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THE CHEMISTRY OF INDOLES (1-AMINOINDOLES), III[1]

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In our previous work[1b] we described a facile method for the synthesis of 1-aminoindoles. Now we wish to call attention to the use of 1-aminoindoles as useful starting materials for the preparation of various types of novel heterocyclic compounds.

I. Preparation of 1-Alkylideneaminoindoles

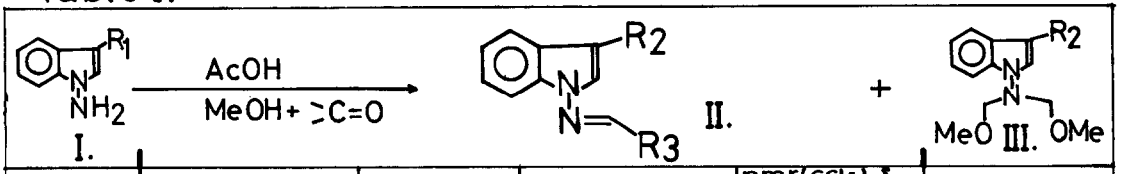
i) Reaction with formaldehyde: 1-Aminoindoles (Ia-c) reacted with formaldehyde in MeOH under the Mannich conditions very rapidly to afford unstable 1-methyleneaminoindoles (IIa-c) and 1-bis(methoxymethyl)aminoindoles (IIIb,c). The stability of these compounds was significantly dependent upon the nature of the 3-substituents, increasing gradually in the order $H < CH_3 < CH_2NMe_2 < CH_2\phi$. With 3-benzylindole, stable 1-bis(methoxymethyl)amino-3-benzylindole (IIIc) and 1-methyleneamino-3-benzylindole (IIc) were obtained and the former compound could easily be converted to the latter in 93.7% yield by treatment with AcOH-MeOH. One of the N-methylene protons of 1-methyleneaminoindoles was easily discernible from the other protons and appeared as a doublet in the region of δ 6.59-6.76 (CCl_4) (Table I).

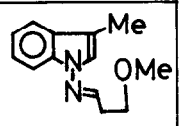
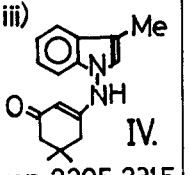
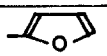
ii) Reaction with acetaldehyde: Acetaldehyde gave the corresponding 1-ethylideneaminoindoles (IId,e) in AcOH-MeOH (Table I).

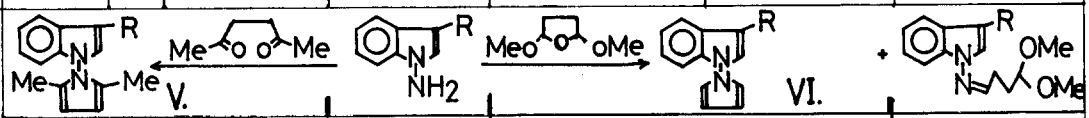
iii) Reaction with 1,3-diketone: 1-Aminoskatole reacted with dimedone to give the corresponding enaminoketone (IV) in 87.4% yield.

iv) Reaction with α,β-unsaturated aldehyde: α,β-Unsaturated aldehydes, such as acrolein, crotonaldehyde, cinnamaldehyde and furfural reacted with 1-aminoindoles, yielding 1-allylideneaminoskatole (IIf), 1-(2-butenylideneamino)-indoles (IIg,j), 1-cinnamylideneaminoindoles (IIh,k) and 1-furfurylideneaminoskatole (IIi), respectively (Table I).

Table I. Preparation of 1-Alkylideneaminoindoles



	R_1		R_2	R_3	mp	Yield %	nmr(CCl4). δ. >N-N=C-H	Yield %
i)	a) Me	a)	Me	H	oil	20.2	6.59 d. J=11 Hz	—
	b) H	b)	$-CH_2-N(Me)_2$	H	〃	76.6	6.76 〃	b) oil 7.7
	c) $-CH_2\phi$	c)	$-CH_2-\phi$	H	〃	27.4	6.73 d. J=10.5	c) 〃 49.8
ii)	a) Me	d)	Me	Me	〃	90.4	in a region of 6.80 ~ 7.76	
	b) H	e)	H	Me	〃	73.5	(CDCl3) 6.14 q. J=5.5	
iv)	a) Me	f)	Me	$-CH=CH_2$	〃	64.7	7.81 d. J= 8.5	+ oil 17.6%
		g)	Me	-CH=CH-Me	455-465	91.6	7.58 d. J= 8.0	iii) 
		h)	Me	-CH=CH-φ	87-88	95.5	7.78 d. J= 8.0	
		i)	Me		oil	100.0	8.06 s.	IV.
	b) H	j)	H	-CH=CH-Me	71.5-72	96.2	7.90 d. J= 8.0	mp 230.5-231.5
		k)	H	-CH=CH-φ	124.5-125	90.6	7.95 d. J= 8.0	Y. 87.4%

v) 

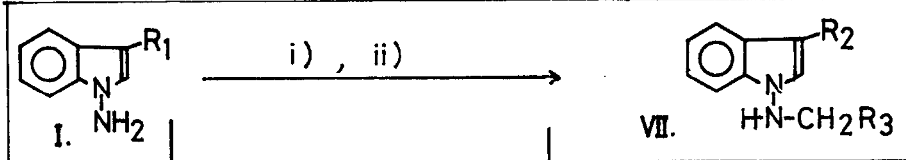
a) mp 107.5-108.5	90.3%	a) R= Me	a) oil 49.3 %	oil 21.5 %
b) mp 80-81	96.9%	b) R= H	b) 〃 33.0 %	—

v) Reaction with 1,4-diketone: 1-Aminoindoles (Ia,b) easily condensed with acetonylacetone and 2,5-dimethoxytetrahydrofuran to afford 1-(2,5-dimethylpyrrol-1-yl)indoles (Va,b) and 1-(pyrrol-1-yl)indoles (IVa,b), respectively (Table I).

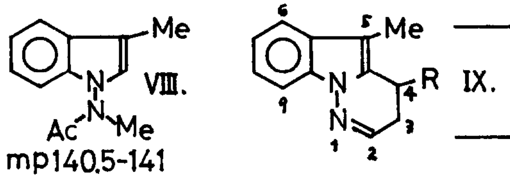
II. Preparation of 1-Alkylaminoindoles

Reduction of 1-alkylideneaminoindoles with $NaBH_4$ smoothly produced the corresponding 1-alkylaminoindoles (VIIa-e). The results are summarized in Table II, showing the overall yields from 1-aminoindoles. Structural proof was obtained from the result that 1-methylaminoskatole, as a representative of the series,

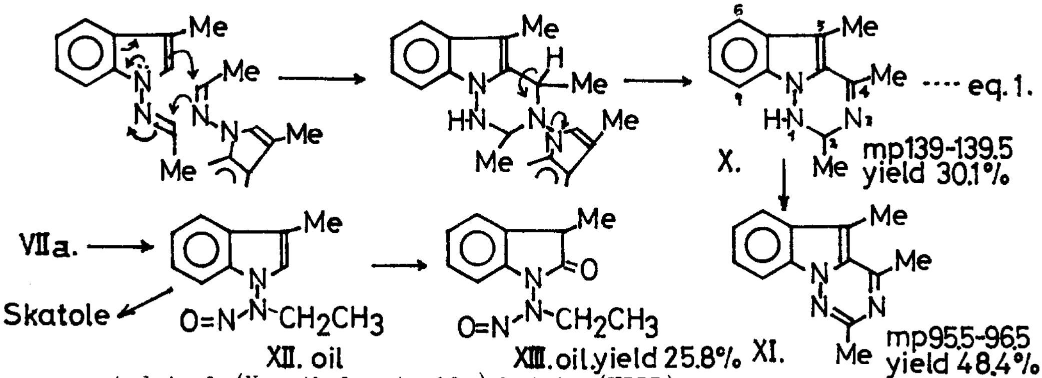
Table II. Preparation of 1-Alkylaminoindoles



	Reaction Conditions		R_2	R_3	Overall Yield %
a) R_1 = Me	i) CH_3CHO-AcOH ii) $NaBH_4$	a)	Me	Me	oil 80.7
	i) HCHO-AcOH ii) 〃	b)	Me	H	〃 72.3
b) R_1 = H	i) CH_3CHO-AcOH ii) 〃	c)	H	Me	〃 72.1
	i) HCHO-AcOH ii) 〃	d)	H	H	mp 33-34 63.6
	i) HCHO-AcOH-Me_2NH ii) 〃	e)	CH_2NMe_2	H	oil 21.3



a) R = Me	mp 84-85	yield 80.0%
b) R = Ø	oil	yield 59.4%



was converted to 1-(N-methylacetamido)skatole (VIII) by Ac_2O in quantitative yield. The same product (VIII) was obtained from reaction of the sodium salt of 1-acetamidoskatole (known compound)[1b] with MeI in 64.1% yield, together with 11.9% yield of 1-(N-methylpropionamido)skatole (mp 76.5-77.5).

III. Preparation of Indolo-Heterocycles

Treatment of 1-(2-butenylideneamino)skatole (IIg) and 1-cinnamilideneamino-skatole (IIh) with Lewis acid in benzene smoothly brought about cyclisation between the γ-carbon atom of the alkenylidene group and the indole C-2, affording the corresponding 3,4-dihydro-4,5-dimethyl-pyridazino(2,3-a)indole (IXa) and

3,4-dihydro-4-phenyl-5-methyl-pyridazino(2,3-a)indole (IXb), respectively. On the other hand, treatment at reflux temperature of 1-ethylideneaminoskatole (IId) with p-toluenesulfonic acid in benzene afforded 1,2-dihydro-2,4,5-trimethyl-as-triazino(1,6-a)indole (X) in 30.1% yield. One explanation of this is an initial formation of a Diels-Alder type adduct as an intermediate, followed by the liberation of skatole (eq. 1). Though another double bond isomer is possible, the structure was confirmed as shown mainly by the nmr spectrum, in which the protons attached to nitrogen-1 and carbon-2 appeared as a doublet (δ 3.73, J=10) and a multiplet (δ 4.46), respectively, and where on the addition of D_2O the former signal disappeared and the latter changed to a quartet of quartet (J=1.5,6.0). The compound (X) was readily oxidized either on exposure to air or by the action of chloranil to give 2,4,5-trimethyl-as-triazino(1,6-a)indole (XI).

IV. Possibility as a Protecting Group

1-Ethylaminoskatole (VIIa) was quantitatively converted to 1-(N-nitrosoethylamino)skatole (XII) by the action of HNO_2. The nmr spectrum showed the presence of restricted rotational isomers. Reaction of this nitroso compound with base, $LiAlH_4$ or Zn-AcOH gave skatole in almost quantitative yield in addition to a small amount of unidentified products. This fact reveals the possibility that the N-nitrosoalkylamino moiety can serve as a protecting group for the indole nitrogen. Attempts are now in progress to determine the fate of the N-alkyl group in this reaction using 1-nitroso-1,2,3,4-tetrahydro-pyridazino(2,3-a)indole derivatives. The action of HNO_2 on 1-aminoskatole caused only deamination, contrary to our expectation that some sort of nucleophile would be introduced into either the indole nitrogen or the benzene nucleus.

V. Oxidation

1-(N-Nitrosoalkylamino)indoles could be converted to the corresponding oxindole derivatives (XIII) by the action of *m*-chloroperbenzoic acid.

Rearrangements of both 1-alkylideneaminoindoles and 1-alkenylideneaminoindoles and their reaction with various dienophiles will be published elsewhere. Biological evaluation of the compounds described in this work is now in progress.

1. This report should be considered as part III of a series entitled "The Chemistry of Indoles"
   a) Part 1: Tetrahedron Letters, 2451 (1973).
   b) Part 2: Tetrahedron Letters, 461 (1974), and references therein.

All compounds gave satisfactory elemental analysis.