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Synthesis, Spectral Studies and Anti-Inflammatory Activity of Some New 2-Aryloxybenzimidazoles

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2-Chloro-1-methylbenzimidazole reacts with various phenols to yield the corresponding ethers. ^{1}H-NMR-spectra of these compounds were studied in deuteriochloroform and trifluoroacetic acid. Fragmentation of one of the ethers in the mass spectrometer is discussed. Anti-inflammatory studies for compounds **2** are reported.

Synthese, spektrale Eigenschaften und entzündungshemmende Wirkung einiger neuer 2-Aryloxybenzimidazole

2-Chlor-1-methylimidazol reagiert mit verschiedenen Phenolen zu den entsprechenden Ethern. ^{1}H-NMR Spektren dieser Verbindungen in Deuterochloroform und Trifluoressigsäure sowie ihre entzündungshemmende Wirkung werden untersucht. Die massenspektrometrische Fragmentierung wird am Beispiel eines der Ether diskutiert.

The benzimidazole nucleus is responsible for various biological activities[1]. Introduction of a phenoxy moiety at various positions of the benzimidazole ring has resulted in useful muscle relaxants[2], local anaesthetics[3] and pesticides[4]. Interestingly the 1-dialkylaminoalkyl derivatives of 2-phenoxy and 2-thiophenoxybenzimidazoles have exhibited excellent analgesic activities[5–8]. However the parent ethers possessing useful imino ether configuration have been less studied. It was thought of interest to synthesise 1-methyl-2-phenoxybenzimidazoles in order to study their spectroscopic and biological properties.

The compounds synthesised are enrouted under scheme-A. 2-Hydroxybenzimidazole prepared by refluxing equimolar quantities of o-phenylenediamine and urea in boiling amylalcohol, was converted to 2-chloro-1-methylbenzimidazole (**1**) by the method of *Harrison* et al.[9]. The condensation of phenols was accomplished by refluxing equimolecular quantities of **1** and phenols in dry DMF in presence of anhydrous potassium carbonate for 24 h. The ethers **2** were colourless crystalline solids obtained in fairly good yields. The compounds prepared are listed in table 1.

Preliminary screening on rats indicated no sedation or depression of general motor activity up to a dose level of 200 mg/kg body weight. Antiinflammatory studies carried out according to the method of *Winter* et al.[10] indicated that both the introduction of the long chain octyl group and more methyl groups in the phenoxy moiety enhance the activity.

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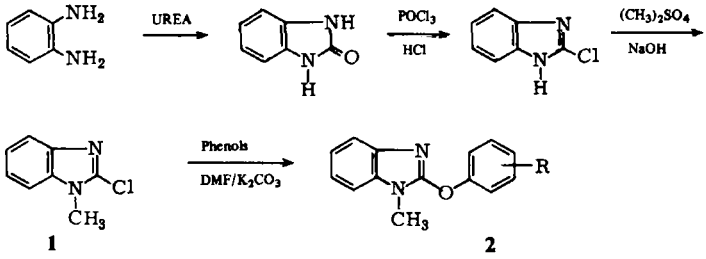


Tab. 1: *Compounds* **2**

2	R	M.P. °C	Yield %	Formula	Analysis Required C	H	N	Found C	H	N
a	4'–CH_3	136	75	$C_{15}H_{14}N_2O$	80.4	5.88	11.8	80.1	5.80	11.9
b	2'–CH_3	114	76	$C_{15}H_{14}N_2O$	80.4	5.88	11.8	80.2	5.74	11.9
c	4'–Cl	113	81	$C_{14}H_{11}ClN_2O$	65.0	4.25	10.8	64.8	4.08	10.7
d	2'–Cl	74–75	80	$C_{14}H_{11}ClN_2O$	65.0	4.25	10.8	65.1	4.12	10.6
e	2'–OCH_3	151	78	$C_{15}H_{14}N_2O_2$	70.9	5.51	11.0	70.7	5.40	11.2
f	3'–OCH_3	80	79	$C_{15}H_{14}N_2O_2$	70.9	5.51	11.0	70.7	5.39	10.9
g	4'–OCH_3	118–119	80	$C_{15}H_{14}N_2O_2$	70.9	5.51	11.0	70.6	5.68	11.2
h	2'3'–CH_3	106–107	84	$C_{16}H_{16}N_2O$	76.2	6.35	11.1	76.1	6.18	11.3
i	2'6'–CH_3	135–137	82	$C_{16}H_{16}N_2O$	76.2	6.35	11.1	76.0	6.22	11.2
j	4'-Octyl	119–120	83	$C_{22}H_{28}N_2O$	78.6	8.33	8.3	78.3	8.12	8.3
k	α-Naphthyl	118	82	$C_{18}H_{14}N_2O$	78.8	5.10	10.2	78.7	5.20	10.0

Infrared spectra

In the infrared spectra (KBr) the bands observed in the regions of 1180–1250 cm^{-1}; 1450–1600 cm^{-1} and 1580–1620 cm^{-1} are due to C–O–C,C=C– (arom), and C=N stretching vibrations respectively.

^{1}H-NMR-Spectra

A qualitative study of the ^{1}H-NMR-spectra of some of these compounds has been done in two solvents: deuterochloroform and trifluoroacetic acid. Though all the protons showed downfield shift in the latter solvent the significant shift was observed with the N-CH_3 protons due to the protonation of the unsaturated nitrogen atom[11]. The chemical shift values are given in table 2 and 3. It is quite interesting to note that the o-methoxy and N-methyl protons appear very close in deuterochloroform solution which are clearly separated in TFA solution. Exactly the reverse is observed in the case of p-OCH_3 group. The data also indicate some steric influence of the ortho substituent in the phenoxy moiety on the shift of N-methyl protons in deuterochloroform solution. However, in TFA solution no such observation is possible because of the solvent effect and the shift of N-CH_3 protons is almost unaltered.

Tab. 2: *Proton Chemical Shifts δ (ppm) of* **2** ($CDCl_3$, TMS int. ref.)

2	R	N–CH_3	Ar–H	R
d	o–Cl	3.8	7.1–7.6	–
c	p–Cl	3.66	7.2–7.5	–
b	o–CH_3	3.78	7.0–7.5	2.33
a	p–CH_3	3.66	7.1–7.6	2.38
e	o–OCH_3	3.76	7.0–7.6	3.73
g	p–OCH_3	3.82	6.9–7.5	3.70

Tab. 3: *Proton Chemical Shifts* δ (ppm) *of* **2** (TFA, TMS int. ref.)

2	R	N–CH_3	Ar–H	R
d	o–Cl	4.16	7.6–7.8	–
c	p–Cl	4.10	7.4–7.8	–
b	o–CH_3	4.10	7.5–7.7	2.4
a	p–CH_3	4.10	7.4–7.8	2.56
e	o–OCH_3	4.13	7.3–7.8	4.0
g	p–OCH_3	*	7.3–7.7	*

Mass spectra

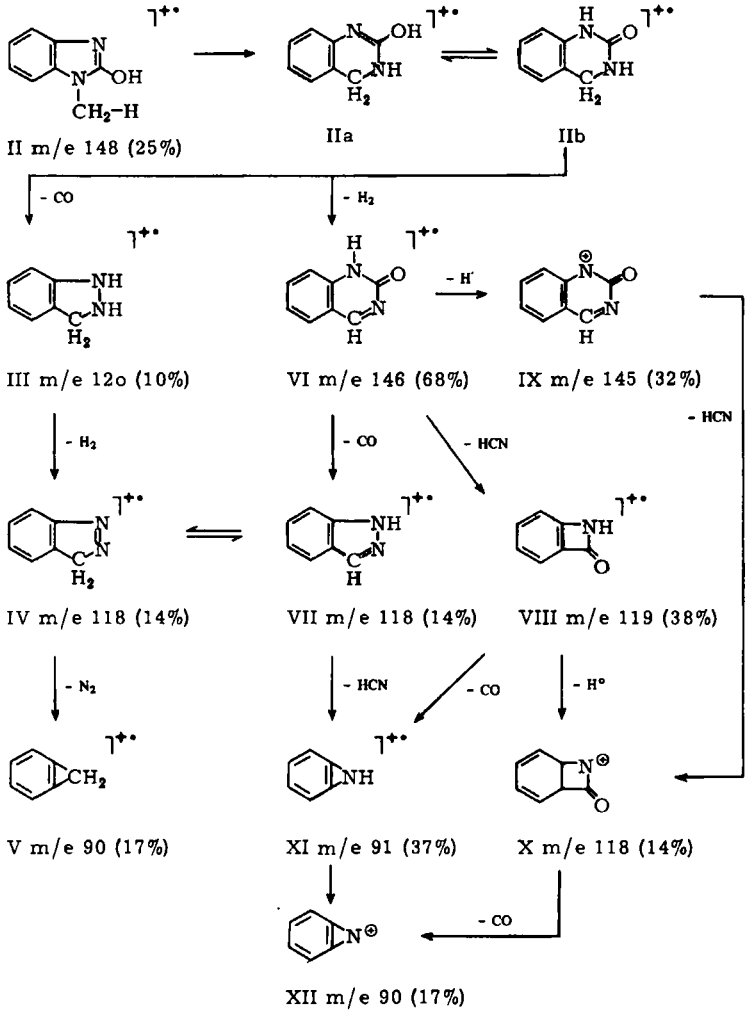
The mass spectral analysis has been carried out in the case of 1-methyl-2-(o-methoxy)phenoxybenzimidazole **(2e)**.

The molecular ion ($M^{+\cdot}$) m/e 254 (69 %) accounts for the second largest peak in the mass spectrum of this compound. Loss of methoxyl radical from the molecular ion leads to an even-electron ion which is the base peak (100 %) at m/e 223. The spectrum also exhibits the (M+1), (M–H), (M–CH_3) and (M–CH_2O) peaks at 255, 253, 239, and 224 m/e values respectively.

The main fragmentation expected to occur is through the well known *McLafferty* rearrangement[12] by the transfer of an α-hydrogen atom from the methoxy group to the aryl-ether oxygen resulting in the formation of an odd-electron ion II with the expulsion of formaldehyde and benzyne. The ion II may further fragment in the following two ways.

Scheme I: In analogy to the ring expansion explained in the case of benzimidazoles[13] and N-methyl pyrroles and indoles[14,15] the ion II gives rise to the hydroxydihydroquinazolinium ion IIa which can tautomerise to its keto form IIb. The keto form IIb is likely to expel either a molecule of carbon monoxide to give the dihydroindazolium ion III or a hydrogen molecule to give VI. The ion III further disintegrates losing neutral fragments of hydrogen and nitrogen to afford the ions IV and V resp. The following three ways seem to be probable for the fragmentation of the ion VI m/e 146 (68 %). It may either give the odd-electron ions VII and VIII on expulsion of carbon monoxide or hydrogencyanide or it may yield the even-electron ion IX by losing a hydrogen radical. The ion IX then may lose a molecule of hydrogen cyanide to give ion X, which in turn may lose carbon monoxide to give the even-electron ion XII which can also be obtained from the ions VII and VIII through the odd-electron ion XI.

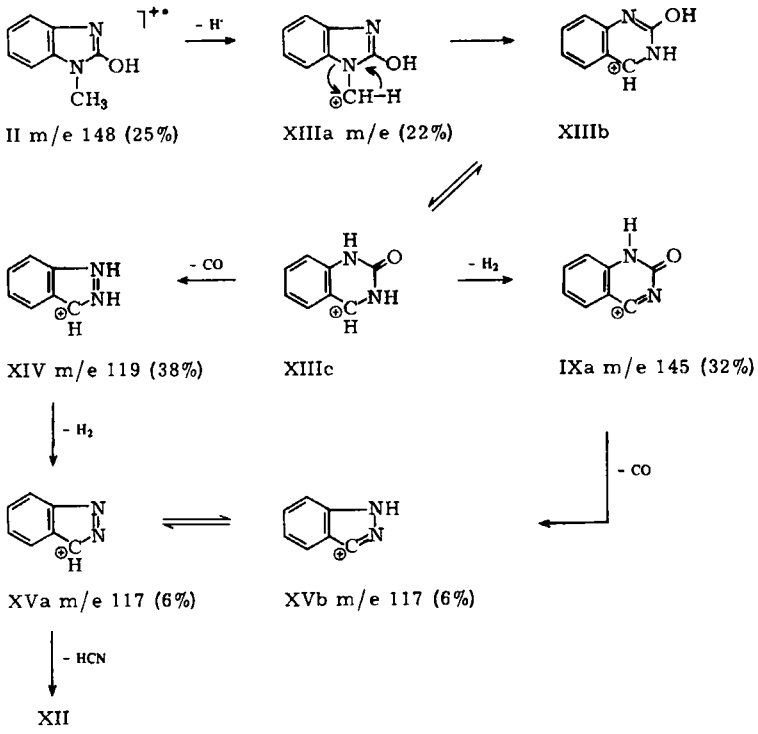
Scheme 1



Scheme 2: The odd-electron ion II, on the other hand may lose a hydrogen radical to give the even-electron ion XIIIa, which can undergo ring expansion to give the quinazolinium ion XIIIb. The keto form XIIIc may expel carbon monoxide to give XIV or a molecule of hydrogen to give the ion IXa which is the resonance structure of ion IX seen in scheme 1. Both these ions XIV and IXa, end up into the same ion XVa after losing either a hydrogen molecule or a molecule of carbon monoxide resp. The ion XVa then may lose a hydrogen cyanide molecule to give the ion XII which was also seen in scheme 1.

Scheme 3: The molecular ion produces the even-electron ion XVIII through the following two routes: i) initial loss of a formaldehyde molecule results in the odd-electron ion XVI which may then lose a

Scheme 2



methyl radical to give XVIII; ii) the molecular ion may first lose a methyl radical and then expel formaldehyde to give XVIII. Further ion XVIII might eliminate a benzyne molecule to give XIXa which can exist as XIXb also. The keto form XIXb may then yield XX after the loss of a carbon monoxide molecule, which in turn may disintegrate by expelling neutral fragments of hydrogen cyanide and nitrogen to give the ions XXI and XXII resp.

Scheme 4: The odd-electron ion XVI obtained, by elimination of a formaldehyde molecule as seen in scheme 3, may further undergo fragmentation by the homolytic cleavage of the ether linkage on either side to result into four daughter ions XXIII, XXIV, XXVa and XIIIa. The ion XIIIa, after a hydride ion transfer changes to XIIIa, the further fragmentation of which has already been explained in scheme 2. The ion XXVa after a hydride ion transfer from the N-methyl group, changes to XXVb which can undergo ring expansion to give the quinazolinium ion XXVc which may then lose a molecule of hydrogen cyanide from the heterocyclic ring to give the ion XXVI which in turn may further lose another molecule of hydrogen cyanide or hydrogen to produce the ions XXIII and XXVII resp. The phenoxide ion XXIV is known to expel carbon monoxide molecule to give the cyclopentadienyl ion[16].

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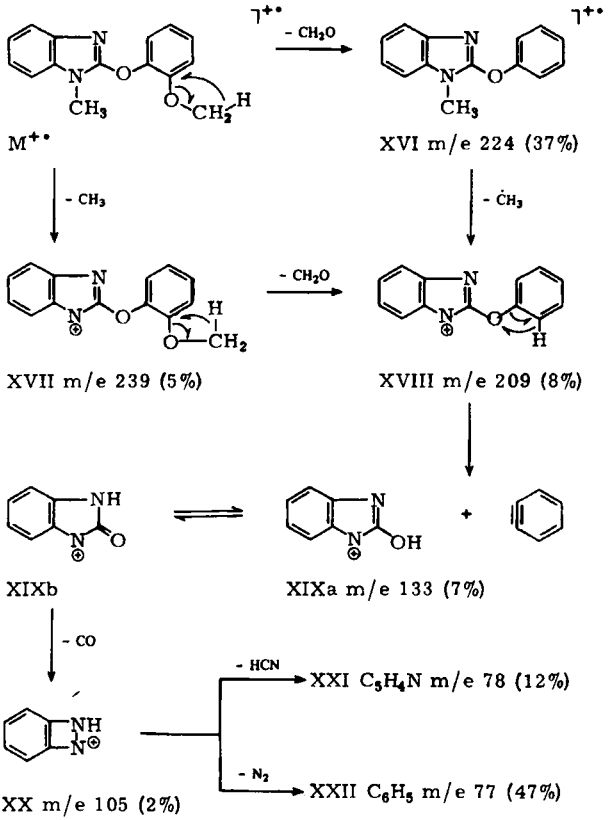
Scheme 3



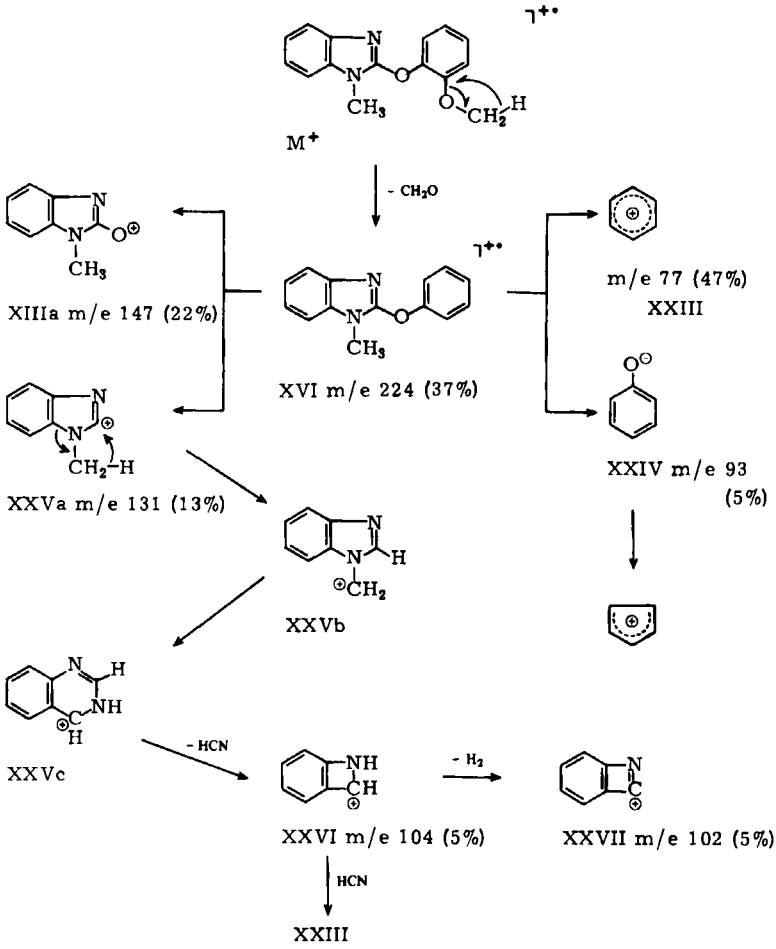
Experimental

MP: taken in open capillaries (uncorr.). *IR spectra:* Carl Zeiss UR-10 spectrophotometer: *NMR spectra:* Varian A-60; *MS:* Varian Mat CH 7 at 70eV utilizing direct insertion.
2-Hydroxybenzimidazole[17], *2-chloro-1-methyl benzimidazole* were prepared according to the earlier methods. The condensation of phenols was carried according to *Pailer* and *Gossinger*[18]. All the compounds were crystallised from ethanol.

Pharmacology

Albino rats of either sex weighing about 100–150 g were used for toxicity as well as anti-inflammatory studies.
All the compounds under study were administered orally as a suspension in gum accacia (4 %) at a dose level of 100 mg/kg body weight. After 1 h carrageenan (1 %, 0.1 ml) was injected into the plantar surface of the rat's hind paw. The edema formation was measured 3 h after injection and compared with that of carrageenan alone and with the test compound for calculation of percentage of inhibition. Results are shown in table 4.

Scheme 4



Tab. 4: Antiinflammatory Activity

2	% Inhibition of inflammation
b	11.1
c	11.1
d	14.8
e	25.9
i	41.8
j	38.5

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Molekülkomplexe und Radikalbildung mit Procain**

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Es werden die Reaktionen von Procain als Elektronendonator mit Polynitroaromaten, mit Iod und mit verschiedenen π-Acceptoren wie 7,7,8,8-Tetracyanochinodimethan (TCNQ), Chloranil, Tetracyanoethylen (TCNE) und 2,4,5,7-Tetranitrofluorenon (TeNF) untersucht. Je nach Lösungsmittelpolarität entstehen dabei verschieden gefärbte Charge-Transfer-Komplexe bzw. Radikale, die zur Bestimmung von Procain in Coffein-Mischungen und zur dünnschichtchromatographischen Detek-

** Herrn Prof. Dr. *H. Oelschläger* zum 60. Geburtstag gewidmet.

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