INDOLE DERIVATIVES.

121.* CONVENIENT METHOD FOR THE PREPARATION OF N-ALKYLINDOLES

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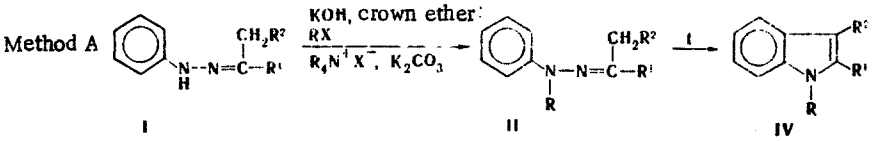
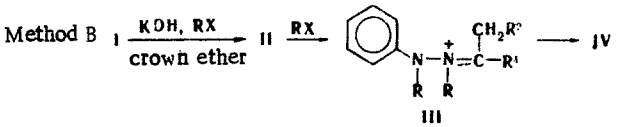
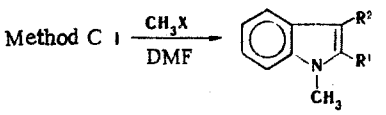
A new method was developed for the synthesis of N-alkylindoles from phenylhydrazones of aldehydes and ketones that makes it possible to obtain diverse N-alkylindoles under mild conditions.

We have previously described the synthesis of N-alkylindoles under conditions of interphase base catalysis (method A) [2]. In the present research we have established that an interphase catalyst (a tetraalkylammonium halide and K_2CO_3 or a crown ether, KOH, and 1 mole of RX) accelerates only the formation of the N-alkylhydrazone (II), which subsequently undergoes thermal cyclization. Although the latter undergoes cyclization to an indole substantially faster than unsubstituted hydrazone I, the rate of this cyclization does not depend on the catalyst concentration.







If a crown ether, KOH, and excess alkyl halide are used as the catalyst, the initially formed hydrazone II undergoes cyclization to N-alkylindole IV with the intermediate formation of dialkyl derivative III (method B). The rate of this reaction is considerably higher than the rate of thermal cyclization of hydrazone II to an N-alkylindole and depends on the nature of the alkylating agent. It is apparent from Table 1 that the most effective cyclizing agents are methyl iodide and methyl p-toluenesulfonate.

The cyclization of N-alkylhydrazones to N-alkylindoles was first described by Grandberg [3], after which it was studied by Posvic and co-workers [4]. Grandberg also showed that a mixture of 2-methylindole and 1-benzyl-2-methylindole is formed by the action of benzyl chloride on acetone phenylhydrazone (method C) [5].

Our methods differ from those described in the literature in that an unsubstituted phenylhydrazone undergoes cyclization, and a mixture of a crown ether, KOH, and an alkylating agent is used as the catalyst. It seemed of interest to compare the synthetic possibilities of methods A and B with method C — cyclization of the phenylhydrazone to an N-alkylindole under the influence of an alkylating agent in the absence of interphase catalysis.

*See [1] for Communication 120.

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TABLE 1. Effect of the Nature of the Alkylating Agent on the Cyclization of Acetophenone N-butylphenylhydrazone to 1-Butyl-2-phenylindole in DMF

RX	t, °C	Time, h	Yield, %
BuBr	180	2	60*
$ClCH_2Ph$	150	15	56
$BrCH_2Ph$	80	20	58
$BrCH_2CH=CH_2$	80	24	60
MeI	80	20	83
MeOTs	80	20	78
Me_2SO_4	60	20	12
$MeSO_3C_6H_3(NO_2)_2$-2,4	60	5	69
$MeOCH_2Cl$	20	10	Resinification

*In sulfolane.

TABLE 2. Effect of the Nature of the Alkylating Agent on the Cyclization of Acetophenone Phenylhydrazone by Method C

RX	t, °C	Time, h	Yield, %	Solvent
BuBr	180	5	39*	Sulfolane
$BrCH_2Ph$	150	20	0†	DMF
$Et_3O^+BF_3^-$	150	20	0†	DMF
Me_2SO_4	80	20	Resinification	DMF
Me_2SO_4	80	20	Resinification*	—
MeOTs	80	20	72	DMF
MeI	80	20	82	DMF
$MeSO_3C_6H_3(NO_2)_2$-2,4	60	7	58	DMF

*Formation of two products, as described in [5].
†Alkylation takes place but cyclization does not.

TABLE 3. Results of Cyclization of Phenylhydrazones of Aldehydes and Ketones to N-Alkylindoles

R^1	R^2	Yield of N-Alkylindole, %		
		method A, R = Bu	method B, R = Bu	method C, R = Me
H	H	9	15*	Traces
i-Pr	H	8	18*	Traces
H	Me	42	70	23
Me	Me	34	76	40
Ph	H	56	83	82
$C_6H_4NO_2$-4	H	—	56	Traces
COOR	H	33	80	Traces

*The yields are low in connection with the low stability of the phenylhydrazones.

It follows from the data in Tables 2 and 3 that method C is effective only in the case of highly active alkylating agents (MeI) and the most reactive phenylhydrazones, the aliphatic parts of which contain substituents that have a +E (Ph) or a +I (Me) effect. The yields of the N-methylindoles decrease as the donor properties of the groups decrease (40% for R^1 = R^2 = Me, and 23% for R^1 = H, R^2 = Me), and virtually no reaction occurs if one of the groups is a strong electron-acceptor group (COOR, $C_6H_4NO_2$-4); dimethylformamide (DMF) is the most suitable solvent.

The range of application of method B is considerably wider than that of method C. It can be used for the synthesis of diverse N-alkylindoles that contain both electron-donor and electron-acceptor substituents. Although the synthesis of N-alkylindoles by method B is

carried out without the intermediate isolation of N-alkylhydrazones II, N-alkylation and cyclization can be separated in time. This makes it possible to use any necessary alkylating agent in the alkylation step and the most active alkylating agent (methyl iodide or methyl p-toluenesulfonate) in the cyclization step. Owing to the mild temperature conditions and the absence of acid catalysis, the yields of N-alkylindoles are generally good and exceed the yields in methods A and C. Method B can be recommended for the synthesis of diverse N-alkylindoles.

EXPERIMENTAL

The spectra were recorded with Specord 71-IR (IR), Specord UV-vis (UV, ethanol), Varian CFT-20 (80 MHz, PMR, deuteroacetone, tetramethylsilane as the internal standard), and MKh-1303 (mass spectra, U = 50 eV) spectrometers.

Method A is described in [2].

Method B. Equimolar amounts of the phenylhydrazone, KOH, and the alkyl halide were stirred with a centimolar amount of 18-dibenzocrown-6-ether in sulfolane or DMF at 80°C for 2 h, after which a threefold excess of MeI was added, and the mixture was maintained at the same temperature for 16-24 h. It was then diluted with water and extracted with CCl_4, and the extract was chromatographed on silica gel (elution with hexane) to give the N-alkylindole.

Method C. The phenylhydrazone was mixed with a threefold to fivefold excess of MeI in DMF, and the mixture was maintained at 80°C for 20-24 h. It was then worked up as in method B.

The structures of the compounds obtained were confirmed by comparison of the IR and PMR spectra with the spectra of genuine samples of the compounds. The IR spectrum of the previously undescribed butyl 1-butylindole-2-carboxylate did not contain an absorption band of an indole NH group but did contain an absorption band of an ester C=O group at 1713 cm^{-1}. The mass spectrum contained an M^+ peak with m/e 273. UV spectrum, λ_{max} (log ε): 209 (4.27), 229 (4.38), and 295 nm (4.32). PMR spectrum: two t, 0.97 (CH_3); m, 1.56-2.24 (CH_2CH_2); t, 4.30 (OCH_2); t, 4.61 (NCH_2); d, 7.28 (3CH, J_{37} = 0.7 Hz); m, 6.99-7.73 ppm (aromatic protons). Found: C 74.6; H 8.5; N 5.1%. $C_{17}H_{23}NO_2$. Calculated: C 74.7; H 8.4; N 5.1%; M 273.

1-Butyl-2-(p-nitrophenyl)indole. IR spectrum: 1530, 1348 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 234 (4.29); 296 nm (4.20). PMR spectrum: t, 0.74 (CH_3); m, 1.28 (CH_2CH_3); m, 1.62 ($CH_2C_2H_5$); t, 4.24 (NCH_2); d, 6.51 (3CH, J_{37} = 0.8 Hz); m, 7.00-7.85 ppm (aromatic protons). Found: C 73.5; H 6.2; N 9.2%; M^+ 294. $C_{18}H_{18}N_2O_2$. Calculated: C 73.5; H 6.1; N 9.5%; M 294.

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