

HETEROCYCLIC SATURATED COMPOUNDS AS DERIVATIVES OR PRECURSORS OF CHLOROMYCETINE AND OF SOME RELATED STRUCTURES

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Abstract - The review summarizes the diastereoselective synthesis of chloromycetine, of its cyclic acetals or ketals and related structures *via* 1,3-dioxanes, oxazolidines and 1,2-epoxides.

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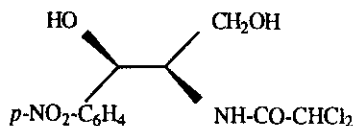
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1. INTRODUCTION

Chloromycetine (-)[(1*R*,2*R*)-2-dichloroacetamido-1-(*p*-nitrophenyl)propane-1,3-diol] is an antibiotic substance obtained from cultures of the soil bacterium *streptomyces venezuelae* or by synthesis. It has been discovered and isolated in 1947,¹ its structural determination² and first synthesis³ have been performed in 1949. During more than four decades, the synthesis of chloromycetine and then of its various analogous and related heterocyclic structures made the object of many papers focused especially on the synthetic pathways.



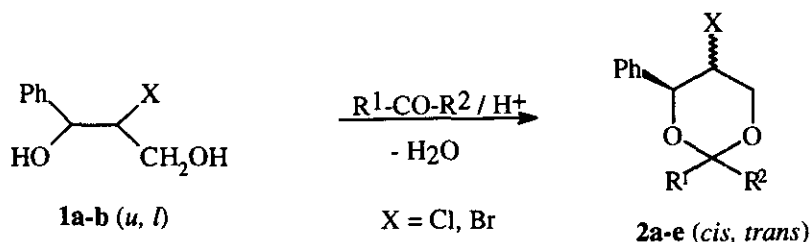
In this review it is our intention to summarize data concerning the heterocyclic saturated derivatives or precursors of chloromycetine and also some compounds of the same type reported as pharmaceuticals,^{4,5} herbicides⁶ or intermediates in the synthesis of crown ethers.⁷ Taking into account the great number of patents covering the subject, including the essential data of the synthesis, the fundamental aspects of the problem were somewhat neglected; therefore a stereochemical point of view is proposed to bring up to date the structural details involved in this domain.

2. SYNTHESIS OF SIX-MEMBERED SATURATED HETEROCYCLES: 1,3-DIOXANES DERIVATIVES

2.1. 5-Halogeno-4-phenyl-1,3-dioxanes and derivatives. These compounds were mentioned since 1951 as possible intermediates in the chloromycetine synthesis,⁸ following a new route *via* heterocyclic saturated compounds; their configuration in relation with the purpose of the whole synthesis was not specified or

discussed by all authors but it could be predicted based *a posteriori* by consideration on the configuration of the starting material used. Two distinct pathways were thus reported.

2.1.1. Direct acetalization and ketalization of 2-halogeno-1-phenylpropane-1,3-diols. Ring closure of racemic like (*l*) as *threo* or unlike (*u*) as *erythro* 2-halogeno-1-phenylpropane-1,3-diols (**1a-b**) with carbonyl compounds was described by several authors to occur under standard conditions,⁹ in good yields (40-90%) (Scheme 1).



Scheme 1

| compound | R ¹ | R ² | X | configuration (yield %) | lit. |
|-----------|---------------------------------|----------------|----|---------------------------------------|----------|
| 2a | H | H | Br | <i>trans</i> (60-90); <i>cis</i> (50) | 10,11,12 |
| 2b | H | H | Cl | <i>trans</i> (86); <i>cis</i> (45) | 10 |
| 2c | Me | Me | Br | <i>trans</i> (90) | 13,14 |
| 2d | H | Ph | Br | <i>trans</i> (-) | 8,15 |
| 2e | (CH ₂) ₃ | | Br | <i>trans</i> (-) | 16 |

The above reaction, in Scheme 1, was considered as the first step in the so-called "Boehringer method" for manufacturing chloromycetine in the fifties period. The halogeno-1,3-diols (**1a-b**) were obtained by hydroxyhalogenation^{10,14,17-19} (bromine and chlorine) of pure *E* and *Z* stereoisomer of cinnamyl alcohol with a diastereospecific *anti*-addition mechanism¹⁰ (Scheme 2)(yields 70-97% for hydroxybromination).

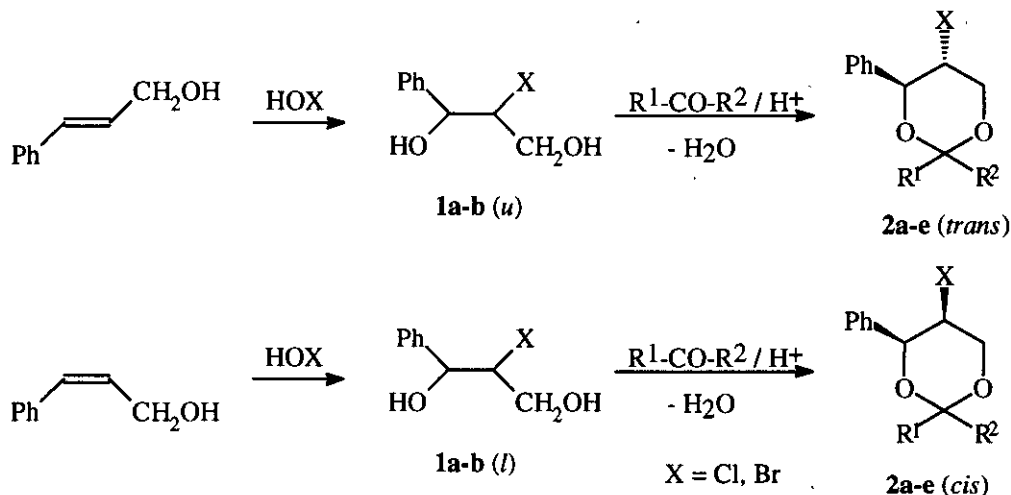
The diastereospecific nature of these additions is ensured¹⁰ by formation of the intermediate bridged bromonium ions which were later considered a key evidence in the dispute on Prins reaction applied to β-halogenostyrenes (see 2.1.2.); however, the whole process is not fully selective.^{14,20}

Some remarks should be noticed in connection to the beginning of this synthesis:

a) the obvious preference to use bromo derivatives, as an essential premise for the later ammonolysis of the halogen.

b) the configuration of compounds (**2**) was frequently designated as "*dl-erythro*" (or "*dl-threo*") in strict

correlation with that of the diols (**1**); the diastereospecificity of the ring closure was neglected in some cases.

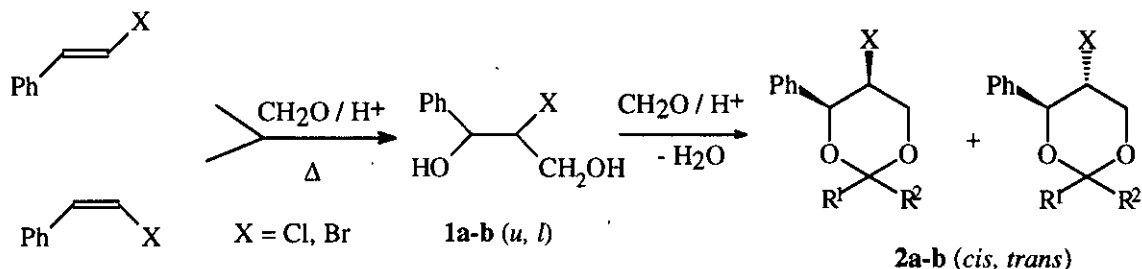


Scheme 2

c) the few instances of theoretical studies in the subject in the first years of the synthesis have shown an obvious tendency of the papers (majority patents) to concentrate on applied research, paying few or no attention to structural details.

2.1.2. Prins reaction of β -halogenostyrenes. The Prins reaction carried out with β -halogenostyrenes was one of the last applications of this cyclocondensation involving β -substituted styrenes.²¹ Their first use as starting materials in 1957 was reported by Chinese authors^{22,23} who developed later a six step synthesis of chloromycetine.²⁴

Subsequent studies^{10-12,25-29} had as a leading concept the following general scheme (Scheme 3).



Scheme 3

Although the existence of 1,3-diols (**1a-b**) (*u* and *l*) as intermediates was neglected^{22,23} the Chinese authors called attention upon both diastereomeric structures (**2a-b**) (*cis* and *trans*) they have obtained as a mixture

(Table 1). However, no assignment was suggested for real configuration of 1,3-dioxanes able to yield chloromycetine.

Table 1 - Data concerning the Prins reaction of β -halogenostyrenes

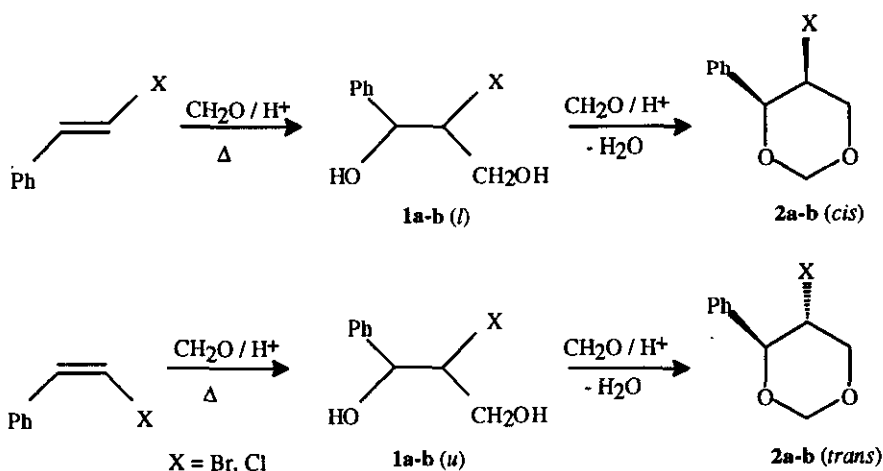
| Substrate | | conc. H ₂ SO ₄ * (mol/l) | Time** (h) | Molar ratio CH ₂ O: substrate | DSR*** and (yield % <i>trans</i>) | lit. |
|------------------------------|--------------|---|---------------|---|---------------------------------------|--------|
| β -bromostyrene | | 1.76 A | 8.0 | 2.9 | 4.46 (-) | 22,23 |
| | | 9.72 W | 5.0 | 2.2 | - (100) | |
| β -chlorostyrene | | 3.00 A | 7.0 | 2.5 | 1.90 (41) | |
| | | 7.80 W | 8.0 | 2.8 | 1.52 (55) | |
| β -bromo- styrene | <i>cis</i> | 0.64 D | 8.0 | 4.0 | 1.21 (-) | 10 |
| | | 1.65 A | 8.0 | 3.0 | 1.25 (17) | |
| | <i>trans</i> | 0.69-0.50 D | 9.0-48.0 | 4.0 | 4.81-11.42 (-) | |
| | | 1.51 A | 4.5 | 3.0 | 4.40 (29) | |
| β -chloro- styrene | <i>cis</i> | 0.17-0.40 D | 12.0-20.0 | 2.0-9.0 | 3.50-11.00 (-) | |
| | <i>trans</i> | 1.29-0.40 D | 12.0-20.0 | 2.0 | 4.10-5.90 (-) | |
| β -bromo- styrene | <i>cis</i> | 3.75-6.75 W | 1.0-18.5 | 9.2-12.2 | 3.76-6.69 (-) | 25,26 |
| | <i>trans</i> | 1.99-8.03 W | 0.2-27.5 | 5.9-18.2 | 14.15-9.00 (-) | |
| β -chloro- styrene | <i>cis</i> | 4.25-6.41 W | 10.0-12.0 | 10.0-11.1 | 3.54-3.34 (-) | |
| | <i>trans</i> | 1.99-6.00 W | 1.0-37.0 | 35.0-57.6 | 0.81-0.49 (-) | |
| β -bromostyrene | | 3.15 D | 8.0 | 3.6 | - (74) | 11,12 |
| | | 0.16-3.50 W | 6.0-21.0 | 2.8-3.5 | 0.95-1.25 (41) | |
| β -chlorostyrene | | 5.19-6.76 W | 12.0-24.0 | 3.5 | 1.82-4.55 (30- 53) | 27, 28 |
| (1:1 <i>cis-trans</i> mixt.) | | 6.94-8.14 W | 0.4-6.0 | 3.5 | 2.76-11.43 (19- 45) | |

* A: AcOH; W: Water; D: Dioxane

** Temperature 85-110 °C

*** DSR: Diastereoselective ratio between *trans*: *cis* 5-halogeno-4-phenyl-1,3-dioxanes (**2a-b**) (GLPC data) at the end of the reaction time (for complementary information see: references²⁹⁻³³).

The major surprising fact observed by certain authors was the difference between the stereoreactivity of *E* and *Z* stereoisomers of cinnamyl alcohol and *E* and *Z* of β -halogenostyrenes as substrates to prepare the same 1,3-dioxanes, (**2a-b**) *cis* or *trans* especially because diols (**1a-b**) were considered as common intermediates in both processes. Thus, if halogenation of cinnamyl alcohol was a diastereospecific *anti*-addition followed by a diastereospecific ring closure (Scheme 2), a similar model for the Prins reaction would have yielded a *trans*-1,3-dioxanes (**2a-b**) from (*Z*)- β -halogenostyrenes and a *cis*-1,3-dioxanes (**2a-b**) from (*E*)- β -halogenostyrenes (Scheme 4).

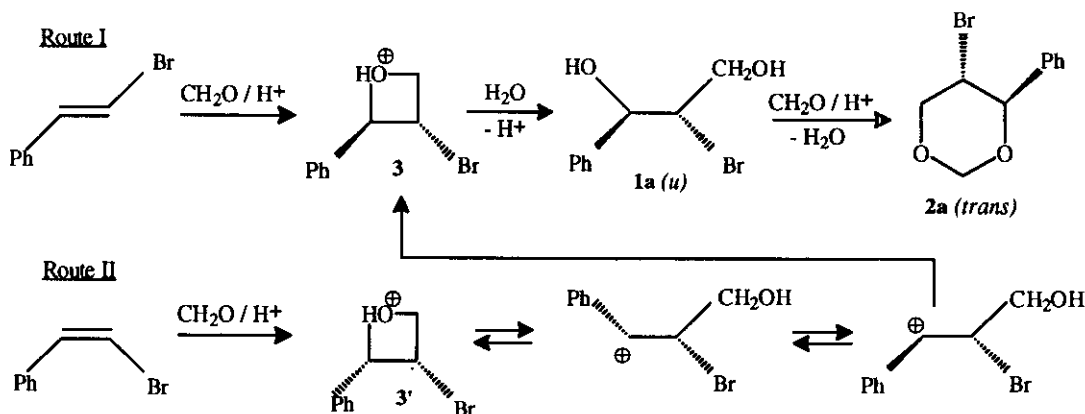


Scheme 4

Data from Table 1 point out no significant diastereospecificity of the reaction in the case of β -bromostyrene while β -chlorostyrene exhibit some diastereospecific behavior in mild conditions. On the other hand, in Scheme 4 it is very easy to observe that if a *syn*-addition model is proposed, the starting substrate and the resulting dioxane have the same configuration (e.g. (*E*)- β -halogenostyrene would give a *trans*-1,3-dioxane).

A *syn* diastereoselective addition was assigned by Bernardi²⁹ at least in the case of β -bromostyrene to explain that both its diastereomers yield *trans*-5-bromo-4-phenyl-1,3-dioxane (**2a**) (Scheme 5).

The four-membered heterocyclic oxonium ions (**3**) and (**3'**) as key intermediates and the isomerization between them due to the steric hindrance in (**3'**) were suggested. Despite their thorough investigations on the subject, Dolby¹⁰ have given no model of the Prins reaction, but they called attention to the influence of the solvent used and the isomerization between 1,3-dioxanes in the diastereoselective evolution of the process.



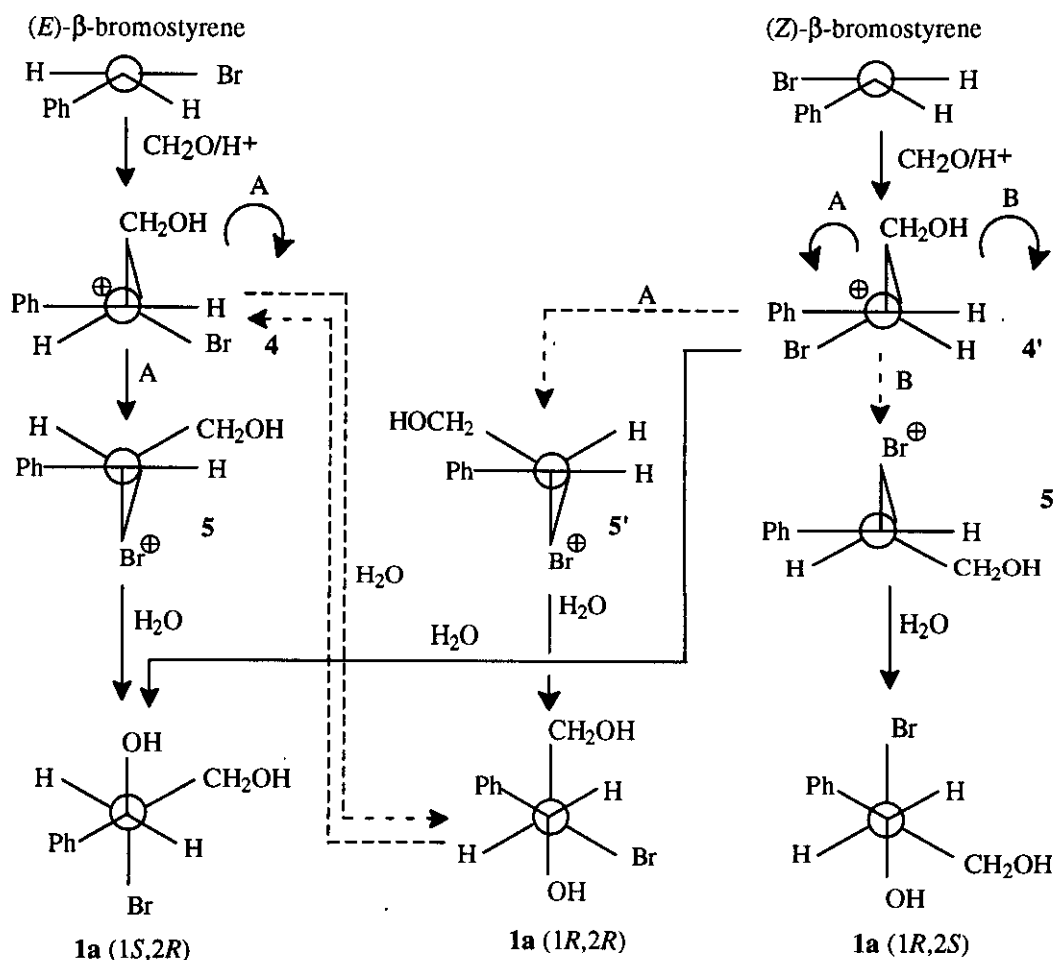
Scheme 5

The diastereoselective Prins reaction involving β -bromostyrene was also generally noticed by all authors^{11,22,23,30-33} and used in the chloromycetine synthesis many years before the complete elucidation of the mechanism by Cousseman.^{25,26} They demonstrated rigorously the electrophilic nature of the reaction, the significant difference between the reactivity of each stereoisomer of halogenostyrene, based on the correlation between Hammett's acidity function (H_0) and the pseudomonomolecular rate constant (k) of the Prins reaction when a large excess of formaldehyde was used (Table 1) ($\text{Log } k = -\alpha H_0 - \gamma$).

Table 2 - Parameters of reactivity (α , γ) in the Prins reaction for some β -substituted styrenes

| Ph - CH = CH - X | Z-stereoisomer | | E-stereoisomer | |
|------------------|-------------------|----------|-------------------|----------|
| | α | γ | α | γ |
| Cl | 1.54 | 8.25 | 1.45 | 7.13 |
| Br | 1.46 | 7.98 | 1.47 | 7.40 |
| Me | 1.65 | 4.39 | 1.70 | 3.95 |
| H | 1.40 (α) | | 3.64 (γ) | |

The α values, in relationship with the influence of the acidity, are approximately the same for all of the compounds studied and the γ -values (Table 2) reflect a greater reactivity of E stereoisomers as compared with Z stereoisomers for all β -substituted styrenes. This was the main evidence for the absence in the transition state of a diminution of the steric hindrance (e.g. Z vs. E stereoisomer); it was the reason for considering a new type of intermediates (Scheme 6).



Scheme 6

The whole reaction mechanism was devised into two steps: the first step was considered as a rate determining stage when configurations were finalized as *unlike* or *like* diol and the second step, diastereospecific and rapid because of a very large excess of formaldehyde (e.g. *unlike* diol \rightarrow *trans* dioxane) when no change of configuration was expected. Moreover, it was determined that a possible isomerization was absent in the case of halogenostyrene and unimportant in that of dioxanes.

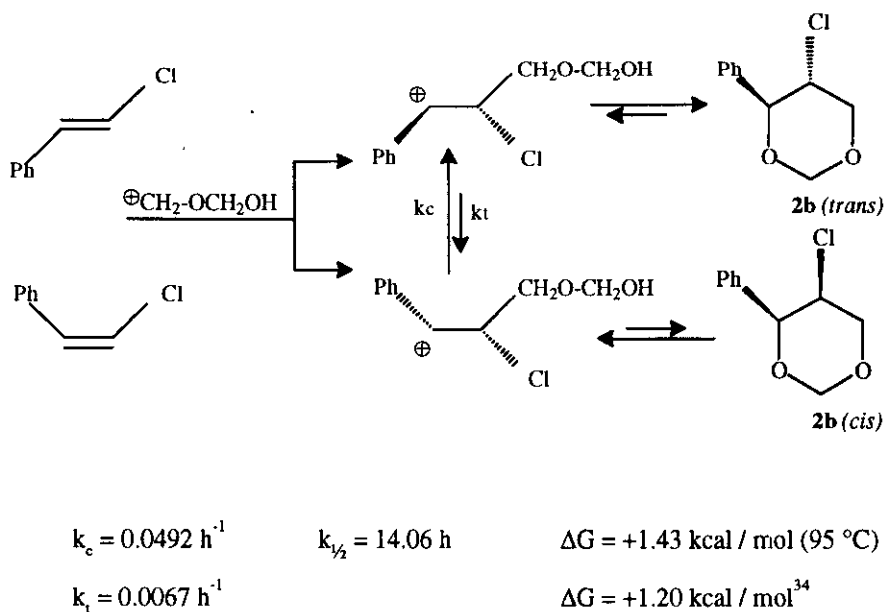
The course of the reaction was found the more diastereoselective when the harder conditions were used (concentration of the catalyst, temperature, excess of formaldehyde), yielding at least 90% *trans*-1,3-dioxane (**2a**) (from pure (E) - β -bromostyrene) and 79% *trans*-1,3-dioxane (**2a**) (from (Z) - β -bromostyrene). This can be explained (Scheme 6) if trigonal bridged ions (**4**) and (**4'**) were admitted; only **4** permits isomerization by rotation (A) to a thermodynamically more stable bromonium ion (**5**) while in the case of **4'** the same rotation

(A) would give a pseudo eclipsed unstable conformer ($5'$).

As a conclusion of the authors,^{25,26} the Prins reaction performed with β -bromostyrene occurs *via* an electrophilic *syn*-addition (from (*E*)- β -bromostyrene) and an *anti*-addition (from (*Z*)- β -bromostyrene) due to a different closure of the diastereotopic faces of the substrate. The reaction is diastereoselective before the ring closure as 1,3-dioxanes, under thermodynamic control (dashed line, Scheme 6).

β -Chlorostyrene showed significant differences (Table 1) because as it was expected, trigonal ions such as **5** have not been considered;^{25,26} thus a normal *anti* addition diastereospecific mechanism was proposed under the same conditions (See Scheme 4). Experimental data confirmed this assignment; from (*E*)- β -chlorostyrene minimum 55% *cis*-1,3-dioxane (**2b**) was obtained and from (*Z*)- β -chlorostyrene minimum 77% *trans*-1,3-dioxane (**2b**) (see Table 1, the DSR values).

Subsequent studies by us^{27,28} proved however a diastereoselective pathway of the Prins reaction starting from β -chlorostyrene. When the excess of formaldehyde was slight (Table 1) the DSR values showed a more obvious preference for the most thermodynamically stable dioxanic diastereomer (*trans* vs. *cis*) as harder conditions were used. The explanation consisted in the equilibration between the two dioxanic diastereomers as depicted in Scheme 7. A *syn* diastereoselective mechanism was suggested, involving a formaldehyde dimer ($^{\oplus}\text{CH}_2\text{-O-CH}_2\text{OH}$) as electrophile which takes into account the concentration of the aldehyde in aqueous media,²⁵ similar to that proposed earlier by Smissman.³⁵

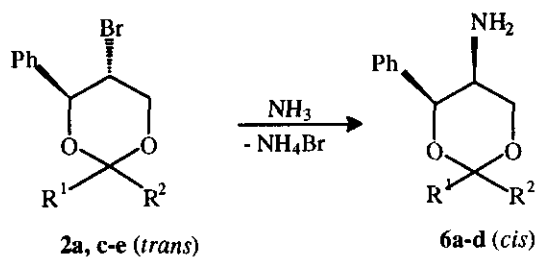


Scheme 7

The behaviour of β -chlorostyrene in the Prins reaction conditions^{27,28} raised also the question of the existence of some side reactions like the polycondensation of the benzylic cations and the polymerization of the substrate with influence on the yield of the reaction (Table 1); this fact is somehow in good agreement with data offered by other authors who avoided to comment upon their own quantitative results.

2.2. 5-Amino-4-phenyl-1,3-dioxane and derivatives. As it was already mentioned, these compounds were subjected in the next step of the synthesis to ammonolysis to give the title compounds. In few cases, ring closure of *l*-phenylserinol itself was reported.

2.2.1. Ammonolysis of 5-bromo-4-phenyl-1,3-dioxane and derivatives. All bromodioxanes (**2a, c-e**) subjected to ammonolysis were *trans*-bromo derivatives (designed, where this feature was specified, as "*dl-erythro*"). The inversion of configuration at C⁵ was mentioned by no author but the structure of the resulting aminodioxanes (**6a-d**) has been occasionally designed as "*dl-threo*" (Scheme 8). Some quantitative data are listed in Table 3.



Scheme 8

Table 3 - Synthesis of 5-aminodioxanes (**6**)

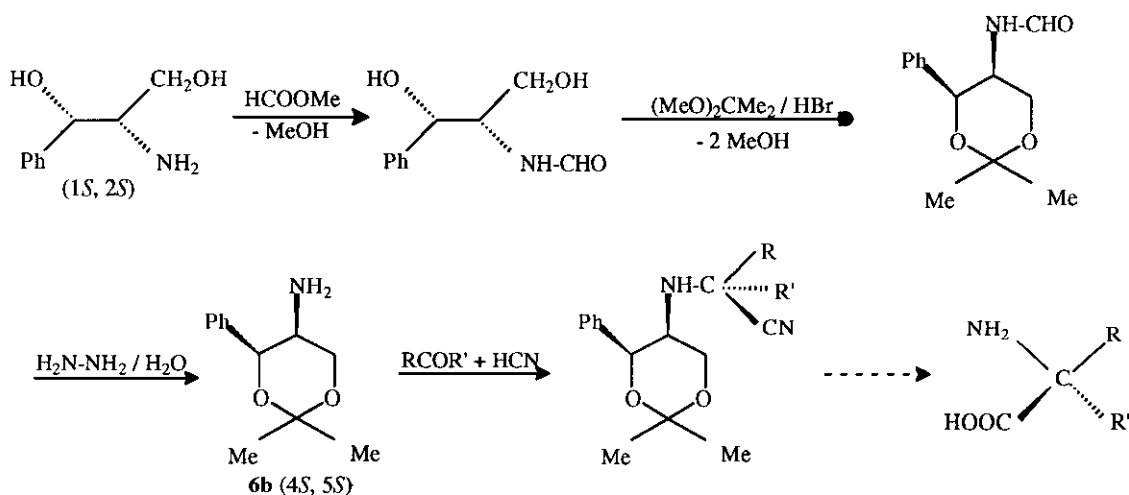
| N° compd. | Substrate R ¹ R ² | Ammonolysis agent | Time (h) | Pressure (atm) | Temp. (°C) | Yield (%) | lit. |
|--------------|--|---|-------------|-------------------|---------------|--------------|------|
| 6a* | H H | NH ₃ (g)-EtOH | 4 | - | 180 | 70 | 36 |
| | | NH ₃ (g)-MeOH | 14 | - | 150 | 75 | 37 |
| | | NH ₃ (aq)-EtOH | - | 60-70 | 180 | 50 | 12 |
| | | (NH ₄) ₂ CO ₃ -H ₂ O** | 12 | - | 80 | - | 33 |
| 6b | Me Me | NH ₃ (g)-EtOH | - | - | - | - | 16 |
| | | NH ₃ (aq)-H ₂ O | - | 55 | 145 | - | 14 |
| 6c | H Ph | NH ₃ (g)-EtOH | - | - | 130-40 | - | 16 |
| 6d | (CH ₂) ₅ | NH ₃ (g)-EtOH | 9-10 | - | 95-100 | 50 | 16 |

* Complementary data, see Zee³⁸ (Synthesis of racemic *cis*-5-amino-4-phenyl-1,3-dioxane starting from β -nitrostyrene), Brugemann³⁹ (Curtius degradation of 5-carboxamido-4-phenyl-1,3-dioxane to yield the *trans*-diastereoisomer).

** Complementary data, see Batteur³³ (amidolysis of *trans*-5-bromo-4-phenyl-1,3-dioxane with dichloroacetamide).

It may be concluded that all aminodioxanes (**6**) summarized in Table 3 are, in fact, cyclic acetal or ketals of *l*-phenylserinol, very close to the desired structure (chloromycetine).

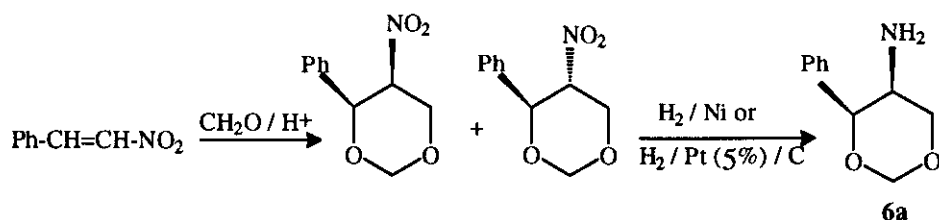
2.2.2. Direct acetalization and ketalization of *l*-phenylserinol. Diastereospecific ring closure of *l*-phenylserinol to give a cyclic ketal was reported by Nordin,⁴⁰ following data previously communicated by Ohara⁴¹ and Kamiya⁴² (the last one working with the *u* form). Only the 2,2-dimethyl ketal was synthesized to be used as pure (4*S*,5*S*) enantiomer in the manufacture of optically active amino acids (overall yield of the synthesis was 78%),(Scheme 9).^{40,43}



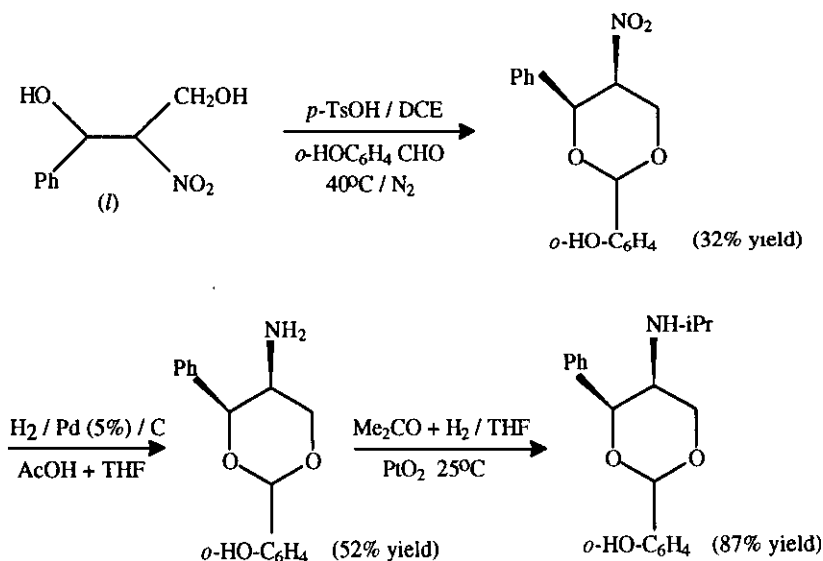
Scheme 9

2.2.3. Via 5-nitro-4-phenyl-1,3-dioxane. The diastereomers of 5-nitro-4-phenyl-1,3-dioxane were for the first time obtained by Zee in 1983 by means of a Prins reaction carried out with β -nitrostyrene.³⁸ Reduction of the nitro group afforded *cis*-5-amino-4-phenyl-1,3-dioxane (**6a**) (Scheme 10) and thus a new pathway towards chloromycetine was discussed.^{38,44}

Diastereospecific ring closure of *l*-2-nitro-1-phenylpropane-1,3-diol as a 2-substituted-1,3-dioxane was claimed in 1992 by Mikite⁴ to give after reduction and *N*-alkylation, 5-*N*-alkylamino-4-phenyl-2-substituted 1,3-dioxanes as pharmaceutical compositions (Scheme 11).



Scheme 10



Scheme 11

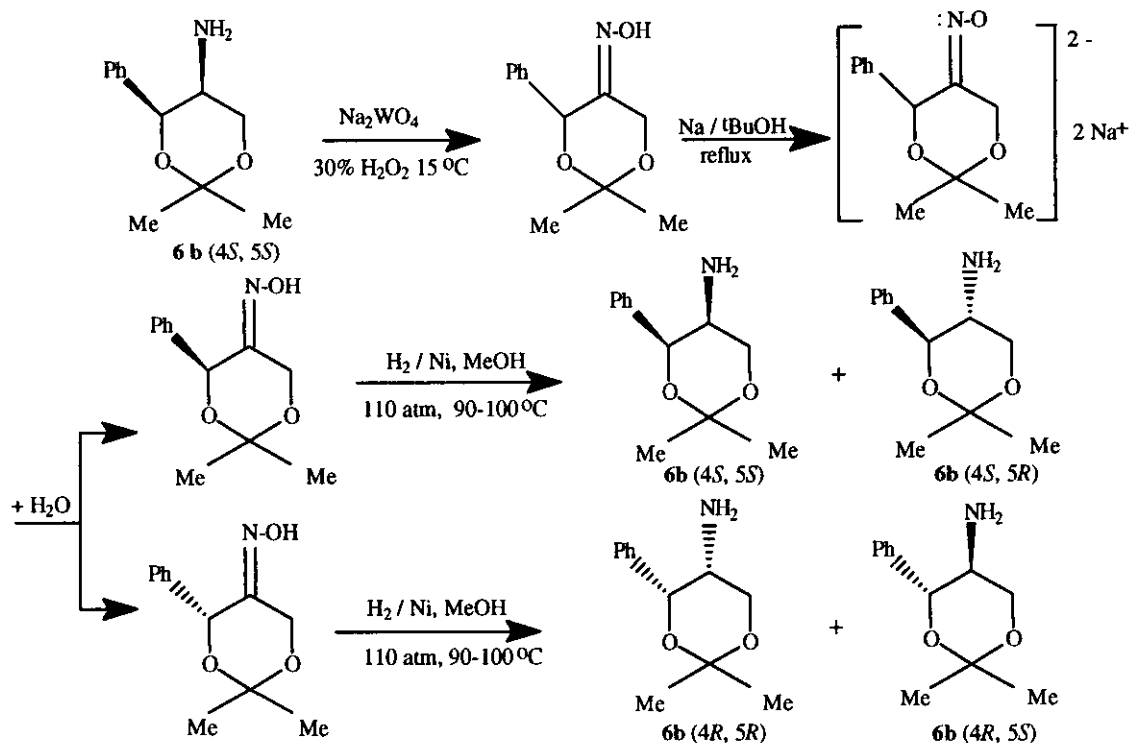
It is to be observed that reduction of the 5-nitro group is a general method to obtain 5-aminodioxanes with no significant side reaction.⁴⁵⁻⁴⁸

2.2.4. Resolution of racemic mixtures of 5-amino-4-phenyl-1,3-dioxane and derivatives; utilization of inactive enantiomers. In connection with chloromycetine synthesis as soon as the amino group has been introduced, Japanese authors proposed since 1955 the resolution of the racemic mixtures^{14,49,50} by using successively D-tartric and D-dibenzoiltartric acids.

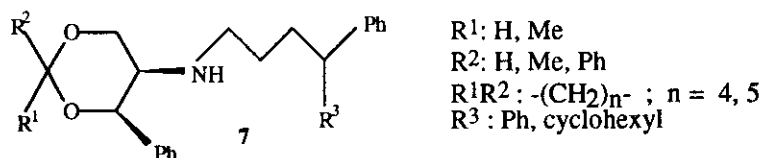
Thus, from the racemic mixture of (±)-*cis*-5-amino-4-phenyl-2,2-dimethyl-1,3-dioxane (**6b**) the two stereoisomers were separated. The (4*R*,5*R*) enantiomer was processed to give chloromycetine while the (4*S*,5*S*) enantiomer was subjected to different reactions to yield supplementary amounts of the active compound (Scheme 12).⁵¹

The essential feature of the Scheme (successive cancellation of the two adjacent chiral centers by oxidation of the amino group as an activating hydroxyimino group and the acid-base exchange at C⁴) had been previously

examined by Kamiya⁴² but the yields and diastereoselectivity were poor (molar ratio racemic **6b cis**: racemic **6b trans** about 7:1, yield of hydrogenation about 70%). Best results were claimed by Ohara⁵¹ (about 90% yield every step, Scheme 12).



An application of the resolution involving the acetals of the *l*-phenylserinol was reported in Boehringer patent⁵ (1965). Thus, racemic mixtures or pure enantiomers (**7**) were claimed to have cardiovascular properties although the desired configuration was not specified.





The synthesis consisted in direct *N*-alkylation of the amino group or *N*-acylation followed by standard reduction. Both pathways gave satisfactory yields (58-76%).

2.3. 4-(*p*-Nitrophenyl)-1,3-dioxane and derivatives. Three synthetic pathways were developed according to three very different points of view as it follows.

2.3.1. Direct nitration of 4-phenyl-1,3-dioxane and derivatives. The main data about direct nitration of these compounds and of some related saturated heterocycles (Scheme 13) are listed in Table 4.

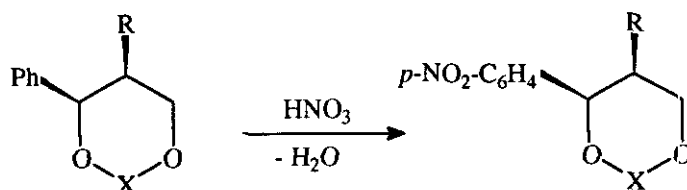
Table 4 - Direct nitration of 4-phenyl-1,3-dioxanes and derivatives

| Substrate | | Nitration agent (solvent) | Molar ratio HNO ₃ : substrate | Temp. (°C) | Yield(%) <i>p</i> -isomer | lit. |
|--------------------------|--|---|--|---------------|------------------------------|------------|
| R | X | | | | | |
| Br | -CH ₂ - | HNO ₃ +Ac ₂ O | 10.57:1 | -5 | 39 | 11,31 |
| | | HNO ₃ (CHCl ₃) | 6.97:1 | -5 | 25 | 26 |
| | | HNO ₃ +H ₂ SO ₄ | - | - | - | 22 |
| Cl* | -CH ₂ - | HNO ₃ (AcOH,CHCl ₃) | 8.65-5.0:1 | 0-5 | 0-17 | 52 |
| | | HNO ₃ +Ac ₂ O (CHCl ₃) | 3.22-10.64:1 | -5+10 | 4-37 | 52 |
| | | HNO ₃ +H ₂ SO ₄ (AcOH) | 3.65-5.97:1 | -1+20 | 13-35 | 52 |
| -NH-CO-CHCl ₂ | -SO- | HNO ₃ 100% | 40.21:1 | -30 | - | 53 |
| | -CO- | HNO ₃ 100% | 24.46:1 | -20 | - | 53 |
| | -CH ₂ -** | HNO ₃ (CHCl ₃) | 4.96:1 | -20 | 88 | 36 |
| | -CMe ₂ -** | HNO ₃ +H ₂ SO ₄ | - | - | - | 33 |
| |  ** | HNO ₃ +Ac ₂ O (CHCl ₃) | 4.00:1 | -15-0 | - | 54, 55 |
| | | HNO ₃ +(EtCO) ₂ O(CHCl ₃) | 5.19:1 | -10+3 | - | 54 |
| -NH-CO-Me | -CMe ₂ - | HNO ₃ +H ₂ SO ₄ | 8.80:1 | -5 | 70 | 56*** |
| -NH-CO-Et | -CMe ₂ - | HNO ₃ +H ₂ SO ₄ | - | - | - | 56*** |
| -NH-CO-Pr | -CMe ₂ - | HNO ₃ +H ₂ SO ₄ | - | - | - | 56*** |
| -NH ₂ | -CMe ₂ - | HNO ₃ (CHCl ₃) | 14.18:1 | -30 | 69 | 56, 14, 57 |
| |  | HNO ₃ +H ₂ SO ₄ | 5.86:1 | -15 | - | 56*** |
| | >CH-Ph | - | - | -15 | - | 56*** |

* Similar yields starting from *trans*-diastereomer

** Obtained by dichloroacetylation of the corresponding aminodioxanes in high yields (85-95%)^{12,14,36,58-60}

*** Subsequent processing in one pot synthesis by hydrolysis and treatment with benzaldehyde to afford the Schiff base of *l-p*-nitrophenylserinol as racemic mixture or enantiomers.

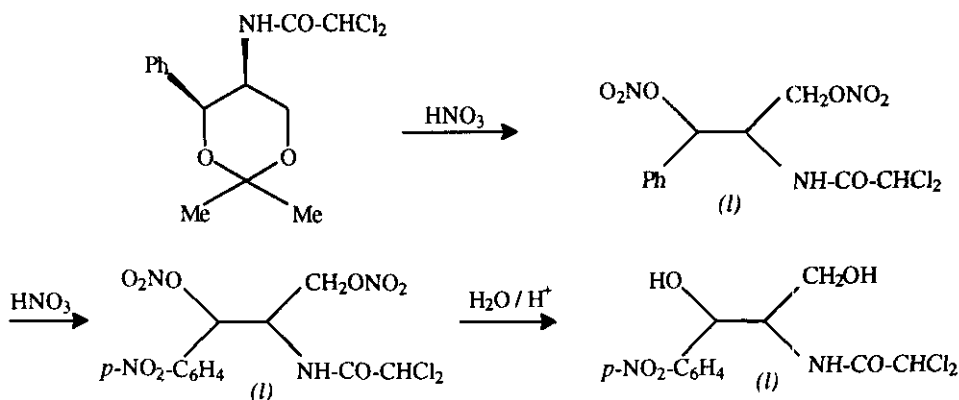


Scheme 13

The above listed studies focused on *cis*-1,3-dioxanes (or related compounds such as 1,3-oxathiane or carbonate) as racemic mixtures or (*4R,5R*) enantiomers (resolution of acetonide of *L*-phenylserinol^{14,56}); yields cover a wide range but, as a general remark, they are poor, taking into account that the nitro group was introduced in an advanced step of the synthesis.

The formaldehyde acetals ($X = -CH_2-$) gave the smallest yields despite an unusual excess of nitration agent, while nitration of phenylcyclohexane⁶¹ yields 50-60% *para* nitro isomer when the excess of HNO_3 is only 15% (2 h at 0-5°C); thus, a preliminary interaction between the nitration agent and the heterocyclic oxygen atoms may be suggested. Subsequent studies⁵² demonstrated that at least in the case of halogenodioxanes ($R = Cl, Br$; $X = -CH_2-$) the regioselectivity is normal for this type of reaction (molar ratio 3:1 *para* vs. *ortho* when the conversion was up to 90%).

Nitration of acetone derivatives (and it is to be assumed that this has the same course with other ketals and acetals depicted in Table 4) gave higher yields; in 1955, Ikuma⁵⁵ reported transesterification of the ketal to give an acyclic dinitro derivative of *L*-phenylserinol as the real substrate which is nitrated (Scheme 14).

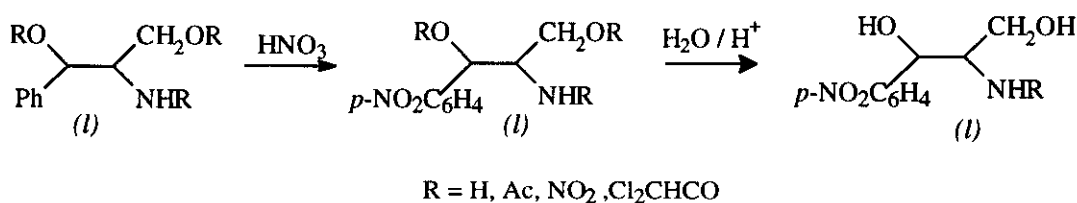


Scheme 14

Based on Ikuma's evidences,⁵⁵ the introduction of the nitro group in order to obtain chloromycetine was

re-examined along the following three directions:

a) no use of heterocyclic saturated structure (e.g. 1,3-dioxanes) was considered from the beginning of the synthesis, because it may be assumed that acetalization and ketalization had been made as a protection of the hydroxyl groups against the nitration agent; *O*- and (or) *N*-acyl derivatives of *l*-phenylserinol were nitrated in high yield (up to 60%) with a better regioselectivity (Scheme 15).^{49,62-76} Nitration took place at very low temperatures (-70 to -10°C) in the presence of a large excess of nitration agent (10-60:1 molar ratio).



Scheme 15

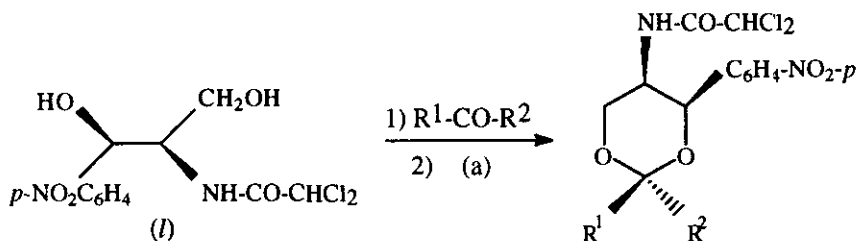
b) *N*-acetyl derivatives of *cis*-5-amino-4-phenyl-2-substituted-1,3-dioxanes were nitrated and processed by hydrolysis in one step synthesis (Table 4); if the *N*-acetyl group was *N*-dichloroacetamido, hydrolysis was carried out selectively, in the presence of ferroammonium sulphate, sulfamic acid or urea.^{56,64}

c) 5-Amino-4-phenyl-2-substituted 1,3-dioxanes were nitrated as ammonium salts (no protection of the amino group) to yield, after hydrolysis of the resulting dinitro esters and subsequent treatment with benzaldehyde, Schiff bases of *l*-*p*-nitrophenylserinol. In some cases resolution of the racemic aminodioxanes preceded nitration.^{14,56}

It is generally admitted that nitration should succeed and not precede ammonolysis; poor results have been mentioned when *trans*-halogeno-1,3-dioxanes [see (2a-b) in 2.1.1] were first nitrated and then submitted to ammonolysis (yields about 30-50%).^{31,52}

2.3.2. Direct acetalization and ketalization of chloromycetine. Few attention was paid to ring closure of chloromycetine (as a diastereospecific process) even though the first reference in the subject⁷⁷ was a Parke Davis patent issued in 1952. Different authors^{58,78-80} agreed that cyclization of chloromycetine occurs in conditions different from usual acetalization and ketalization, due to the steric hindrance of the starting *l*-1,3-diol. No alteration of configuration during the process was yet reported (Scheme 16).

Conformational details are also discussed, based on high resolution ¹H-nmr spectra.^{79,80} If the phenyl group is absent, ring closure of 2-dichloroacetamido-2-methylpropane-1,3-diol takes place in standard conditions.^{9,81}



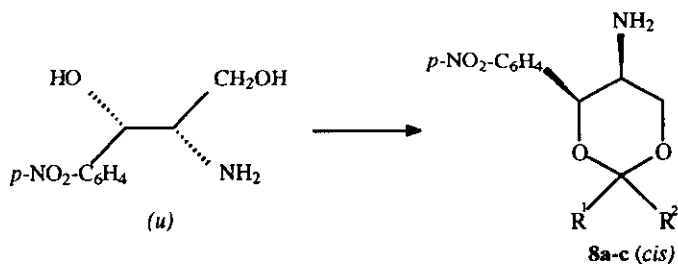
(a) : P_2O_5 or H_2SO_4 ; ⁷⁷ or conc. aq. HCl ; ⁷⁸ or molecular sieve / THF; ⁷⁹ or P_2O_5 / THF. ⁸⁰

R^1, R^2 , (yield): Me, Me, (90); Me, Et, (22); Me, ^tBu, (traces); $-(CH_2)_5-$, (70); $-(CH_2)_4-$, (80); Et, Ph, (4); H, Ph, (60); H, *p*-MeO- C_6H_4- , (80); H, *m*-HO- C_6H_4- , (82); Et, Et, (-); Et, H, (-); Ph- CH_2CH_2- , H, (-); Me, H, (84).

Scheme 16

2.3.3. Direct acetalization and ketalization of *p*-nitrophenylserinol. The first ring closure of racemic *u-p*-nitrophenylserinol was first examined by Nagawa ^{49,58} (reaction with acetone). The reactivity of the amino group was blocked by using the hydrobromide of the substrate to obtain a cyclic ketal.

Later studies by us (to be published) have concluded that no common method of cyclisation is useful but a specific one is needed for each carbonyl compound used (see also 3.1-3.2) (Scheme 17). The key feature is the complete cancellation of nucleophilicity of the amino group. The *cis*-5-amino-4-(*p*-nitrophenyl)-1,3-dioxane and derivatives (racemic mixtures or pure enantiomers) were then converted in *N*-acetyl derivatives and dioxanic Schiff bases.

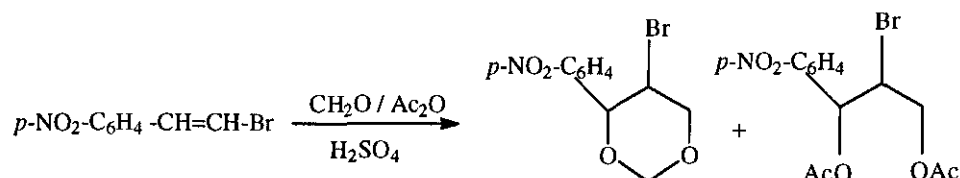


| compound | R^1 | R^2 | reagent | yield(%) |
|-----------|------------|--|---|----------|
| 8a | H | H | 1:1 $CH_2O + H_2SO_4$ ($0^\circ C$) | 60-70 |
| 8b | Me | Me | $P_2O_5 + Me_2CO + HCl$ ($0^\circ C$) | 50-60 |
| 8c | $(CH_2)_5$ | <i>p</i> -TsOH + cyclohexanone + benzene | 18 (under kinetic control) | |

Scheme 17

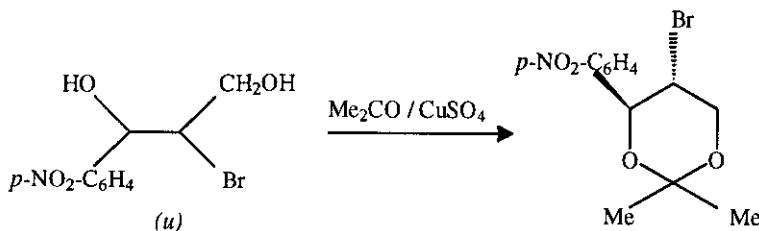
As in the case of chloromycetine, no epimerization was detected: all cyclisations were diastereospecific to give (4*R*,5*R*) or (4*S*,5*S*) compounds (**8a-c**).

2.3.4. Prins reaction of *p*-nitro- β -bromostyrene. The use of *p*-nitro- β -bromostyrene in Prins reaction to yield 5-bromo-4-(*p*-nitrophenyl)-1,3-dioxane is a minor pathway in chloromycetine chemistry. The Prins reaction carried out by Batteur³³ afforded a mixture of compounds due to reaction conditions; no structural and quantitative information was mentioned concerning the products (Scheme 18).



Scheme 18

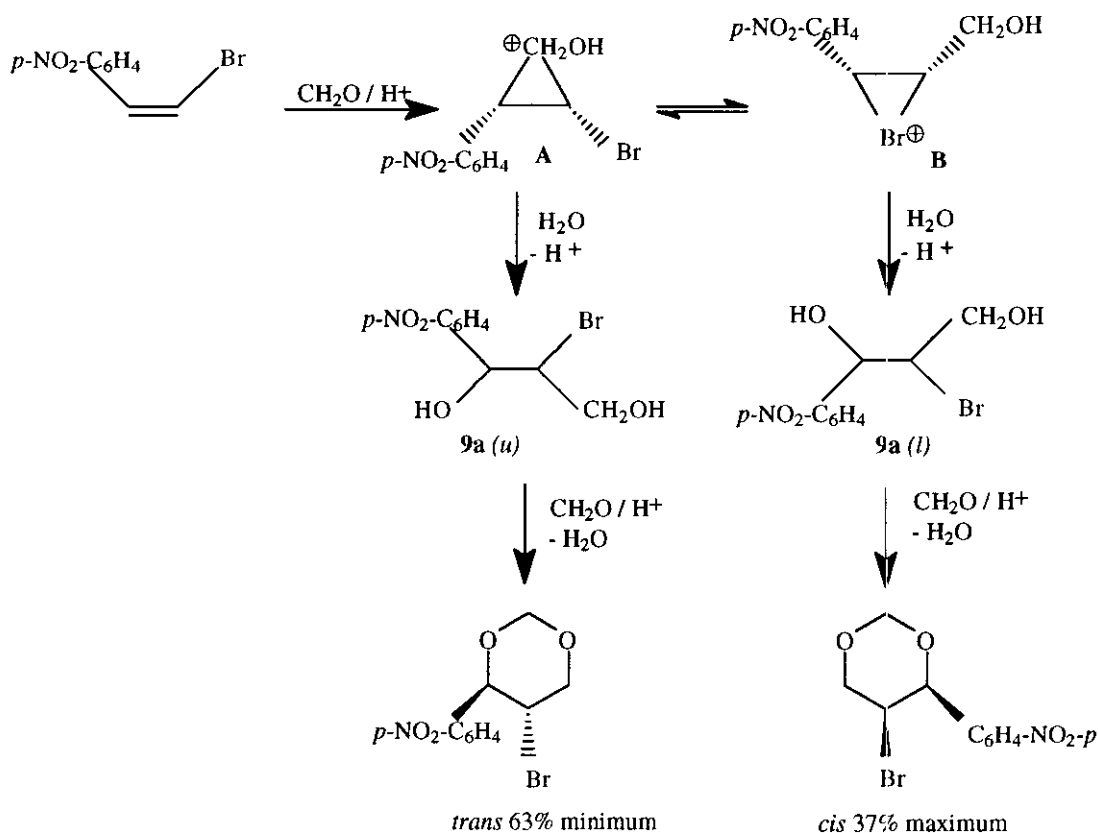
A related method was reported in Boehringer's patent;¹³ the racemic *u*-2-bromo-1-(*p*-nitrophenyl)-propane-1,3-diol (presumably obtained by bromination of (*E*)-*p*-nitrocinnamyl alcohol) was ketalized with acetone to give a dioxanic structure (designed as "*dl*-erythro")(Scheme 19).



Scheme 19

In 1964 Bernardi and Leone²⁹ proposed a *syn*-addition to (*Z*)- and (*E*)-*p*-nitro- β -bromostyrenes to yield the corresponding 1,3-dioxanes in a diastereospecific process (e.g. from (*Z*)-*p*-nitro- β -bromostyrene, *cis*-1,3-dioxanes). Further experiments by Coussemant²⁶ pointed out that at least in the case of (*Z*)-*p*-nitro- β -bromostyrene, a minimum 63% *trans*-1,3-dioxane was expected (Scheme 20).

Based on Olah previous data³² about the stability of open *p*-nitrobenzylic cations, Coussemant²⁶ assumptions focused on the equilibrium $A \rightleftharpoons B$. In (B) steric hindrance is greater than in (A) (bulky substituents are somehow eclipsed) but the three-membered heterocycle includes a more polarizable atom, a situation stabilized by the withdrawing group from the aromatic system. Thus, diastereoselectivity decreases [*trans*-1,3-dioxane vs. *cis*-1,3-dioxane, see 2.1.2. Scheme 6, the same reaction from (*Z*)- β -bromostyrene] from 79% (unsubstituted benzene) to 63% (*p*-nitrophenyl derivative).

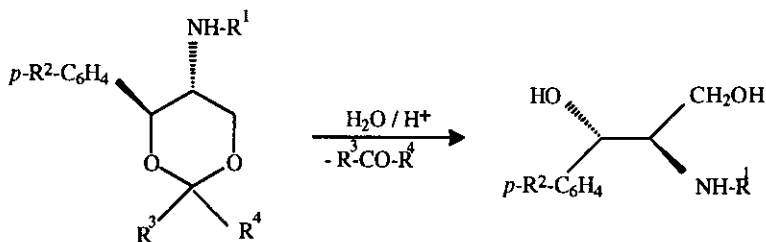


Scheme 20

2.4. Ring cleavage of 4-phenyl-1,3-dioxane and derivatives. When ring cleavage of these compounds included in the chloromycetine synthesis was carried out (Scheme 21), the reactivity of the dioxanic substrates was very different, as it may be seen in Table 5.

It may be concluded from data listed in Table 5 that the appropriate moment for performing the ring cleavage is after ammonolysis but before nitration, in good agreement with the higher yields obtained when acyclic forms were nitrated (See 2.3.1.). No epimerization was noticed during hydrolysis of the dioxane ring (e.g. involving the benzylic carbon). As it is expected, acetals of formaldehyde were less reactive, except for the ring cleavage catalyzed by $\text{ZnCl}_2 / \text{Ac}_2\text{O}$, Zee⁴⁴ isolated a diacetyl derivative which was subsequently hydrolyzed in alkaline medium (the same treatment earlier reported in Boehringer's patent³⁶).

All structures discussed were designed as "*dl-threo*" *cis* in direct connection to chloromycetine. However, the nitro compounds exhibited lower reactivity in ring cleavage (Isagulyants³¹); moreover, *cis*- and *trans*-5-halogeno-4-(*p*-nitrophenyl)-1,3-dioxanes could not be equilibrated (like their phenyl analogous) or hydrolyzed by none of the methods depicted in Table 5.³²



Scheme 21

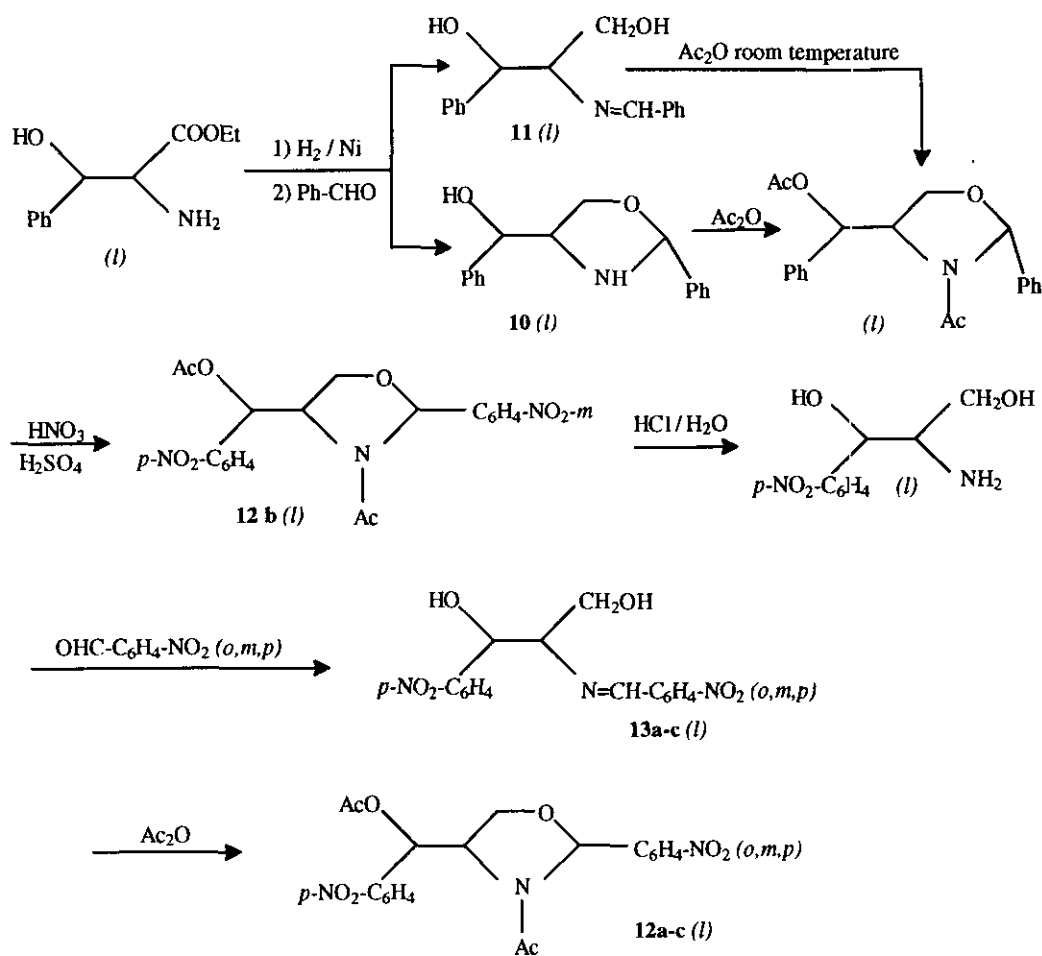
Table 5 - Ring cleavage of various 4-phenyl -1,3-dioxanes

| Substrate | | | | Hydrolysing agent | Time (h) | Temp. (°C) | Yield (%) | lit. |
|-----------------------|-----------------|----------------|----------------|---|----------|------------|-----------|-------|
| R ¹ | R ² | R ³ | R ⁴ | | | | | |
| -CO-CHCl ₂ | NO ₂ | H | H | ZnCl ₂ - Ac ₂ O | 12 | 15 | 84 | 36,44 |
| -CO-Ph | H | H | H | ZnCl ₂ - Ac ₂ O | 48 | 20 | 20 | 12 |
| H | NO ₂ | H | H | KU-2 Amberlyst15-MeOH | 4-48 | 65 | 37-30 | 31,52 |
| -CO-Ph | H | H | Ph | 1% HCl - EtOH | 0.5 | 78 | 95 | 16 |
| -CO-Ph | NO ₂ | Me | Me | H ₂ N-SO ₃ H - H ₂ SO ₄ | - | - | 28 | 14 |
| -CO-Me | H | Me | Me | 1% HCl - EtOH | - | - | 92 | 16 |
| -CO-CHCl ₂ | H | Me | Me | 1% HCl - EtOH | - | - | - | 16 |

3. SYNTHESIS OF FIVE-MEMBERED SATURATED HETEROCYCLES: 1,3-OXAZOLIDINES DERIVATIVES

Certain authors have reported the preparation of some five-membered saturated heterocycles, derivatives of *l*-phenylserinol or its nitro, *N*- or *O*-acylated forms when, in the end of chloromycetine synthesis, an appropriate protection of the amino group by treatment with carbonyl compounds was considered. It is well known that *l*-phenylserinol is an essential precursors of chloromycetine, available in different other synthetic pathways (e.g. starting from *u*-2-bromo-1-phenylpropane-1,3-diol^{17,68,83,84} or *l*-phenylserine and its functional derivatives^{65,67,70-72,85-100}).

3.1. Various substituted 1,3-oxazolidines. In 1954 Umezawa and Suami⁸⁶ assigned an oxazolidine structure for the product obtained by hydrogenation of racemic *l*-phenylethylserinate (presumably based on Collin's earlier structural proposal concerning the reaction of *l*-*p*-nitrophenylserinol with benzaldehyde¹⁰¹) (Scheme 22).

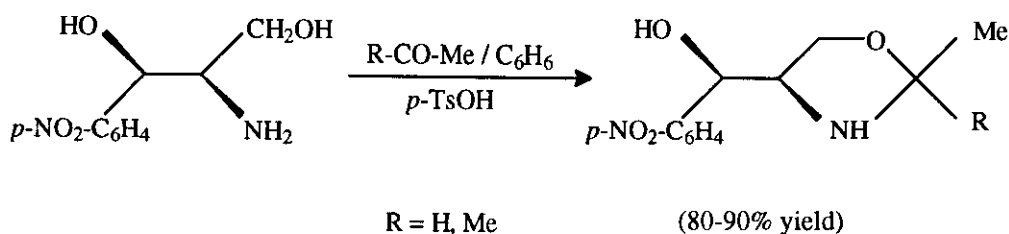


Scheme 22

The structure of the compound obtained after hydrogenation was differently assigned: either as 4-phenylhydroxymethyl-2-phenyl-oxazolidine (10)⁸⁶ or as *l*-2-benzylidenamino-1-phenylpropane-1,3-diol (11) (a Schiff base of *l*-phenylserinol¹⁰⁰). The possibility of a ring chain tautomerism^{102,103} (Schiff-base \rightleftharpoons oxazolidine) was not discussed and not examined by other authors [however the double acetylation with rearrangement of Schiff bases (11, 13a-c) (Scheme 22) suggested this type of tautomerism].

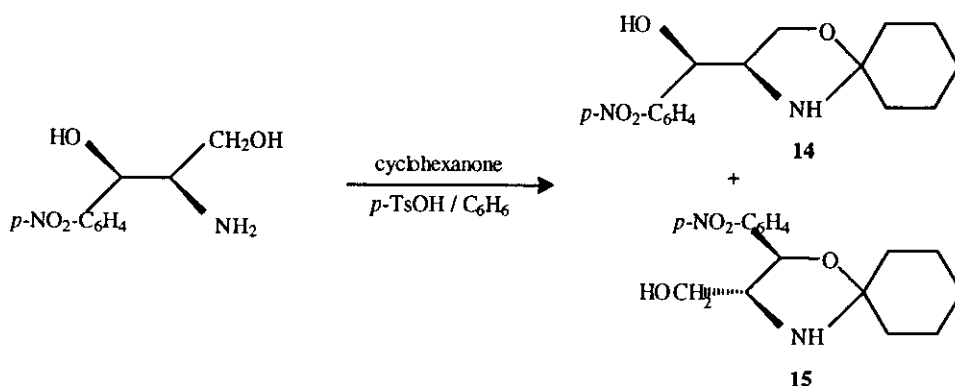
The right structure of oxazolidine (12b) was studied by comparison with the compounds (13a-c) obtained by treatment of *l*-*p*-nitrophenylserinol with *o*, *m*, *p* isomers of nitrobenzaldehyde.

Based on ir spectra only, in 1956 Pedrazzoli and Tricerni¹⁰⁴ assumed an oxazolidine structure for the compound obtained from the reaction of enantiomeric (*1R,2R*)-*p*-nitrophenylserinol with nonaromatic carbonyl compounds (e.g. acetaldehyde and acetone)(Scheme 23).



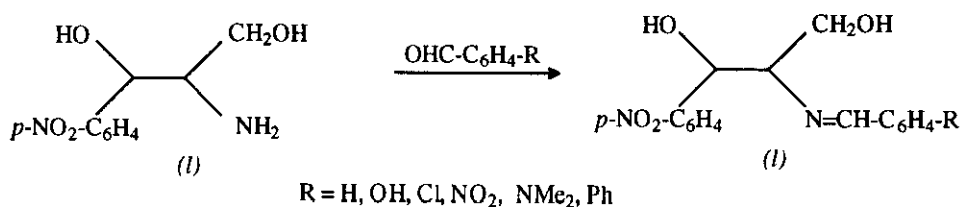
Scheme 23

The regioselectivity of ring closure in reaction with acetone was demonstrated by us (to be published) (Scheme 23) by means of high resolution ^1H -nmr spectroscopy; nevertheless, the similar ring closure with cyclohexanone (Scheme 24) was not fully regioselective, yielding a 7:1 (**14**:**15**) mixture of the two spiro oxazolidines⁷⁹ (under thermodynamic control; see 2.3.3. compound (**8c**) obtained under kinetic control).



Scheme 24

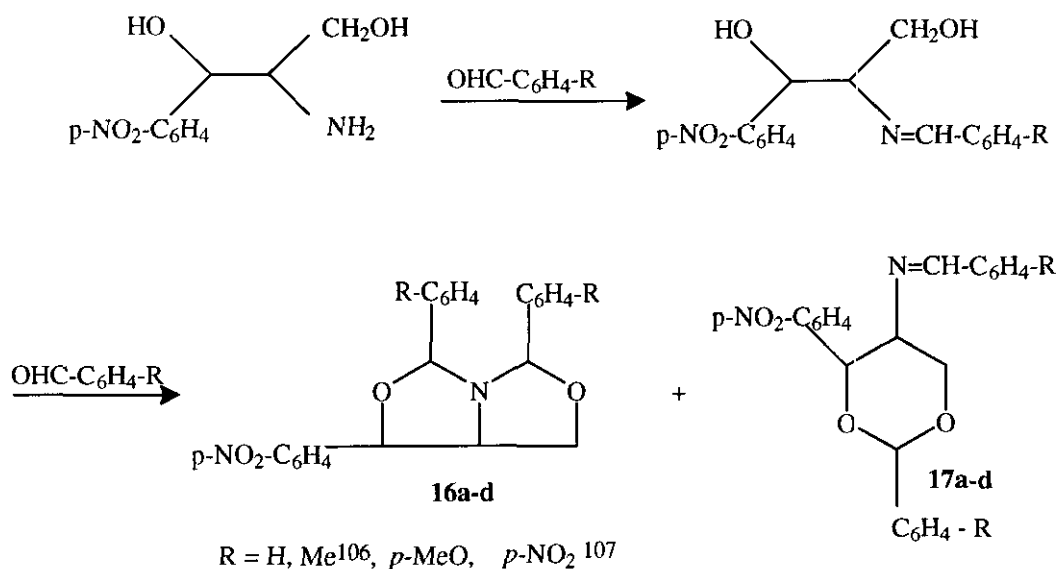
In reaction with aromatic aldehydes, only Schiff bases were reported, starting from *l*-*p*-nitrophenylserinol.¹⁰⁴⁻¹⁰⁶



Scheme 25

3.2. 1-Aza-4-(*p*-nitrophenyl)-3,7-dioxo-2,8-disubstituted bicyclo[3.3.0]octanes. In their above quoted study,¹⁰⁴ Pedrazzoli and Triccerri noticed the unexpected reactivity of Schiff-bases, derivatives of *l* and *u* *p*-nitrophenyl-

serinol with excess of aromatic aldehydes when little or no acetalization occurred but bicyclo derivatives were isolated (Scheme 26).



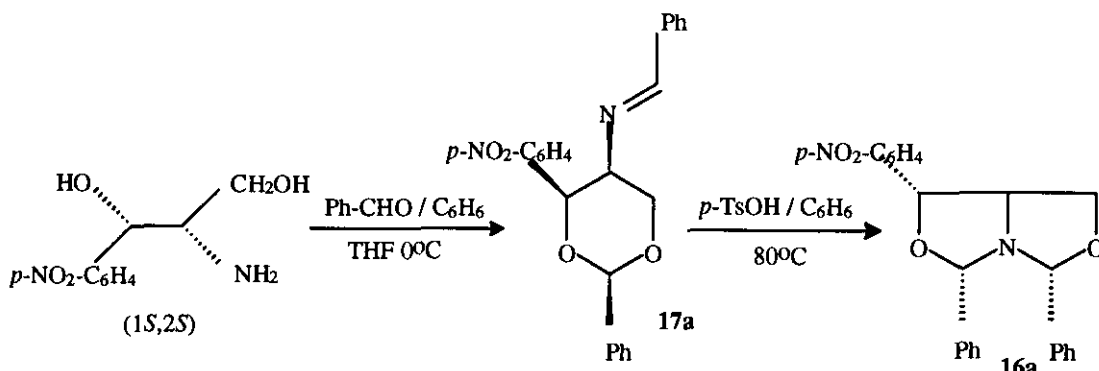
Scheme 26

The identity of this new types of compounds was discussed¹⁰⁴ using ir and uv data with no assumption about their stereochemistry; Italian authors emphasized, however, the maintaining of configuration of the starting skeleton, (*l*, *u* respectively) by hydrolysis in acidic media. Edgerton^{105,107} called attention to the fact that compounds (16) of *l* type should be considered as mixtures of *cis-trans* isomers (no data). The reaction mechanism was also discussed.^{104,105} It was found that Schiff bases of *p*-nitrophenylserinol are isolable intermediates to yield compounds (16) (supplementary details, see Nagawa's study⁴⁹); dioxanes (17) were isolated as by-product only when the substrate was *l* type (R=H); anyhow this side reaction remained unclear.

Recent studies by us⁸⁰ gave additional data. It was clearly found that compound (16a, R=H) is a mixture of four diastereomers (in 32:26:22:20 ratio, from 360 MHz ¹H-nmr spectrum). Yet, (2*R*,4*S*,5*S*)-5-(*E*)-benzylidenamino-4-(*p*-nitrophenyl)-2-phenyl-1,3-dioxane (17a, R=H) was obtained in one pot synthesis from (1*S*,2*S*)-*p*-nitrophenylserinol as single product. It was subsequently isomerized to (2*S*,4*S*,5*S*,8*R*)-1-aza-4-(*p*-nitrophenyl)-2,8-diphenyl-3,7-dioxabicyclo[3.3.0]octane (16a, R=H), the major component of the above mixture (Scheme 27).

It may be concluded that in the reaction with *p*-nitrophenylserinol, aromatic aldehydes yield Schiff bases, 1,3-dioxanes and substituted 1-aza-3,7-dioxabicyclo[3.3.0]octanes. The reactivity of nonaromatic aldehydes

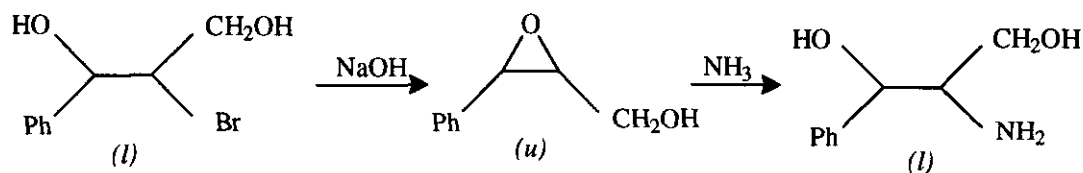
seems to be different: they give oxazolidines (see 3.1) or bicyclo derivatives¹⁰⁵ (formaldehyde and isobutyraldehyde).



Scheme 27

4. SYNTHESIS OF THREE-MEMBERED SATURATED HETEROCYCLES: 1,2-DISUBSTITUTED EPOXIDES

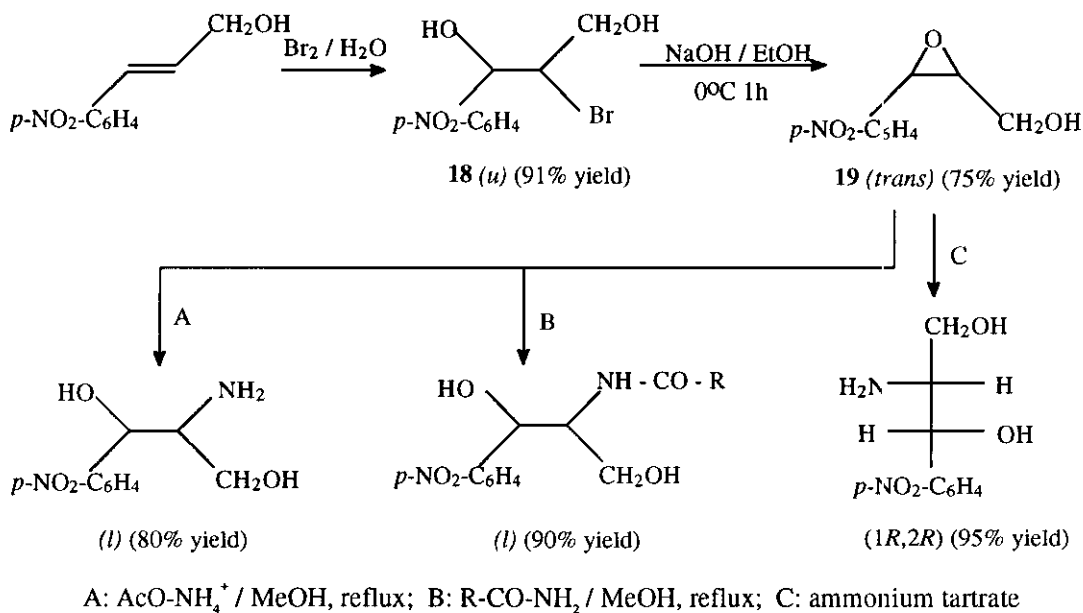
In 1961, a Boehringer's patent¹⁷ presented a new route in order to obtain *l*-phenylserinol starting from *l*-2-bromo-1-phenylpropane-1,3-diol; it was an applicative development of Bretschneider earlier work⁸⁴ (Scheme 28).



Scheme 28

The starting bromodiol was obtained by diastereospecific *anti* bromination (see 2.1.1. Scheme 2) of (*Z*)-cinnamyl alcohol. The diastereospecific feature of the whole process was ensured by a double inversion of configuration due to the anchimeric assistance of the benzylic hydroxyl group. Following a similar scheme, Krebs¹⁰⁸⁻¹⁰⁹ reported the preparation of chloromycetine starting from (*E*)-*p*-nitrocinnamyl alcohol (Scheme 29). Thus, bromination of (*E*)-*p*-nitrocinnamyl alcohol gave *u*-2-bromo-1-(*p*-nitrophenyl)propane-1,3-diol (**18**); its ring closure yielded *trans*-1-hydroxymethyl-2-(*p*-nitrophenyl)ethylenoxide. The *trans* configuration of **19** was specified to emphasize that ring cleavage with ammonium acetate (A) or amide (B) gave racemic *l*-*p*-nitrophenylserinol (A) or *N*-acylated derivatives (including chloromycetine if R = CHCl₂) (B). This

unusual and unexpected ring cleavage of the epoxidic heterocycle (**19**) (nucleophilic attack from the same side of the heterocyclic oxygen) was not explained. When ring cleavage was carried out with L-(+)-ammonium tartrate (**C**), the same unusual steric behaviour was reported, at the same time with resolution of the racemic *l*-*p*-nitrophenylserinol.



Scheme 29

ACKNOWLEDGMENTS

We wish to thank Dr. A. Dehnel for his help and especially for reading the manuscript and suggesting improvements

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