Azole Chemistry. IX.[1] A New Synthesis of Fused Pyrimidines: Tetrahydropyrimido[1,2-*a*]benzimidazoles

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2-Aminobenzimidazole and 2-amino-5,6-dimethylbenzimidazole react with various epoxy bromides in hot 2-butanone to give, after basification, 3-hydroxy-1,2,3,4-tetrahydropyrimido-[1,2*a*]benzimidazoles. The spectral properties of these heterocycles are discussed.

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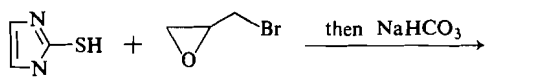
L'amino-2 benzimidazole et l'amino-2 diméthyl-5,6 benzimidazole réagissent avec divers bromures d'époxydes dans la butanone chaude pour conduire après basification aux hydroxy-3 tétrahydro-1,2,3,4 pyrimido-[1,2*a*] benzimidazoles. On discute des propriétés spectrales de ces hétérocycles. [Traduit par le journal]

The reaction of epoxy bromides with mercaptoazoles such as 2-mercaptoimidazole (1) and 5-mercapto-1-phenyl-1,2,3,4-tetrazole (2) represents a convenient synthetic approach to fused 1,3-thiazines (*e.g.*, **1** → **2**). A question arises as



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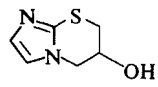

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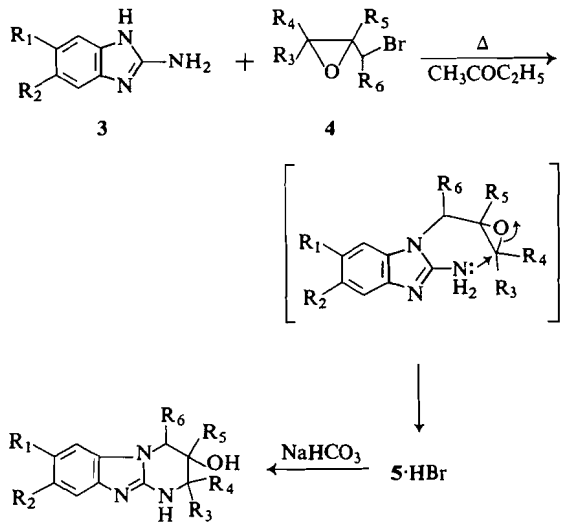
to whether amino azoles could also undergo this type of cyclization process and afford six-membered ring heterocycles containing two nitrogen atoms. Should such a transformation occur, it would provide a new and simple entry into fused, potentially pharmacologically active, pyrimidines. We now wish to report the synthesis of some tetrahydropyrimido[1,2-*a*]benzimidazoles, formed by treatment of 2-aminobenzimidazole and 2-amino-5,6-dimethylbenzimidazole with various epoxy bromides.

Results and Discussion

When an equimolar mixture of 2-aminobenzimidazole (**3**, $R_1 = R_2 = H$) or 2-amino-5,6-dimethylbenzimidazole (**3**, $R_1 = R_2 = CH_3$) and an epoxy halide (**4**) were refluxed in 2-butanone for 1–4 days, the hydrobromide salt of **5** was formed, either as an oil or as a solid. The salt was converted into its free base upon treatment with sodium bicarbonate. The reaction times, yields, and analytical data of the 3-hydroxy-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles (**5**) are listed in Table 1.



3 **4**

5·HBr

5

The initial step in the reaction process involves alkylation at a ring nitrogen to give the substituted 2,3-epoxypropane intermediate. Ogura and co-workers (3) have presented evidence for

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TABLE 1. Products obtained from reaction of epoxy bromides (**4**) with **3**

	3	**4**				Reaction time,	Yield	Melting		Analytical data % calcd. (found)		
5	R_1, R_2	R_3	R_4	R_5	R_6	days	(%)	point (°C)	formula	C	H	N
a	H	H	H	H	H	1	17	205(dec.)	$C_{10}H_{11}N_3O$	63.48 (63.29)	5.82 (5.88)	22.22 (21.68)
b	H	H	H	CH_3	H	2	23	230–232	$C_{11}H_{13}N_3O$	65.03 (64.77)	6.40 (6.64)	20.69 (20.21)
c	H	H	H	H	CH_3	3	7	230(dec.)	$C_{11}H_{13}N_3O$	65.03 (64.77)	6.40 (6.51)	20.69 (21.19)
d	H	CH_3	CH_3	H	H	4	24	240–242	$C_{12}H_{15}N_3O$	66.36 (66.51)	6.91 (6.47)	—
e	CH_3	H	H	H	H	4	31	175(dec.)	$C_{12}H_{15}N_3O$	66.36 (66.68)	6.91 (6.73)	—
f	CH_3	H	H	H	CH_3	2	10	260(dec.)	$C_{13}H_{17}N_3O$	67.53 (67.08)	7.35 (7.32)	—

TABLE 2. Infrared and u.v. spectral data for **5**

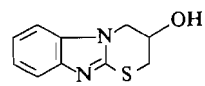
5	Infrared (KBr disc) ν (cm^{-1}) OH	CO	N=C—N	δNH	Ultraviolet (ethanol) max (log ε) nm
a	2500–3380	1095 or 1110	1568(br)	1620	228(3.72), 253(3.69), 291(3.72)
b	2550–3350	1159	1578	1627	—
c	2600–3350	1080	1580	1628	—
d	2600–3400	1098	1577	1632	—
e	2600–3400	1095 or 1115	1570	1620	233(3.69), 250(3.62), 299(3.67)
f	2600–3300	1078	1565	1628	231(3.61), 256(3.51), 302(3.57)

the occurrence of condensation at a ring nitrogen, rather than at the amino group nitrogen, of **3**, $R_1 = R_2 = H$, in the synthesis of the related imidazo[1,2-*a*]benzimidazole system. Annelation of the pyrimidine ring to the benzimidazole then occurs by ring opening of the intermediate epoxide.

The structures of the 3-hydroxy-1,2,3,4-tetrahydropyrimido-[1,2-*a*]benzimidazoles were assigned on the basis of analytical data and spectral results. Solid state i.r. spectra (Table 2) of **5** showed sharp, characteristic carbon–oxygen stretching vibrations between 1078 and 1159 cm^{-1} (1, 2). Broad bands were observed in the region of 3400–2500 cm^{-1} and were assigned to the hydrogen–bonded stretch of the hydroxyl and amino functions (carbon–hydrogen stretching absorptions overlap in the 3050–2825 cm^{-1} region). An intense absorption appeared at 1580–1565 cm^{-1} which is due to ν(N=C—N) of the benzimidazole portion of the molecule (4).

The heterocycles (**5**) were insufficiently soluble in solvents commonly used for n.m.r. purposes. The u.v. spectra for several of the tetrahydropyrimido[1,2-*a*]benzimidazoles were recorded (Table 2) and show three absorption maxima at 228–233, 250–256, and 291–302 nm. The latter maximum is probably due, at least in part, to an $n \rightarrow \pi^*$ transition.

Electron impact mass spectra of two of the heterocycles provided important information regarding their structures. The isomeric compounds **5***b* and **5***c* each gave a parent molecular ion peak at *m/e* 203. A major fragmentation pathway of **5***b* was elimination of acetaldehyde to give an ion of *m/e* 159, possibly of structure **6**. The fused 1,3-thiazine **8**, also loses acetaldehyde



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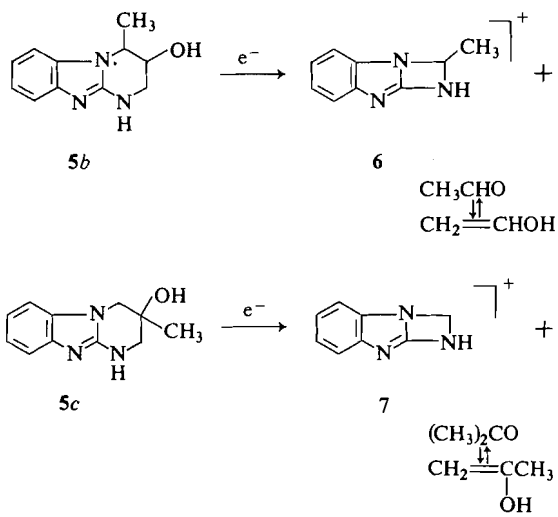
on fragmentation of the molecular ion (5). The tertiary alcohol **5***c* loses acetone on electron impact to afford a fragment of proposed structure **7** (*m/e* 145).

An oily by-product was formed in most of these reactions, easily separated from **5** by solubility differences. Nuclear magnetic resonance spectra of the oils lack signals due to aromatic protons. The oil is probably a polymer of the epoxy bromide.



5*b* **6** **5***c* **7**

Experimental

General

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Elemental analyses were determined by Hoffmann-LaRoche Microanalytical Laboratory and by Pascher Mikroanalytisches Laboratorium, Bonn, Germany. Infrared spectra were obtained on a Perkin-Elmer 457 spectrometer and u.v. spectra were recorded on a Perkin-Elmer 202 spectrometer. Mass spectra were determined using a Varian MS902 spectrometer.

Epoxy Bromides

Epibromohydrin was commercially available. 1-Bromo-2,3-epoxy-3-methylbutane was prepared by dehydrohalogenation of 1,2-dibromo-3-methyl-3-butanol (6). Dehydrohalogenation of 2,3-dibromobutan-1-ol yielded *threo*-3-bromo-1,2-epoxybutane (7). Halogenation of 2-methyl-2-propen-1-ol gave 1,2-dibromo-2-methyl-3-propanol (8), which was then dehydrohalogenated to yield 1-bromo-2,3-epoxy-2-methylpropane (9).

General Procedure for the Reaction of 2-Aminobenzimidazole or 2-Amino-5,6-dimethylbenzimidazole with Epoxy Bromides

Equimolar amounts of the heterocycle and epoxy halide (15.6 mmol) were refluxed with stirring in 2-butanone (125–225 ml) for 1–4 days, until either the color of the solution changed or a precipitate was formed, signifying that a reaction had occurred. The reaction mixture was allowed to cool to room temperature and work-up was then effected as follows for the individual cases:

(*a*) R_1—R_6=H: the hydrobromide salt of **5***a* precipitated out of solution. If was filtered and dried. Conversion to the free base was accomplished by dissolving the salt in hot water (~300 ml), adding a small amount (5 ml) of *N*,*N*-dimethylacetamide, and basifying the solution with 5% aqueous sodium bicarbonate (to a p*H* of 8). The solution was then continuously extracted with methylene chloride. Pentane was added to the residue obtained by flash evaporation of the methylene chloride extract in order to induce precipitation of pure **5***a*.

(*b*) R_1—R_4=R_6=H, R_5=CH_3: the reaction mixture was filtered and the filtrate was concentrated to a dark oil. The oil was dissolved in ethanol and basified as described in *a*. Continuous extraction with methylene chloride, followed by solvent evaporation, gave a semi-solid from which **5***b* was isolated by addition of ether and subsequent filtration. The heterocycle was washed well with acetone.

(*c*) R_1—R_5=H, R_6=CH_3: isolation of 5*c*·HBr and basification was effected as in *b*. A small quantity of an unidentified precipitate was filtered and the filtrate was extracted continuously with methylene chloride. Flash evaporation of the organic extract gave a yellow oil which, upon standing, deposited the fused azole. The heterocycle was filtered and washed with acetone. Evaporation of the filtrate gave an oil, possibly of polymeric composition (n.m.r. $(CD_3)_2CO$: δ 2.02s, 2.87s, 3.03s).

(*d*) R_1=R_2=R_5=R_6=H, R_3=R_4=CH_3: the work-up used was that of *b* up to the point of flash evaporation of the methylene chloride extract. The oil was dissolved in the minimum amount of tetrahydrofuran. Pentane was added and the reaction mixture was then allowed to stand overnight at room temperature. Decantation of the solution gave an orange oil from which **5***d* slowly crystallized on standing.

(*e*) R_1=R_2=CH_3, R_3—R_6=H: the reaction was worked up as described for **5***b*.

(*f*) R_1=R_2=R_6=CH_3, R_3=R_4=R_5=H: the reaction was worked up as described for **5***c*.

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