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# Cleavage of Saturated Nitrogen-containing Heterocycles at the C-N Bond by Electrophilic Agents

E.I.Levkoeva and L.N.Yakhontov

The review deals with reactions involving the opening of saturated nitrogen-containing rings at the C-N bond under the influence of acids, their anhydrides, esters, acid halides, and a number of other electrophilic agents. The use of the reverse Ritter reaction and of the Braun reaction for the cleavage of saturated heterocycles containing a secondary nitrogen atom is discussed.
The bibliography includes 137 references.

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## I. INTRODUCTION

The cleavage reactions of saturated nitrogen-containing heterocycles at the C — N bond are widely used to establish the structures of natural compounds and are of definite preparative value in organic synthesis.

Various methods for the rupture of endocyclic C — N bonds in saturated systems have been described in the literature. In the first place mention should be made of the cleavage of quaternary ammonium bases and their salts by the Hofmann and Emde methods involving heat treatment or treatment with alkalis, amalgams, and alkali metals in liquid ammonia.

These methods, which have been used successfully in the study of the structures of alkaloids and other complex heterocyclic systems, have been discussed in detail in fairly complete reviews[1-7]. Methods for the dissociation of C — N bonds in the catalytic dehydrogenation of alkaloids and on their distillation with zinc dust have been analysed in other reviews[8,9].

More specific are examples, described in various publications, of the cleavage at the C — N bonds of saturated cyclic amines in hydrogenolysis[10], the Wolff-Kishner[11-13] and Clemmensen[14-19] reduction reactions, and also as a result of oxidative[20] and electrochemical processes[21,22], in rearrangements[23-25], in transamination reactions[5,26], and in various tautomeric conversions[27-32].

In recent years attention has been increasingly drawn to a wide variety of methods for the opening of the C — N bond of saturated heterocyclic rings with a secondary or tertiary nitrogen atom by a number of electrophilic agents.

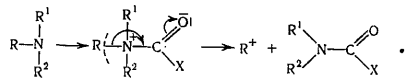
In view of the lack of reviews on reactions of this kind, it is desirable to give a general account of data from a fairly large number of publications.

The present review consists of two sections: the first deals with the cleavage reactions of saturated heterocycles containing a tertiary nitrogen atom by acids, anhydrides, acid halides, and esters and the second deals with the dissociation of C — N bonds of saturated cyclic secondary amines under the conditions of the reverse Ritter reaction and the Braun reaction.

The cleavage of tertiary cyclic amines by cyanogen bromide using the Braun method has not been included in the present paper, since the problem is dealt with in a fairly complete review[33] where the mechanism, conditions, and applications of this reaction are discussed in detail.

## II. CLEAVAGE OF SATURATED HETEROCYCLES CONTAINING A TERTIARY NITROGEN ATOM

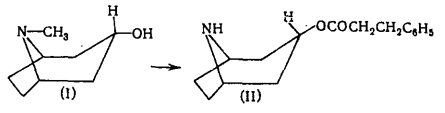
One of the methods for the dissociation of the C — N bond in tertiary amines involves their conversion into quaternary compounds by interaction with carboxylic acids or their derivatives: anhydrides, acid halides, chlorocarbonic esters, phosgene, and certain other electrophilic agents. The functional group attached to nitrogen withdraws the electron pair from the bond mainly as a result of its $-E$ effect, facilitating further dissociation:



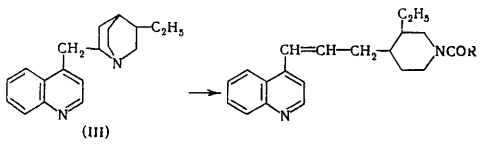
The cleavage of many tertiary cyclic amines has been achieved by this mechanism, the carbonium cation $R^+$ being subsequently stabilised either by the abstraction of a proton and the formation of a double bond or as a result of attack by nucleophilic agents (halide ions, water, alcohols, nitrogenous bases, etc.) with conversion into derivatives having the corresponding functional groups.

### 1. Dissociation of the C — N Bond by Acids

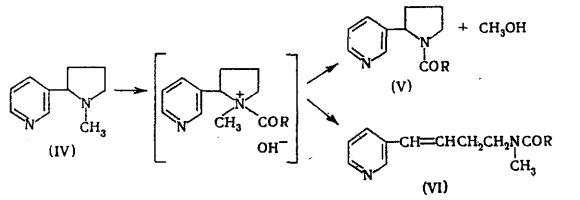
Saturated heterocyclic systems with a tertiary nitrogen atom are usually resistant to organic and inorganic acids. For example, *N*-methylpyrrolidine and *N*-methyl-1, 2, 3, 4-tetrahydroisoquinoline undergo only *N*-demethylation without ring opening on refluxing with benzoic, palmitic, acetic, or dihydrocinnamic acids[34]. When tropine(I) is heated to 200°C in the presence of dihydrocinnamic acid, the corresponding nortropine ester (II) is formed[34]:



Ring opening by acids is achieved only in compounds where the C — N bond is weakened owing to electron-accepting or bulky substituents at the carbon atom adjoining the nitrogen atom. Thus the quinuclidine ring is readily opened by acids when the $\alpha$-position relative to the nitrogen atom contains a bulky substituent which is involved in addition in the formation of a conjugated bond system after ring opening. Similar cleavage takes place with dihydrodeoxycinchonine (III):[35]

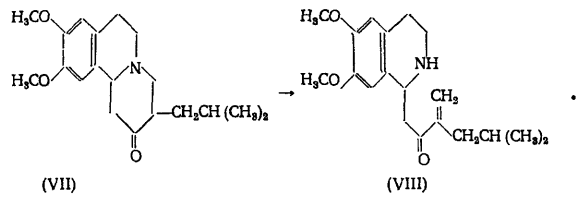


When nicotine (IV) is heated with benzoic or dihydrocinnamic acid until it starts to boil slightly, a product (VI) with an open pyrrolidine ring is formed together with *N*-acylnornicotine (V); the amount of compound (VI) increases with reaction temperature[36]:



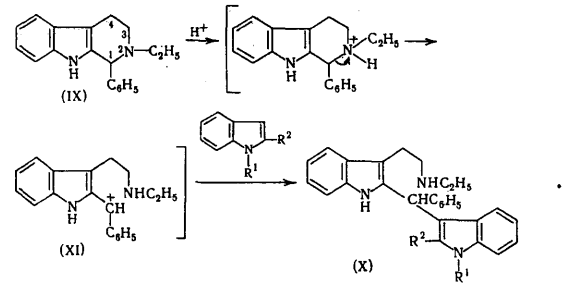
The acid cleavage of the C — N bond in saturated nitrogen-containing rings has been used to establish the structures of a number of natural compounds. Studies on the chemistry of Pereiro alkaloids containing the indoline group[37] and the *Voacanga africana* alkaloids—voacamine and voacorine, which are derivatives of 1, 2, 3, 4-tetrahydro-$\beta$-carboline[38]—may be quoted as examples.

In the course of the synthesis of emetine, Brossi et al.[39] showed that, when substituted benzoquinolizine (VII) is refluxed with acetic acid, the piperidine ring is cleaved and an unsaturated compound (VIII) is formed:



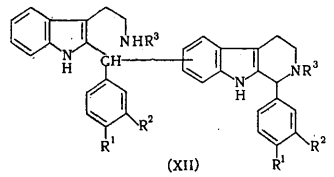
The mechanism of the opening of nitrogen-containing rings by acids has been examined in detail for the reactions of 1-aryl-1, 2, 3, 4-tetrahydro-$\beta$-carbolines[40].

When 2-ethyl-1-phenyl-1, 2, 3, 4-tetrahydro-$\beta$-carboline (IX) is heated with various indole derivatives in the presence of acetic and phosphoric acids, condensation products of type (X) are formed in high yields:



The cleavage of compound (IX) in an acid medium takes place exclusively at the $C_{(1)}$ — N bond, since only in this case is a mesomerically stabilised carbonium ion (XI) (similar to the diphenylmethyl cation) formed. The authors suggest that the $C_{(1)}$ — N bond is polarised owing to the protonation of the 2-N-nitrogen atom and attack by the nucleophilic agent (indole) at the 1-C atom, which leads ultimately to the dissociation of the ring. The carbonium cation (XI) formed interacts with the most reactive position (the 3-position) of the indole molecule. If the 3-position is occupied, the condensation involves the 2-position, which is much less reactive. In the case of 2, 3-disubstituted indoles, the reaction involves the benzene ring. Dimers of 1-aryl-1, 2, 3, 4-tetrahydro-$\beta$-carbolines (XII), which

are structural analogues of the alkaloid voacamine, were synthesised similarly[40]:

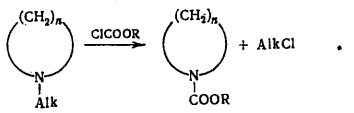


(XII)

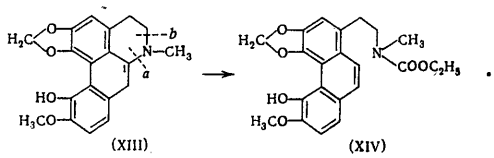
When the aryl substituent at 1-C is replaced by an alkyl substituent, the addition of indole does not take place, since the stabilisation of the carbonium cation (XI), which is essential for the reaction, cannot take place. The introduction of electron-accepting groups in the *para*-position of the phenyl substituent at 1-C enhances appreciably the reactivity of the compounds.

## 2. Dissociation of the C — N Bond by Chlorocarbonic Esters

Chlorocarbonic esters are regarded as "group agents" for the opening of the piperidine ring in 1,2,3,4-tetrahydroisoquinolines. The capacity of tetrahydroisoquinoline to be cleaved readily at the $C_{(1)}$ — N bond under the influence of ethyl chlorocarbonate was first observed as early as 1921 by Gadamer and Knoch[41]. Subsequently it was shown[42-44] that different quinoline, isoquinoline, pyridine, piperidine, and pyrrolidine derivatives do not undergo ring opening under these conditions. When chlorocarbonic esters are allowed to react with *N*-alkyl piperidines[43,44], tropane[44], or *N*-alkylpyrrolidines[42], only *N*-dealkylation processes take place with formation of alkyl chlorides and *N*-alkoxycarbonyl derivatives of the initial heterocycles:

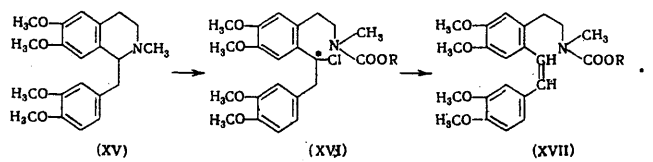


On the other hand, the majority of 1,2,3,4-tetrahydroisoquinolines readily undergoes selective dissociation at the $C_{(1)}$ — N bond on treatment with chlorocarbonic esters and are converted in quantitative yields into the corresponding open-chain urethanes. For example, the alkaloid bulbocapnine (XV), the Hofmann degradation of which is not unambiguous (it can occur via pathway *a* and *b*), gives rise only to compound (XIV) on treatment with ethyl chlorocarbonate, i.e. it is cleaved only at the $C_{(1)}$ — N bond[41]:



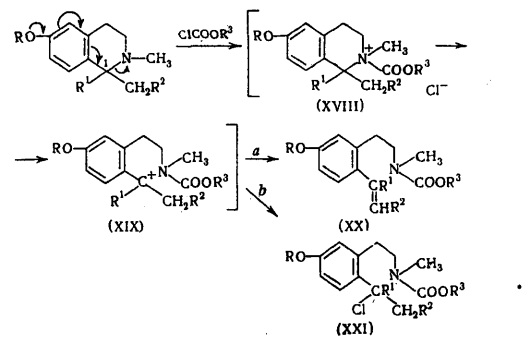
(XIII) (XIV)

When (-)-laudanosine (XV) interacts with chlorocarbonic esters, the initial product is the optically active chloroderivative (XVI), which splits off hydrogen chloride in the presence of alkali and gives rise to compound (XVII):[41,45]



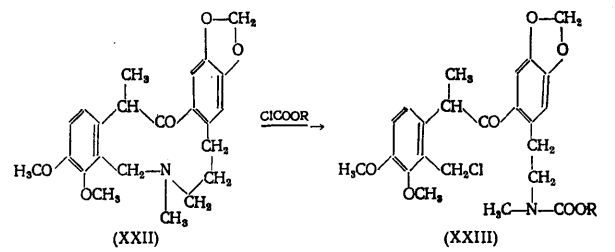
(XV) (XVI) (XVII)

Knabe and coworkers[45-49] examined the effects of substituents in the benzene ring on the ease of dissociation of the $C_{(1)}$ — N bond in 1,2,3,4-tetrahydroisoquinolines and proposed a possible reaction mechanism. They established that, on treatment with chlorocarbonic esters, the piperidine ring in *N*-methyl-1,2,3,4-tetrahydroisoquinoline cannot be cleaved, which can be accounted for by the inadequate polarity of the $C_{(1)}$ — N bond in this compound. The introduction of electron-donating groups in the *ortho*- or *para*-position of the benzene ring enhances the polarisation of the $C_{(1)}$ — N bond and facilitates the addition of the chlorocarbonic ester residue to the nitrogen atom. This results in the formation of a quaternary compound of type (XVIII) in which the $C_{(1)}$ — N bond is readily dissociated and the carbonium cation (XIX) thus obtained may be stabilised in two ways: (a) with elimination of a proton and formation of the unsaturated compound (XX); (b) via attack by a chloride ion with formation of the chloroderivative (XXI):



(XVIII) (XIX) (XX) (XXI)

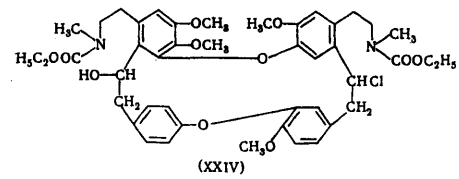
If the carbon atom adjoining 1-C does not have a proton capable of being split off, for example in the alkaloid corycavidine (XXII), a stable chlorourethane (XXIII) is formed[50]:



(XXII) (XXIII)

Otherwise, as mentioned above for (-)-laudanosine (XV), an unsaturated compound can be readily obtained.

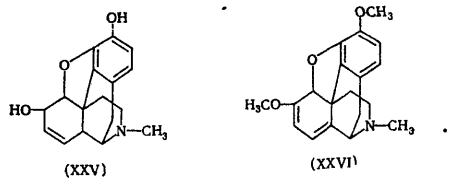
When the methyl ether of hydroxyacanthine is cleaved by chlorocarbonic ester in the presence of potassium hydroxide, the initially formed carbonium cations are stabilised by the addition of chloride and hydroxide ions with formation of compound (XXIV):[46,51]



(XXIV)

The reaction of chlorocarbonic esters with morphine (XXV) and codeine is known to result only in the acylation of the alkaloid at the hydroxy-group, while in the reaction

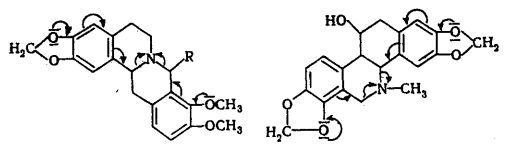
with thebaine (XXVI) the opening of the piperidine ring takes place with an almost quantitative yield[41,52]:



(XXV) (XXVI)

The example of thebaine shows that an aromatic system is not essential for ring opening. It is sufficient that the electron-donating substituent is conjugated with an allylamine residue.

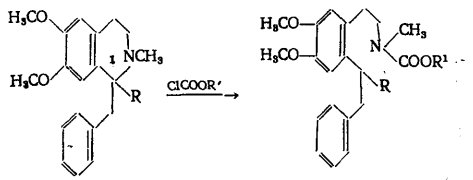
It is interesting that alkaloids of the tetrahydroberberine group (XXVII), which have, as it were, a "double benzylamine structure", do not undergo the opening of the piperidine ring when acted upon by chlorocarbonic esters[46,48]:



(R = H, $CH_2C_6H_5$) (XXVII) (XXVIII)

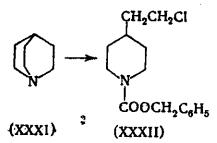
Initially it was suggested[46] that the opposed electron shifts in the two benzylamine systems in compounds of this type may reduce the polarisation of the C — N bond and prevent the reaction with chlorocarbonic ester. However, the alkaloid chelidonine (XXVIII), which also has a "double benzylamine structure", is readily cleaved at the C — N bond under these conditions[41].

Evidently not only electronic but also steric factors, primarily the degree of screening of the nitrogen atom attacked, play a major role in these processes. Indeed, whereas the yield of the urethane (XXIXa) from 1-benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (XXXa) is nearly quantitative[48], the introduction of a methyl group in the 1-position reduces the yield of compound (XXIXb) to 29% and the 1-ethyl homologue (XXXc) does not form the corresponding urethane (XXIXc) at all under standard conditions[49].



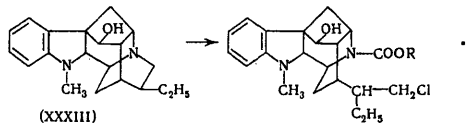
(XXX) [R = H (*a*), $CH_3$ (*b*), or $C_2H_5$ (*c*)] (XXIX)

Further studies showed that the cleavage of heterocycles at the $C_{(1)}$ — N bond by chlorocarbonic esters is not confined to substituted 1,2,3,4-tetrahydroisoquinolines or analogous systems in which electron-donating substituents are conjugated with the allylamine residue. It was possible to cleave the quinuclidine ring in an aprotic medium with the aid of these esters. When unsubstituted quinuclidine (XXXI) was treated with benzyl chlorocarbonate, the urethane (XXXII) was obtained in 88% yield[44]:



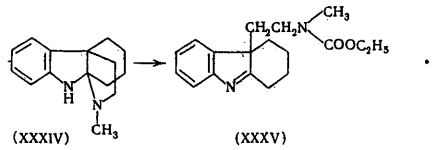
(XXXI) (XXXII)

It has been shown for 21-deoxyajmaline (XXXIII) that bicyclic systems with a nitrogen bridge are cleaved when acted upon by benzyl chlorocarbonate in a higher yield (98%) than on treatment with the corresponding ethyl ester (yield 55%)[44]:



(XXXIII)

Ethyl chlorocarbonate has been successfully used for the dissociation of the N — C bond also in *N*-methylechibolinе (XXXIV).[53] This involves the opening of the condensed pyrrolidine ring, the urethane (XXXV) being isolated in a yield of 65%:

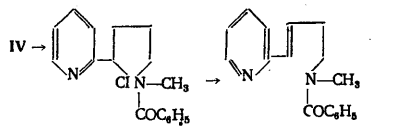


(XXXIV) (XXXV)

3. Dissociation of the C — N Bond by Acid Halides

Since acid halides are powerful electrophilic agents, they should apparently have found a wide application in reactions involving the cleavage of heterocyclic tertiary amines. However, the reaction of acid halides with tertiary amines containing even one α-hydrogen atom usually gives rise to the corresponding ketens. Therefore mainly phosgene or benzoyl halides, which are incapable of the formation of ketens, were used previously in C — N bond dissociation reactions.

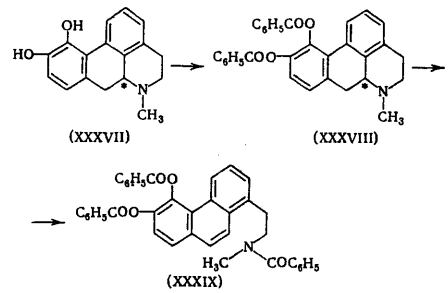
Thus, as early as 1894, a study of the reaction of benzoyl chloride with nicotine (IV) established that, when a mixture of these substances is heated to 200°C, *N*-benzoylmetanicotine (XXXVI) is formed[54,55]:



(XXXVI)

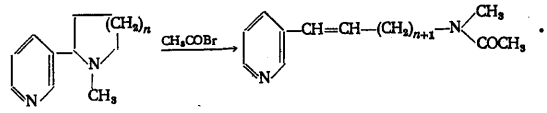
A thorough investigation of the products of this reaction led to a convincing proof of the structural formula of nicotine[54-56].

In the determination of the structure of apomorphine (XXXVII), its cleavage was also achieved with the aid of benzoyl chloride[57]. The optically active dibenzoyl derivative (XXXVIII) formed initially in this reaction reacts further with the excess benzoyl chloride, which results in the opening of the piperidine ring and the formation of an optically inactive non-basic product (XXXIX):



(XXXVII) (XXXVIII) (XXXIX)

Recently it was suggested that, with amines which are cleaved particularly readily, the amount of keten formed from the acid halide can be reduced to a minimum[58]. Indeed the reaction of acetyl bromide with nicotine (IV) yielded *N*-acetylmetanicotine (XLa) in 46 — 52% yield, while *N*-methylanabasine gave a 23% yield of the product (XLb), which is formed on opening of the piperidine ring:

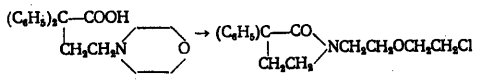


(IV) (XL) (*a*) $n=1$; (*b*) $n=2$

Appreciable amounts of keten were not detected in these reactions.

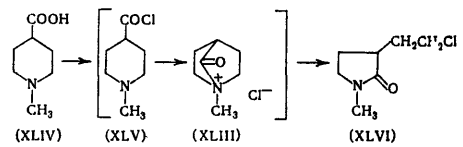
The cleavage of the piperidine ring of thebaine (XXVI) was achieved with the aid of acetyl and benzoyl chlorides in moist ethyl acetate, the corresponding codeinoacylnormethines being obtained in yields of about 90%.[52]

The intramolecular acylation of the chlorides of $\gamma$-aminoacids with a tertiary ring nitrogen atom has been the subject of a special study[59]. It was found that the reaction of $\gamma$-*N*-pyrrodinyl-, $\gamma$-*N*-piperidinyl-, and $\gamma$-*N*-morpholinyl-$\alpha\alpha$-diphenylbutyric acids (XLI) with thionyl chloride results in the opening of the heterocycle and the formation of the corresponding chloroalkyl derivatives of the *N*-substituted $\alpha$-pyrrolidinone (XLII):



(XLI) (XLII)

A similar reaction occurred in the synthesis of the bicyclic lactam (XLIII) as a result of the interaction between thioonyl chloride and *N*-methylisonipecotic acid (XLIV).[59] Compound (XLIII) proved to be extremely unstable and was converted under the reaction conditions into $\beta$-chloroethyl-*N*-methyl-$\alpha$-pyrrolidinone (XLVI):



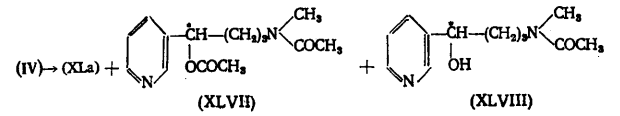
(XLIV) (XLV) (XLIII) (XLVI)

## 4. Dissociation of the C — N Bond by Acid Anhydrides

Acid anhydrides (mainly acetic anhydride) are fairly widely used for the cleavage of tertiary amines, including saturated nitrogen-containing heterocycles.

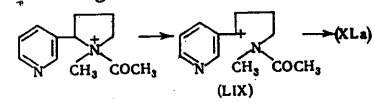
Tiffeneau's classical studies[60] showed that acid anhydrides cleave most effectively tertiary amines in which the nitrogen atom is linked to the benzyl residue and that the nature of the substituents in the benzine ring is important.

The ease of opening of the pyrrolidine ring in nicotine was also explained by its belonging to amines of the "benzyl type"[55]. In a recent study[61] of the effect of structural factors on the cleavage of tertiary amines by acetic anhydride, the interaction of the latter with nicotine (IV) was examined in detail. 1-Acetoxy-4-(*N*-methylacetamido)-1-($\beta$-pyridyl)butane (XLVII) and 1-hydroxy-4-(*N*-methylacetamido)-1-($\beta$-pyridyl)butane (XLVIII), which on vacuum distillation are converted into compound (XLa), were isolated from the reaction product together with *N*-acetylmetanicotine:



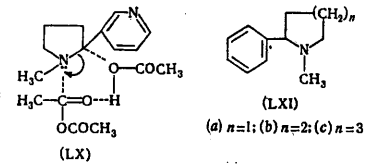
(XLVII) (XLVIII)

It is very likely that the formation of compound (XLa) from nicotine proceeds via the intermediate carbonium cation (LIX), which is stabilised subsequently by the elimination of a proton and the formation of a double bond conjugation with the pyridine ring:



(LIX)

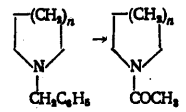
The presence of the hydroxy-derivative (XLVIII) and the acetoxy-derivative (XLVII) among the reaction products might be regarded as due to the addition of a hydroxy-group and an acetic acid residue respectively to the carbonium cation (LIX). However, the products obtained on stabilisation of the carbonium cation (LIX) should be racemates, while compounds (XLVIII) and (XLVII) proved to be optically active. Since the yield of the products of the cleavage of nicotine by acetic anhydride increases in the presence of water[62] or acetic acid[61], it was suggested[63] that the reaction proceeds simultaneously via two mechanisms: (1) via the formation of the carbonium cation (LIX), which gives rise immediately to *N*-acetylmetanicotine (XLa); (2) via a six-membered transition state of type (LX), which leads to compounds (XLVII) and (XLVIII).



(LX) (LXI)

(*a*) $n=1$; (*b*) $n=2$; (*c*) $n=3$

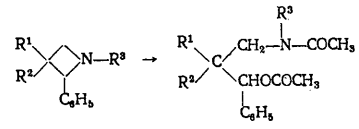
It has been shown[61] that a benzene analogue of nicotine—*N*-methyl-$\alpha$-phenylpyrrolidine (LXIa)—is cleaved like nicotine on its interaction with acetic anhydride. On the other hand, the reaction of *N*-benzylpyrrolidine and *N*-benzylpiperidine, which do not contain substituents in the $\alpha$-positions of the ring, with acetic anhydride in the presence of acetic acid involves the dissociation of the exocyclic C — N bond only:



It is noteworthy that the course of the above reaction is determined not only by the nature of the substituents at the nitrogen and $\alpha$-carbon atoms but also by the size of the ring undergoing cleavage. Thus *N*-alkylpiperidines remain unchanged even after refluxing for 100 h with acetic anhydride and acetic acid. Under the same conditions, *N*-alkylpyrrolidines and *N*-alkylhexamethyleneimines form the corresponding acyclic amides, albeit in low yields (11 — 14%). Similarly the piperidine ring in *N*-methyl-$\alpha$-phenylpiperidine (LXIb) is cleaved by acetic anhydride with much more difficulty than the five- or seven-membered ring in compounds (LXIa, c)[61].

The four-membered ring of *N*-alkylazetidines (LXII) is opened very readily on heating with acetic anhydride.

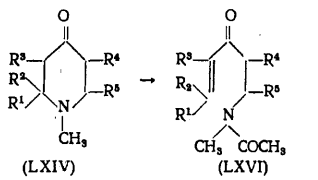
This results in the formation of quantitative yields of the corresponding $\gamma$-acetamidoacetates (LXIII):[64]



(LXII) (LXIII)

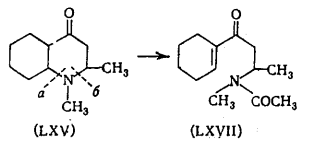
The nature of the substituents at the $\beta$-carbon atom in azetidine does not have a significant influence on the ease of ring opening and in the presence of a substituent at the $\alpha$-carbon atom the C — N bond adjoining the substituent is dissociated[64,65].

A number of studies have been made[66,67] on the interaction of acetic anhydride with *N*-methylpiperidine-4-ones (LXIV) and *N*-methyldecahydro-4-quinolones (LXV) containing methyl groups in various positions in the piperidine ring. It was established that at room temperature or on heating the components to 100°C, the piperidine ring is not cleaved. The corresponding $\beta$-acylaminoketones (LXVI) are formed in maximum yields (60 — 80%) on refluxing with acetic anhydride for 2.5 — 10 h.



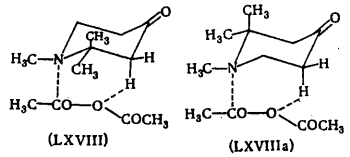
(LXIV) (LXVI)

It has been noted[66,67] that the opening of the piperidine ring always takes place with formation of "amidoketones" (LXVI) in which the vinyl group is alkylated to the maximum extent, i.e. the dissociation takes place at the most straining C — N bond. 1,2-Dimethyldecahydro-4-quinolone (LXV) is converted into a cyclohexene derivative (LXVII) on refluxing with acetic anhydride. There is no cleavage at the N — C($CH_3$) bond. Consequently the effect of the cyclohexane ring, responsible for the cleavage of the piperidine fragment via pathway *a*, is much greater than that of the methyl group:



(LXV) (LXVII)

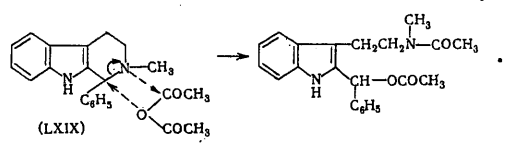
In the discussion of the possible mechanism of the opening of the $\gamma$-piperidine ring in compound (LXIV), it was suggested[67] that the reaction proceeds via a six-membered intermediate state (LXVIII):



(LXVIII) (LXVIIIa)

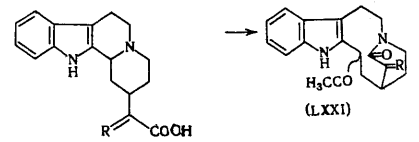
However, the formation of (LXVIII) has not been demonstrated experimentally. On the other hand, one should note that the existence of such an intermediate state does not account for the preferential dissociation of the C — N bond adjoining the most alkylated carbon atom. Indeed, it would in fact appear that the geminal substituents at the $\alpha$-carbon atom should hinder the formation of the transition state (LXVIII) and should facilitate the formation of (LXVIIIa).

Therefore it appears more likely that such reactions take place via four-membered intermediate complexes of type (LXIX), proposed by Freter and coworkers[40,68] in their description of the interaction of 1-phenyl-1,2,3,4-tetrahydro-$\beta$-carboline derivatives with acetic anhydride:



(LXIX)

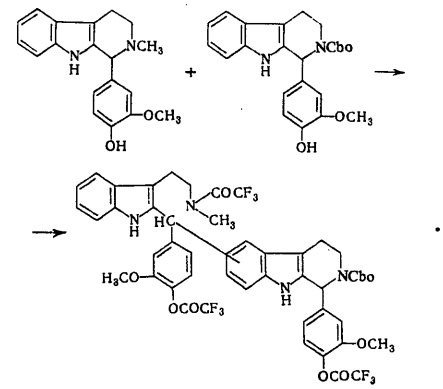
The piperidine ring of dihydrocorynantheine (LXX) was opened similarly in the presence of acetic anhydride and the cleavage products were isolated in the form of acetoxylactams (LXXI):[69]



(LXXI)

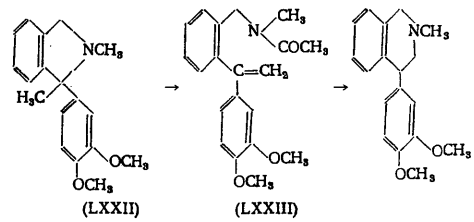
(LXX): R = $H_2$, $CH_3OCH$

Catalytic amounts of carboxylic acids may have a definite influence on the mechanism of the reactions under consideration. In order to eliminate acid catalysis, the C — N bond in 1,2,3,4-tetrahydro-$\beta$-carbolines was dissociated by trifluoroacetic anhydride in tetrahydrofuran (THF):[40]



However, the presence of phenolic hydroxyls in the initial compounds, the acylation of which involves the formation of trifluoroacetic acid, invalidates the conclusions of this investigation to some extent.

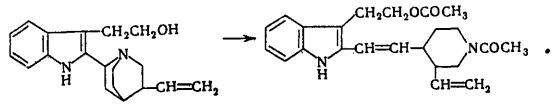
A novel method of converting the isoindoline structure into the 1,2,3,4-tetrahydroisoquinoline structure was described recently[70]. When acted upon by acetic anhydride, isoindoline (LXXII) is cleaved to the unsaturated amide (LXXIII), which then undergoes ring closure in a highly alkaline medium to a 1,2,3,4-tetrahydroisoquinoline derivative:



(LXXII) (LXXIII)

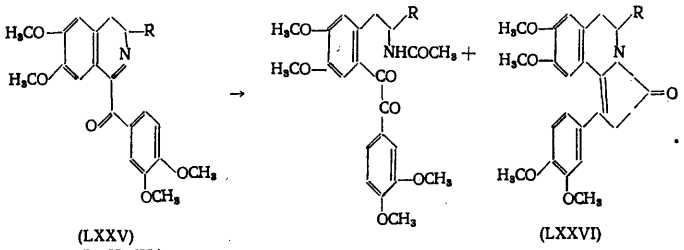
An interesting example of the use of acetic anhydride for the opening of a nitrogen-containing ring is provided by a study[71] undertaken to demonstrate the structure of

cinchonamine (LXXIV). The quinuclidine ring in this alkaloid is dissociated by acetic anhydride at the C — N bond adjoining the carbon atom linked to the indole component of the molecule:



(LXXIV)

It should be noted that unsaturated rings, such as the 3,4-dihydroisoquinoline ring in compound (LXXV), are also readily cleaved on refluxing with acetic anhydride. However, in these cases the process is complicated by the formation of side products of type (LXXVI):[72]



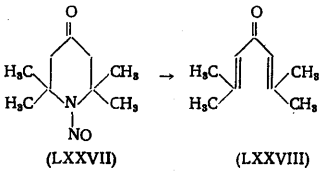
(LXXV) (R=H, $CH_3$)

(LXXVI)

## III. CLEAVAGE OF SATURATED HETEROCYCLES CONTAINING A SECONDARY NITROGEN ATOM

The C — N bond in saturated secondary amines is appreciably stable. Its thermal dissociation can be achieved only on heating to 350 — 400°C. However, the ease of dissociation of this bond may be increased by introducing certain substituents both at the nitrogen and at the $\alpha$-carbon atom. For this purpose, the nitrogen atom should contain strongly electron-accepting groups, namely NO,[73] COR,[74] $SO_2C_6H_5$,[75] Br,[75,76] and others and the $\alpha$-carbon atom should be linked to bulky geminal substituents which increase the strain in the C — N bond[77,78], or to allylic substituents which facilitate the stabilisation of the carbonium cation formed as a result of the dissociation of the C — N bond.

As an example one may quote 2, 2, 6, 6-tetramethyl-*N*-nitrosopiperidin-4-one (LXXVII), which on heating to 80°C yields phorone (LXXVII):[73]

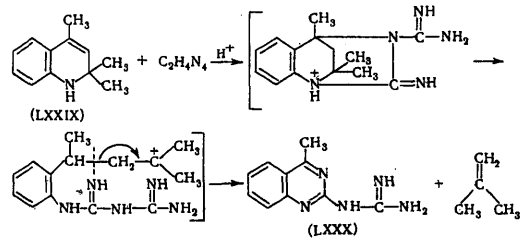


(LXXVII) (LXXVIII)

Two factors operate at once in this case: those associated with the electron-accepting nitroso-group at the nitrogen atom and the two bulky substituents at the $\alpha$-carbon atom, which leads to a comparatively easy dissociation of the ring.

The introduction of electron-accepting polyfunctional groups at the nitrogen atom usually entails not only the dissociation of the C — N bond weakened thereby but also further reactions (various intramolecular condensations and rearrangements) which frequently lead to unexpected compounds.

For example, 2, 2, 4-trimethyl-1, 2-dihydroquinoline hydrochloride (LXXIX) reacts with dicyanodiamide in aqueous solution to give a 68% yield of 2-guanidino-4-methylquinazoline hydrochloride (LXXX):[79,80]



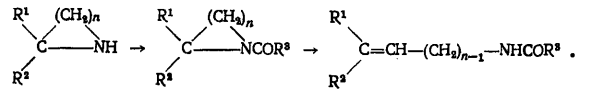
(LXXIX)

(LXXX)

The most thoroughly investigated reactions involving the opening of saturated secondary cyclic amines include the reactions of their *N*-acyl derivatives with the dissociation of the endocyclic C — N bond under the conditions of acid hydrolysis on heating (the reverse Ritter reaction) and also under the influence of compounds such as phosphorus pentoxide under the conditions of the Braun reaction.

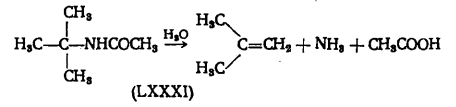
### 1. Dissociation of the C — N Bond under the Condition of the Reverse Ritter Reaction

In order to open the rings of saturated cyclic secondary amines containing geminal substituents at the $\alpha$-carbon atom, the following method is frequently employed nowadays: the amine is converted into an *N*-acyl derivative, which is then cleaved to an unsaturated acyclic compound on heating in an acid medium:



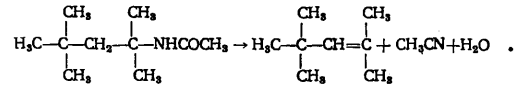
A similar cleavage of amides in which the nitrogen atom is linked to a quaternary carbon atom is known as the reverse Ritter reaction.

It has been shown[74] for t-butylacetamide (LXXXI), which is hardly hydrolysed by alkalis[81], that in an acid medium compounds of this kind readily decompose into an olefin, ammonia, and an acid via the following mechanism:



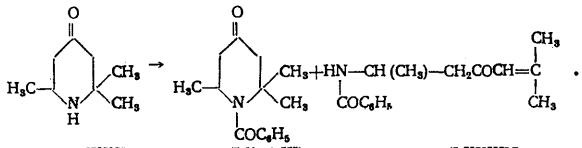
(LXXXI)

Steric hindrance at the $\alpha$-carbon atom makes amides with this structure inert in relation to other substances. These compounds do not react with Grignard reagents and with acylating substances and are not reduced by hydrogen even at elevated temperatures and pressures. However, on heating to boiling, the most unstable of them decompose with formation of the corresponding nitriles and unsaturated compounds[74]:



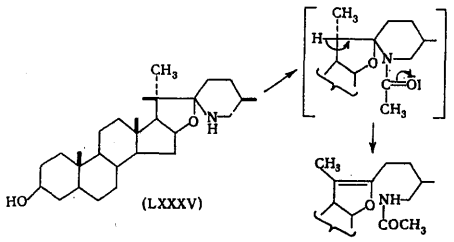
An *NN*-disubstituted amide usually yields an unsaturated monoamide. For example, the interaction of vinyl diacetoneamine [2, 2, 6-trimethyl-4-oxopyrrolidine] (LXXXII) with benzoyl chloride gives rise, together with the

expected *N*-benzoyl derivative (LXXXIII), to its cleavage product—the acyclic amide (LXXXIV):[82]



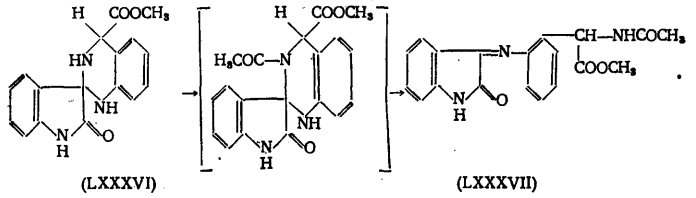
(LXXXII) (LXXXIII) (LXXXIV)

In the *N*-acetyl derivatives of the steroid alkaloids solasodine tomatidine (LXXXV), the piperidine ring is cleaved extremely readily under the conditions of the reverse Ritter reaction: after refluxing for 15 min in the presence of acetic or propionic acid and even at room temperature in the presence of hydrochloric or perchloric acid[83]:



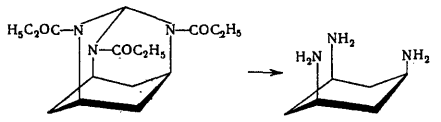
(LXXXV)

In the determination of the structures of isamic acid esters (LXXXVI), the tetrahydropyrimidine ring was opened under the influence of acetic anhydride with formation of the compound (LXXXVII), which has a highly strained system of conjugated bonds[84]:



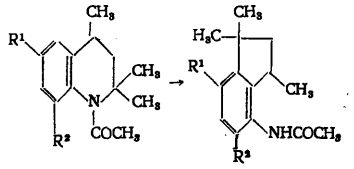
(LXXXVI) (LXXXVII)

When *NN'N"*-Tripropionyl-2,4,10-triaza-adamantane (LXXXVIII) is heated with concentrated hydrochloric acid, *cis*-1,3,5-triaminocyclohexane (LXXXIX) is formed[85]:



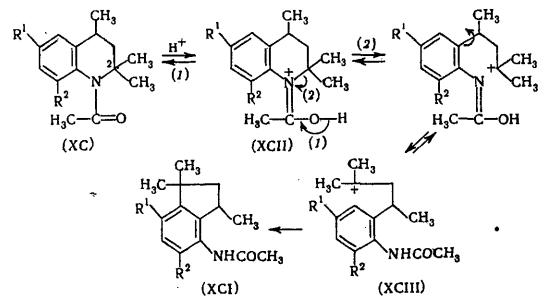
(LXXXVIII) (LXXXIX)

Electrophilic substitution reactions in an acid medium involving sterically hindered cyclic amides can be accompanied by the cleavage of the ring via the reverse Ritter reaction. Thus nitration of substituted 1-acetyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines (XC) (at 100°C for 1 h) in the presence of sulphuric or polyphosphoric acid led to the isolation of the corresponding indane derivatives (XCI):[86]



(XC) (XCI)
($R^1$ и $R^3$=H, Br, $NO_2$)

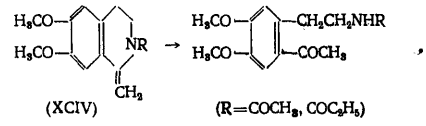
It is believed[86] that the protonation of the amide carbonyl with formation of the unstable ion (XCII) plays a decisive role in the rearrangement:



(XC) (XCII) (XCI) (XCIII)

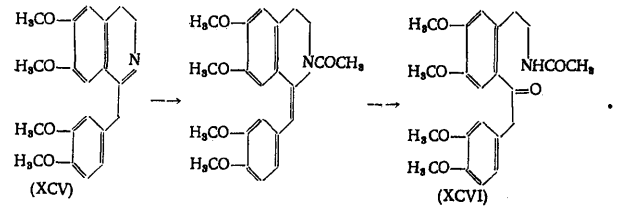
The ion (XCII) may be stabilised either by the loss of a proton (pathway *1*) or by conversion into the carbonium ion (XCIII) (pathway *2*). Then in compound (XCIII) the free *ortho*-position in the benzene ring is attacked with formation of the indane derivative (XCI). The authors[86] state that examination of atomic models demonstrates an appreciable steric interaction between the carbonyl group of the amide and the *gem*-dimethyl substituents at 2-C. After the removal of one methyl group, the strain of the $C_{(2)}-N$ bond is appreciably reduced. Thus *gem*-dimethyl groups at the $\alpha$-carbon atom on the one hand facilitate the dissociation of the $C_{(2)}-N$ bond and on the other hand stabilise the intermediate ion (XCIII).

The opening of the piperidine ring in 2-acyl-1-methylene-1,2,3,4-tetrahydroisoquinolines (XCIV) in the presence of hydrochloric acid is facilitated by the electron-donating effect of the benzene ring with methoxy-groups in the 6- and 7-positions[87]:



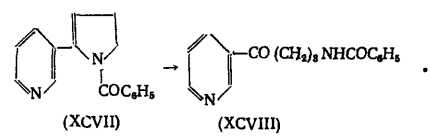
(XCIV) (R=$COCH_3$, $COC_2H_5$)

The dihydroisoquinoline ring of the intermediate in the synthesis of norapormorphine (XCV) is cleaved similarly to compound (XCIV); its *N*-acetyl derivative, containing the benzylidene substituent at 1-C, is converted on heating with hydrochloric acid into the corresponding deoxybenzoin (XCVI):[88]



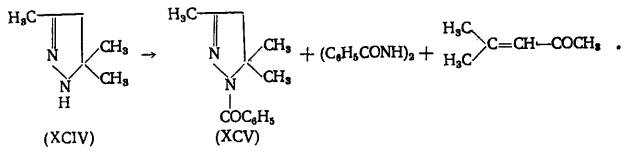
(XCV) (XCVI)

The cleavage of *N*-benzoylmyosmine (XCVII) leading to compound (XCVIII), may serve as an example of the opening of the $\Delta^2$-pyrroline ring[89]:



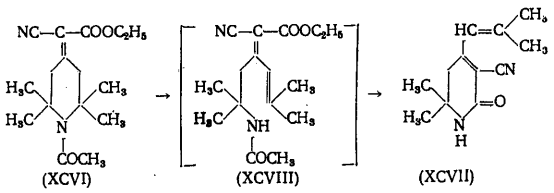
(XCVII) (XCVIII)

When pyrazolines are acylated by acid chlorides, the dissociation of C — N bonds and ring opening are also observed[90–93]. Benzoylation of 3, 5, 5-trimethylpyrazoline (XCIV) leads to the formation of dibenzoylhydrazine and mesityl oxide together with the expected amide (XCV):[93]



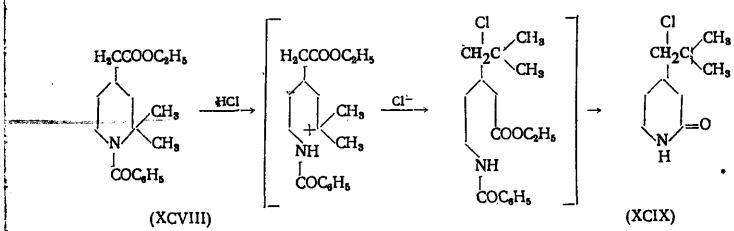
(XCIV) (XCV)

Heating of *N*-acetyl derivatives of piperidine with geminal substituents in the α-position also leads to relatively easy dissociation of the $C_{(\alpha)}$ — N bond accompanied in many cases by further reactions of the substance. For example, 1-acetyl-4-(cyanoethoxycarbonylmethylene)-2, 2, 6, 6-tetramethylpiperidine (XCVI) is converted on heating to 130°C into dehydro-2-piperidinone (XCVII)—a product of the intramolecular condensation of the unsaturated amide (XCVIII):[94]



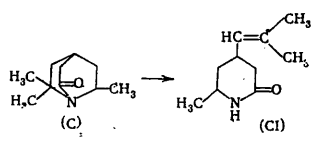
(XCVI) (XCVIII) (XCVII)

When *N*-benzoyl-4-ethoxycarbonylmethyl-2, 2-dimethylpiperidine (XCVIII) is refluxed with hydrochloric acid, a substituted 2-piperidinone (XCIX) [95] is formed, probably via the following mechanism:



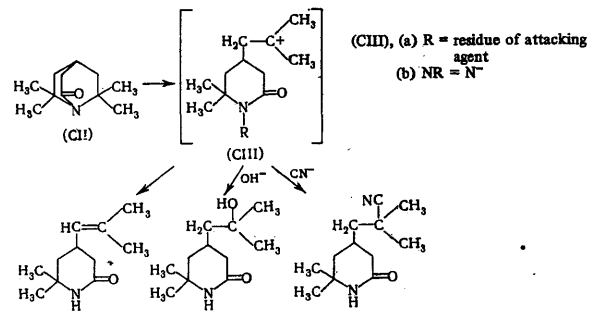
(XCVIII) (XCIX)

In many cases the products of the reverse Ritter reaction were not isolated and their formation was inferred from the change in the infrared spectrum of the reaction mass. For example, after 6, 6, 7-trimethyl-2-quinuclidone (C) ($\nu_{C=O}$ = 1750 $cm^{-1}$) has been allowed to stand for a long time, an absorption band appears in the infrared spectrum in the region of 1640 $cm^{-1}$; it was assigned to absorption by the amide carbonyl of the open-chain form (CI):[96]



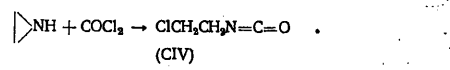
(C) (CI)

A similar cleavage of 6, 6, 7, 7-tetramethyl-2-quinuclidone (CII) takes place even more readily[97]. Here the unstable carbonium cation (CIII) is probably formed initially and then stabilised either by the addition of nucleophilic agents or as a result of the elimination of a proton with formation of an unsaturated compound:



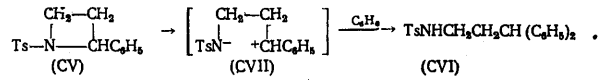
(CII) (CIII), (a) R = residue of attacking agent (b) NR = $N^-$

Evidently the cleavage of cyclic secondary amines by phosgene or sulphonyl chlorides belongs to reactions of this type. Under the influence of phosgene, aziridine readily gives rise to β-chloroethyl isocyanate (CIV):[98]



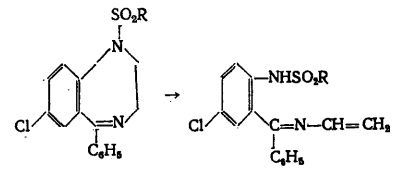
(CIV)

The introduction of the tosyl or methanesulphonyl group at the nitrogen atom also favours ring opening at the C — N bond. On refluxing in benzene, 2-phenyl-*N*-tosylazetidine (CV) is converted into the acyclic sulphonamide (CVI), which is formed as a result of the Friedel — Crafts alkylation of benzene by the cleavage product of the azetidine ring (CVII):[99]



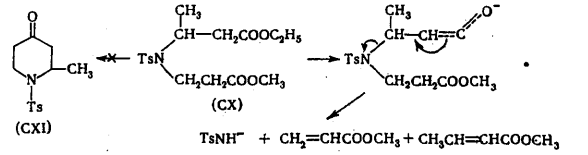
(CV) (CVII) (CVI)

When an attempt was made to remove with the aid of sodium hydride the tosyl (or methanesulphonyl) group from substituted 1, 4-benzodiazepines (CVIII), the vinylimines (CIX) were obtained, their structure being demonstrated by synthesis[100]:



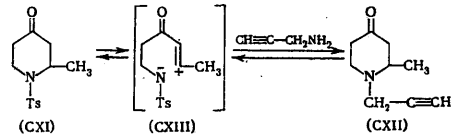
(CVIII) (CIX)

Mistryukov and Aronova[101] observed that, under the conditions of the Dieckmann reaction, the *N*-tosyl derivative (CX) does not give rise to the corresponding γ-piperidinone (CXI) but is decomposed under the influence of sodium hydride via the following mechanism:



(CXI) (CX)

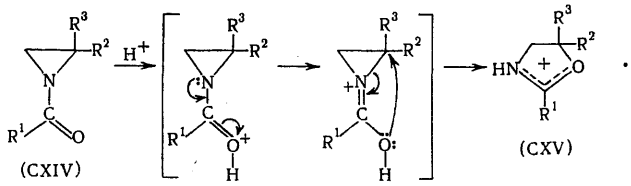
An attempt to split off in a similar way toluenesulphonamide from compound (CXI) was unsuccessful[101]. When 2-methyl-*N*-tosylpiperidin-4-one (CXI) was treated with propargylamine, only traces of the expected 2-methyl-*N*-propargylpiperidin-4-one (CXII) were detected:



(CXI) (CXIII) (CXII)

It is believed[101] that this is either due to the considerable shift of the equilibrium (CXI) ⇌ (CXIII) towards the cyclic form (CXI) or to the reduced nucleophilic properties of the open-chain form (CXIII) owing to the negative charge on the sulphonamide nitrogen.

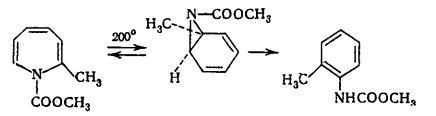
There are numerous publications on the cleavage, under the conditions reverse of the Ritter reaction, of small rings (azetidines and aziridines) with different electron-accepting residues at the nitrogen atom[102-107]. Thus, in a highly acidic medium, substituted 1-acylaziridines (CXIV) are converted quantitatively into the corresponding oxazolonium cations. The study of the $^1$H NMR spectra at −55°C led to the hypothesis[104] that initially the amide group in compound (CXIV) is *O*-protonated with rapid opening of the aziridine ring and conversion into the *O*-protonated oxazolone, the latter being immediately converted into the oxazolonium ion (CXV):



(CXIV) (CXV)

($R^1$ = $CH_3$, $C_6H_5$)

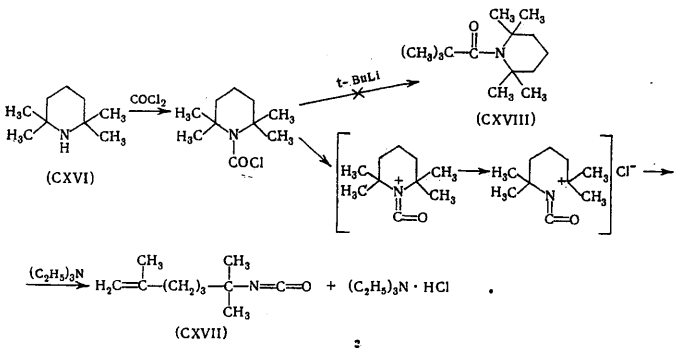
The reactions of 1-*H*-azepines accompanied by aromatisation may be regarded as of the same type. On heating to 200°C, *N*-methoxycarbonylazepines substituted in the 2-position are known to be converted[108,109] in high yields into aromatic urethanes:



In the presence of dilute acids, these processes take place much more readily, frequently at room temperature[109-111]. When the molecule contains several substituents, isomers may be formed as a result of sigmatropic migrations[109].

In a study dealing with amide conjugation in cyclic systems[112], it was noted that attempts at the synthesis of sterically hindered amides, where a planar disposition of the −N−C=O group is impossible, lead to molecular rearrangement already in the course of acylation. This leads to the formation of the usual conjugated amide system. An increase of steric hindrance by the branching of the alkyl substituents in the amine molecule promotes the dissociation of the C−N bond with formation of a stable t-alkyl cation.

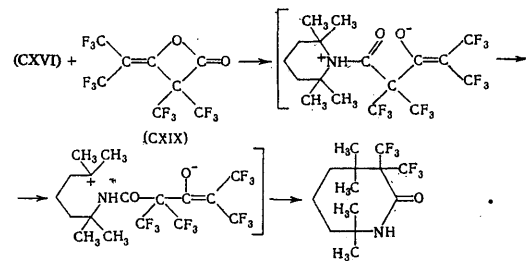
When 2, 2, 6, 6-tetramethylpiperidine (CXVI) reacts with phosgene in the presence of lithium t-butoxide, only the isocyanate (CXVII) is obtained and the expected cyclic amide (CXVIII) is hardly formed:



(CXVI) (CXVIII)

(CXVII)

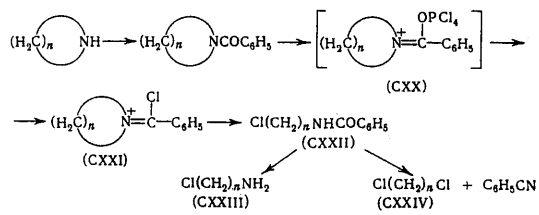
Examination of atomic models showed that the most favourable steric conditions for cleavages of this kind obtain in screen β-lactones as acylating agents. For example, on reaction with the β-lactone (CXIX), 2,2,6,6-tetramethylpiperidine (CXVI) undergoes the following transformations[112]:



(CXIX)

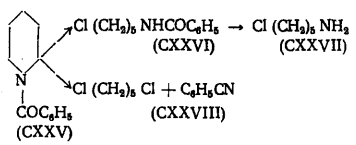
## 2. The Braun Reaction

The dissociation of the C−N bond in secondary cyclic amines can be achieved by a method developed by Braun[113,114]. For this purpose, the benzoyl derivative of the amine is heated with phosphorus pentachloride at 115−120°C. This results in the formation of the unstable tetrachlorophosphoranoate (CXX)† which then readily decomposes to the corresponding chloroimino-derivative (CXXI). Hydrolysis of compound (CXXI) yields a substituted benzoylamine (CXXII), the hydrolysis of which gives the monochloro-substituted amine (CXXIII). Further interaction of compound (CXXI) with phosphorus pentachloride at 180−200°C yields the dichloro-derivative (CXXIV) and benzonitrile:



(CXX) (CXXI) (CXXII) (CXXIII) (CXXIV)

For example, when *N*-benzoylpiperidine (CXXV) was allowed to react with phosphorus pentachloride at 120°C, the product was 1-(*N*-benzamido)-5-chloropentane (CXXVI), the alkaline hydrolysis of which leads to 1-amino-5-chloropentane (CXXVII). An increase of reaction temperatures to 200°C results in the formation of 1,5-dichloropentane (CXXVIII) and benzonitrile[114]:



(CXXV) (CXXVI) (CXXVII) (CXXVIII)

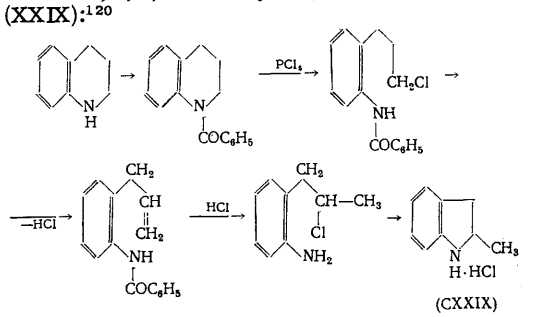
Apart from phosphorus pentachloride, phosphorus pentabromide[116], phosgene[117], and thionyl chloride[117,118] may be used in the Braun reaction. An attempt has been made to employ thionyl bromide also[117], but, on heating, the latter decomposes readily and acts as a brominating

† The lifetime of tetrachlorophosphoranoate derivatives of amides is usually very short. However, in the case of acid amides, containing powerful electron-accepting substituents, these compounds have been isolated and characterised [for example, the products of the interaction of trichloroacetamides with phosphorus pentachloride: $CCl_3C(OPCl_4)$ = NR].[115]

agent, leading to the formation of a large number of side products.

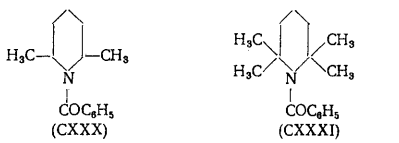
The scope of the Braun reaction is fairly wide and it has been used to open the rings of pyrrolidine[119], 1,2,3,4-tetrahydroquinoline[114,120-122] and its derivatives[123,124], indoline[125] and its derivatives[124,126,127], the alkaloids coniine[128], camphidine[129], etc.

The Braun reaction can be used also for the contraction of nitrogen-containing rings; this was demonstrated in the conversion of 1,2,3,4-tetrahydroquinoline into 2-methylindoline (XXIX):[120]



(CXXIX)

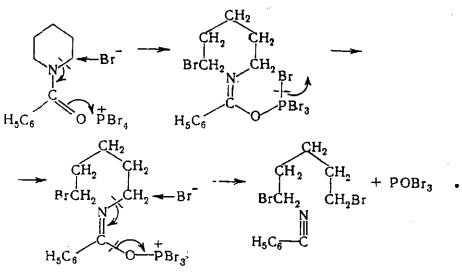
A number of studies have been made on the mechanism of the Braun reaction[130-136], in which the structure of the intermediates, the effects of substituents in the amine and acyl components of the molecule, and the kinetics of the individual stages of the process were considered. Leonard and Nommensen[134] studied several series of *N*-disubstituted benzoylamines in order to determine the effect of the screening of the $\alpha$-carbon atom by alkyl substituents on the course of the Braun reaction. During this investigation, it was established that, whereas *N*-benzoylpiperidine reacts with phosphorus bromide to form 1,5-dibromopentane in 78% yield[114], the yield of the corresponding dibromide decreases with increasing steric hindrance at the $\alpha$-carbon atom. With *N*-benzoyl-2,6-dimethylpiperidine (CXXX), the reaction takes place only to the extent of 19% and the tetramethyl derivative (CXXXI) does not form an aliphatic halogeno-derivative at all[134]:



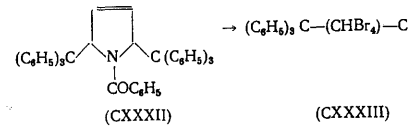
(CXXX) (CXXXI)

Similarly the yield of alkyl halides in the Braun reaction decreases with increasing screening also in the series of *N*-benzoyl derivatives of the isomeric heptyl- and butyl-amines, which supports a bimolecular reaction mechanism.

In addition, it has been shown for *N*-benzoyl-s-butylamine that, in the presence of an asymmetric carbon atom, the situation is reversed. On the basis of these findings, it has been suggested[134] that the bimolecular process in the reaction under consideration may be represented in the following way:

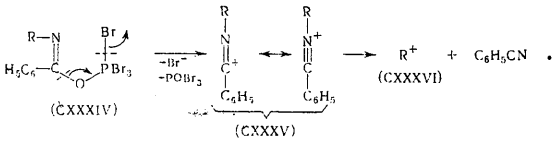


At the same time in a number of cases it has proved possible to achieve the Braun reaction with amides where the approach $\alpha$-carbon atom is hindered by substituents. Thus the interaction of *N*-benzoyl-2,5-di(triphenylmethyl)-$\Delta^3$-pyrroline (CXXXII) with phosphorus pentabromide yields 1,2,3,4-tetrabromo-1,4-di(triphenylmethyl)butane (CXXXIII) in 15% yield[137]:



(CXXXII) (CXXXIII)

Probably such sterically hindered amides react via a different mechanism involving an intermediate "carbonium-ammonium" ion. Leonard and Nommensen illustrate this mechanism by the reaction of *N*-alkylbenzoylamines with phosphorus pentabromide[134]:



(CXXXIV) (CXXXV) (CXXXVI)

The first attack by phosphorus pentabromide leads to the abstraction of a proton from the amide nitrogen and the formation of the intermediate (CXXXIV) which on decomposition can give rise to the "carbonium-ammonium" ion (CXXXV). The latter decomposes on heating into benzonitrile and the carbonium ion (CXXXVI), which, depending on its structure and the nature of the surrounding medium, can be converted into an olefin (with elimination of a proton) or can react with the available bromide ions to form an alkyl bromide.

Certain aspects of the Braun reaction have been investigated in recent years[135,136]. Various conclusions concerning the influence of the screening of the $\alpha$-carbon atom in the amine part of the molecule have been confirmed and it has been shown for *N*-benzoylamine that the Braun reaction can be achieved as a rule with high yields when there are no substituents at the $\alpha$-carbon atom[136].

Comparison of the yields of alkyl halides from substituted *N*-benzoylamines established that they correspond to the stability of the carbonium ion (CXXXVI). For example, the yield of benzyl chloride is 20 — 50%, while benzyl chlorides substituted in the *ortho*-position are formed in 80 — 85% yield.

New hypotheses have arisen in recent years concerning the role of the acyl residue in the Braun reaction. Earlier much importance was not attached to the nature of this part of the molecule. Braun used for acylation benzoyl chloride, which is most readily available, although he believed that any aromatic acid halide may be used for this purpose[114]. Leonard and Nommensen noted[134] that the screening of the $\alpha$-carbon atom in the acyl part of the amide molecule does not affect the yield of the halogeno-derivative. However, Carlson[118,136] showed that the yields of substituted benzyl chlorides from the corresponding *N*-benzoylbenzylamines are higher than from the analogous *N*-acetylbenzylamines. This finding can also be accounted for by the fact that the phenyl group promotes the stabilisation of the intermediate ion of type (CXXXV) to a greater extent than does the methyl group.

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Ordzhonikidze All-Union Institute of Chemistry and Pharmacology, Moscow

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