INDOLE CHEMISTRY

XXIX.* PROTOTROPIC REARRANGEMENT OF 3-ALKYL-
AND 3-ARYLINDOLES

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Judging from the PMR spectra, the protonation of various 3-alkyl- and 3-arylindoles in sulfuric and trifluoroacetic acids proceeds primarily at the 3 position. Prototropic shift of a radical to form 2-substituted indoles occurs on heating with these acids, and better results are obtained with polyphosphoric acid. Ideas regarding the mechanism of the process are presented.

The indole molecule is a π-electron cyclic system in which the maximum electron density is found on the β-carbon atom [2]. The attack of an electrophilic agent (including the proton) should therefore be directed to this position [2]. The cation localization energy calculated for this case is a minimum, and the cation formed is consequently the most stable one [3]. Moreover, the increased index of multiplicity of the $C_2 = C_3$ bond presupposes that indole has properties characteristic for double bonds. In fact, in addition to electrophilic substitution in the 3 position of the indole molecule [4], the addition of the reagent at this bond is observed in a number of cases [5, 6].

If protonation of indole compounds proceeds at the 3 position, heterolytic opening of the $C_2 = C_3$ double bond occurs simultaneously with predominant localization of the charge on the α-carbon atom [2]. In this respect, indole reminds one of cyclic enamines, the protonation of which proceeds primarily at the carbon atom [7]. The proton can also attack the nitrogen atom during the formation of crystalline salts with inorganic acids [8]. This protonated form is only 1-3 kcal/mole less stable than the β-protonated form [2, 3]. However, the possibility of N-protonation was postulated only on the basis of an interpretation of the IR spectroscopic data and was not observed when other methods were used. At the same time, all of the data on the electrophilic substitution of alkylindoles in acidic media [2] and PMR spectroscopy of indoles in acids [8] favor β-protonation. The presence of a strong positive charge on the α-carbon atom during protonation of the indole molecule explains the fact that β-substituted indoles are less basic by a factor of 10^3 than α-alkyl derivatives [8], in which the alkyl substituent stabilizes the molecule through its inductive effect. The protonation of a structure with a substituent in the β-position is consequently less stable energically than the same structure with the same substituent in the α-position. The first should therefore be converted to the second under certain conditions. In fact, it is known that the corresponding 2-substituted indoles [9-12] are formed by the action of Lewis acids ($ZnCl_2$, $AlCl_3$) on 3-methyl-, 3-phenyl-, 3-benzyl-, and 3-tert-butylindoles at high temperatures, but all of these experiments were carried out under different conditions, and it is therefore difficult to compare them.
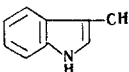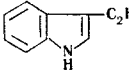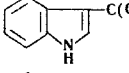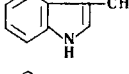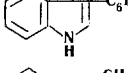
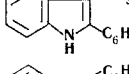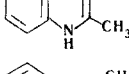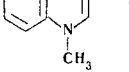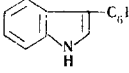We have investigated the effect of proton acids (polyphosphoric, sulfuric, and trifluoroacetic acids) on the behavior of a series of 3-substituted indoles. Characteristic changes that correspond to a change in the structure of the molecule during the addition of a proton to the 3 position are observed in the PMR spectra of 3-substituted indoles (Table 1) on passing from neutral solvents to acids. The signal of the 3-H

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*See [1] for communication XXVIII.

TABLE 1. PMR Spectra of 3-Substituted Indoles in Concentrated Sulfuric Acid*

	Aliphatic region	3-H	2-H	Benzene ring protons
3-CH$_3$ indole	CH$_3$ 2,30 (d, J 6Hz)	4,91 (q, J 6Hz)	9,57 (d, J 6Hz)	8,17
3-C$_2$H$_5$ indole	CH$_3$ 0,93 (t) CH$_2$ 2,01 (m)	4,29 (t)	9,29 (d)	7,00—7,80
3-C(CH$_3$)$_3$ indole	CH$_3$ 1,16 (s) †	4,27 (s)	9,22 (d)	7,30—8,00
3-CH$_2$C$_6$H$_5$ indole	CH$_2$ 3,25 (d) †	4,58 (t)	9,08 (d)	7,00—7,80
3-C$_6$H$_5$ indole	—	5,91 (s)	9,54 (d, J 6Hz)	7,40—8,50 (m)
3-CH$_3$, 2-C$_6$H$_5$ indole	CH$_3$ 1,63 †	5,55 (q)		7,60—8,20
3-C$_6$H$_5$, 2-CH$_3$ indole	CH$_3$ 3,09 (s) [2,63 †]	5,65 (s) [5,53 †]		7,20—8,80
3-CH$_3$, N-CH$_3$ indole	3-CH$_3$ 2,02 (d, J 6Hz) N—CH$_3$ 4,62	4,75 (q, J 6Hz)	9,46 (s)	8,21
3-C$_6$H$_5$, N-CH$_3$ indole	N—CH$_3$ 4,56	5,87 (s)	9,40 (s)	7,30—8,50

*The chemical shifts are presented on the δ scale in parts per million. The abbreviations are as follows: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.
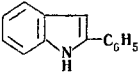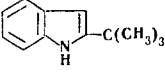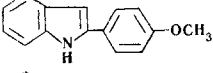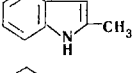†The spectra were recorded from solutions in a mixture of H$_2$SO$_4$ and CF$_3$COOH (1 : 10).
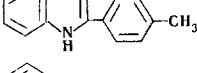
proton appears at 5-6 ppm and is split into a quartet in 3-methylindoles or into a triplet if there is an adjacent methylene group. In the case of 3-phenyl- and 3-tert-butylindoles, the 3-H signal appears as a singlet. In addition, the signal of the 2-H proton appears at 9.0-9.5 ppm and is split into a doublet in the case of N-unsubstituted indoles. 2-Substituted indoles are stronger bases and are protonated not only in sulfuric acid but also in trifluoroacetic acid (Table 2). The protonation of 3-substituted indoles by trifluoroacetic acid is incomplete, and the spectrum is the superimposition of the spectra of the protonated and unprotonated form. For example, in the case of skatole, both a doublet of the methyl group at 1.37 ppm (protonated form) and a singlet of the methyl group at 2.26 ppm (unprotonated form) are observed in the spectrum. However, the spectrum becomes complicated after a certain time, which is apparently associated with polymerization of the skatole.

2-Substituted indoles are formed in high yields when all of the studied 3-substituted indoles are heated with polyphosphoric acid to 100-150°. Exce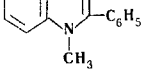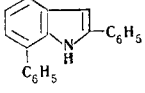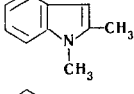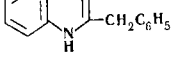ptions to this are 3-methyl- and 1,3-dimethylindoles, for which the yield is 10-50%, and a considerable amount of resinous reaction products is formed. It is known that such compounds are generally extremely acidophobic and are readily resinified by the action of acidic agents [13]. The reaction in trifluoroacetic acid and sulfuric acid requires more time, and the yield of rearrangement products decreases.

The degree of ease of migration of the radicals is CH$_3$ < C(CH$_3$)$_3$ < CH$_2$C$_6$H$_5$ < C$_6$H$_5$, which is in agreement with the order of the stability of the corresponding cation. We have already published a brief communication regarding this [14].

TABLE 2. PMR Spectra of 2-Substituted Indoles in Concentrated Sulfuric Acid*

	3-H	Aromatic region	Aliphatic region
indole-2-C_6H_5 (N-H)	5,09 (4,78)	7,70—8,10 (7,80—8,20)	
indole-2-$C(CH_3)_3$ (N-H)	4,68 (4,42)	7,40—8,00 (7,40—7,80)	$C(CH_3)_3$ 1,80 (1,51)
indole-2-(C_6H_4-OCH_3)	5,28	7,62 8,00—8,70	CH_3 4,44
indole-2-CH_3	4,69	7,92 Broad singlet	CH_3 3,27
indole-2-(C_6H_4-CH_3)	5,00	7,60—8,5	CH_3 2,77
indole-2-C_6H_5 (N-CH_3)	5,07	8,00—8,20	CH_3 4,52
indole-2-C_6H_5 (N-C_6H_5)	5,31 (4,87)	7,80—8,80 (7,70—8,20)	
indole-2-CH_3 (N-CH_3)	4,80	8,16 Broad singlet	2-CH_3 3,25 N—CH_3 4,40
indole-2-$CH_2C_6H_5$ (N-H)	4,75 or 4,85 (4,33 or 4,44)	7,70—8,30 (7,10—7,70)	CH_2 4,85 or 4,75 (4,44 or 4,33)

*The chemical shifts are given on the δ scale in parts per million. The chemical shifts in spectra recorded from trifluoroacetic acid solutions are given in parentheses.

TABLE 3. Rearrangement of 3-Substituted Indoles to the 2-Substituted Isomers by the Action of Polyphosphoric Acid
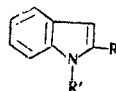
R'	R	Reaction temp., °C	Reaction time, min	Yield,%	Mp, °C found	Mp, °C literature data
H	C_6H_5	100	15	90	189—190	189—190 [17]
H	$CH_2C_6H_5$	100	15	80	84	86 [18]
H	$C(CH_3)_3$	100	60	50	77	73—74[19]
H	CH_3	130	240	10	58—59	56—59[20]
CH_3	C_6H_5	100	15	83	102	100—101[20]
CH_3	CH_3	140	420	50*	—	56 [21]
H	2,7-$(C_6H_5)_2$	150	15	90	115	116—117 [22]

*Determined by gas—liquid chromatography with a 3-m-long column packed with polyethylene glycol 30,000 on microspheric brick at a column temperature of 202°C and a gas (nitrogen) carrier rate of 100 ml/min. Two peaks with retention times of 1.4 and 1.7 min were obtained.

A mixture of only 2-tert-butylindole and 2-phenylbenzofuran is formed, according to gas-liquid chromatographic analysis, when an equimolecular mixture of 3-tert-butylindole and 3-phenylbenzofuran (which is readily isomerized by the action of acids to 2-phenylbenzofuran [15]) is heated. Moreover, crossed alkylation (arylation) products are not observed, which makes it possible to assume that the isomerization proceeds intramolecularly (see [16]).

Thus electrophilic attack of the 3 position of the indole ring by the proton with heterolytic opening of the C_2–C_3 bond apparently occurs initially. Preprotonation is a primary and necessary act, since 3-phenylindole is recovered quantitatively when it is heated to 200° without acid.
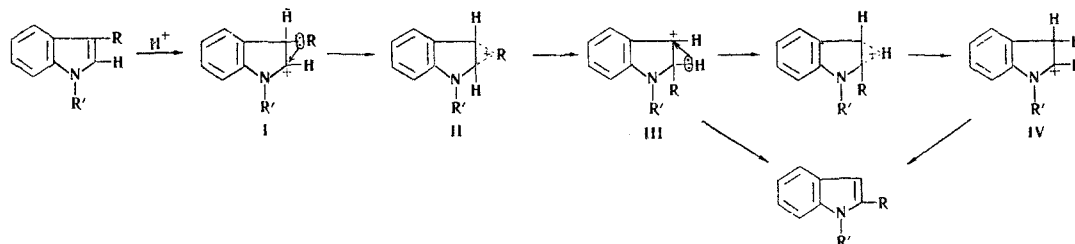
In ion I, the electrons that form the bond between radical R and the ring interact with the strong positive charge on the α-carbon atom, which leads to migration of the substituent to form ion III (possible through intermediate, nonclassical cation II). The proton then migrates, which leads to a more stable cation (IV), although direct deprotonation of IV to form the rearrangement product cannot be excluded. It is possible that the migration of the radical and proton is a synchronous process.

Thus indoles with alkyl or aryl substituents in the pyrrole ring are capable of isomerization in acidic media on heating. In this case, the relative stabilities of the protonated forms of the isomers play the decisive role; i.e., in other words, in conformity with the Le Chatelier principle, the less basic 3-isomer is converted to the more basic 2-isomer. In a number of cases, particularly for 3-alkylindoles, in which the cation formed is sterically accessible, the process is complicated by competetive polymerization.

EXPERIMENTAL

The PMR spectra were obtained with an RS-60 spectrometer with hexamethyldisiloxane as the external standard. Thin-layer chromatography on a loose layer of activity II aluminum oxide with elution by ether–petroleum ether (1:1) and development by iodine vapors, as well as gas–liquid chromatography with a Tswett-1 chromatograph, were used to evaluate the purities of the substances obtained.

The starting 3-phenyl-, 3-benzyl-, and 3-tert-butylindoles were obtained by the action of an organomagnesium compound on isatin with subsequent reduction of the reaction product [12].

Rearrangement of 3-Substituted Indoles in Polyphosphoric Acid. A 1-mmole sample of the 3-substituted indole was added to polyphosphoric acid (from 5 ml of 85% orthophosphoric acid and 10 g of phosphorus pentoxide), and the mixture was heated with constant stirring. At the end of the reaction, the mixture was poured over ice and extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water and dried with magnesium sulfate. The solvent was removed to give the 2-isomer. The yields and reaction time and temperature are presented in Table 3.

Rearrangement of 3-Benzylindole by the Action of Trifluoroacetic Acid. A solution of 300 mg (0.001 mole) of 3-benzylindole in 10 ml of trifluoroacetic acid was refluxed for 18 h. The acid was then removed by vacuum distillation, a small amount of water was added to the residue, and the mixture was extracted with ether. According to chromatography on aluminum oxide, the 3-substituted isomer was not present in the reaction mixture. The ether was evaporated, and the residual mass was recrystallized from petroleum ether to give 100 mg (30%) of pure 2-benzylindole with mp 84°.

Rearrangement of 3-Phenylindole in Sulfuric Acid. A mixture of 100 mg (0.0005 mole) of 3-phenylindole and 5 ml of concentrated sulfuric acid was allowed to stand at room temperature for 10 days. The mixture was then poured over ice and extracted with ether. The ether extract was washed with sodium bicarbonate solution and water and dried with magnesium sulfate. The ether was evaporated to give 10 mg (10%) of 2-phenylindole with mp 188–189°.

<u>Joint Rearrangement of 3-Phenylbenzofuran and 3-tert-Butylindole.</u> A mixture of 0.5 g (~0.003 mole) of 3-phenylbenzofuran and 0.5 g of 3-tert-butylindole was added to polyphosphoric acid (from 50 g of phosphorus pentoxide and 25 ml of 85% phosphoric acid) heated to 150°, and the mixture was heated at this temperature for 2 h. The mixture was poured over ice and extracted with ether. The extract was washed with water, the ether was vacuum evaporated, and the residue was dissolved in petroleum ether. The solution was filtered through a thin layer of aluminum oxide, and the petroleum ether was removed by vacuum distillation to give 0.8 g (80%) of colorless crystals. Gas—liquid chromatography with a 3-m-long column packed with polyethylene glycol 2000 on microspheric brick at a column temperature of 220° and a gas (nitrogen) carrier rate of 39 ml/min gave four peaks with retention times of 17.5, 22, 27, and 37 min. The intensity ratio was 2:38:6:32. The peaks correspond to 3-phenylbenzofuran, 2-phenylbenzofuran, 3-tert-butylindole, and 2-tert-butylindole.

LITERATURE CITED

1. N. N. Borisov, R. S. Sagitullin, and A. N. Kost, Khim. Geterotsikl. Soedin., 48 (1972).
2. A. N. Kost, L. G. Yudin, V. A. Budylin, and V. I. Minkin, Dokl. Akad. Nauk SSSR, 176, 1096 (1967).
3. R. Herman, Int. J. Quant. Chem., 2, 165 (1968).
4. W. Sumpter and F. Miller, Heterocyclic Compounds with Indole and Carbazole Systems, New York (1954).
5. K. Shofield, Quart. Rev., 4, 382 (1950).
6. S. Plant and M. Tomlinson, J. Chem. Soc., 955 (1933).
7. K. Blaha and O. Cervinka, Advances in Heterocyclic Chemistry, 6, 182 (1966).
8. R. Hinmann and E. Whipple, J. Am. Chem. Soc., 84, 2534 (1962).
9. K. Biswas and A. Jackson, Tetrahedron, 25, 227 (1969).
10. E. Fisher and T. Schmidt, Ber., 21, 1811 (1888).
11. G. R. Clemo and J. C. Seaton, J. Chem. Soc., 2582 (1964).
12. M. Bettembourg and S. David, Bull. Soc. Chim. France, 772 (1962).
13. B. G. F. Smith, Advances in Heterocyclic Chemistry, 2, 303 (1963).
14. V. A. Budylin, A. N. Kost, and E. D. Matveeva, Vestnik MGU, Ser. Khim., No. 3, 121 (1969).
15. W. Davies and S. Middleton, J. Chem. Soc., 822 (1958).
16. N. P. Buu-Höi, Bull. Soc. Chim. France, 1104 (1967).
17. C. Blad and A. Wilds, J. Org. Chem., 21, 1013 (1956).
18. J. Pikl. J. Am. Chem. Soc., 55, 2105 (1933).
19. F. Piozzi and M. R. Langualla, Gazz. Chim. Ital., 93, 1382 (1963).
20. H. Kussman, D. Farnswortt, and B. Witkop, J. Am. Chem. Soc., 74, 3949 (1952).
21. I. Degen, Ann., 236, 153 (1886).
22. A. N. Kost, I. P. Sugrobova, and A. P. Yakubov, Zh. Organ. Khim., 1, 124 (1965).