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Indole and 3-methylindole are completely converted by alcohols into *N*-alkyl or *N*-isoalkyl derivatives in the presence of aluminium alkoxides and Raney Nickel; 2-methylindole gives lower yields. Pyrroles suffer *N*- and *C*-alkylation but the initially formed *N*-alkylpyrroles are reduced into *N*-alkylpyrrolidines in the reaction mixtures.

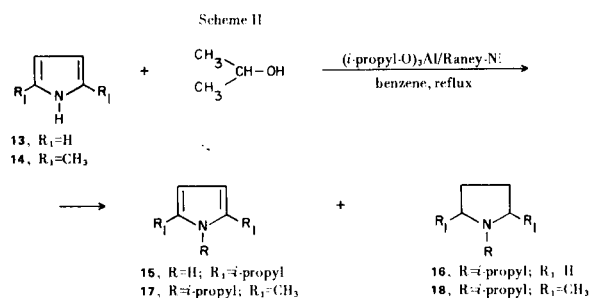
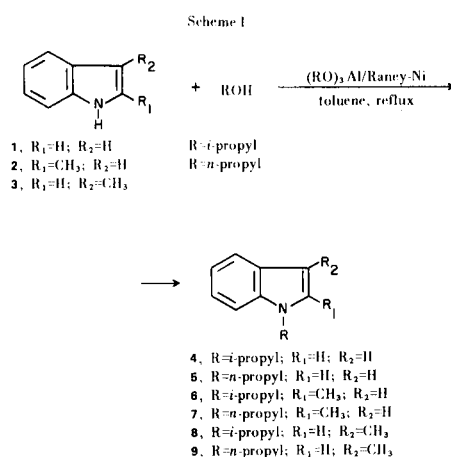
The occurrence of these *N*-alkylations is at variance with the *C*-alkylation of indoles and pyrroles which takes place by means of alcohols and sodium alkoxides. This suggests that the reaction occurs between the substrate and the reagent both coordinated by aluminium.

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Indoles (1) and pyrroles (2) are *C*-alkylated by alcohols in the presence of sodium or potassium alkoxides. The first step of these reactions is likely to be a nucleophilic attack of the conjugate base of the substrate to the carbonyl compound (3) which is in equilibrium with the alcohol in the presence of alkoxide at high temperature.

Fluorene (4) is alkylated in a similar way and the presence of nickel catalysts favours the reaction; on the other hand, anilines (5) condense with alcohols with the catalysis of Raney nickel to give the *N*-alkyl derivatives, and an equilibrium alcohol-carbonyl compound is achieved in this condition (6). It is well known that this equilibrium is also favoured by aluminium alkoxides (7), therefore it appeared reasonable to us to try these reductive condensations using this reagent coupled with Raney nickel. We have so described a synthetic method which allowed us to *N*-alkylate indole with secondary alcohols (8). This anomalous, regioselective alkylation prompted us to examine more deeply this system in order to add the general understanding of the catalysis applied to the chemistry of pyrroles and indoles. The present paper deals with a study on the reactions of indoles, pyrroles and other heterocyclic compounds with the system alcohol/aluminium alkoxide/Raney nickel.

Indole **1** reacted slowly in refluxing toluene with an excess of isopropanol and aluminium isopropoxide catalyzed by Raney nickel (Scheme I); after 24 hours the substrate disappeared (tlc). *N*-isopropylindole **4**, identified through its physical and spectral properties (9), was isolated as the sole product. No detectable amount of 3-isopropylindole was found in the reaction mixture (gc). We obtained similar results by using as solvents cyclohexane or an excess of isopropanol instead to toluene. When Raney nickel was replaced with palladium on charcoal, palladium on barium sulphate or with powdered nickel, no reaction took place; we did not observe any reaction either in the presence of Raney nickel alone. Indole



did not react with *t*-butyl alcohol/aluminium *t*-butoxide, but it gave **4** with *t*-butyl alcohol and aluminium isopropoxide thus in agreement with an alcohol-alkoxide exchange. This has suggested (8) that it should be possible to use aluminium *t*-butoxide (10) as a condensing agent, coupled with different alcohols.

The yield was lower in the case of 2-methylindole **2** and the reaction mixture contained a basic product (see later). 3-Methylindole **3** gave the corresponding *N*-isopropyl derivative **8** in yields comparable with that of indole itself, while 2,3-dimethylindole was recovered

Table I
N-Alkylation of Indoles and Pyrroles

Starting Material	Alcohol	Reflux Time (hours)	Product	Yield %	Distillation °C/mm Hg	Indexes of Refraction (n_D^{20})	Analyzed for	Found % (Calcd.)		
								C	H	N
1	isopropyl alcohol	24	4	90	58-60 (a)/0.4	(b)	(b)			
1	<i>n</i> -propyl alcohol	48	5	90	60-64 (a)/0.5	(b)	(b)			
2	isopropyl alcohol	36	6	40	88-90 (a)/0.6	1.5776	C ₁₂ H ₁₅ N	83.10 (83.18)	8.84 8.73	8.06 8.09
2	<i>n</i> -propyl alcohol	48	7	20	86-89 (a)/0.5	1.5775	C ₁₂ H ₁₅ N	82.80 (83.18)	8.91 8.73	8.29 8.09
3	isopropyl alcohol	18	8	92	80-82 (a)/0.5	1.5711 (c)	C ₁₂ H ₁₅ N	83.01 (83.18)	9.01 8.73	7.98 8.09
3	<i>n</i> -propyl alcohol	48	9	32	80-81 (a)/0.5	1.5694	C ₁₂ H ₁₅ N	83.02 (83.18)	8.85 8.73	8.13 8.09
13	isopropyl alcohol	48	15	34	110-112 (a)/31	1.4861 (d)	C ₁₀ H ₁₇ N	79.28 (79.40)	11.33 11.34	9.39 9.26
			16	40	123-124 (e)/760	1.4365	C ₇ H ₁₅ N	74.17 (74.27)	13.71 13.36	12.12 12.37
14	isopropyl alcohol	96	17	23	88-89/28	1.4700	C ₉ H ₁₅ N	78.52 (78.77)	11.40 11.02	10.08 10.21
			18	62	137-138/760	1.4339	C ₉ H ₁₉ N	76.65 (76.52)	13.62 13.56	9.73 9.92

(a) Bath temperature given. (b) Known compounds (9). (c) Literature value (13): $n_D^{20} = 1.5706$. (d) Value given at 25° literature value (14): $n_D^{20} = 1.487$. (e) Literature (15) b.p. = 121°/760 mm Hg.

unchanged. In view of these facts the reaction appears to be sensitive to the steric hindrance.

A primary alcohol like *n*-propyl alcohol behaved in a similar way; reactions were routinely carried out using aluminium *n*-propoxide previously prepared and purified (see Experimental). Experiments in which aluminium *n*-propoxide was prepared *in situ* (distilling off excess alcohols) before adding the substrate and Raney nickel, afforded the same results. Indole **1** gave compound **5** but the reaction was slow if compared with that of indole with isopropyl alcohol.

The compounds **2** and **3** gave only low yields of the corresponding *N*-*n*-propyl derivatives **7** and **9** respectively, along with unreacted materials and basic products.

Indole failed to react with methanol in the presence of aluminium methoxide and Raney nickel; this behaviour is coherent with a previous observation (11) which was explained by the instability of formaldehyde in the presence of Raney nickel (12).

As far as the basic by-products are concerned, they were obtained in the reactions carried out on 2- or 3-methylindoles with a long time of reflux. They were examined *via* gc-ms, and the recorded mass spectra allowed us to assign the structures of a *N,N'*-disubstituted aniline, indoline or octahydroindole (see Experimental) to them. On the basis of the behaviour of 2,3-dimethylindole (recovered unchanged) and pyrroles (see later) we suppose that these basic products arise from the hydrogenation and/or hydrogenolysis of *N*-alkylindoles formed

during the reaction course.

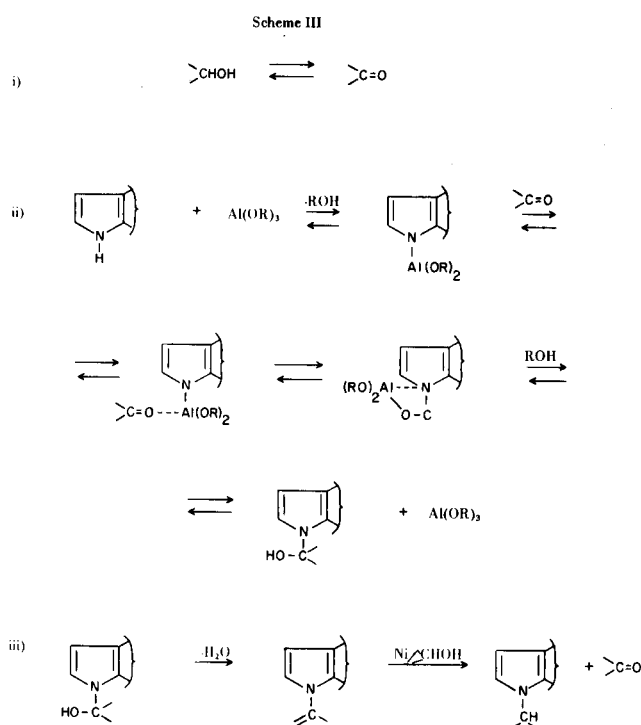
Pyrrole **13** reacted with isopropanol/aluminium isopropoxide/Raney-nickel in a benzene solution giving a mixture of 2,5-diisopropylpyrrole **15** and *N*-isopropylpyrrolidine **16**. In a similar way 2,5-dimethylpyrrole **14** gave a small amount of *N*-isopropyl-2,5-dimethylpyrrole **17** and *N*-isopropyl-2,5-dimethylpyrrolidine **18** (Scheme II).

Separate experiments showed that *N*-alkylpyrroles were converted into the corresponding pyrrolidines in this catalytic reaction mixture, therefore the isolation of pyrrolidines should be a consequence of the hydrogenation of the *N*-alkylpyrroles formed at the beginning of the reaction.

Other heterocyclic compounds were tested: imidazole, benzimidazole, 3,5-dimethylpyrazole and benzopyrazole were recovered unchanged from the reaction mixture.

The role of aluminium alkoxides merits some considerations. In spite of the fact that the alkylation of indoles and pyrroles with alcohols and sodium alkoxide occurs at C₃ and C₂, respectively, aluminium alkoxide induces the *N*-alkylation, which is the only reaction in the case of indoles. Suppose a similar pathway is operative in these reductive condensations, such a difference can be explained by the hypothesis that the key step of the process (*i.e.*, the condensation of the substrate and the carbonyl compound) occurs when both are ligands of aluminium.

The entire process could be schematically represented as follows:



By this scheme we are also able to explain why pyrroles suffer *C*- and *N*-alkylation: they are 1,2 ambident nucleophiles and the C_2 carbon too is accessible to the electrophilic carbon; on the contrary indoles are 1,3 nucleophiles and the C_3 is not accessible to the reagent.

The occurrence of hydrogenation and/or hydrogenolysis of heteroaromatic nucleus is of some consequence. If the nitrogen lone pair involved in the aromatic π bonds can interact with aluminium, this should lower the aromatic character of the nucleus and such side reactions became possible. Once again the electron gap of aluminium, in conjunction with the electron donor capability of nitrogen, can explain this peculiar behaviour of aluminium alkoxide, as compared to that of sodium alkoxide.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra (carbon tetrachloride) were recorded on a Perkin Elmer 257 infrared spectrophotometer. Pmr spectra (deuteriochloroform; reported in δ) were taken on a Perkin Elmer R 32 and a Joel C 60 HL spectrometers using tetramethylsilane as internal reference. Indexes of refraction were obtained on a Bausch and Lomb Abbe refractometer. Elemental analyses were kindly performed by ACRAF Research Laboratories, Rome. Gas chromatographic analyses were carried out with a Perkin Elmer F 11 (flame ionization detector; nitrogen as carrier). Mass spectra coupled with gas chromatographic analyses were performed by an AEI MS 12 mass spectrometer interfaced by a Biemann separator with a Varian 1400 gas chromatograph (flame ionization detector; helium as carrier). Gc determinations were made using a 2 m, 1/8 in. column packed with OV 17 (2%) and a 2 m, 1/8 in.

column packed with Versamide 900 (4%) and sodium hydroxide (0.5%) for basic compounds, both on Chromosorb G 80-100 mesh. Analytical thin layer chromatographies were run on glass plates coated with a 0.25 mm layer of silica gel 60 F²⁵⁴ (Merck) using 7:3 *n*-hexane-benzene as eluent. Spots were observed with UV light and developed with iodine. Preparative column chromatography was performed on silica gel 60, 70-230 mesh (Merck) (crude products/silica gel = 1:30) in a 85:15 *n*-hexane-benzene mixture.

Raney nickel W-2 (16), weighed as settled catalyst, was freshly prepared, deionized according to the method reported (17), stored under absolute ethyl alcohol and washed with toluene (benzene for pyrroles) before using. Aluminium isopropoxide was commercially available (Carlo Erba Reagent). All solvents and alcohols were previously distilled from sodium metal. Solvents and excess alcohols were removed under vacuum; for pyrroles distillation of solvents through a Vigreux column under atmospheric pressure was necessary. All products are easily oxidable in the air.

Aluminium *n*-Propoxide.

The reaction was carried out following a procedure used for aluminium isopropoxide (18). The crude material was vacuum distilled using a Liebig air condenser, b.p. 210-215° (1.5 mm Hg). A liquid nitrogen trap, along with a potassium hydroxide (solid) tower, should be used along the pump line in order to avoid mercuric vapours escape through the pump.

N-Alkylation of Indoles 1 to 3 and Pyrroles 13 and 14. General Procedure.

A 10% solution (w/v) in toluene (benzene for pyrroles) of the substrate (0.03 mole) and the appropriate alcohol (0.21 mole) was vigorously stirred under reflux in the presence of the corresponding aluminium alkoxide (0.12 mole) and Raney nickel (100% w/w of the substrate). After the appropriate time the mixture was cooled, diluted with ethyl ether and complexes were decomposed with 5% aqueous sodium hydroxide. After separation the aqueous layer was thoroughly extracted with ethyl ether. The filtered organic solution was treated three times with 2*M* chloridric acid, washed with 5% aqueous sodium hydrogen carbonate and saturated sodium chloride, then dried over sodium sulphate. Evaporation of the solvents and the excess alcohols gave the crude products. The chloridric solution was basified (CpH 11-12) with 30% aqueous sodium hydroxide and exhaustively extracted with ether. The organic layer was washed with saturated sodium chloride and dried (sodium sulphate). Solvent removal gave the basic fraction. The reaction times, yields and physical properties of the products are given in Table I. Purification and spectroscopic properties (19) are listed below.

N-Isopropylindole (4).

A short path distillation (see Table I) of the crude product gave 4; ir: ν max 1465, 1320, 1305 cm^{-1} ; pmr: δ 7.5-6.8 (complex, 5, aromatic), 6.35 (d, 1, $J = 3$ Hz, R-N-CH=CH-), 4.58 (sym m, 1, $J = 5$ Hz, -CH<), 1.46 (d, 6, $J = 5$ Hz, -CH₃). Spectroscopic properties are in accordance with those depicted in the literature (9). Neither starting material nor basic fraction was detected.

N-*n*-Propylindole (5).

Distillation in a Hickmann apparatus (see Table I) of the crude product afforded 5; ir: ν max 1465, 1340, 1320 cm^{-1} ; pmr: δ 7.6-6.7 (complex, 5, aromatic), 6.32 (d, 1, $J = 3$ Hz, R-N-CH=CH-), 3.65 (t, 2, $J = 7$ Hz, >N-CH₂-), 1.56 (se., 2, $J = 7$

Hz, $-\text{CH}_2-$), 0.67 (t, 3, $J = 7$ Hz, $-\text{CH}_3$). Spectroscopic properties agree with those listed in the literature (9). Starting material and basic fraction were absent in the reaction mixture.

N-Isopropyl-2-methylindole (6).

Column chromatography followed by distillation (see Table) gave **6**, ir: ν max 1460, 1415, 1390, 1375, 1315 cm^{-1} ; pmr: δ 7.4-6.8 (complex, 4, aromatic), 6.03 (s, 1, $\text{R}-\dot{\text{N}}-\text{CR}'=\text{CH}-$), 4.52 (sym m, 1, $J = 5$ Hz, $-\text{CH}<$), 2.32 (s, 3, $-\text{CH}_3$), 1.53 (d, 6, $J = 5$ Hz, $-\text{CH}_3$). Starting material (49%) was recovered unchanged, m.p. 58-60°. The basic fraction (0.360 g.) was examined *via* gc-ms. The only product present was presumably *N*-ethyl-*N*-isopropyl-2-methylaniline **10**; ms: *m/e* (rel intensity) 177 (53), 162 (20), 149 (71), 134 (50), 107 (100), 91 (24), 77 (24), 65 (20).

N-*n*-Propyl-2-methylindole (7).

The crude product was distilled collecting the fraction distilling up to 120° (0.8 mm Hg). Chromatographic purification followed by further distillation (see Table I) afforded the pure **7**; ir: ν max 1455, 1395, 1355, 1310 cm^{-1} ; pmr: δ 7.6-7.0 (complex, 4, aromatic), 6.21 (s, 1, $\text{R}-\dot{\text{N}}-\text{CR}'=\text{CH}-$), 3.96 (t, 2, $J = 5$ Hz, $>\text{N}-\text{CH}_2-$), 2.35 (s, 3, $-\text{CH}_3$), 1.73 (se., 2, $J = 5$ Hz, $-\text{CH}_2-$), 0.9 (t, 3, $J = 5$ Hz, $-\text{CH}_3$). The starting indole (67%) was also present, m.p. 59-60°. The most abundant product (gc-ms) in the basic fraction (0.7 g.) was an amine to which we have assigned the structure of *N*-*n*-propyl-2-methyloctahydroindole **11**; ms: *m/e* (rel intensity) 181 (25), 166 (91), 152 (59), 138 (100), 81 (20).

N-Isopropyl-3-methylindole (8).

Distillation of the crude product gave as the only product **8**; ir: ν max 1465, 1390, 1375, 1365, 1310; pmr: δ 7.5-6.75 (complex, 5, aromatic), 4.46 (sym m, 1, $J = 5$ Hz, $-\text{CH}<$), 2.27 (s, 3, $-\text{CH}_3$), 1.37 (d, 6, $J = 5$ Hz, $-\text{CH}_3$). The basic fraction was absent.

N-*n*-Propyl-3-methylindole (9).

Purification by column chromatography gave **9** as a less polar product. Distillation (see Table I) followed; ir: ν max 1475, 1395, 1375, 1340 cm^{-1} ; pmr: δ 7.5-6.6 (complex, 5, aromatic), 3.92 (t, 2, $J = 7$ Hz, $>\text{N}-\text{CH}_2-$), 2.26 (s, 3, $-\text{CH}_3$), 1.79 (se., 2, $J = 7$ Hz, $-\text{CH}_2-$), 0.9 (t, 3, $J = 7$ Hz, $-\text{CH}_3$). The starting indole (55%) was recovered, m.p. 94-95°. In the basic fraction (0.650 g.), the main product (gc-ms) presumably had the structure of *N*-*n*-propyl-3-methylindoline **12**; ms: *m/e* (rel intensity) 175 (30), 146 (100).

2,5-Diisopropylpyrrole (15).

Distillation (109-110°/31 mm Hg) of the crude product followed by column chromatography and a second distillation (see Table I), afforded the pure **15** which crystallized on standing (m.p. 20°; ir: ν max 3460, 3340 (broad), 1455, 1415, 1375, 1360, 1160, 1035, 905 cm^{-1} ; pmr: δ 7.55 (broad, 1, $>\text{N}-\text{H}$), 5.6 (d, 2, $J = 3$ Hz, $=\text{CH}-\text{CH}=\text{}$), 2.82 (sym m, 2, $J = 7$ Hz, $-\text{CH}<$), 1.24 (d, 12, $J = 7$ Hz, $-\text{CH}_3$). The basic fraction (1.9 g.) was distilled at atmospheric pressure using a Vigreux column (see Table I) to give the pure *N*-isopropylpyrrolidine **16**; ir: ν max 2960, 2780, 1380, 1370, 1325, 1200, 1180 cm^{-1} ; pmr: δ 2.6-2.0 (m, 5, $-\text{CH}_2-\dot{\text{N}}-\text{CH}_2-$ and $>\text{CH}-\text{N}<$), 1.9-1.6 (m, 4, $-\text{CH}_2-\text{CH}_2-$), 1.05 (d, 6, $-\text{CH}_3$). Starting pyrrole was not among the products.

N-Isopropyl-2,5-dimethylpyrrole (17).

Distillation carried using a short Vigreux column (see Table I) gave **17** as a pure product; ir: ν max 2960, 1460, 1395, 1370,

1290, 1205, 1130, 1020 cm^{-1} ; pmr: δ 5.72 (s, 2, $=\text{CH}-\text{CH}=\text{}$), 4.4 (sym m, 1, $J = 5$ Hz, $>\text{CH}-\text{N}<$), 2.25 (s, 6, $-\text{CH}_3$), 1.45 (d, 6, $-\text{CH}_3$). 2,5-Dimethylpyrrole was not recovered. The basic fraction (3.2 g.) was distilled through a short Vigreux column at atmospheric pressure (see Table I) to give *N*-isopropyl-2,5-dimethylpyrrolidine **18**; ir: ν max 2950, 2860, 1455, 1380, 1370, 1330, 1205; pmr: δ 3.2-2.7 (m, 3, $>\text{N}-\text{CH}<$), 2.0-1.2 (m, 4, $-\text{CH}_2-\text{CH}_2-$), 1.06 (d-d, 12, $-\text{CH}_3$).

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