VI the most significant information comes from the spin–spin coupling constants for the =CH and CH=N protons (J = 10-13 Hz, [1]). This spin coupling was not observed in VII due to both the low values of these constants in pyrazoles [6] and to prototropic processes in compounds of this type.

The availability of the enamine fragment and the NH proton in compounds V and VI makes them promising reagents for heterocyclizations involving dihalo electrophiles. In particular, it was found that reaction of hydrazone Va with trisphosgene and with phenyldichlorophosphine in the presence of triethylamine gives pyrazolone VIII and diazophospholine IX respectively.



The latter was identified by ^{31}P NMR spectroscopy and characterized as the phosphinesulfide X. PMR Spectra were also run to provide further structural evidence. The most diagnostic information comes from the chemical shift of the proton of the CH=N group which is shifted to low field (8.04-8.13 ppm) as a singlet in the pyrazoline VIII and as a doublet in the diazophospholine X (H–P spin–spin coupling, J = 14 Hz).

EXPERIMENTAL

PMR Spectra were recorded on a Varian 200 MHz instrument using $CDCl_3$ or DMSO-D_6 solvent and TMS internal standard. ^{31}P NMR Spectra were recorded on a 200 MHz Bruker machine.

TABLE 1. PMR Spectral Parameters for Compounds Synthesized (δ, ppm, J, Hz)

Compound	Solvent	$C_{(3)}-(CH_3)_2$ s	$N-CH_3$ s	=CH	CH=N	H-7	H-5	Aryl and other protons
VII	$CDCl_3$	1,69	2,55	6,11	7,48	6,56, J = 7,8	6,72	3,60 (1H,m, NH—Me), 7,17 (1H, dd H-6), 10,7 (1H, m -NH—N=)
Va	$CDCl_3$	1,57, 1,62	3,12, 3,20	5,29, 5,50	7,61, 8,00	—	—	6,58...7,25 (9H, m Ar), (*E*, *Z*, syn-anti isomers
Vb	$CDCl_3$	1,58, 1,63	3,18, 3,24	5,18, 5,49, J = 13,5	7,73, J = 7,8 7,89	6,68, J = 7,8	6,89	6,97 (2H, d, 12,12'-H), 7,07 (2H, d 12,12'-H), 8,13 (2H, d, 13,13'-H, J = 9), 7,13...7,20 (2H,m, 4-H, 6-H)
Vc	$CDCl_3$	1,62	3,52, 3,31	5,56, J = 10,5	8,31, J = 10,5	7,90, J = 9,6	6,97	7,9 (1H, d, 12-H, J = 9,6), 8,24 (1H, dd , 13-H, J = 9,9), 9,13 (1H, d, 13-H, J = 2,7, J = 0,9), 7,20...7,24 (2H, m 4-H, 6-H)
VI	DMSO	1,47	3,09	5,23 (10,2)	8,16 (10,2)	—	—	6,07 (2H, s, NH_2), 6,79...6,83 (2H, m H-7, H-5), 7,14 (1H, dd , H-6), 7,25 (1H, d, H-7, J = 7,2)
VIII	$CDCl_3$	1,78	3,94	—	8,04	—	—	7,99 (2H,d, 12,12'-H, J = 4), 7,1...7,5 (7H,m, Ar)
X	$CDCl_3$	1,73, 174	3,46	—	8,13 d, J = 14	—	—	8,03 (2H, d, 12,12'-H, J = 7), 6,72...7,40 (12H, m, Ar)

Elemental analytical data for N and P in compounds Va-c, VI-VIII, and X agreed with that calculated.

ω-Formyl-1,3,3-trimethyl-2-methyleneindoline Phenylhydrazone (Va). A mixture of aldehyde Ia (4.02 g, 0.02 mole) and phenylhydrazine (2.16 g, 0.02 mole) in ethanol (10 ml) was refluxed for 2 h. The precipitate was filtered, washed with ethanol, and crystallized from propanol to give product (63%) with mp 153-155°C.

ω-Formyl-1,3,3-trimethyl-2-methyleneindoline 4-Nitrophenylhydrazone (Vb). A mixture of aldehyde Ia (2.29 g, 11.4 mmole), p-nitrophenylhydrazine (1.75 g, 11.4 mmole), and acetic acid (1 ml) in ethanol (20 ml) was refluxed for 1.5 h. The precipitate was filtered, washed with isopropanol, and crystallized from methanol-isopropanol (1:1) to give product (82%) with mp 210-212°C.

ω-Formyl-1,3,3-trimethyl-2-methyleneindoline 2,4-Dinitrophenylhydrazone (Vc). A mixture of aldehyde Ia (1.69 g, 8.4 mmole), 2,4-dinitrophenylhydrazine (1.66 g, 8.4 mmole), and acetic acid (2 ml) was refluxed in isopropanol (25 ml) for 4 h. The precipitate was filtered, washed with isopropanol, and purified by refluxing in isopropanol to give product (82%) with mp 235-237°C. Chromatography using ether-hexane (2:1) gave a spot with R_f 0.58.

ω-Formyl-1,3,3-trimethyl-2-methyleneindoline Semicarbazone (VI). A mixture of Ia (4.02 g, 0.02 mole), semicarbazide (2.23 g, 0.02 mole), and pyridine (10 ml) was refluxed in ethanol (20 ml) for 4 h, the reaction being monitored by chromatography. After addition of water (20 ml), the product was extracted with chloroform, dried, the solvent evaporated, and petroleum ether added. The solid product was pulverized, filtered, washed with ethanol and then petroleum ether, and dried to give product (40%) with mp 191-192°C.

5-(1-Methyl-1-(2-methylaminophenyl)ethyl)pyrazoline (VII). Hydrazine hydrate (4 g, 0.08 mole) was added to aldehyde Ia (16.08 g, 0.08 mole) in methanol (20 ml). The product was refluxed for 3 h and petroleum ether (50 ml) added with vigorous stirring. The precipitate was filtered, washed with petroleum ether, and crystallized from methanol-water (1:2) to give product (76%) with mp 118-120°C.

1-Phenyl-4-(1',3',3'-trimethylindolin-2'-ylidene)pyrazolin-5-one (VIII). Triethylamine (2.05 g, 0.02 mole) was added to hydrazone Va (2.95 g, 0.01 mole) in benzene (30 ml). The product was cooled to 0-5°C and a solution of trisphosgene (1 g, 0.0337 mole) in benzene (10 ml) added dropwise. The precipitated triethylamine hydrochloride was filtered off and the

solution evaporated. The product was triturated with petroleum ether and crystallized from n-decane to give product (11%) with mp 182-184°C.

1,5-Diphenyl-4-(1′,3′,3′-trimethylindolin-2′-ylidene)-5-thio-1,2,5-diazophospholine (X). Dichlorophenylphosphine (0.97 g, 0.0054 mole) in pyridine (5 ml) was added to hydrazone Va (1.58 g, 0.0054 mole) in pyridine (25 ml) and stood at 20°C for 24 h. The reaction mixture showed one signal in the ^{31}P NMR spectrum at 20 ppm.

The mixture was treated with sulfur (0.173, 0.0054 mole) and stirred until completely soluble (2-3 h). Pyridinium chloride was filtered of and solvent evaporated. Crystallization gave product (63%) with mp 206-208°C. ^{31}P NMR Spectrum (pyridine): 55.06, 56.18 ppm.

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