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THE REACTION OF EPOXIDES WITH 1,4-BENZODIAZEPINES, MECHANISM AND STRUCTURAL ASSIGNMENTS

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Abstract—The reaction of epoxides with the imine moiety of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones yields oxazolo[3.2-d][1.4]-benzodiazepin-6-(7*H*)-ones. A SN-2 initiated two-step mechanism is proposed. The reaction of propylene oxide with 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one affords a mixture of epimers which are resolved and to which structures are assigned.

THE synthesis of oxazolidines by the addition of aliphatic epoxides to Schiff bases was reported in 1962.[1] We were interested in broadening the scope and understanding of this reaction concomitant with our continuing interest in novel heterocyclic systems, in particular those related to quinazolines and 1,4-benzodiapines.[2] Oda, *et al.*,[1] had limited themselves to the Schiff bases of aldehydes as starting materials. It thus seemed appropriate to examine the reaction of epoxides with Schiff bases of greater steric requirements. Such Schiff bases are present in the 1,4-benzodiazepines **1** and **5** both of which offered in addition, the prospect of the novel fusion of the oxazolidine and the benzodiazepine moities.[3]

RESULTS

An excess of ethylene oxide was allowed to react with 7-chloro-1.3-dihydro-1-methyl-5-phenyl-2*H*-1.4-benzodiazepin-2-one (**1**)[4] in the presence of aluminium chloride (Scheme I). The red reaction mixture was hydrolyzed and worked up to give a 74% yield of a compound which corresponded to the simple addition product of ethylene oxide and **1**. The IR spectrum of the product in chloroform revealed the absence of the imine (1610 cm^{-1}) and the retention of the amide (1665 cm^{-1}) adsorptions.

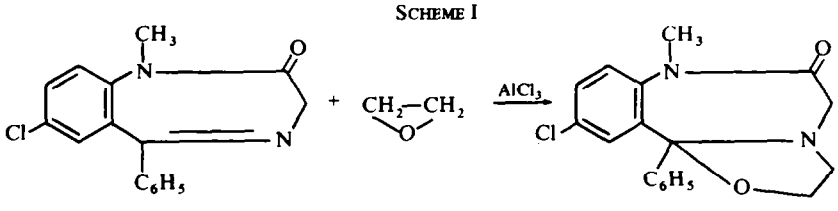
The UV and NMR spectra were compatible with the expected structure and the mass spectrum showed the anticipated M^+ (328) and exhibited a fragmentation pattern consistent with that anticipated for the assigned structure **2**.

An alternate synthetic approach to **2** by way of the classical preparation of oxazolidines[5] was obvious and is demonstrated in the sequence **3** → **4** → **2**. When compound **3**[6] was allowed to react with 2-aminoethanol, **2** was obtained in 38·5% yield. Under the reaction conditions of refluxing ethanol and triethylamine, the intermediate **4** was cyclized directly and no effort was made toward its isolation.

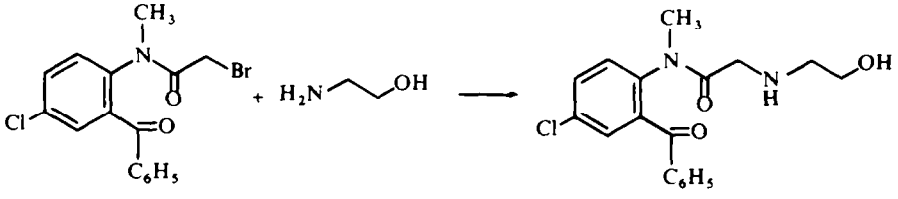
Although Oda *et al.*[1] had established the structure of the addition products of Schiff bases with propylene oxide as 5-methyl-oxazolidines and had accordingly

suggested a SN-2 type mechanism, it was of interest to us that only one product was revealed in cases where the presence of epimers would have been expected. Since we were interested in both the mechanism of the reaction and in establishing the presence or absence of both epimers and since the latter might shed light on the former, we chose to repeat our experiments with **5**[4] using propylene oxide as a reactant (Scheme II). The state of the literature[7] suggested that indeed the expected product would be a 5-methyloxazolidine and in addition, our alternate synthetic approach could establish

SCHEME I



1 **2**



3 **4**

the substitution of the product. It was of additional interest that geometrical isomerization at the 2,5-positions of oxazolidines had apparently not been studied although a number of derivatives containing two asymmetric centers have been reported.

Thus, the reaction of **5** with propylene oxide (Scheme II) was examined. Although we observed that the reaction would proceed with any of the four catalysts tried (aluminium trichloride, titanium tetrachloride, boron trifluoride and stannic chloride), the latter appeared to give the best results. A benzene solution of **5** containing stannic chloride and three equivalents of propylene oxide was stirred under dried nitrogen for 15 hr at room temperature. An aliquot was removed, hydrolyzed and analyzed by TLC.* Two new compounds in a ratio of about 3:2 had appeared, but constituted less than 10% of the reaction mixture. The reaction was then heated to 80° and examined by TLC periodically. After a total of 22 hr, the presence of a 3:2 (approximate) ratio of two new compounds (**A** and **B**) to the exclusion of **5** was seen.

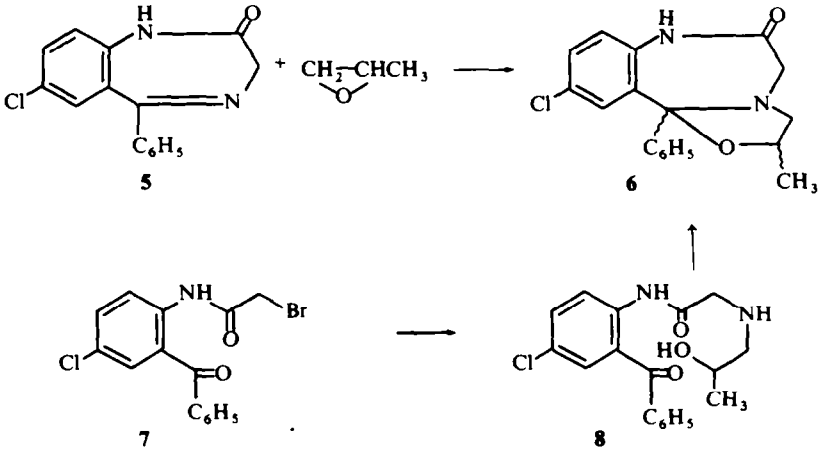
The two new materials co-crystallized from a number of different solvents giving a sharp melting crystalline product. However, the presence of a mixture was revealed by

* The TLC analyses were made on an alumina Eastman chromagram sheet 6062, eluted with a 3:2 mixture of hexane-ethyl acetate. Product ratios were based on visual estimates and corresponded quite well with NMR defined ratios.

both the NMR spectrum and by TLC on alumina. The isomeric nature of the mixture was attested to by the elemental analysis and by the mass spectrum.

The alternate synthetic approach utilizing 7[6] as the starting material and proceeding by way of **8** gave the oxazolidine **6** in which the location of the Me group could be unequivocally assigned. The product **6**, derived from **8**, was identical with that obtained from **5**, even the isomer ratios being essentially the same. Each of the two products then was clearly a 5-methyloxazolidine.

SCHEME II



In order to obtain more accurate determinations of the epimer ratios and in the hope of obtaining some insight into the configuration of the two epimers, DMF solutions of the product mixtures were analyzed by NMR. The mixture showed two Me doublets, at δ 1·27 and 1·15, j = 6·5 Hz, in a ratio of 3:2. Since the major product exhibited the greater R_f on alumina, the mixture was chromatographed on a column of alumina giving a mixture highly enriched in the faster moving of the two compounds. Recrystallizations gave a single compound, melting at 188–189°, with a three proton doublet at δ 1·27 which was identified as the "low field" isomer **A**. Attempts to chromatographically purify the "high field" isomer **B** were fruitless, but a chemical approach was devised. The treatment of a 3:2 mixture of the two epimers with an excess of hot boron trifluoride etherate gave essentially total conversion to **B**. In the purification of **B**, it was observed that successive recrystallizations led to mixtures increasingly contaminated with **A**. In fact, the best sample of **B** analyzed by the NMR technique showed a contamination with 14% of **A**, although unrecrystallized samples containing nearly pure **B** were seen to exist by TLC analysis.

The increase in the ratio of **A** to **B** with repeated recrystallizations suggested the possibility of a remarkably facile epimerization. Accordingly, samples of relatively pure **A** and **B**, dissolved in the NMR solvent DMF, were heated. A 7:2 mixture of **A**:**B** was heated for 2 hr at 85° and reexamined to show a new ratio of 2:1, after an additional 2 hr at 125°, the ratio was 3:2. When a 1:3 mixture of **A**:**B** was heated to 56·5° in DMF for 50 min, a new ratio of 3:2 was observed. Upon continued heating, the ratio of 3:2 remained unchanged. It is of some interest that the epimerization

occurs at room temperature over a period of days in DMF and that a similar isomer ratio is obtained in refluxing ethanol, chloroform and carbon tetrachloride. The ease of epimerization at a given temperature, as evidenced by the time required to obtain a 3:2 mixture, increases in a series carbon tetrachloride, ethanol and DMF.

Additionally, it was observed that in the conversion of **A** to **B** with boron trifluoride, a crystalline compound could be isolated. The material was shown by its elemental analysis to contain two molecules of boron trifluoride for each molecule of **6**.

The IR spectrum of the complex was distinguished by its strong absorption in both KBr and Nujol at 1725 cm^{-1}, a hypsochromic shift at 35 cm^{-1} from the amide. Amides are reported to exhibit such shifts in strongly acidic solutions and spectral studies indicate protonation predominately on the carbonyl O atom[8] although an alternative rationale, protonation on the amide nitrogen has not been rigorously excluded for all cases. It is interesting that when less than one equivalent of boron trifluoride is present both **A** and **B** rapidly epimerize to the equilibrium mixture which, when then treated with an excess of two equivalents of boron trifluoride, yields after work-up, essentially pure epimer **B**.

DISCUSSION

The reaction of propylene oxide with an imine to yield a 5-methyloxazolidine was visualized as proceeding by way of one of two possible mechanisms.* The first is shown in Fig 1. It is anticipated that such a one-step mechanism would lead pre-

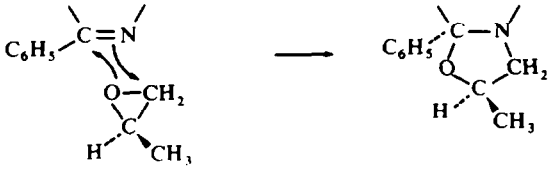


FIG 1

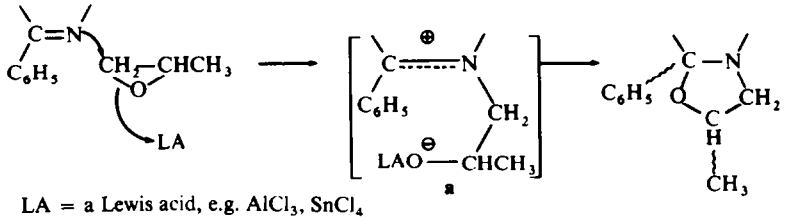
dominately to the *trans* isomer (methyl and phenyl 1,3-*trans*) as shown. That two isomers were obtained in a 3:2 ratio from the reaction of propylene oxide with **5** speaks against a one-step mechanism unless one incorporates an epimerization intermediate.

Such an intermediate is shown as **a** in our preferred mechanism shown in Fig 2.†

One may assume that in the presence of a Lewis acid, the first step is SN-2 as shown (a SN-1 first step would yield a 4-substituted oxazolidine) but the one-step formation of the oxazolidine (Fig 1) followed by heterolytic cleavage to **a** cannot be rigorously excluded. Since the dipolar intermediate **a** is planar at the carbonium-immonium ion, the oxanion may then attack from either side of that plane. In such

* Since 4-methyloxazolidines have not been isolated from these reactions, no mechanism involving the formation of a carbonium ion derived from the epoxide is considered likely.

† Blackett *et al.*[9] have recently discussed the mechanism of 1,3-dioxolane formation from epoxides and carbonyl compounds. They concluded that a mechanism analogous to that shown in Fig 2 best explained their results.



LA = a Lewis acid, e.g. $AlCl_3$, $SnCl_4$

FIG 2

an attack, the steric effect of the Me is less than that in the one-step mechanism shown in Fig 1. Thus, a mixture of the *cis* and *trans* isomers would be anticipated in which the *trans* isomer should be the more abundant if, as the Drieding models suggest, in intermediate **a** during ring closure, the transannular interaction of Me is less than its 1,3-interaction with phenyl.

The similarity of isomer ratios in the two separate syntheses of **6** prompted us to consider the possibility of a common intermediate. Indeed, one could anticipate that in the presence of a Lewis acid, both synthetic routes might proceed via the intermediate **a**.

The conformation of 7-chloro-5-(2,4-dichlorophenyl)-4,5-dihydro-1,4-dimethyl-3*H*-1,4-benzodiazepin-2-one has been established by X-ray analysis.[10] In that model, as expected on steric grounds, the 5-phenyl substituent is equatorial on a boat diazepine ring. Using the defined structure as a guide, by the appropriate addition of carbon and oxygen, one may construct the oxazolobenzodiazepine, **6**. Examination of such a Drieding model reveals that in the cyclized compound **6**, the 1,3-interaction of Me with a *cis* phenyl is approximately the same as the Me transannular interaction with the amide moiety of the diazepine ring in the *trans* isomer (Fig 3). Thus. the steric stability of the two isomers should be similar although as mentioned above, the stereochemistry of the intermediate **a** would favor cyclization to the *trans* epimer. Thus, a prediction might be made that the more abundant of the epimers in an equilibrium mixture would then be the *trans* isomer. However, such speculations offer a tenuous basis for structural assignment and may serve only as corroborative evidence.

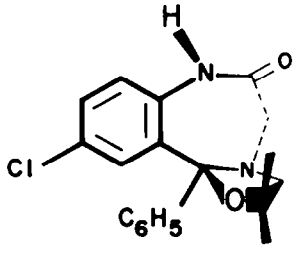


FIG 3

An examination of the boron trifluoride complex of **6** however offers a compelling argument for the assignment of the epimeric structures. The location of the first equivalent of boron trifluoride in the complex cannot be made with certainty. but we feel that it is at the tertiary nitrogen for steric and basicity reasons. Certainly

though, a catalytic amount of boron trifluoride, is promoting oxazolidine cleavage, presumably by attack at the ether oxygen. The location of the second boron trifluoride at the amide is indicated by the effect shown in the IR spectra on the CO frequency and the boron appears to be complexed with either the amide nitrogen or with the oxygen, the latter case being the most likely.[8] In the case of the former, the amide nitrogren would become tetrahedral and by assigning the boron trifluoride the equatorial position, the amide proton would become axial, significantly increasing the trans-annular interaction with Me in the *trans* epimer (Fig 4). If. as seems more likely, the boron is associated with the oxygen of the CO, the result would be to shorten the N—C bond of the amide function in the model shown in Fig 3 by giving it increased double bond character thus changing the conformation of the diazepine

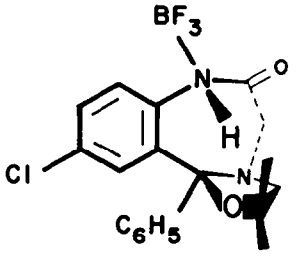
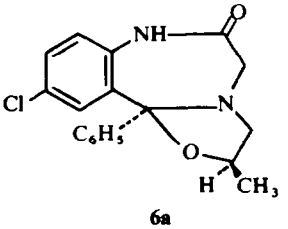


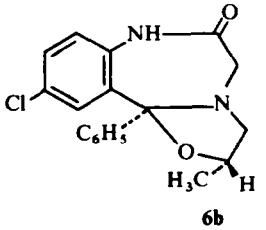
FIG 4

ring, and to provide a bulky group at the CO oxygen. Both of these effects would favor the isolation of the *cis* epimer, first by increasing in the intermediate the trans-annular steric hinderance to cyclization to the *trans* isomer, thus increasing the equilibrium ratio of *cis* to *trans* product over that from the uncomplexed intermediate and secondly by so sterically crowding the cyclized *trans* isomer as to greatly increase its propensity to disproportionate to that intermediate.

Thus, we suggest that if one epimer were to result from either of the two boron trifluoride complexes discussed. that epimer would be *cis*. Accordingly. we assign the



6a
trans



6b
cis

trans configuration **6a** to the more stable isomer **A** and the *cis* configuration **6b** to isomer **B**. Furthermore, this is in agreement with our expectation that of the two epimers, the *trans* would be the major component in an equilibrium mixture.*

* The epimerization reaction is invisible in **2**, but revealed in **6** by the relocation of a Me group to form an additional chiral center. The isomerization reaction between **6a** and **6b** is a 5-membered ring example of the second type of invisible and revealed reactions as defined by Cram.[11]

EXPERIMENTAL*

10-Chloro-7-methyl-2,3,5,11b-tetrahydro-11b-phenyloxazolo[3.2-d][1,4]benzodiazepin-6(7H)-one (**2**)

A. From **1**. A mixture of dried benzene (100 ml) and $AlCl_3$ (5·0 g) under a Dry Ice-acetone cooled condenser was stirred and treated with **1**[4] (10·0 g, 35 mmol), giving a yellow solid. Stirring was continued for 20 min and after the addition of dry hexane (35 ml), the mixture was cooled in an ice bath. Upon the addition of ethylene oxide (7 ml) the yellow solid dissolved, giving a red mixture. The mixture was warmed to room temp and was stirred overnight. Benzene was removed from the mixture by evaporation and the residue was partitioned between CH_2Cl_2 and iced NH_4OH. Filtration removed a large portion of the Al salts and the organic layer was separated, washed with water, dried and evaporated. The resultant residue was washed with ether to give colorless crystals (8·5 g, 73·9%), m.p. 179–184°. Two recrystallizations from CH_2Cl_2–hexane gave colorless rods, m.p. 182–184°. (Found: C, 65·87; H, 5·21; N, 8·77. $C_{18}H_{17}ClN_2O_2$ requires: C, 65·75; H, 5·21; N, 8·52%).

B. From **3**. A soln of **3**[6] (6·4 g, 20 mmol), ethanolamine (12·2 g, 200 mmol), Et_3N (50 ml) and EtOH (300 ml) was stirred overnight at reflux. The mixture was concentrated to 6·4 g of a semi-solid residue from which **2** (2·5 g, 38·5%) was obtained as an ether-insoluble crystalline solid, m.p. 180–183°, spectroscopically identical with that prepared from **1**.

10-Chloro-2.3.5.11b-tetrahydro-2-methyl-11b-phenyloxazolo[3.2-d] [1.4]benzodiazepin-6(7H)-one (2, 11b *trans*) (**6a**)

A soln of **5**[4] (5·4 g, 20 mmol) and $SnCl_4$ (20 mmol) in dry benzene (300 ml) was treated with propylene oxide (60 mmol) and stirred under dry N_2 for 22 hr at 80°. The mixture was concentrated *in vacuo* to a residue which was partitioned between CH_2Cl_2 and NH_4OH. The organic phase was washed with water, dried and concentrated to give a crystalline residue. Recrystallization from EtOAc gave colorless prisms, m.p. 178–183°, of a mixture of **6a** and **6b**. The mixture was dissolved in $CHCl_3$ and chromatographed over Woelm neutral alumina grade I. A mixture highly concentrated in **6a** was collected in 30% EtOAc-70% hexane. Recrystallizations from CH_2Cl_2 gave colorless prisms, m.p. 188–189°. (Found: C, 65·95; H, 5·21; N, 8·22. $C_{18}H_{17}ClN_2O_2$ requires: C, 65·75; H, 5·21; N, 8·52%).

10-Chloro-2,3,5,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3.2-d][1.4]benzodiazepin-6(7H)-one (2, 11b *cis*) (**6b**)

The above mixture of **6a** and **6b** (1·0 g sample, 3 mmol), was stirred 17 hr at 80° with BF_3-etherate (25 ml). The mixture was poured over ice (200 g) and was carefully treated with NH_4OH to give a pH of 8. The resultant solid was removed by filtration and was air dried to give **6b** (0·9 g; 90%). Two recrystallizations from $CHCl_3$–hexane gave colorless prisms, m.p. 172–174°. (Found: C, 65·68; H, 5·07; N, 8·32. $C_{18}H_{17}ClN_2O_2$ requires: C, 65·75; H, 5·21; N, 8·52%).

5-Chloro-2[2-(hydroxypropylamino)acetamido]benzophenone (**8**)

To a soln of **7**[6] (35·3 g, 0·1 mole), Et_3N (100 ml) and EtOH (600 ml) 1-amino-2-propanol (22·5 g, 0·3 mole) was added. The mixture was stirred at room temp for 65 hr. The solvent was removed *in vacuo* and the residue partitioned between water and EtOAc. The organic layer was dried and concentrated to give a colorless oil. An ether soln of the oil was treated with dry HCl to form the hydrochloride salt which was recrystallized from EtOH to give colorless prisms, m.p. 194–195°. (Found: C, 56·65; H, 5·45; N, 7·21. $C_{18}H_{19}ClN_2O_3.HCl$ requires: C, 56·41; H, 5·26; N, 7·30%).

The equilibrium mixture of **6a** *and* **6b** *from* **8**. A pyridine soln of **8** (8·0 g, 23 mmol) was stirred 17 hr at reflux in the presence of pyridine hydrochloride (0·5 g). The mixture was concentrated *in vacuo* to a residue which was crystallized from EtOH as colorless crystals (3·7 g, 49·3%), m.p. 184–185°. This mixture was identical spectrally and by TLC with that obtained from the $SnCl_4$ catalyzed reaction of propylene oxide with **5**.

* M.ps were determined microscopically on a hot stage and are corrected. The NMR data were determined on a Varian A-60 instrument, the IR spectra were determined on a Beckman IR-9 spectrophotometer, the UV spectra were determined on a Cary Model 14 spectrophotometer and the mass spectra were determined by means of a CEC 21-110B instrument at 70 eV by direct insertion. Dry solvents were prepared by elution over a column of Woelm neutral alumina, activity grade I. Solns were dried by stirring over $MgSO_4$.

10-*Chloro*-2,3,5-11b-*tetrahydro*-2-*methyl*-11b-*phenyloxazolo*[3.2-*d*][1.4]*benzodiazepin*-6(7*H*)-*one* (2.11b *cis*), dihydrated, di(boron trifluoride)salt.

A soln of the equilibrium mixture of **6a** and **6b** (1·0 g; 3 mmol) in dry chloroform (25 ml) was treated with BF_3–etherate (2 ml). The mixture was stirred 17 hr and a hydroscopic yellow crystalline solid (1·2 g. 80%) was removed by filtration, m.p. 138–142° dec. (Found: C, 43·20; H, 4·11; N, 6·04. $C_{18}H_{12}ClN_2O_2.2BF_3.2H_2O$ requires: C, 43·20; H, 4·32; N, 5·60%).

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