ALKYLATION OF INDOLE SODIUM SALT AS AMBIFUNCTIONAL NUCLEOPHILIC SYSTEM

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Abstract—The relationship between the structure of alkyl halides and the relative reactivity of nucleophilic centers existing in an ambifunctional nucleophilic system and in particular the alkylation reactions of the indole sodium salt in THF with primary, secondary, tertiary, allyl and benzyl halides has been investigated.

In the course of alkylation of the indole salts, the reactivity of the less electronegative center (position 3 of the indole nucleus) increases the higher the SN_1 character of the reacting species and the greater the interaction of the cation with the ambient indole anion. This is in accordance with the results reported for pyrrole, enol and phenol ambient systems. For a number of alkyl, allyl and benzyl indole derivatives, the methods of separation and the spectrographic characteristics (IR, UV, NMR) of pure products are reported.

The determination of the echinuline[1] structure and the total synthesis[2] of the hexahydroechinuline have clarified the structural correlations between the echinuline and ergot alkaloids[3], and drawn attention to the biogenetic mechanism whereby isoprene chains are inserted into echinuline.[4] This problem requires in the first instance an investigation of the alkylation of the indole nucleus. The preceding studies concerning the action of alkyl halides on indole and its salts include: (*a*) the direct action of alkyl halides on indole[5] occurring only under drastic conditions and yielding a mixture of polyalkylated derivatives and indolenine compounds; (*b*) the alkylation of indolylmagnesium halides[6] with few exceptions attacks position 3, e.g. with 3-alkylindolylmagnesium halides[7] the 3-position is attacked with formation of indolenines; (*c*) the alkylation of indole sodium salt was considered to involve attack prevailingly in 1-position.[8]

The use of other alkylating agents has been limited to the action of alcohols on

[1] G. Casnati, R. Cavalleri, F. Piozzi and A. Quilico, *Gazz. Chim. Ital.* **92**, 105 (1962); G. Casnati, A. Quilico and A. Ricca, *Gazz. Chim. Ital.* **92**, 129 (1962).

[2] G. Casnati, M. R. Langella, F. Piozzi, A. Ricca and A. Umani Ronchi, *Gazz. Chim. Ital.* **94**, 1221 (1964).

[3] C. Casnati, A. Quilico and A. Ricca, *Gazz. Chim. Ital.* **92**, 133 (1962).

[4] *a* A. J. Birch, G. E. Blance, S. David and H. Smith, *J. Am. Chem. Soc.* 3128 (1961); *b* A. J. Birch and K. R. Farrar, *J. Chem. Soc.* 4277 (1963); *c* A. H. Jackson and A. S. Smith, *Tetrahedron* **21**, 989 (1965).

[5] W. C. Sumpter and F. M. Miller, *Heterocyclic Compounds with Indole and Carbazole Systems* p. 31, Interscience, New York (1954).

[6] B. Oddo, *Gazz. Chim. Ital.* **41**, (I), 221 (1911).

[7] T. Hoshino, *Liebigs Ann.* **500**, 35 (1932); *Abstracts of Japan Chem. Lit.* **6**, 390 (1932) (*C.A.* **27**, 291 (1933)); *Pro. Imp. Acad.* (*Tokio*) **8**, 171 (1932) (*C.A.* **26**, 4814 (1932)).

[8] *a* H. Pleininger, *Chem. Ber.* **87**, 127 (1954); *b* K. T. Potts and J. E. Saxton, *Org. Synth.* **40**, 68 (1960); M. Nakazaki and S. Isoe, *Nippon Kagaku Zasshi*, **76**, 1159 (1955) (*C.A.* **51**, 17877f (1957)); *d* M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 838 (1959); *Chem. Abstr.* **54**, 13096g (1960).

indole in the presence of a base[9]; contradictory results have been obtained with other alkylating agents.[10]

It has however been established that alkylation of the indole system occurs in the pyrrole nucleus and generally at 1- and 3-positions although alkylation of the 2-position has been reported.[11]

Although ambifunctional nucleophilic systems have been the subject of many investigations[12], the reactivity of the indole nucleus, typical for ambifunctional nucleophilic systems, has received very little attention.[13]

On the other hand the relationship between the structure of alkyl halide and the relative reactivity of nucleophilic centers existing in an ambifunctional nucleophilic system is not clear at this time[14]; this problem has been investigated for the indole system and is the subject of the present paper.

TABLE 1. REACTION OF INDOLE SODIUM SALT WITH ALKYL BROMIDE

Alkyl halide	Reaction time, hr	Relative weight % composition							
		Indole		1-alkylindole		3-alkylindole		1,3-dialkylindole	
		a	b	a	b	a	b	a	b
C$_2$H$_5$Br	1·5	7	—	81·5	—	2	—	9·5	—
	3	5·5	—	85	—-	2	—	7·5	—
n-C$_3$H$_7$Br	1	18·2	15·6	72	74	3·5	3·4	6·3	7
	3	11	11·6	78	77·6	3·4	3·1	7·6	7·7
	24	7·5	—	81·7	—-	3·3	—	7·5	—
iso-C$_5$H$_{11}$Br	1	38·6	—	54·6	—	4	—	2·8	—
	3	19·2	13·5	72·5	77	3·9	2·7	4·4	6·7
	6	—	12·4	—	78	—	2·8	—	6·8
	24	11·5	—	79·5	—	3·7	—	5·3	—
sec-C$_3$H$_7$Br	1	68	71·2	20·7	19·6	9·5	7·8	1·8	1·4
	3	51	51	33	33·5	11·7	11·2	4·3	4·3
	24	24	25	51·5	53	13	12	10·5	9
	48	23·8	—	52·7	—	13·1	—	10·4	—
sec-C$_5$H$_{11}$Br^c	1	78·3	—	12·3	—	6·6	—-	0·8	—-
	3	66	—	19·1	—-	9·9	—	1·8	—-
	24	41	40·3	33·9	35·9	14·5	15·4	4·7	4·7
tert-C$_5$H$_{11}$Br	24	84·8	85·5	8·3	7·9	6·4	6	—	—

    ^{a} First run.
    ^{b} Second run.
    ^{c} Little percentages of three by-products were found in these experiments.

[9] E. F. Pratt and L. W. Botimer, *J. Am. Chem. Soc.* **79**, 5248 (1957); L. W. Botimer, Univ. Microfilms (Ann Arbor, Mich) No. 59-6835; *Dissertation Abstr.* **20**, 3068 (1960).
[10] T. Kubota, *J. Chem. Soc. Japan*, **59**, 399, 407, 409 (1938) (*C.A.* **32**, 9080 (1938)).
[11] E. Funakubo and T. Hirotani, *Ber. Dtsch. Chem. Ges.* **69**, 2129 (1935); see also ^{4c}.
[12] For a review see: R. Gompper, *Angew. Chem. (Intern. Ed. Engl.)* **3**, 560 (1964).
[13] N. Lerner, Univ. Microfilms (Ann Arbor, Mich) No. 64-6837; *Dissertation Abstr.* **24**, 4982 (1964).
[14] W. J. Le Noble and J. E. Puerta, *Tetrahedron Letters* No. 10, 1087 (1966).

RESULTS AND DISCUSSION

The reaction between alkyl bromides and the indole sodium salt in THF was investigated under conditions that would ensure (a) an homogeneous phase so as to exclude the heterogeneous factors which can alter the reaction course;[15] (b) the use of a solvent (THF) with a limited power of cationic specific solvation[16] and practically negligible anionic solvation so as to exclude as much as possible a direct influence of the solvent on the reaction. The results obtained by heating under reflux stoichiometric amounts of indole sodium salt and the halide in THF are reported in Table 1 and indicate (a) a low conversion in alkylated products from secondary and tertiary bromides and (b) in every case 1,3 alkylation products.

The low yields obtained with secondary and tertiary alkyl bromides is due to concurrent elimination reactions between the alkyl halide and the indole sodium salt. Isopropyl bromide yields propylene, whilst with tertiary amyl bromide 2-methyl-2-butene and 2-methyl-1-butene are obtained.[17]

The 1,3-dialkyl derivatives, always observed during these and the following reactions, may be due to proton transfer between C-alkylated indole and the sodium salt of indole.[18] The indole alkylation reactions[19] could be represented according to the following scheme[20]:

Scheme 1
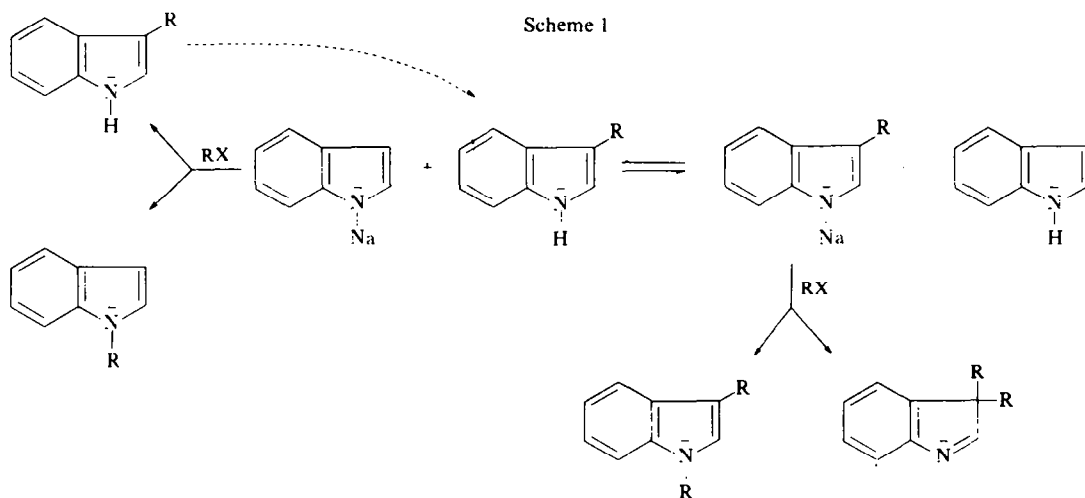
[15] R. Gompper. *Angew. Chem. (Intern. Ed: Engl.)* **3**, 567 (1964).

[16] B. Tchoubar, *Bull. Soc. Chim. Fr.* 2069 (1964); A. J. Parker, in *Advances in Organic Chemistry* Vol. 5, pp. 1–46. Interscience, New York (1965).

[17] In the course of the alkylation of tryptophan sodium salt in liquid NH_3, an attack has been observed on the indole nitrogen atom with primary halides, whilst with i-PrI and tert-butI the product was recovered unchanged; the authors attribute the unsuccessful alkylation to steric factors even if unsaturated hydrocarbons have been neglected. S. Yamada, *Chem. Pharm. Bull.* **13**, 88 (1965).

[18] For a similar equilibrium between pyrrole and 2-allyl-pyrrole sodium salt see: C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos and L. A. Vander Werf, *J. Am. Chem. Soc.* **84**, 46 (1962).

[19] It has been proved that there is no reaction when the unsalified indole is warmed by refluxing in THF with allyl halide or when the indole sodium salt is similarly treated with N-alkylindole.

[20] The writing here used is not the representative one of the particular structure of the indole sodium salt. in the way it is present in the reaction.

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In order to corroborate such as assumption two kinds of experiments were undertaken. An equimolecular mixture of scatole and indole sodium salt was alkylated with i-amyl bromide in THF and the products from both indole and scatole sodium salt were separated.[21]

Scheme 2

$R = C_5H_{11}$
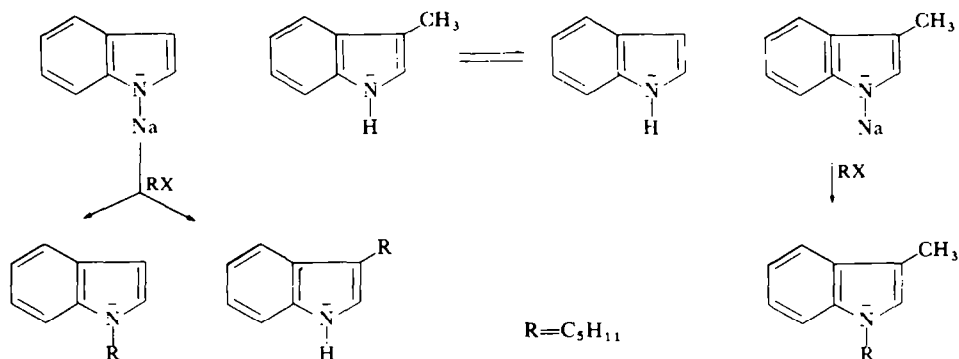
Alkylation of the indole sodium salt with allyl bromide in the presence of excess indole depressed the formation of dialkylated products although dialkylation took place even if the ratio indole–sodium salt was 2/1.[22]

TABLE 2. ALKYLATION OF INDOLE SODIUM SALT WITH ALLYL
BROMIDE IN THF:
DIFFERENT RATIOS OF INDOLE AND INDOLE SODIUM SALT

Molecular ratio of reagents	Products[a]			
Indole:NaH:RX	1-allyl indole	3-allyl indole	1,3-diallyl indole	b
1:1:1	53·2	24·6	19·1	3·1
1,25:1:1	50·8	30·3	15·9	3·0
2:1:1	51·5	39·4	9·1	—

[a] Relative weight % composition, excluding unreacted indole.
[b] The product was not identified.

An understanding of the origin of the dialkylated products and the cause of the low yields obtained in the alkylation with secondary and tertiary halides, has made the evaluation of the relative reactivity of the nucleophilic 1- and 3-positions of the indole ambifunctional anion possible. In a first approximation the ratios between N-alkylindole and 3-alkylindoles (comprehensive of 3-alkylindole, 1,3-dialkylindole,

[21] It is clear that the relative percentages of the alkylated products do not characterize the equilibrium reported in scheme 1 in that the relative speeds of alkylation of indole and 3-alkylindole sodium salts may be noticeably different among them and as to the speed of the proton transfer.
[22] This result is particularly meaningful in that on the ground of the acidities relating to the indole and scatole it has to be presumed that the equilibrium reported in scheme II is shifted to left.

3,3-dialkylindolenine) are a measure of the relative reactivity of the nucleophilic 1- and 3-positions in the particular conditions of the operation. On the other hand, as the reactions were studied under identical conditions, the reactivities must depend only on the nature of the alkyl halide; in this way it has been possible to point out (see Table 1) a reactivity increment in the less electronegative center, i.e. at C in 3 of the indole nucleus, this increment is the higher the more reacting halide acquires a SN_1 character. These results have been corroborated (see Table 3) by investigating the alkylation reactions with allyl or benzyl reagents and comparing the reactivity of alkyl iodides and bromides.

TABLE 3. ALKYLATION OF INDOLE SODIUM SALT WITH ALKYL, ALLYL, BENZYL BROMIDE AND ALKYL IODIDE

Alkyl halide	Relative weight % composition				
	Indole	1-alkylindole	3-alkylindole	1,3-dialkylindole	3,3-dialkylindolenine
CH_3—Br[a]	—	96	—	4	—
CH_3I[a]	—	85	—	15	—
C_2H_5—Br	18·6	76·5	2·3	2·6	—
C_2H_5—I	13·1	63·6	12·8	10·5	—
$C_6H_5CH_2$—Br	15	37·5	17·5	24·5	5·5
$CH_2=CH—CH_2$—Br	15·2	38·3	26·1	17·7	2·7[b]

[a] Excess of NaH and alkyl halide.
[b] The product was not identified.

On the other hand these results assume a precise meaning only if evaluated with reference to the operative conditions.

According to recent investigations on dissociative and associative phenomena of the ion-pairs in organic solvents[23] it was presumed that in this case the indole sodium salt was present as an equilibrium of ion pairs in different states of aggregation. Further, keeping in mind the THF physico-chemical characteristics[24] (dielectric constant, cation and anion specific solvation powers) and the concentrations used it was considered that under the conditions used the higher states of aggregation (aggregates or intimated ion-pairs) prevailed. If it is assumed possible that the indole ion, even if present in small amounts, could control the reaction course, then the free indole anion would have to react with the nitrogen atom (1-position)[25] even with reagents having a strong SN_1 character, while in actual fact an increment of reactivity with carbon (3-position) was observed with such reagents. Therefore a weakening of the interaction between sodium cation on the indole anion shifts the attack noticeably towards the nitrogen atom (1-position) even with SN_1 reagents.

[23] About the equilibria in THF among ion aggregates, contact ion-pairs, solvent separated ion-pairs, free ions see: T. E. Hogen-Esch and J. Smid. *J. Am. Chem. Soc.* **88**. 307 (1966).
[24] C. Carvajal, K. J. Tölle, J. Smid and M. Szwarc, *J. Am. Chem. Soc.* **87**, 5548 (1965).
[25] In the indole anion made free by the action of the cation and of the solvent, it has to be considered that the N is more nucleophilic, in that it represents the center of the ambient system with higher electronic density; further an attack to carbon (in 3-position) involves a non-aromatic transition stage, unlike what occurs for the attack to nitrogen atom.

This assumption has been verified by alkylating the indole sodium salt with allyl bromide in DMF, the latter being a solvent chosen on account of its dielectric constant and cationic selective solvation power.[26]

TABLE 4. ALKYLATION OF INDOLE SODIUM SALT WITH
ALLYL BROMIDE IN THF[a] AND DMF[b]

Solvent	Relative weight % composition				
	Indole	1-allyl-indole	3-allyl-indole	1,3-diallyl-indole	c
THF	14·5	45·5	21	16·3	2·7
DMF	15·2	80	1	3·8	--

[a] In refluxing THF.
[b] T 65°.
[c] The product was not identified.

Similar results were obtained with pyrrolylmagnesium bromides.[27] In this case, reaction took place at the more electronegative center, i.e. the nitrogen atom, with reagents having a clear SN_1 character, if the magnesium coordinating power was weakened by means of solvation effects (Table 5).

These results and the data reported for alkylations with alkyl halides of pyrrole[28], phenol[29] and enol[30] systems, support the following general statement: the reactivity

TABLE 5. ALKYLATION OF PYRRYLMAGNESIUM BROMIDE[a] IN Et_2O AND HMPT[b]

Alkyl halide	Solvent	N-alkyl pyrrole[c]	C-alkyl pyrroles[c]
CH_3-I	Et_2O	0	100
	HMPT	97·5	2·5
iso-$C_5H_{11}Br$	Et_2O	0	100
	HMPT	95·5	4·5
$CH_2=CH-CH_2-Br$	Et_2O	0	100
	HMPT	12	88
	HMPT[d]	31·5	68·5

[a] Pyrrylmagnesium bromide at initial concentration of 0·1M; room temperature.
[b] HMPT is hexamethylphosphotriamide.
[c] Relative weight % of N- and C-alkylpyrroles, excluding unreacted pyrrole.
[d] Pyrrylmagnesium bromide at initial concentration of 0·033M.

[26] F. Madaule-Aubry, Bull. Soc. Chim. Fr. 1457 (1966); see also [16].
[27] G. Casnati and A. Pochini, La Chim. e l'Industria, 48, 262 (1966).
[28] P. A. Cantor and C. A. Vander Werf, J. Am. Chem. Soc. 80, 970 (1958).
[29] [a] B. Miller and H. Margulies, J. Org. Chem. 30. 3895 (1965); [b] N. Kornblum, R. Seltzer and P. Haberfield, J. Am. Chem. Soc. 85, 1149 (1963); [c] V. A. Zagorevsky, J. Gen. Chem. (USSR) 28, 488 (1958) (C.A. 52, 14572c (1958)); [d] D. Y. Curtin and R. R. Fraser, J. Am. Chem. Soc. 80, 6017 (1958).
[30] [a] G. Briger and W. M. Pelletier, Tetrahedron Letters 3555 (1965); [b] D. S. Stotz: Univ. Microfilms (Ann Arbor, Mich.) Order No. 65-9829; Dissertation Abstr. 26, (4) 1921–2 (1965); [c] W. J. Le Noble and J. E. Puerta, Tetrahedron Letters 1087 (1966).

of the less electronegative center existing in the ion-pairs of the ambifunctional nucleophilic systems of the indole, pyrrole, phenol and enol type, with alkyl and benzyl halides increases as the electrophilic character (SN_1) of the reacting species and the interaction of the cation with the ambifunctional nucleophilic anion[31] increases.

These conclusions agree with the interpretation proposed by Nesmejanow.[32] Indeed the same problem has been recently discussed on the basis of a different statement[33] by some authors, who have examined[14] the relationship between the structure of alkyl halides and the reactivity of enolic systems. The statement which we point out is on the other hand in agreement with some structural features peculiar to the type of ion-pairs studied. It is generally accepted that the cation in an ion-pair is situated on the more electronegative atom[34] and therefore it must influence the course of the relative reactivity of the two centers present on the ambident anion. In effect the cation present in the ion-pair (a) greatly reduces the reactivity of the more electronegative center[15], (b) partially weakens the reactivity of the less electronegative center making the attack of the more reactive species (e.g. reagents with a more marked SN_1 character) possible, (c) and acts more efficiently as a positive electrostatic shield in the final stages, the more enhanced the electrophilic character of the reagent.

EXPERIMENTAL

Reagents. The purity of indole (RP-C. Erba) and of 3-methylindole (Fluka), was checked by TLC and GLC.NaH (Fluka), a 50% dispersion in mineral oil, was titrated by gas volumetric analysis. All alkyl halides were obtained from commercial sources; their purity was found by GLC to be more than 99%, with the exception of 2-bromopentane (95%) and tert-amylbromide (91%). This latter, after several distillations (107–108°/752 mm Hg), was obtained 98% pure. All reactions were carried out under dry nitrogen, saturated with THF, in order to avoid a concentration of the solutions.

Solvents. Tetrahydrofuran, after standing over KOH, was distilled from Na, then from LiAlH₄. Dimethylformamide, after standing first over KOH, then over CaO was distilled "in vacuo" under a nitrogen flow.

GLC and TLC analyses. Qualitative and quantitative GLC analyses of the reaction mixture, unless differently stated, were carried out with a A-350 Wilkens Aerograph (thermal conductivity detector), using in all experiments a 60 ml/min helium flow rate, on a 20% Apiezon L column with a.w. Chromosorb W (30/60 mexh). All the components of the reaction mixture, after their separation, were purified till GLC analyses with a Wilkens Aerograph Hy-Fi 600 chromotograph (flame ionization detector) on 10% Apiezon L column with silanized Chromosorb W pointed out only one peak; they were later identified and compared with the reaction mixtures. TLC analyses of the products were performed with a 80/20 cyclohexane ethylacetate mixture as an eluent on activated silica gel G (Merck) plates, using for the detection the Ehrlich reagent.

IR spectra were determined with a Perkin Elmer "Infracord 137" spectrophotometer[35] and proved to

[31] This statement is clearly not extensible to those cases wherein the steric effects make more difficult the approach of the reacting species to one of the centers of the ambident anion system. S. T. Yoffe, E. E. Kugutcheva and M. I. Kabachnik, *Tetrahedron Letters* 593 (1965).

[32] A. N. Nesmejanov and M. I. Kabachnik, *Zh. Obsch. Khim.* **25**, 41–87 (1955).

[33] Some authors have disclosed contrasts among the experimental results obtained during the alkylation of ambifunctional nucleophilic systems of pyrrole[28] or enol type[14] with a general statement checked by Kornblum for NO_2^- anion: according to our opinion the conclusions valid in this case, inferred by Kornblum for the NO_2^- anion, are not extensible to the pyrrolic, enolic or indolic systems just because of the different nature of the ambident anions under examination. N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.* **77**, 6269 (1955).

[34] R. Gompper, *Angew. Chem. (Intern. Ed. Engl.)* **3**, 566 (1964).

[35] In liquid film with exception of benzylindoles spectra, which were determined in KBr.

be valuable for structural assignment. Each alkylindole exhibited the following characteristic bands:[36] 1620–1615 (w), 1600–1575 (w), 1450–1470 (ms or s), 1015-1010 (m), 774–762 (w or m, sometimes absent in 1,3-dialkylindoles) and 744–738 (s) cm^{-1}. Beside above mentioned bands the following characteristic absorptions were found for: 1-*alkylindoles*: 1510–1515 (ms), 1315–1330 (m or ms), 1300-1315 (ms), 885 (w) and 714–719 (m) cm^{-1}: 3-*alkylinsolwa*: 3400–3370 (s) (NH), 1330–1340 (m) and 1090–1100 (m) cm^{-1}: 1,3-*dialkylindoles* no characteristic band.

UV spectra determined in 95% ethanol with a DK2 Beckmann spectrophotometer, showed characteristic absorption at the following wavelengths: 1-*alkylindoles*: 219–222, 5 mμ (log ε ∻ 4·5), 274–276 mμ (log ε ∻ 3·7), 281–283 mμ (log ε ∻ 3·8), 292–294 mμ (log ε ∻ 3·7); 3-*alkylindoles*: 221·5–223·5 mμ (log ε ∻ 4·5), 275–277 mμ sh. (log ε ∻ 3·7), 281–283 mμ (log ε ∻ 3·8), 290·5–291 mμ (log ε ∻ 3·7); 1,3-*dialkylindoles*: 224–228 mμ (log ε ∻ 4·5), 288·5–292 mμ (log ε ∻ 3·7).

NMR spectra were measured with a Varian A-60 Spectrometer. Chemical shifts are in ppm (δ) from TMS as internal standard. The position of the side chain presents in C-alkylindoles were determined by the value of chemical shifts of H-2 and H-3 in the indole ring[37] and by the difference in chemical shifts of H-2 signals with diluition[38] and with solvents of increasing polarity.[39] The reported data of chemical shifts were obtained in CCl$_4$ solutions, unless otherwise noted. The concentrations are in the range 45–65 mg/ml.

Standard reaction of indole sodium salt with alkyl bromides

A solution of 5 g (0·043 mole) of indole in 15 ml of anhydrous THF was slowly added to the suspension of 2·05 g of NaH, previously washed with hexane, in 20 ml of anhydrous THF. During the addition, an instantaneous gas evolution occurred; this gas was collected and measured: the result showed that the reaction was practically over at room temperature. Then the reaction mixture was refluxed for 15 min. A solution of 0·043 mole of alkyl bromide in 15 ml of anhydrous THF was added in 5 min, at room temperature, to the indole sodium salt solution; the mixture was then allowed to reflux.

To determine the progress of the reaction at any time, samples of 3 ml were withdrawn and analysed by GLC after hydrolysis with saturated aqueous ammonium chloride. The reaction was stopped by adding at 0° a solution of saturated aqueous ammonium chloride; the mixture was then extracted with ether. The ether solution washed with water, was dried over Na$_2$SO$_4$ and concentrated under reduced pressure at room temperature.

Reaction between indole sodium salt and ethyl bromide

Five g of indole, 2·05 g of NaH and 4·65 g of ethyl bromide were allowed to react as described in the standard reaction. Analyses of the reaction mixture both by GLC (on 20% Apiezon L, 190°; for % mixture composition see Table 1) and by TLC pointed out (besides unreacted indole) the presence of three products, which were separated by chromatography on a silica gel column.[40]

1,3-*diethylindole*[41] (colourless liquid) UV absorption λ$_{max}$: 227 mμ (log ε = 4·58), 290 mμ (log ε = 3·78). NMR spectrum: 6·70 δ broad triplet (H-2) (J$_2$, CH$_2$ ∻ 1 c/s); 6·6–7·6 δ (4 aromatic H); N—CH$_2$: 4·02 δ (q, J = 7·0 c/s); ⟩C—CH$_2$: 2·72 δ (q, J = 7·0 c/s); 2CH$_3$: 1·38 δ, 1·30 δ (2 triplets, J = 7·0 c/s). (Found: N 7·97. C$_{12}$H$_{15}$N requires: N, 8·09%.)

1-*ethylindole* (colourless liquid)[43]-UV absorption λ$_{max}$: 221 mμ (log ε = 4·55), 276 mμ (log ε = 3·77), 282 mμ (log ε = 3·79), 293·5 mμ (log ε = 3·66). NMR spectrum: 6·90 δ (H-2), 6·33 δ (H-3) (2d, J$_{2-3}$ = 3·0 c/s); 6·7–7·7 δ (4 aromatic H); N—CH$_2$—CH$_3$: 3·97 δ (2 H) (q); 1·33 δ (3 H) (t, J = 7·0 c/s). Found: C, 82·72; H, 7·52; N, 9·69. C$_{10}$H$_{11}$N requires: C, 82·72; H, 7·64; N, 9·65%.)

3-*ethylindole*[42] constituting only the 2% of the reaction mixture, was identified by comparison (IR, UV,

[36] A. R. Katritzky and A. P. Ambler, in *Physical Methods in Heterocyclic Chemistry* Vol. 2, pp. 211–212. Academic Press, London (1963).

[37] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Am. Chem. Soc.* **82**, 2184 (1960).

[38] M. G. Reinecke, H. W. Johnson, Jr. and J. F. Sebastian, *Chem. & Ind.* 151 (1964).

[39] R. V. Jardine and R. K. Brown, *Canad. J. Chem.* **41**, 2067 (1963).

[40] The products are eluted in the following order: 1,3-dialkylindole with hexane–benzene: 95/5. 1-alkyl-indole and 3-alkylindole with hexane–benzene 90/10.

[41] R. L. Hinmann and J. Lang, *J. Am. Chem. Soc.* **86**, 3805 (1964).

[42] E. Leete and L. Marion, *Canad. J. Chem.* **31**, 775 (1953).

TLC and GLC) with a sample of 3-ethylindole prepared by reduction of 3-acetylindole with $LiAlH_4$ (solid: m.p. 42°)-UV absorption λ_{max}: 223·5 mμ (log ε = 4·55), sh: 276·5 mμ (log ε = 3·73), 283 mμ (log ε = 3·76), 291 mμ (log ε = 3·70). NMR spectrum: 6·59 δ (H-2) (doublet of triplets, J_{1-2} = 2·0, $J_{2\cdot CH_2}$ = 1·0 c/s); 6·7–7·6 δ (4 aromatic H + NH); $>C—CH_2—CH_3$: 2·72 δ (q) (2H); 1·29 δ (t) (3H) (J = 7·5 c/s).

Reaction of indole sodium salt with n-propyl bromide

Five g of indole, 2·05 g of NaH and 5·25 g of n-propyl bromide were allowed to react (two runs) as described in the standard reaction.

GLC analyses (on 20% Apiezon L, 200°; for % composition of the mixture see Table 1) of the reaction mixtures pointed out besides unreacted indole the presence of three products. The components of the reaction mixture were separated by chromatography on a silica gel column (hexane–benzene) as described for the reaction with ethyl bromide.[40]

1,3-*dipropylindole* (colourless liquid)-UV absorption λ_{max}: 227·5 mμ (log ε = 4·53), 291 mμ (log ε = 3·73). NMR spectrum: 6·68 δ broad triplet ($J_{2\cdot CH_2}$ ≁ 1 c/s); 6·7–7·6 δ (4 aromatic H); N—CH_2: 9·88 δ (t, J = 7·0 c/s); 2—CH_2—CH_3: 1·72 δ (m) (4H); two triplets (6H) at 0·98 δ (J = 6·5 c/s) and 0·87 δ (J = 7·0 c/s). (Found: N, 7·0. $C_{14}H_{19}N$ requires: N, 6·96%.)

1-*propylindole*[43]-UV absorption λ_{max}: 221 mμ (log ε = 4·55), 276 mμ (log ε = 3·77), 282 mμ (log ε = 3·78), 294 mμ (log ε = 3·67). NMR spectrum: 6·84 δ (H-2), 6·32 δ (H-3) (2d, J_{2-3} = 3·0 c/s); 6·7–7·6 δ (4 aromatic H); N—CH_2—CH_2—CH_3: 3·88 δ (t) (2 H), 1·71 δ sextet (2 H), 0·81 δ (t) (3 H) (J = 7·0 c/s). (Found: N, 8·65. $C_{11}H_{13}N$ requires: N. 8·80%.)

3-*propylindole*[44] obtained by chromatography on silica gel was further purified by preparative GLC (on 20% Apiezon L, 190°) (colourless liquid)-UV absorption λ_{max}: 223·5 mμ (log ε = 4·59), sh 276 mμ (log ε = 3·75), 282 mμ (log ε = 3·8), 291 mμ (log ε = 3·72). NMR spectrum: 6·64 δ (H-2) doublet of triplets ($J_{1,2}$ ≁ 2, $J_{2\cdot CH_2}$ ≁ 1 c/s); 6·7–7·7 δ (4 aromatic H + NH) $>C—CH_2—CH_2—CH_3$: 2·68 δ (t) (2 H), 1·70 δ sextet (2H), 0·96 δ (t) (3 H) (J = 7·0 c/s). (Found: N, 8·58. $C_{11}H_{13}N$ requires: N, 8·80%.)

Reaction of indole sodium salt with isoamyl bromide

The reaction was carried out (two runs) as described in the standard procedure, letting react 5 g of indole, 2·05 g of NaH and 6·45 g of isoamyl bromide. GLC analyses (on 20% Apiezon L, 230°; for % mixture compositions see Table 1) of the mixtures pointed out besides indole three products. The reaction products were separated by chromatography as previously described (Silica gel–hexane/benzene).[40]

1,3-*diisoamylindole* (colourless liquid)-UV absorption λ_{max}: 227·5 mμ (log ε = 4·54), 291·5 mμ (log ε = 3·75). NMR spectrum: 6·71 δ (H-2) broad singlet ($J_{2\cdot CH_2}$ ≁ 1 c/s); 6·8–7·6 δ (4 aromatic H); N—CH_2: 3·95 δ (broad triplet, J = 7·0 c/s); $>C—CH_2$ ≁ 2·7 δ (m); 2—CH_2—$CH(CH_3)_2$: 1·3–1·9 δ (m) (6 H); 0·98 δ (d) and 0·95 δ (d) (12 H). (Found: C, 83·81; H, 10·82; N, 5·38. $C_{18}H_{27}N$ requires: C, 83·99; H, 10·57; N, 5·44%.)

1-*isoamylindole*[43] (colourless liquid)-UV absorption λ_{max}: 221 mμ (log ε = 4·57), 276 mμ (log ε = 3·78), 282 mμ (log ε = 3·79), 294 mμ (log ε = 3·67). NMR spectrum: 6·88 δ (H-2) and 6·38 δ (H-3) (2 d, $J_{2,3}$ = 3·0 c/s); 6·8–7·7 δ (4 aromatic H); N—CH_2: 3·93 δ (broad triplet, J ≁ 7·0 c/s); —CH_2—$CH(CH_3)_2$: 1·25–1·80 δ (m) (3 H), 0·90 δ (d, J = 5·5 c/s) (6 H). (Found: C, 83·24; H, 8·90; N, 7·46. $C_{13}H_{17}N$ requires: C, 83·37; H, 9·15; N, 7·48%.)

3-*isoamylindole* obtained by chromatography on silica gel was further purified by preparative GLC (on 20% Apiezon L, 220°) (colourless liquid)-UV absorption λ_{max}: 223·5 mμ (log ε = 4·55), sh 276·5 mμ (log ε = 3·74), 283 mμ (log ε = 3·78), 291 mμ (log ε = 3·72). NMR spectrum: 6·75 δ (H-2) doublet of triplets (broad) ($J_{1,2}$ ≁ 2 and $J_{2\cdot CH_2}$ ≁ 1 c/s); 6·8–7·7 δ (4 aromatic H + NH); $>C—CH_2$: ≁ 2·6 δ (m); —CH_2—$CH(CH_3)_2$: 1·6 δ (m) (3H), 0·97 δ (d) (6 H). (Found: N, 7·20. $C_{13}H_{17}N$ requires: N, 7·48%.)

Reaction of indole sodium salt with 2-bromopropane

The reaction was carried out (two runs) as described in the standard procedure (5 g of indole, 2·05 g of

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[44] G. F. Smith and A. E. Walters, *J. Chem. Soc.* 940 (1961).

NaH and 5·25 g of 2-bromopropane). The reaction apparatus having been connected, before the adding of 2-bromopropane, to a gas collector. GLC analysis (on silica gel, 20°, 50 ml/min hydrogen flow rate) of these gas pointed out, besides nitrogen, a peak having the same T_R of the synthetic propene. Reaction mixture was found to consist besides of indole of three products (GLC analyses on 30% Apiezon L, 200°; for % mixture compositions see Table 1). The products were separated by chromatography as previously described.[40]

1,3-*diisopropylindole* (colourless liquid)-UV absorption λ_{max}: 227·5 mμ (log ε = 4·55), 291 mμ (log ε = 3·74). NMR spectrum: 6·82 δ (H-2) broad singlet ($J_{2,CH_2} \sim$ 1 c/s); 6·7–7·7 δ (4 aromatic H); N—CH< : 4·53 δ (quintet, J = 6·5 c/s) (1 H); >C—CH< : 3·16 δ (quintet, J = 6·5 c/s) (1 H); 2—C(CH$_3$)$_2$: 1·45 δ and 1·35 δ (2d, J = 6·5 c/s). (Found: N, 7·18. C$_{14}$H$_{19}$N requires: N, 6·96%.)

1-*isopropylindole*[43] (colourless liquid) UV absorption λ_{max}: 221 mμ (log ε = 4·56), 276 mμ (log ε = 3·76), 282 mμ (log ε = 3·77), 294 mμ (log ε = 3·65). NMR spectrum: 6·96 δ (H-2) and 6·34 δ (H-3) (2d, $J_{2,3}$ = 3·5 c/s); 6·8–7·7 δ (4 aromatic H); N—CH(CH$_3$)$_2$: 4·41 δ quintet (1 H), 1·33 δ (d) (6 H) (J = 6·5 c/s). (Found: C, 83·01; H, 8·20; N, 9·03. C$_{11}$H$_{13}$N requires: C, 82·97; H, 8·23; N, 8·80%.)

3-*isopropylindole*[45] (colourless liquid)-UV absorption λ_{max}: 223 mμ (log ε = 4·54), sh 276·5 mμ (log ε = 3·73), 282 mμ (log ε = 3·76), 291 mμ (log ε = 3·69). NMR spectrum: 6·50 δ (H-2) doublet of doublet ($J_{1,2}$ = 2·5 and J_{2,CH_2} = 1·0 c/s), 6·7–7·7 δ (4 aromatic H + NH); >C—CH(CH$_3$)$_2$: 3·13 δ quintet (1 H) and 1·31 (d) (6 H) (J = 6·8 c/s). (Found: C, 82·68; H, 8·23; N, 8·77. C$_{11}$H$_{13}$N requires: C, 82·97; H, 8·23; N, 8·8%.)

Reaction of indole sodium salt with 2-bromopentane

The reaction was carried out (two runs) as described in the standard procedure (5 g of indole, 2·05 g of NaH and 6·45 g of 2-bromopentane). GLC analyses (on 20% Apiezon L, 220°; for % mixture compositions see Table 1) of the reaction mixtures pointed out besides indole, three main products and slight amounts of three by-products, which had a T_R essentially alike to the former ones and are probably due to the impurities of the 2-bromopentane used. The products were first separated by chromatography on a silica gel column[40] then as the by-products are not separable by this technique, all the three main products were purified by preparative GLC (on 20% Apiezon L; 180°).

1,3-*di-(1'-methyl) butylindole* (colourless liquid)-UV absorption λ_{max}: 228 mμ (log ε = 4·51), 292 mμ (log ε = 3·76). NMR spectrum: 6·77 δ (H-2) broad singlet; 6·7–7·6 δ (4 aromatic H); N—CH—CH$_3$: 4·37 δ sextet (3 H) and 1·33 δ (d) (1 H) (J = 7·0 c/s); >C—CH—CH$_3$: 3·0 δ sextet (3 H) and 1·45 δ (d) (1 H) (J = 6·5 c/s); 2 —CH$_2$—CH$_2$—CH$_3$: 0·8–2 δ complex pattern (14 H). (Found: N, 5·55. C$_{18}$H$_{27}$N requires: N 5·44%.)

1-(1'-*methyl*) butylindole (colourless liquid)- UV absorption λ_{max}: 221·5 mμ (log ε = 4·53), 276 mμ (log ε = 3·76), 283 mμ (log ε = 3·77), 294 mμ (log ε = 3·64). NMR spectrum: 6·95 δ (H-2) and 6·40 δ (H-3) (2d, $J_{2,3}$ = 3·0 c/s); 6·8–7·6 δ (4 aromatic H); N—CH—CH$_3$: 4·26 δ sextet (1 H) and 1·26 δ (d) (3 H) J = 6·8 c/s); —CH$_2$—CH$_2$—CH$_3$: 0·7 δ complex pattern (7 H). (Found: C, 83·22; H, 9·17; N, 7·39. C$_{13}$H$_{17}$N requires: C, 83·37; H, 9·15; N, 7·48%.)

3-(1'-*methyl*) butylindole (colourless liquid)-UV absorption λ_{max}: 223·5 mμ (log ε = 4·54), sh 276·5 mμ (log ε = 3·72), 282 mμ (log ε = 3·74), 291 mμ (log ε = 3·68). NMR spectrum: 6·70 δ (H-2) broad doublet ($J_{1,2}$ = 2·5 c/s); 6·8–7·7 δ (4 aromatic H + NH): >C—CH—CH$_3$: 3·16 δ sextet (1 H) and 1·30 δ (d) (3 H) (J = 7·0); —CH$_2$—CH$_2$—CH$_3$: 1·1–1·9 δ (m) (4 H), 0·88 δ broad triplet (3 H). (Found: N, 7·32. C$_{13}$H$_{17}$N requires: N, 7·48%.)

Reaction of indole sodium salt with tert-amyl bromide

Five g of indole, 2·05 g of NaH and 6·45 g of tert-amyl bromide were allowed to react (two runs) as described in the standard procedure, the reaction apparatus having been connected, before the adding of the alkyl halide, to a dry-ice/methanol trap through the reflux condenser kept at a constant temperature of 45°. Under a slow nitrogen flow besides a small amount of THF, some products with a low b.p. were

[45] Trenkler *Liebigs Ann.* **248**, 106.

collected. One g of such a mixture was ozonized at 0° for 1 hr in glacial acetic acid (50 ml). The ozonized solution, after decomposition with water and zinc dust, was directly distilled in sulphuric 2,4-dinitrophenylhydrazine, and a precipitate of 2,4-dinitrophenylhydrazones was obtained. By chromatography on silica gel, eluiting with hexane–ethylether (10/1) acetone and ethyl-methyl-ketone 2,4-dinitrophenylhydrazones were separated and identified by mixed m.p. with authentic samples. From the obtained reaction mixture containing besides indole, two products (GLC analysis with 20% Apiezon L, 220°; for % mixture compositions see Table 1), most of the indole was eliminated by crystallization with hexane; from the mother liquor the two products were separated by chromatography as previously described.[40]

1-*tert*-amylindole (colourless liquid)-UV absorption λ_{max}: 222·5 mμ (log ε = 4·58), 275 mμ (log ε = 3·78), 281 mμ (log ε = 3·80), 292 mμ (log ε = 3·71). NMR spectrum: 6·97 δ (d) (H-2); 6·32 δ (d, $J_{2,3}$ = 3·5 c/s); 6·8–7·7 δ (4 aromatic H); —C(CH$_3$)$_2$—CH$_2$—CH$_3$: 1·53 δ (s) (6 H), 1·95 δ (q) (2 H), 0·50 δ (t) (3 H) (J = 7·0 c/s). (Found: C, 83·50; H, 9·04; N, 7·69. $C_{13}H_{17}N$ requires: C, 83·37; H, 9·15; N, 7·48%.)

3-*tert*-amylindole (colourless liquid)-UV absorption λ_{max}: 222·5 mμ (log ε = 4·58), sh 276 mμ (log ε = 3·72), 282 mμ (log ε = 3·76), 291 mμ (log ε = 3·70). NMR spectrum: 6·73 δ (d, $J_{1,2}$ = 2·5 c/s) (H-2); 6·7–7·8 δ (4 aromatic H); —C(CH$_3$)$_2$—CH$_2$—CH$_3$: 1·35 δ (s) (6 H), 1·82 δ (q) (2 H) and 0·68 δ (t) (3 H) (J = 7·0 c/s). (Found: N, 7·20. $C_{13}H_{17}N$ requires: N, 7·48%.)

Reaction of indole sodium salt with 3-methylindole and isoamylbromide

1·3 g (0·011 mole) of indole in 10 ml of anhydrous THF was added at room temperature to a suspension of 0·45 g of NaH (0·010 mole about) in 5 ml of anhydrous THF; the mixture was then refluxed for 30 min: the amounts of gas evolved was in agreement with the theoretic value. To avoid the presence of NaH in the reaction mixture, some more indole (75 mg in 5 ml of dry THF) was added: no gas was evolved. Afterwards, at room temperature it was added first 1 g (0·013 mole) of 3-methylindole in 5 ml of anhydrous THF, then 1·5 g (0·01 mole) of isoamylbromide in 5 ml of the same solvent.

The reaction mixture was refluxed for 24 hr, hydrolysed then by water and ammonium chloride, subjected to extraction with ether and the ether solution, washed with water, was dried on Na_2SO_4. The solvent was removed at room temperature under reduced pressure and GLC analysis of the residue (Wilkens Aerograph Hy-Fi, 600 chromatograph, on 10% Apiezon L column with silanized Chromosorb W, 210°) indicated the following composition: Indole 20%, 3-methylindole 32%, 1-isoamylindole 27%, 1-isoamyl-3-methylindole 19%, 3-isoamylindole 2%.

Preparation of 1-isoamyl-3-methylindole[4c]

1·31 g of 3-methylindole in 5 ml of anhydrous THF was slowly added to a suspension of 0·48 g of NaH, previously washed with hexane, in 10 ml of anhydrous THF; the mixture was refluxed for 30 min: the evolved gas amount was in accordance with the theory.

1·51 g of isoamylbromide in 5 ml of anhydrous THF was then added, the mixture was allowed to reflux for 24 hr. The reaction mixture was treated as usual, and by chromatography on silica gel column eluting with hexane–benzene (95/5) it was possible to separate 1·5 g of 1-isoamyl-3-methylindole, which was found 100% pure by GLC analysis (on 20% Apiezon L, 210°). UV absorption λ_{max}: 227·5 mμ (log ε = 4·54), 291 mμ (log ε = 3·76). NMR spectrum: 6·66 δ (q) (H-2) and 2·26 δ (d) ($>$C—CH$_3$) (J = 1·0 c/s); 6·8–7·6 δ (4 aromatic H); N—(CH$_2$)$_2$—CH(CH$_3$)$_2$: 3·87 δ (t, $J \simeq$ 7·0 c/s) (2 H), 1·2–1·9 δ (m) (3H); 0·96 δ (d) (6 H). (Found: C, 83·23; H, 9·26; N, 7·09. $C_{14}H_{19}N$ requires: C, 83·53; H, 9·51; N, 6·96%.)

Reaction of indole sodium salt with allyl bromide in refluxing THF

First run. To a suspension of 2·05 g of NaH, washed with hexane, in 20 ml of anhydrous THF a solution of 5 g (0·043 mole) of indole in 15 ml of THF anhydrous was slowly added. To the refluxing mixture 5·17 g (0·043 mole) of allyl bromide in 15 ml of anhydrous THF was added over a period of 30 min. The reaction mixture was refluxed for another 24 hr, treated then as usual, to give a mixture which by GLC analysis (on 20% Apiezon L, 220°; for % mixture compositions see Table 2) was found to comprise, besides indole, four products. The products were separated by chromatography on silica gel column: elution with hexane–benzene (95/5) gave a mixture of 1,3-diallylindole and 1-allylindole, and with hexane–benzene (90/10) a mixture of 3-allylindole and indole. The polarity of the eluent was then gradually changed up to benzene–methanol (1/1) obtaining a product which was not identified.

1,3-diallylindole and 1-allylindole were separated by preparative GLC (on 20% Apiezon L, 220°); pure 3-allylindole was obtained by distillation at 120°/0·05 mm Hg.

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1,3-*diallylindole* (colourless liquid)-IR spectrum: —CH_2—CH=CH_2: 1640, 990, 918 cm^{-1}. UV absorption λ_{max}: 225 mμ (log ε = 4·50), 287 mμ (log ε = 3·75). NMR spectrum: 6·73 δ broad singlet ($J_{2,CH_2} \curlyvee$ 1·0 c/s), (H-2); 6·7–7·6 δ (4 aromatic H); N—CH_2: 4·60 δ (doublet of triplets, $J_{CH_2-CH=}$ = 5·0, J_{allyl} = 1·5 c/s); $\geqslant$C—CH_2—: 3·44 δ (doublet of quartets, $J_{CH_2-CH=}$ = 6·0, 2 equal J_{allyl} = 1·0 c/s); 2—CH=CH_2: 5·6–6·4 δ (2 H), 4·8–5·3 δ (4 H) complex patterns. (Found: N, 7·0. $C_{14}H_{15}N$ requires: N, 7·10%.)

1-*allylindole*[8c] (colourless liquid)-IR spectrum: —CH_2—CH=CH_2: 1640, 990 and 925 cm^{-1}. UV absorption λ_{max}: 220 mμ (log ε = 4·57), 274 mμ (log ε = 3·82), 281 mμ (log ε = 3·81), 292·5 mμ (log ε = 3·68). NMR spectrum: 6·92 δ and 6·36 δ (2d, $J_{2,3}$ = 3·0 c/s); 6·8–7·6 δ (4 aromatic H); N—CH_2—: 4·62 δ (doublet of triplets, $J_{CH_2-CH=}$ = 5·0, J_{allyl} = 1·5 c/s); —CH=CH_2: 5·93 δ (10 lines) (1 H); 5·13 and 5·0 δ (2 doublets of quartets, J_{cis} = 10·0, J_{trans} = 16·0, J_{gem} = 1·5, J_{allyl} = 1·5, $J_{NCH_2-CH=}$ = 5·0 c/s). (Found: N, 9·07. $C_{11}H_{11}N$ requires 8·91%.)

3-*allylindole*[8c] (colourless liquid)-IR spectrum: —CH_2—CH=CH_2: 1640, 990 and 918 cm^{-1}. UV absorption λ_{max}: 222·5 mμ (log ε = 4·54), sh 275 mμ (log ε = 3·75), 281 mμ (log ε = 3·78), 290·5 mμ (log ε = 3·70). NMR spectrum: 6·7 δ (H-2) (doublet of triplets, $J_{1,2} \curlyvee$ 2, $J_{2,CH_2} \curlyvee$ 1·0 c/s); 6·6–7·7 δ (4 aromatic H + NH); $\geqslant$C—CH_2: 3·47 δ (doublet of quartets, $J_{CH_2-CH=}$ = 6·0, 2 equal J_{allyl} = 1·0 c/s); CH=CH_2: 6·00 δ (12 lines) (1 H), 5·10 δ and 5·02 δ (2 doublets of quintets, J_{cis} = 9·00, J_{trans} = 17·0, J_{gem} = 2·2, J_{allyl} = 1·0 c/s, $J_{CH_2-CH=}$ = 6·0 c/s). (Found: C, 83·94; H, 7·0, N, 8·90. $C_{11}H_{11}N$ requires: C, 84·04; H, 7·05; N, 8·91%).

Second run. The reaction was carried out as described in the first run, but in this case, 2·05 g of NaH, 6·25 g (0·053 mole) of indole and 5·15 g (0·043 mole) of allyl bromide were allowed to react.

The resulting mixture consisted of five components (for % mixture composition see Table 2).

Third run. The reaction was carried out as previously described, but in this case 2·05 g of NaH, 10 g (0·086 mole) of indole and 5·17 g (0·043 mole) of allyl bromide were allowed to react. The resulting mixture consisted of five products (for % mixture composition see Table 2).

Reaction of indole sodium salt with methyl bromide

To a suspension of 3·075 g (0·064 mole about) of NaH, previously washed with hexane, in 20 ml of anhydrous THF, a solution of 5 g (0·043 mole) of indole in 15 ml of anhydrous THF was added. To the mixture, refluxed for 15 min, it was added at room temperature a solution of 6·1 g (0·064 mole) of methyl bromide in 15 ml of anhydrous THF. After 12 hr at room temperature, the mixture was treated as usual; analysis by means of GLC (on 20% Apiezon L, 190°; for % mixture composition see Table 3) of the resulting material indicated the presence of two products. By distillation (130°/20 mm Hg) it was obtained a 99% pure product, which by comparison (IR, UV and NMR) was identified as 1-methylindole. The second product was identified as 1,3-dimethylindole by comparison (GLC and TLC) with a pure sample.

Reaction of indole sodium salt with methyl iodide

The reaction was carried out as previously described, but in this case, 9·1 g (0·064 mole) of methyl iodide replaced the methyl bromide. Two products were obtained: 1-methylindole and 1,3-dimethylindole; for % mixture composition see Table 3.

Reaction of indole sodium salt with ethyl bromide in THF at room temperature

The reaction was carried out as described in the standard reaction, but at 15° ($\mp$2) for 24 hr; a mixture was obtained consisting of four products (for % mixture composition see Table 3).

Reaction of indole sodium salt with ethyl iodide in THF at room temperature

The reaction was carried out as described in the previous reaction, but in this case 6·65 g (0·043 mole) of ethyl iodide replaced the ethyl bromide. The resulting mixture consisted of four products (for % mixture composition see Table 3).

Reaction of indole sodium salt with allyl bromide in THF at room temperature

It has been operated on the same amounts and according to the same procedure as previously described as to the reaction with the same halide (see first run p. 3781 but the run was effected at 15° (+2) for 24 hr. GLC analysis (on 20% Apiezon L, 220°; for % mixture composition see Table 3) of the resulting mixture pointed out five components, which were identified by GLC comparison.

Reaction of indole sodium salt with benzyl bromide at room temperature

To a solution of 0·043 mole of indole sodium salt prepared from 5 g of indole and 2·05 g of NaH, 7·3 g (0·043 mole) of benzyl bromide in 15 ml of anhydrous THF were added at room temperature over a period of 30 min. After the addition the reaction mixture was allowed to react for 24 hr at 15° (∓2) and then treated as usual, obtaining a mixture of five components (GLC analysis on 20% Apiezon L with a programmed temperature course from 210° up to 280°; for % mixture composition see Table 3) which was subjected to chromatography on silica gel. Elution with hexane–benzene (95/5) gave a product (m.p. 43–44°, from ethanol) which was identified as 1-benzylindole; further elution with hexane–benzene (90/10) gave a first product (m.p. 72–73°, from hexane identified as 1,3-dibenzylindole, then a product with m.p. 52° (indole) and finally a product (m.p. 110–111°, from hexane) identified as 3-benzylindole. The polarity of the eluent was then gradually changed up to benzene–methanol (1/1) obtaining a product identified as 3,3-dibenzylindolenine (m.p. 115–117°, from hexane).

1-*benzylindole*[8a]-UV absorption λ_{max}: 219 mμ (log ε = 4·56), 274 mμ (log ε = 3·82), 281 mμ (log ε = 3·81), 292 mμ (log ε = 3·68). NMR spectrum (CDCl$_3$): 6·53 δ (d, J = 3·0 c/s) (H-3), 6·9–7·8 δ (9 aromatic H + H-2), N—CH$_2$: 5·28 δ (s). (Found: C, 86·96; H, 6·31; N, 6·56. C$_{15}$H$_{13}$N requires: C, 86·92; H, 6·32; N, 6·76%.)

1,3-*dibenzylindole* UV absorption λ_{max}: ≈ 224 mμ (log ε = 4·57), 288·5 mμ (log ε = 3·83). NMR spectrum: 6·66 δ broad singlet (H-2), 6·7–7·5 δ (14 aromatic H), N—CH$_2$: 5·0 δ (s), C—CH$_2$: 4·01 δ (s). (Found: C, 88·90; H, 6·26; N, 5·01. C$_{22}$H$_{19}$N requires: C, 88·85; H, 6·44; N, 4·71%.)

3-*benzylindole*[46] UV absorption λ_{max}: 221·5 mμ (log ε = 4·57), 275 mμ (log ε = 3·77), 281 mμ (log ε = 3·79), 290·5 mμ (log ε = 3·72). NMR spectrum (CDCl$_3$): 6·80 δ (doublet of triplets, J_{2,CH_2} ≈ 1, $J_{1,2}$ ≈ 2 c/s) (H-2); 6·8–7·8 δ (9 aromatic H + NH); —C—CH$_2$: 4·08 δ (d, J_{2,CH_2} = 1 c/s). (Found: C, 86·90; H, 6·33; N, 6·67. C$_{15}$H$_{13}$N requires: C, 86·92; H, 6·32; N, 6·76%.)

3,3-*dibenzylindolenine*-UV absorption λ_{max}: 210 mμ (log ε = 4·48), 259 mμ (log ε = 3·61). NMR spectrum (CDCl$_3$): 8·11 δ (s) (H-2), 6·7–7·5 δ (14 aromatic H), —C(CH$_2$—)$_2$: 3·17 δ (s) (4 H). (Found: C, 88·90; H, 6·41; N, 5·10. C$_{22}$H$_{19}$N requires: C, 88·85; H, 6·44; N, 4·71%.)

Reaction of indole sodium salt with allyl bromide in DMF at 65°

Indole sodium salt was prepared in THF as usual (5 g of indole, 2·05 g of NaH); the solvent, removed first by distillation under anhydrous nitrogen atmosphere then under reduced pressure, was replaced by 35 ml of DMF. To this solution 5·17 g (0·043 mole) of allyl bromide in 15 ml of DMF was added at a constant temperature of 65° over a period of 30 min. After 1 hr, the mixture composition was constant; the mixture was then hydrolyzed and treated as usual obtaining four products (GLC analysis on 20% Apiezon L, 220°; for % mixture see Table 4).

[46] R. H. Conforth and R. Robinson, *J. Chem. Soc.* 680 (1942).