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STEREOCHEMISTRY OF THE RING OPENING OF SOME STILBAZOLE OXIDES

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Abstract—The *trans* and *cis* forms of 3- and 4-stilbazole oxide and *trans*-2-(*p*-methoxystyryl)pyridine oxide have been prepared from the corresponding stilbazoles, by addition of HClO and HBrO, followed by dehydrohalogenation of the halohydrins with base. The configurations of the epoxides have been confirmed by their NMR spectra. The stereochemistry of the ring opening of the above mentioned compounds with HCl, HBr and CCl_3COOH has been investigated and compared with that of the similar reactions of the stilbene oxides, very pronounced differences in steric course being observed. The reactions of the stilbazole oxides with the hydrogen halides take place with complete inversion, those with CCl_3COOH with decreasing degrees of inversion in going from the 2- to the 3- and to the 4-pyridyl derivatives.

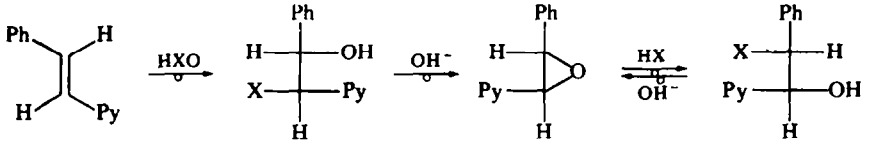
AN INCREASING amount of data, which have become available in recent years on the cleavage by acids of epoxides carrying aryl substituents on the oxirane ring,[1] indicates that the stereochemistry of these reactions depends to a very large extent on several factors, such as configuration and conformation of the epoxide, solvent, type of reagent, etc.: anything from a complete retention to a complete inversion of configuration can be expected, in contrast with cleavages by base, which in almost all known cases take place exclusively with inversion.[1a, 2]

The purpose of the work described in the present paper was to extend our previous investigations on the stereochemistry of the ring opening of stilbene oxides[1b, 1d, 1e] to their pyridyl analogues, i.e. the stilbazole oxides. The preparation of *trans*- and *cis*-2-stilbazole oxide (**7** and **19**) and of the corresponding chlorohydrins (**4a**, **10a**, **16a** and **22a**) and bromohydrins (**4b**, **10b**, **16b** and **22b**) has been described in a previous paper.[3] In order to get a more complete picture the work has now been extended with the study of the oxides of *trans*- and *cis*-3- and 4-stilbazole (**8**, **9**, **20** and **21**) and of *trans*-2-(*p*-methoxystyryl)pyridine (**28**), with particular reference to the stereochemistry of their reactions with hydrogen halides and with trichloroacetic acid.

As had been previously found[3] for the 2-stilbazoles (**1** and **13**), it was not possible to convert the 3- and 4-stilbazoles (**2**, **3**, **14** and **15**) into the corresponding epoxides by reaction with peroxy acids. Peroxybenzoic, peroxyacetic or *p*-nitroperoxybenzoic acid readily transform all these compounds into the corresponding N-oxides, which, even in the presence of a large excess of the oxidizing agent, do not react further to give epoxides. Evidently, the electron-withdrawing effect of the positive nitrogen of the N-oxide prevents the electrophilic attack by the peroxy acid on the double bond. Even *trans*- or *cis*-(*p*-methoxystyryl)pyridine (**25** and **26**), in which it was hoped that the electron-donating properties of the methoxy group would counterbalance the unfavourable effect of the N-oxide group, could not be epoxidated. The desired epoxides were therefore prepared from the corresponding stilbazoles, through addition of hypoalogenous acids, followed by dehydrohalogenation of the halohydrins by base.

The chlorohydrins **4a**, **6a**, **16a** and **18a** can be obtained by stereospecific *trans* additions from the hydrochlorides of the stilbazoles **1**, **3**, **13** and **15** with aqueous hypochlorite, while both the *trans* and *cis* methoxy derivatives **25** and **26** give only the *erythro*-chlorohydrin **27a**; the same result is obtained when t-butyl hypochlorite is used instead of sodium hypochlorite.

CHART 1

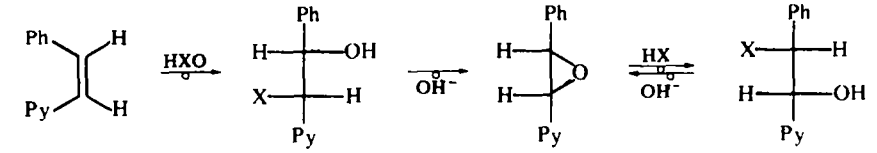


1: Py = 2-C_5H_4N
2: Py = 3-C_5H_4N
3: Py = 4-C_5H_4N

4a: Py = 2-C_5H_4N, X = Cl
4b: Py = 2-C_5H_4N, X = Br
5b: Py = 3-C_5H_4N, X = Br
6a: Py = 4-C_5H_4N, X = Cl
6b: Py = 4-C_5H_4N, X = Br

7: Py = 2-C_5H_4N
8: Py = 3-C_5H_4N
9: Py = 4-C_5H_4N

10a: Py = 2-C_5H_4N, X = Cl
10b: Py = 2-C_5H_4N, X = Br
11a: Py = 3-C_5H_4N, X = Cl
12a: Py = 4-C_5H_4N, X = Cl
12b: Py = 4-C_5H_4N, X = Br

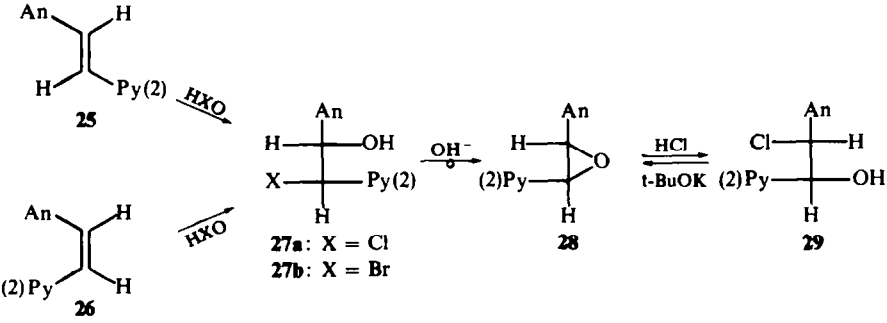


13: Py = 2-C_5H_4N
14: Py = 3-C_5H_4N
15: Py = 4-C_5H_4N

16a: Py = 2-C_5H_4N, X = Cl
16b: Py = 2-C_5H_4N, X = Br
17b: Py = 3-C_5H_4N, X = Br
18a: Py = 4-C_5H_4N, X = Cl
18b: Py = 4-C_5H_4N, X = Br

19: Py = 2-C_5H_4N
20: Py = 3-C_5H_4N
21: Py = 4-C_5H_4N

22a: Py = 2-C_5H_4N, X = Cl
22b: Py = 2-C_5H_4N, X = Br
23a: Py = 3-C_5H_4N, X = Cl
24a: Py = 4-C_5H_4N, X = Cl
24b: Py = 4-C_5H_4N, X = Br



27a: X = Cl
27b: X = Br

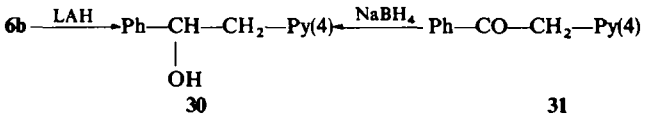
28

29

An = *p*-$CH_3OC_6H_4$—

The bromohydrins **4b**, **5b**, **6b**, **16b**, **17b**, **18b** and **27b** can be synthesized in fair to good yields by reacting aqueous solutions of the stilbazole hydrochlorides with N-bromosuccinimide. Also in these cases the reactions involve *trans* additions, except for *cis*-methoxystilbazole **26**, which leads to the *erythro*-bromohydrin **27b**.

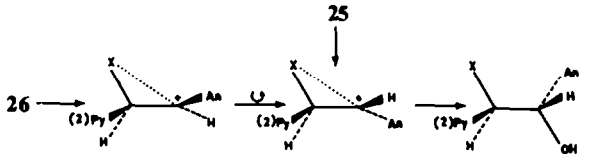
The fact that the electrophilic attack by the halogen takes place α to the pyridyl group had been proved in the case of the transformation of **1** into **4a** and **4b**, and of **13** into **16a** and **16b**,[3] and has now been confirmed for the bromohydrin **6b**, by reducing it with LAH to 1-phenyl-2-(4-pyridyl) ethanol (**30**), also obtained by sodium borohydride reduction of 4-phenacylpyridine (**31**). There can be no reasonable doubt about the fact that also the other halohydrins, which were obtained by similar reactions,



30 **31**

are of the same type, as such an orientation would be expected from the consideration of the two carbonium ions, **32** and **33**, which could arise from the electrophilic attack on the stilbazoles: **32** is certainly much more stable than **33**, particularly if the pyridine moiety is protonated.

32 **33**



The configurations of the halohydrins were assigned on the basis of the fact that the addition of hypohalogenous acid normally takes a *trans* course, and were confirmed by their conversion into the epoxides (see below). The fact that in the case of the methoxy derivatives **25** and **26** both stereoisomers give only the *erythro* compounds (**27a** and **27b**) can be explained by the longer life-time of the stabilized intermediate carbonium ion, which could allow the cisoid cation **34**, formed from the *cis*-stilbazole **26**, to pass to the more stable transoid conformation **35**, before the nucleophilic attack, that would therefore lead to the *erythro* halohydrin **36**. A similar behaviour had been observed, for instance, by Curtin *et al.*[4] in the bromination of *trans*- and *cis*-*p*-methoxystilbene, which led in both cases to the *erythro*-dibromide.

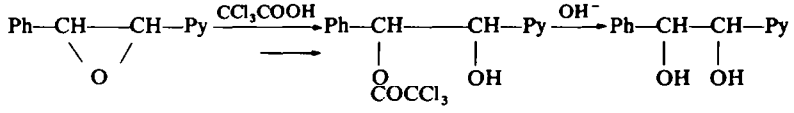
The conversion of the halohydrins into the epoxides **7**, **8**, **9**, **19**, **20**, **21** and **28** was achieved in good yield by the treatment with sodium hydroxide of their solutions in 2-propanol. In all known cases transformations of this type take place with inversion, *erythro*-halohydrins giving the *trans*-epoxides and *threo*-halohydrins the *cis*-epoxides. The configurations of the epoxides, and consequently those of the starting halohydrins were confirmed by their NMR spectra. It is known from the literature[5]

that oxirane protons resonate at higher fields when they are *cis*, than when they are *trans* to a Ph group; furthermore, the coupling constants between *cis* protons are larger than those between *trans* protons.[5,6] The data in Table 4 are in perfect agreement with these assumptions. The three *trans* epoxides (**8**, **9** and **28**, H *cis* to Ph) show their oxirane proton bands in the range 3·81–4·08 ppm (δ scale); the two *cis* epoxides (**20** and **21**) at 4·39–4·51 ppm. The coupling constants are ca. 2 c/s for two of the three *trans* epoxides (in the spectrum of **8** only a singlet is visible for both protons), ca. 4 c/s for the two *cis* compounds. These NMR spectra will be discussed more fully, together with those of other epoxides, in a separate paper.

When the epoxides mentioned above were reacted with hydrogen bromide or chloride, halohydrins were formed, which were found to be different from the ones obtained from the stilbazoles with hypohalous acids; this could be ascertained particularly well for the 2-pyridyl[3] and 4-pyridyl series, in each of which all eight possible bromo- and chlorohydrins were prepared. All the halohydrins were formed by *trans* opening of the epoxide ring, as shown by the fact that they were reconverted into the starting epoxides by sodium hydroxide in 2-propanol; only in the case of the methoxy chlorohydrin **29** the *threo* glycol **46** was isolated instead of the epoxide, displacement by hydroxyl of the halogen activated by the anisyl group being evidently easier than the epoxide ring closure. It was however possible to convert **29** into the epoxide **28** by the use of potassium t-butoxide in benzene.

The fact that the halohydrins obtained from the epoxides are different from those formed from the stilbazoles evidently indicates that they must have the halogen atom α to the Ph group. This is in agreement with the normal course of the reactions of aryl epoxides with acids,[1] in which the ease of bond breaking determines the direction of ring opening; the nucleophilic attack by the halide ion therefore occurs more easily on the benzylic carbon, rather than on the one which is α to the protonated pyridyl group.

The opening of the stilbazole oxides (**37**) with trichloroacetic acid is less stereospecific than that with hydrogen halides. This reaction, which is much slower than the similar one of the stilbene oxides,[1b,1e] because of the electron-attracting properties of the pyridinium group, gives mono(trichloroacetic) esters (**38**), which are easily hydrolyzed to the glycols **39**. The configuration of the latter compounds was established by their preparation from the stilbazoles through *cis* dihydroxylation with osmium tetroxide. Table 1 summarizes the stereochemical results of the ring opening reactions with trichloroacetic acid.



37 **38** **39**

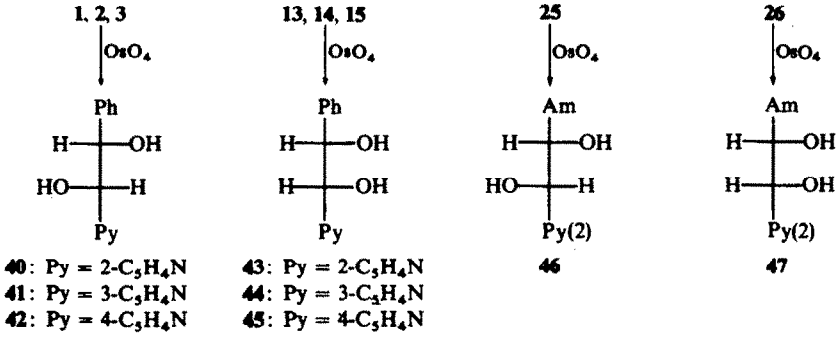
A comparison of the reactions of the stilbazole oxides with those of the stilbene oxides reveals some very pronounced differences. It had been previously found[1e] that *trans*-stilbene oxide reacts with hydrogen chloride in benzene or chloroform to give exclusively the *threo*-chlorohydrin (complete retention), while *cis*-stilbene oxide gives under the same conditions a mixture of about 80% of the *threo* and 20% of the *erythro* chlorohydrin (80% inversion). The reactions of the same epoxides with

TABLE 1. STERBOCHEMICAL RESULTS OF RING OPENING OF STILBAZOLE WITH CCl_3COOH[a]

	% Inversion	% Retention
trans-Epoxides		
7	>90	<10
8	70	30
9	25	75
28	<10	>90
cis-Epoxides		
19	>90	<10
20	50	50
21	30	70

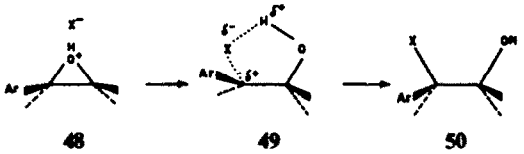
[a] Limit of error in the determinations ±10% (Experimental)

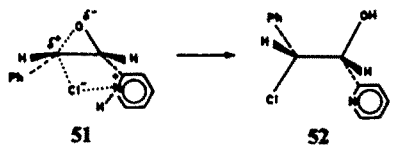
CHART 2



carboxylic acids, and particularly with trichloroacetic acid,[1b,7] are, on the other hand, completely *cis* stereospecific also for the *cis* epoxide; a similar behaviour had been observed for *trans*- and *cis*-*p*-nitrostilbene oxide and several other aryl epoxides.[1d,1f,8]

The *cis* stereochemistry which is often observed for the opening of aryl substituted epoxides by acids in low polarity aprotic solvents has been interpreted as due to a reaction involving the partners of an ion pair (**48**), formed by the protonated epoxide

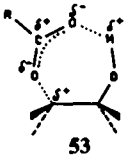




and the anion of the acid, which interact in a "cage" of solvent in such a way that the direction of nucleophilic attack by the anion on the oxirane carbon is determined by the reciprocal orientation of the partners.[1a,*] The fact that the *cis* opening has so far been observed only for oxiranes carrying unsaturated substituents (aryl or alkenyl) indicates that the transition state must have a considerable carbonium ion character, and could therefore be represented as **49**, which would account very well for a *cis* opening to **50**. The excess of inversion observed in the reaction of *cis*-stilbene oxide with hydrogen chloride does not necessarily speak against such a mechanism, as the intermediate of type **49** would be rather unfavourable in this case, the two aryl groups being almost eclipsed. There could therefore be a rotation around the C—C bond to give the more stable transoid conformation before formation of the final product **50**.

Several factors can be responsible for the fact that only *trans* opening is observed in the reaction of the stilbazole oxides with hydrogen halides. The pyridine nitrogen, which is protonated under the conditions of the reaction, must exert an electron-attracting inductive effect on the oxirane ring. This will decrease the degree of protonation of the oxygen atom and that of bond-breaking in the transition state, thus giving to the reaction a more pronounced S_N2-type character and favouring inversion over retention of configuration. The strong positive charge will also provide more polar surroundings and decrease the isolation of the simple ion pair, by attracting more anions. Particularly in the case of the 2-pyridyl derivatives, there could also be a direct transfer of the halide ion from nitrogen to carbon, which would give the inverted halohydrin, as shown in **51** → **52**. Pyridinium bromide is known to be a good agent for the ring opening of epoxides.[9] The direct transfer of halide would be progressively more difficult in going from the 2- to the 3- and to the 4-pyridyl series. A strong support to the latter hypothesis was given by the observation that when *trans*-2-stilbazole oxide (**7**) was treated with an exactly equimolar amount of hydrogen chloride in chloroform it was rapidly transformed into the *erythro* chlorohydrin **10a**; the methoxystilbazole oxide **28** behaved similarly. *trans*-3-Stilbazole oxide (**8**) reacted much more slowly and uncompletely, while the *trans*-4-oxide **9** gave under the same conditions only the hydrochloride of **9**, which was not transformed into the chlorohydrin even after long heating in chloroform. A further indication in favour of the direct transfer of the anion from nitrogen to carbon is given by the data on the reaction with trichloroacetic acid (Table 1), the *trans*- and *cis*-2-stilbazole oxides (**7** and **19**) being the only ones which give an almost complete inversion.

It has been found before that trichloroacetic acid almost always gives larger amounts of *cis* opening product than hydrogen halides.[1b,1e,1f,1g] This could be explained by the fact that the bidentate carboxylic anion could stabilize an intermediate of type **49** (**53**) against rotation around the C—C bond better than a halide anion. Furthermore, the more basic carboxylate anion would be expected to attack the cationoid



53

* The alternative hypothesis of the intermediate formation of a phenonium ion[1e] can now be ruled out by the fact that also epoxides having only one phenyl substituent, and which, being opened on the benzylic bond, cannot form such an intermediate, can give a completely *cis* opening.[1f,g]

center at a faster rate, than the rate of rotation around the C—C bond, thus preventing the passage to the more stable transoid conformation. The data in Table 1 could therefore be accounted for by different contributions of the mechanism of direct transfer of halogen and of that of ion-pair reaction, the latter becoming more important the farther the nitrogen is from the oxirane ring. The only result that does not fit such a picture is that relative to the anisoyl derivative **28**, which belongs to the 2-pyridyl series, but opens almost completely in a *cis* fashion; this could be due to a compensation of the electron attracting properties of the protonated pyridyl group by the electron-releasing ones of the anisyl group, which would give a higher degree of carbonium ion character to the transition state and favour a *cis* mechanism of type **53**.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus. IR spectra were taken on paraffin oil mulls with a Perkin–Elmer Infracord, Mod. 137; UV spectra in EtOH solns with a Perkin–Elmer, Mod. 137 UV, or a Beckman, Mod. DU; NMR spectra on $CDCl_3$ solns on a Varian DA-60 I spectrometer with TMS as internal standard. GLC were run on a Perkin–Elmer, Mod. F 20, apparatus with a flame ionization detector. Comparisons between compounds were made on the basis of their IR spectra. Pet ether refers to the fraction, b.p. 30–50°. $MgSO_4$ was always used as the drying agent.

The preparation of compounds **1**, **4a**, **4b**, **7**, **10a**, **10b**, **13**, **16a**, **16b**, **19**, **22a**, **22b**, **40** and **43** has already been described.[3]

trans-3-*Stilbazole* (**2**), m.p. 76–78° (lit.,[10] m.p. 77–79°) and cis-3-*stilbazole* (**14**), b.p. 80–81°/0·1 mm, n_D^{19} 1·6263 (lit.,[10] b.p. 103–104°/0·3 mm, n_D^{25} 1·620) were prepared by the method of Clarke *et al.*;[10] their purity was checked by GLC (2-m column, 1% neopentyl glycol succinate on silanized Chromosorb W 80/100, temp 180°, retention times: **14**, 1 min 46 sec; **2**, 4 min 54 sec).

trans-4-*Stilbazole* (**3**), m.p. 129–131° (lit.,[11] m.p. 128°), hydrochloride, m.p. 200–215°(dec) (lit.,[12] m.p. 204°), was obtained in 62% yield by a slight modification of one of the methods of Williams *et al.*[11] involving the heating of equimolar amounts of 4-picoline, benzaldehyde and Ac_2O for 24 hr, followed by addition of an excess of 2N HCl, extraction with ether, alkalinization of the aqueous layer with conc ammonia and crystallization from EtOH.

cis-4-*Stilbazole* (**15**). A soln of 10 g of **3** in 700 ml of benzene was irradiated for 9 hr with a 70 W immersion high-pressure UV lamp under N_2 with external ice cooling. After elimination of the solvent, the semi-solid residue was taken up in pet. ether, the insoluble *trans* isomer was eliminated by filtration and the residual oil was fractionally distilled; the first fraction, 3 g of an oil, b.p. 125–126°/0·8 mm, n_D^{23} 1·6217 (lit.,[11] b.p. 105–106°/0·4 mm, n_D^{25} 1·6215) was found to be **15**, free of the *trans*-isomer **3** (GLC, 2-m 1% SE-52 Silicone Rubber on silanized Chromosorb W 80/100, temp 200°, retention times: **15**, 1 min 10 sec; **3**, 2 min 12 sec). The hydrochloride of **15** crystallized from acetone in long prisms, m.p. 200–205°. (Found: C, 71·91; H, 5·66. $C_{13}H_{11}N \cdot HCl$ requires: C, 71·72; H, 5·56%.)

trans-2-(p-*Methoxystyryl*)*pyridine* (**25**). Williams *et al.*[11] report that **25** cannot be prepared by the method used for the synthesis of **3**. We found, however, that by using a large excess of anisaldehyde it is possible to achieve reasonable yields. A mixture of 28·0 g (0·30 mole) of 2-picoline, 122·5 g (0·90 mole) of anisaldehyde and 30·7 g (0·30 mole) of Ac_2O was refluxed for 30 hr. The product was worked up as described for **3** to give, after crystallization from pet. ether, 36·0 g (57% based on picoline) of **25**, white leaflets, m.p. 72–73°, λ_{max} 330 mμ (ε 34,000) [lit.,[11] m.p. 69°, λ_{max} 325 mμ (ε 36,900, MeOH)]; hydrochloride, m.p. 198–200° (lit.,[13] m.p. 200–201°).

cis-2-(p-*Methoxystyryl*)*pyridine* (**26**) was prepared by photochemical isomerization of 15·0 g **25**, as described for **15**. The treatment with pet. ether led to the recovery of unchanged **25**. Distillation of the pet. ether soluble part gave a first fraction (2·3 g), b.p. 173–175°/1·2 mm, n_D^{23} 1·6360 of **26**, which still contained 6% of the *trans* isomer **25** (GLC, same conditions as for **15**, retention times: **26**, 2 min 42 sec; **25**, 5 min). The next fractions of the distillation contained increasing amounts of **25**. The first fraction was transformed into the hydrochloride, by treatment with HCl in anhyd ether, and the salt was crystallized from acetone to give pure **26**·HCl, m.p. 145–152° (dec); the free base obtained by treatment with 2% NaOH aq, extraction with $CHCl_3$, drying and evaporation, was gas-chromatographically pure, n_D^{23} 1·6320, λ_{max} 305 mμ (ε 10,500), and was characterized as the methiodide: 100 mg of the base was treated with 0·3 ml MeI,

heated for a few min on a steam-bath, taken up in ether and crystallized from EtOH–ether: yellow plates (110 mg), m.p. 160–162°. (Found: C, 50·97; H, 4·56. $C_{14}H_{13}NO \cdot CH_3I$ requires: C, 51·00; H, 4·57%.)

Transformation of the stilbazoles into the bromohydrins

A soln of 5·0 mmole of the stilbazole hydrochloride in 50 ml of water is treated with 0·90 g (5·0 mmole) of solid N-bromosuccinimide and stirred for 1 hr, then made alkaline with satd $NaHCO_3$ aq and extracted with ether. Evaporation of the dried extract gives the crude bromohydrin, which is crystallized as such, or transformed into the hydrochloride or hydrobromide with an ether soln of HCl or HBr, if it is a liquid. The characteristics of the products are given in Table 2.

Transformation of the stilbazoles into the chlorohydrins

(a) A soln of 5·0 mmole of the stilbazole hydrochloride in 60 ml of water is treated with 7·5 mmole of NaOCl[3] in 30 ml of water and stirred for 1 hr at room temp, then made alkaline with satd $NaHCO_3$ aq and extracted with ether. Evaporation of the ether layer and crystallization of the free base or of the hydrochloride leads to the products described in Table 3.

(b) For the preparation of compound **27a** from **25** also the following method was used, in an attempt to achieve a better yield. A soln of 2·11 g (10 mmole) of **25** in 70 ml of water and 2 ml AcOH was treated with 1·08 g (10 mmole) of t-butyl hypochlorite[14] and shaken for 30 min, then made alkaline with satd $NaHCO_3$ aq and extracted with ether. Evaporation of the dried extract gave an oil, which was crystallized from benzene–pet. ether to yield 0·68 g (26%) of **27a**, m.p. 160–162°.

Transformation of the halohydrins into epoxides

A soln of 10·0 mmole of the halohydrin in 25 ml of 2-propanol is treated dropwise with 10 ml of 1N NaOH aq in the presence of phenolphthalein at such a rate as to avoid a build-up of alkali. When the hydrochloride or hydrobromide is used instead of the free base, 20 ml of the alkali is employed. The reaction is quite rapid. After completion of the addition the soln is stirred 10 min, then water is added, the ppt is extracted with ether and the dried extract is evaporated. The residue is extracted again repeatedly with pet. ether to eliminate insoluble side-products. The concentrated soln is cooled at −10° and the ppt is recrystallized from pet. ether. Table 4 summarizes the results.

Transformation of the epoxides into halohydrins

Dry gaseous HCl or HBr (from tetralin and Br_2[15]) is bubbled through a soln of 2·0 mmole of the epoxide in 20 ml dry benzene at room temp to saturation; the ppt of hydrochloride or hydrobromide is collected, washed with benzene and recrystallized. No appreciable difference is observed between the IR spectra of the crude and recrystallized salts. The results are summarized in Table 5.

Some of the reactions were also run in $CHCl_3$ with an exactly equimolar amount of HCl. One mmole of the epoxide in 10 ml dry $CHCl_3$ was treated with 5 ml of a 0·2M soln of HCl in $CHCl_3$; after 30 min the solvent was evaporated *in vacuo* at room temp and the IR spectrum of the residue was examined, with the following results: *trans*-2-stilbazole oxide (**7**) and *trans*-2-(*p*-methoxystyryl)pyridine oxide (**28**) were transformed completely into the chlorohydrins **10a** and **29**. *trans*-3-Stilbazole oxide (**8**) gave a mixture of the chlorohydrin **11a** with much hydrochloride of **8**. *trans*-4-Stilbazole oxide (**9**) gave exclusively the corresponding hydrochloride (**9**·HCl), which, after crystallization from $CHCl_3$-ether, melted at 164–167°. (Found: C, 66·28; H, 5·30. $C_{13}H_{11}NO \cdot HCl$ requires: C, 66·81; H, 5·18%.) The hydrochloride was perfectly stable and was not transformed into the chlorohydrin **12a** even after refluxing for 30 hr in $CHCl_3$.

All the halohydrins of Table 5, except **29**, were retransformed in good yield into the epoxides from which they had been prepared, by treatment with NaOH in 2-propanol, as described above for the preparation of the epoxides. Only **29** was transformed under these conditions into the glycol **46**, m.p. 123–125° (see Table 6). Its transformation into the epoxide was therefore carried out in the following manner: a suspension of 0·30 g (1·0 mmole) of **29**·HCl in 30 ml dry benzene was treated with 0·11 g (1·0 mmole) of K t-butoxide, stirred 30 min, then treated again with 0·22 g of K t-butoxide, stirred again for 90 min and left at room temp overnight; after washing with water, evaporation and crystallization of the residue from pet. ether, 0·1 g of the epoxide **28**, m.p. 51–53°, was obtained.

1-Phenyl-2-(4-pyridyl)ethanol (**30**)

(a) A soln of 0·20 g of 4-phenacylpyridine (**31**)[16] in 10 ml MeOH was treated with one of 0·11 g $NaBH_4$ in 2 ml water and 2 drops 10% NaOH. After two days at room temp, the excess of hydride was destroyed with 2N H_2SO_4, and the soln was made alkaline with ammonia. The base was extracted with ether, the

TABLE 2. BROMOHYDRINS FROM STILBAZOLES

Bromohydrin	Starting compound	Yield %	m.p.	Crystallization solvent	Formula	Analysis C% found	C% required	H% found	H% required
5b[a]	**2**	94	149–151°	C_6H_6	$C_{13}H_{12}BrNO$	55·97	56·13	4·76	4·35
6b[b]	**3**	88	142–144°	C_6H_6–pet. ether	$C_{13}H_{12}BrNO$	56·04	56·13	4·53	4·35
17b·HCl	**14**	90	166–172°	EtOH–Ether	$C_{13}H_{12}BrNO\cdot HCl$	49·65	49·62	4·23	4·16
18b·HCl[c]	**15**	83	170–172°	EtOH	$C_{13}H_{12}BrNO\cdot HCl$	49·85	49·62	4·39	4·16
27b	**26**	80[d]	139–140°	EtOH	$C_{14}H_{14}BrNO_2$	54·52	54·56	4·53	4·58

[a] **5b**·HCl, m.p. 158–160°.

[b] **6b**·HCl, m.p. 165–170° (from EtOH–Ether). (Found: C, 49·56; H, 4·07. $C_{13}H_{12}BrNO\cdot HCl$ requires C, 49·60; H, 4·16%); **6b**·HBr, m.p. 170–172° (from EtOH–ether).

[c] **18b**·HBr, m.p. 173–176° (from EtOH–ether).

[d] 71% yield starting from the *trans*-stilbazole **25**.

TABLE 3. CHLOROHYDRINS FROM STILBAZOLES

Chlorohydrin	Starting compound	Yield %	m.p.	Crystallization solvent	Formula	Analysis C% found	C% required	H% found	H% required
6a·HCl	**3**	60	171–174°	Acetone	$C_{13}H_{12}ClNO\cdot HCl$	57·32	57·79	4·53	4·85
18a·HCl	**15**	50	190–200°(dec)	EtOH–ether	$C_{13}H_{12}ClNO\cdot HCl$	58·02	57·79	4·82	4·85
27a	**26**	66[a]	160–162°	C_6H_6–pet ether	$C_{14}H_{14}ClNO_2$	63·43	63·76	5·29	5·35

[a] 20% yield starting from the *trans*-stilbazole **25**.

TABLE 4. STILBAZOLE OXIDES

Epoxide	Starting compound	Yield %	m.p.	Formula	Analysis C% found	C% required	H% found	H% required	NMR δ[c] (pattern, J)	
8	**5b**	90	36–38°	$C_{13}H_{11}NO$	79·35	79·16	5·60	5·62	3·95	(s)
9	**6b**	88[a]	66–68°	$C_{13}H_{11}NO$	78·91	79·16	5·69	5·62	3·81; 3·82	(q, 1·9 c/s)
20	**17b**·HCl	78	39–41°	$C_{13}H_{11}NO$	78·99	79·16	5·62	5·62	4·39; 4·45	(q, 4 c/s)
21	**18b**·HCl	71	37–39°	$C_{13}H_{11}NO$	79·52	79·16	5·81	5·62	4·38; 4·51	(q, 4·5 c/s)
28	**27b**	88[b]	51–53°	$C_{14}H_{13}NO_2$	74·04	73·99	5·77	5·77	4·03; 4·08	(q, 2 c/s)

[a] Also obtained in 80% yield from **6a**·HCl.
[b] Also obtained in 75% yield from **27a**.
[c] Chemical shifts of oxirane protons ($CDCl_3$ solns, TMS internal standard); s = singlet; q = AB quartet.

TABLE 5. HALOHYDRINS FROM STILBAZOLE OXIDES

Halohydrin	Starting compound	Yield %	Crystallization solvent	m.p.	Formula	Analysis C% found	C% required	H% found	H% required
11a·HCl	**8**	95	EtOH–ether	192–193°	$C_{13}H_{12}ClNO \cdot HCl$	57·94	57·79	4·83	4·85
12a·HCl	**9**	81	Acetone	194–195°	$C_{13}H_{12}ClNO \cdot HCl$	57·28	57·79	4·99	4·85
12b·HBr	**9**	95	EtOH–ether	211–215°	$C_{13}H_{12}BrNO \cdot HBr$	43·98	43·48	3·85	3·65
23a·HCl	**20**	95	EtOH–ether	195–200°	$C_{13}H_{12}ClNO \cdot HCl$	57·35	57·79	4·95	4·85
24a·HCl	**21**	95	EtOH	207–209°	$C_{13}H_{12}ClNO \cdot HCl$	57·40	57·79	4·95	4·85
24b·HBr	**21**	94	EtOH–ether	175–177°	$C_{13}H_{12}BrNO \cdot HBr$	43·64	43·48	3·92	3·65
29·HCl[a]	**28**	84	Acetone–ether	139–141°	$C_{14}H_{14}ClNO_2 \cdot HCl$	56·10	56·01	5·08	5·04

[a] The free base (**29**), m.p. 100–102°, was obtained in only 50% yield by treatment of **29**·HCl with satd $NaHCO_3$, extraction with ether and crystallization from pet. ether (b.p. 80–100°). (Found: C, 63·22; H, 5·52. $C_{14}H_{14}ClNO_2$ requires: C, 63·76; H, 5·35%.)

TABLE 6. 1-PHENYL-2-PYRIDYLETHANE-1,2-DIOLS

Compound	Starting material	Yield %	Crystallization solvent	m.p.	Formula	Analysis C% found	C% required	H% found	H% required
41	**2**	20	C_6H_6–pet. ether	152–154°	$C_{13}H_{13}NO_2$	72·73	72·54	6·06	6·09
42[a]	**3**	65	C_6H_6	177–178°	$C_{13}H_{13}NO_2$	72·21	72·54	6·12	6·09
44	**14**	30	C_6H_6	126–130°	$C_{13}H_{13}NO_2$	72·22	72·54	6·13	6·09
45[a]	**15**	65	C_6H_6	175–176°	$C_{13}H_{13}NO_2$	72·93	72·54	6·01	6·09
46	**25**	42	C_6H_6–pet ether	127–128°	$C_{14}H_{15}NO_3$	68·69	68·55	6·23	6·16
47	**26**	73	C_6H_6–pet. ether	125–126°	$C_{14}H_{15}NO_3$	68·80	68·55	5·93	6·16

[a] A 1-phenyl-2-(4-pyridyl)1,2-ethanediol, m.p. 166°, of unknown stereochemistry has been reported as the reduction product of the corresponding diketone [C. A. Buehler, J. W. Addleburg and D. M. Glenn, *J. Org. Chem.* **20**, 1350 (1955)]. It probably is a mixture of the diastereoisomers **42** and **45**.

soln dried and treated with HCl in dry ether, which precipitated 0·20 g of **30**·HCl; after crystallization from EtOH–ether, prisms, m.p. 172–175°. (Found: C, 66·06; H, 6·02. $C_{13}H_{13}NO$·HCl requires: C, 66·24; H, 5·99%.)

(b) A soln of 0·30 g of **6b** in 90 ml ether was treated with 0·30 g LAH in 80 ml ether and refluxed 1 hr. Water (4 ml) and 2N NaOH (4 ml) were added dropwise and the filtered ether layer was evaporated. The residue was treated as under (a) to give **30**·HCl, m.p. 172–175°.

1-Phenyl-2-pyridylethane-1,2-diols

(a) A soln of 0·5 mmole of the stilbazole, 0·2 ml pyridine and 0·127 g (0·5 mmole) OsO_4 in 6 ml ether was stored for 2 days at room temp. The ppt was then collected, washed with ether, dissolved in 10 ml CH_2Cl_2 and shaken with a soln of 0·2 g NaOH and 0·5 g mannitol in 8 ml water until the organic layer was almost completely colourless. In some cases (particularly for **41** and **44**) this required several treatments and yields were low. The dried CH_2Cl_2 soln was then evaporated and the residue crystallized from benzene, or benzene–pet. ether. The results are given in Table 6.

(b) A soln of 1·0 mmole of the epoxide in 15 ml C_6H_6 was treated with 2·5 ml of a 1M soln of CCl_3COOH in benzene and refluxed 3 hr (under milder conditions the reaction was not complete; only in the case of the epoxide **28**, complete reaction was obtained after 48 hr at room temp). After washing with satd $NaHCO_3$ and evaporation of the solvent *in vacuo*, the residue consisted of a crude ester of type **38** (CO band and at 5·69 μ). No attempt was made to characterize these compounds, but they were directly hydrolyzed to the glycols, by leaving the crude product at room temp 1 hr with 20 ml 5% KOH in EtOH, then diluting with water and extracting with ether. Evaporation of the dried ether soln gave a solid residue of the glycol (yields 80–90%). The crude mixtures were analyzed by TLC on silica containing a fluorescent indicator, a 10/1 mixture of $CHCl_3$ and MeOH being used as the eluant; elution was repeated 4 times and the spots were revealed with UV light (254 mμ); the *threo* compounds migrate more rapidly. The relative amounts of *threo* and *erythro* glycol were estimated by visual comparison of the intensities of the spots with those relative to a series of mixtures prepared with different amounts of the pure glycols obtained by the OsO_4 method; although the precision of the method is not high, the results (Table 1) were certainly valid within a limit of error of ±10%. Only in the case of the glycols **46** and **47**, separation by TLC was not possible; however the IR spectrum of the product obtained from epoxide **28** was practically identical with that of the *threo* glycol **46**, and distinctly different from that of the *erythro* compound **47**; it gave no m.p. depression with the former, but a mixture with the latter showed a depression in m.p.

Stilbazole N-oxides. All attempts to epoxidize the double bond of the stilbazoles led only to the corresponding N-oxides. For instance, a suspension of 2·2 g (12·0 mmole) *p*-nitroperoxybenzoic acid in 20 ml $CHCl_3$ was treated with 1·0 g (4·7 mmole) of **25** in 10 ml $CHCl_3$ and left 48 hr at room temp, then washed with 10% Na_2CO_3 aq, dried and evaporated; the residue was crystallized from benzene to give 0·90 g trans-2-(*p-methoxystyryl*)*pyridine* N-*oxide*, yellow leaflets, m.p. 163–164° (lit.[17] m.p. 157–158°). In a similar way trans-4-*stilbazole* N-*oxide*, m.p. 167–169° (lit.[17] m.p. 173°), and trans-3-*stilbazole* N-*oxide*, m.p. 110–113° were prepared. (Found: C, 79·66; H, 5·74. $C_{13}H_{11}NO$ requires: C, 79·16; H, 5·62%.)

Similar results were obtained with peroxybenzoic acid.

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