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A GENERAL CLEAVAGE REACTION OF 3-SUBSTITUTED INDOLES

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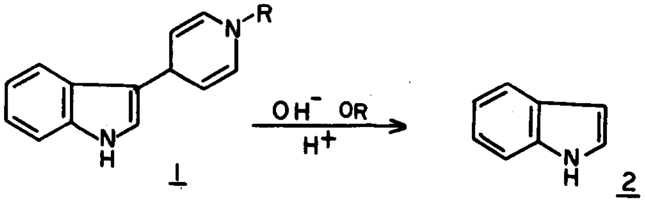
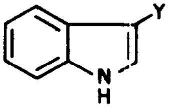
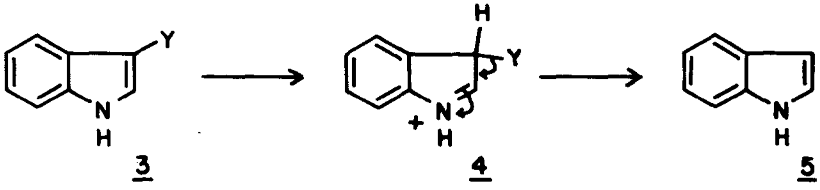
While investigating methods for the conversion of the piperidylindole derivative 1 (R=CN) to 3-(4-pyridyl) indole, we discovered a novel cleavage reaction. When 1 (R=CN) was heated at reflux with 2% potassium hydroxide in ethanol-water for 18 hours, there was obtained a 90% yield of indole (2) instead of the expected hydrolysis product. Similarly, a 41% yield of indole was isolated when 1 (R=CN) was reacted with 4% hydrochloric acid in ethanol-water for 2 hours at reflux.



We have since found that this loss of a substituent from the 3-position of indoles is indeed a general reaction. A large variety of 3-substituted indoles gave the corresponding unsubstituted heterocycle when treated with dilute acid or base (see table). The products from the cleavage reactions were isolated and identified by comparison of their infrared solution spectra and R_f values (silica gel G thin layer chromatographic) with those of authentic samples. Most of the transformations were exceedingly facile and proceeded under mild conditions. Acid catalyzed cleavage was in general less suitable since yields were decreased by competing polymerization reactions.

REACTANT	PRODUCT	CONDITIONS
$\underline{1}$ R = $CO_2C_2H_5$	indole (33%)	1% NaOH in C_2H_5OH/H_2O 18 hrs., 27°
		
Y = $CO_2^- Na^+$	indole (29%)	10% NaOH in H_2O 3 days, 100°
Y = CO_2H	indole[1]	
Y = $CO_2C_2H_5$	indole (80%)	4% H_2SO_4 in C_2H_5OH 18 hrs., 78°
Y = $CO_2C_2H_5$	indole (85%)	.1N $NaOC_2H_5$ in C_2H_5OH 18 hrs., 78°
Y = CHO	indole (20%)	60% KOH in H_2O 1 day, 100°
Y = $COCH_3$	skatole[2]	$NaOCH_3$ in CH_3OH 13 hrs., 210°
Y = $POCl_2$, 2-methyl	2-methylindole (51%)	Na_2CO_3 in acetone/H_2O 20 hrs., 56°
Y = CH_2OH	diindoylmethane[3]	boiling water

A possible mechanism for these cleavage reactions involves conversion of the 3-substituted indole ($\underline{3}$) to its tautomeric indolenine (basic medium) or indolenium salt ($\underline{4}$) (acidic medium). Subsequent cleavage of the substituent (see arrows in $\underline{4}$) would regenerate the aromatic indolic system $\underline{5}$, thus providing significant driving force for the reaction. A recent report that 2-methylindole and 1,2-dimethylindole undergo ready tautomerism in dilute acid or base provides our mechanism with considerable support since most of the cleavage reactions are acid or base catalyzed.



Acylindoles are cleaved with great difficulty. Indole 3-carboxaldehyde did not react when heated at reflux with dilute aqueous base; forcing conditions were necessary for the production of indole. This aldehyde is sufficiently acidic to form a sodium salt when dissolved in dilute aqueous alkali and evidently salt formation hinders tautomerization to the indolenine thus preventing cleavage. Treatment of 3-acetylindole with sodium methoxide at 210° yielded skatole.[2] The mechanism of this transformation probably involves cleavage of the acetyl group from 3-acetylindole to give indole. Since indoles are known to be quite susceptible to alkylation by alcohols in basic medium,[5,6] it appears reasonable to assume that the indole thus formed would be methylated under the reaction conditions. Support for this mechanism is derived from the observation that only 3-ethylindole is formed if the cleavage is carried out using sodium ethoxide in ethanol instead of sodium methoxide. The formation of diindolylmethane from indole 3-carbinol is another example of this type of reaction.[3] Cleavage of the carbinol produces indole which is then alkylated by excess indole 3-carbinol to yield the observed product.

The biosynthesis of tryptophan has been found to involve the intermediate formation of 3-indolylglycerol phosphate 3 ($R=CHOH-CHOH-CH_2OPO_3H_2$).[7] An enzymic reaction causes the cleavage of this to indole which is eventually converted to tryptophan. Since many of the above cleavage reactions occur under very mild conditions, it seems reasonable to assume that the enzymic reaction is occuring by a similar process.

Cleavage of substituents from other heterocyclic systems and the utility of this reaction in providing several protecting groups for the 3-position of indoles will be discussed elsewhere.

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References

(1) T. S. Stevens, in E. H. Rodd, *Chemistry of Carbon Compounds*, Vol. IVA, p. 96. Elsevier, New York (1957).

(2) C. Alberti, *Gazz. chim. ital.*, **67**, 238 (1937).

(3) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

(4) B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2524 (1963).

(5) E. F. Pratt and W. L. Botimer, *J. Am. Chem. Soc.*, **79**, 5248 (1957).

(6) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 1247 (1963).

(7) C. Yanofsky, *J. Biol. Chem.*, **224**, 783 (1957).