MODIFIED POLONOVSKI REACTION, A VERSATILE SYNTHETIC TOOL

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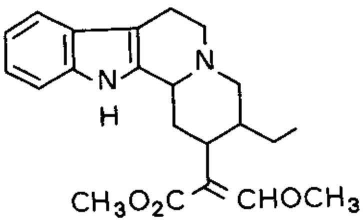
Abstract - Recent synthetic applications of the modified Polonovski reaction are reviewed. In particular, the mechanistic consequences of the reaction are discussed.

Designing the synthesis of a complex organic molecule such as several alkaloids often involves the strategist in questions of formidable difficulty. It can be argued that many of the greatest achievements of synthetic organic chemistry have come within the past two decades, and one can only presume that an increasing rate of new syntheses (sensu stricto, see ref. 1) will be achieved in the future. Of vital importance to the development of new efficient and elegant syntheses is the discovery of new selective chemical transformations, the unit processes which the organic chemist uses as "building blocks" in designing and executing a synthetic strategy and plan in detail. Piperidine unit is an abundant feature of several natural products, as exemplified by corynantheidine 1, (±)-20-epiuleine 2, histrionicotoxin 3, Ψ-pelletierine 4 and morphine 5 in Chart 1. Beyond doubt, the achievement of the correct substitution pattern in the piperidine ring has been a vexed problem.[2] The development of the modified Polonovski reaction[3] has provided a versatile approach to various substituted piperidine systems, in offering a general method of constructing a 5,6-dihydropyridinium system 6 which is susceptible to the attack of carbon nucleophiles in a desired conjugated addition manner. In addition to being a useful means of preparing the dihydropyridine equivalent 6, the modified Polonovski reaction is also amenable to generating α-aminonitriles, synthons of wide applicability in both nucleophilic and electrophilic reactions.

I POLONOVSKI REACTION

I-1 Mechanism

Already in 1927 Max and Michel Polonovski observed that tertiary amines can be demethylated by treating the corresponding N-oxide 7 with acid anhydride.[4] The main products of the reaction were found to be the N-acylated N-demethylamine 8 and formaldehyde (Equation 1).



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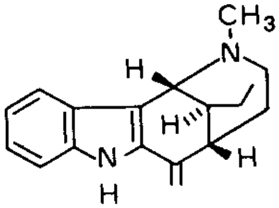

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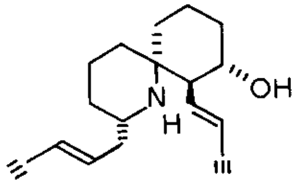

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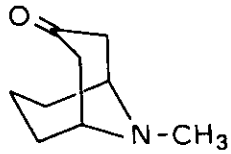

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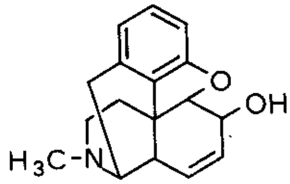

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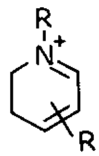

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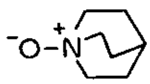

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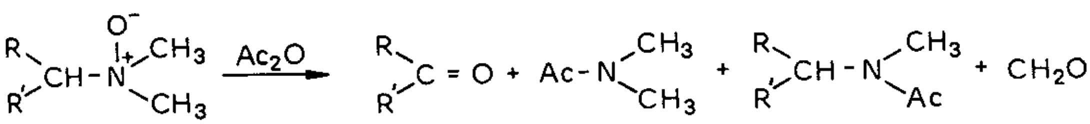
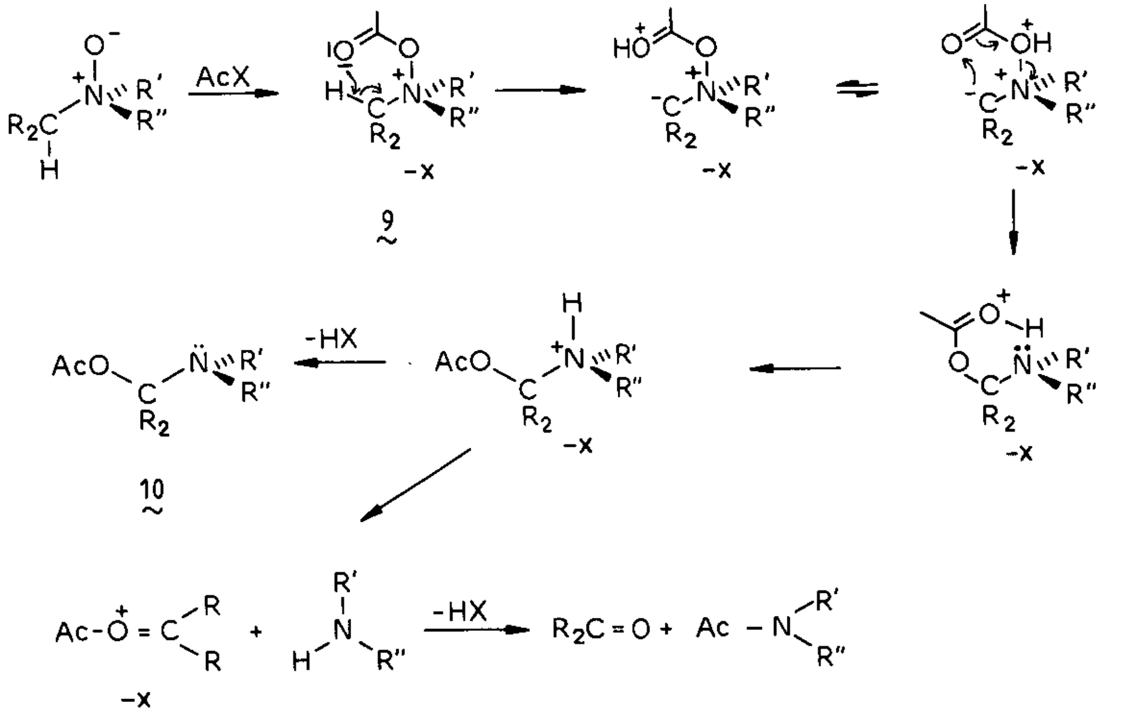
Chart 1



7 8

Equation 1

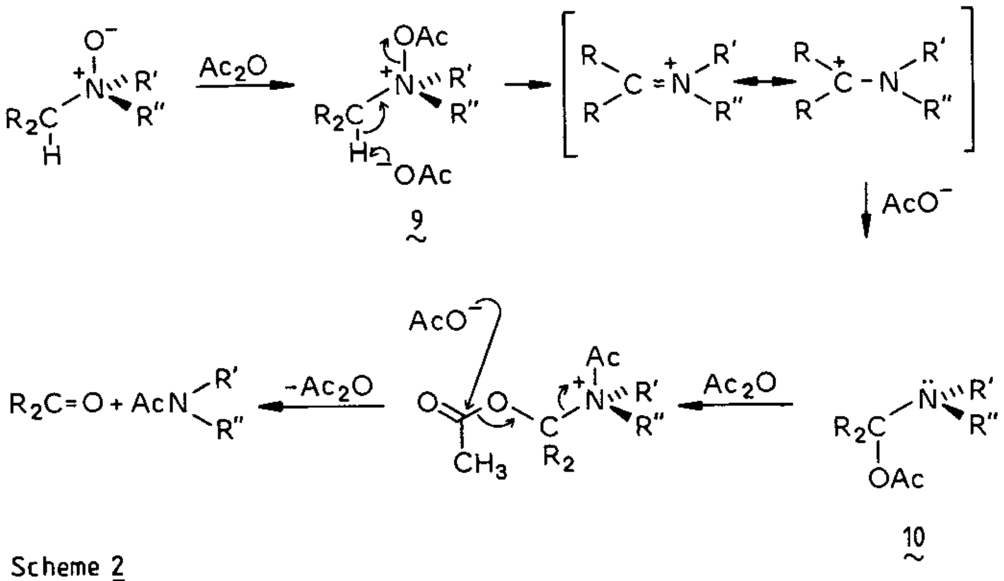


Scheme 1

Only nearly three decades later, in 1954, Wenkert proposed a mechanism for the reaction.[5] This proposition was based on theoretical considerations: to explain the formation of the Polonovski products from compounds with the nitrogen at a bridgehead position,[6] an ylide mechanism was needed so as to avoid violation of the Bredt's rule (Scheme 1).

Huisgen et al.[7] undertook a more careful study on the mechanism of the Polonovski reaction and were able to provide substantial evidence in favor of the mechanism outlined in Scheme 2. They also considered a radical mechanism possibility, as the Polonovski reaction of N,N-dimethyl aryl amine N-oxides had been reported to induce polymerization of styrene.[8] However, this phenomenon was attributed to a side reaction with high temperature coefficient.[7] The intramolecular ylide mechanism of Wenkert[5] was also cast aside, because the reaction was observed to follow a base-catalyzed E_2-elimination scheme.

Later, Huisgen and Kolbeck[9] were able to show that, at least in the case of quinuclidine N-oxide 11, the Bredt's rule was not violated. The only product isolated (in nearly quantitative yield) was the remarkably stable N-acyloxyquinuclidinium salt. The benzoylquinuclidinium compound resisted further reaction to give the Polonovski reaction products.



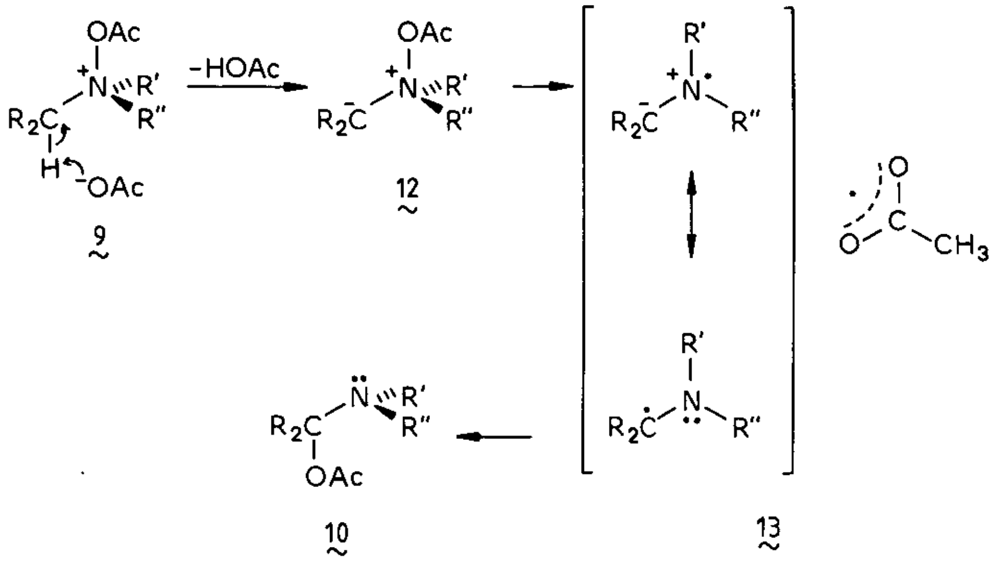
Scheme 2

As previously mentioned, on the basis of the observation that the rearrangement of N,N-dimethylaniline N-oxide in boiling benzene is effective in causing styrene polymerization,[8] a radical mechanism for the Polonovski reaction was advanced. Thus, the ylide 12 was supposed to be cleaved homolytically into the radical pair 13 which would then re-combine to form the aminomethylene ester 10. Referring to the classical work of the two Polonovskis, Craig et al.[10] considered the exothermic nature of the reaction also supportive of a free-radical mechanism.

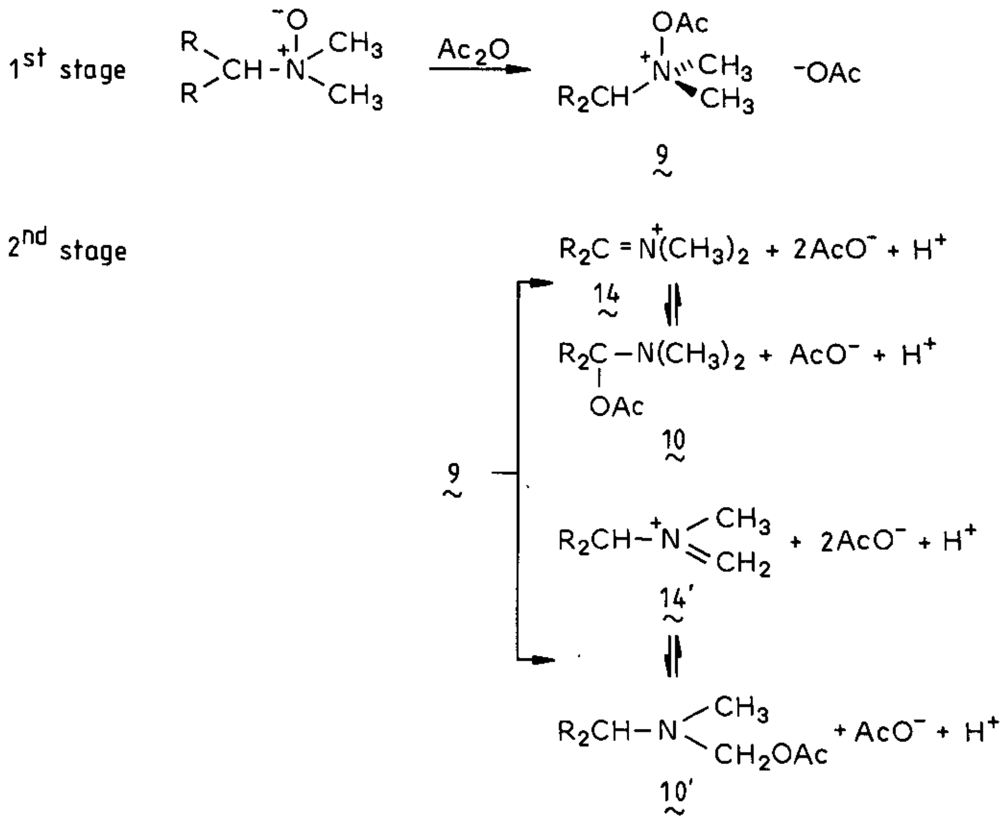
In the course of a rather extensive study of the mechanism of the Polonovski rearrangement by means of ^{18}O labeled acetic anhydride, Oae et al.[11] first proposed that the reaction involves radical mechanism in solvent cage, in accordance with the fact that the acetoxy radical is extremely unstable and short-lived. The facts that the reaction was not affected by the amount or kind of solvents and the addition of radical scavengers, were thought strongly to suggest that the main reaction proceeds through the "radical pair" process shown in Scheme 3.

Later in their studies,[12] the Osaka group came to the conclusion that, in the rearrangements of γ-picoline, acridine, α,N-diphenylnitrone, lepidine, quinaldine and 1-methylisoquinoline N-oxides, the reactions involve at least preponderately an ionic mechanism. It should be pointed out at this point that, although an intramolecular ionic mechanism has often been favored to represent the Polonovski rearrangement, using N^4-oxides of 1,4-benzodiazepines Šunjić et al.[13] unambiguously showed the reaction to proceed in a non-concerted manner.

Conclusive evidence for the mechanism of the Polonovski reaction was obtained by the French group. Studying the reaction by means of ^1H NMR spectroscopy, Michelot[14] was able to identify several crucial intermediates in favor of the mechanism outlined in Scheme 4. The mechanism is essentially



Scheme 3



Scheme 4

identical with the one proposed by Huisgen et al.[7] Further evidence to support this mechanism was gained by Volz and Kiltz[15a], and Volz and Ruchti[15b], who succeeded in isolating the methylene-iminium species 14' and carrying this intermediate on to give the Polonovski reaction products. Quite recently, Gartner[16] has isolated and fully characterized also the acetoxyammonium intermediates 9 as well as the methyleneiminium species 14.

I-2 Acylating reagents - the modified Polonovski reaction

The original Polonovski reaction was conducted using acetic anhydride. It was observed that also other acylating agents can be used in the reaction. Cavé and Michelot[17] pointed out that the acylating reagent has a dramatic effect on the regiochemical course of the Polonovski reaction. Thus, in the reaction trifluoroacetic anhydride and acetyl chloride liberate strong acids, which convert the esters of gem-amino alcohols to the corresponding iminium ion species.

In the modified Polonovski reaction,[18] were the amine N-oxide is treated with trifluoroacetic anhydride,[19] the diminished nucleophilicity and enhanced basicity of the trifluoroacetate ion disfavours the formation of the aminomethylene ester 10'.[16] Two formal pathways for the reaction can thus be expected:[20]

i) an elimination reaction, in which only the C-H bond adjacent to the C-N bond is broken, and thus "normal" Polonovski intermediates are formed.

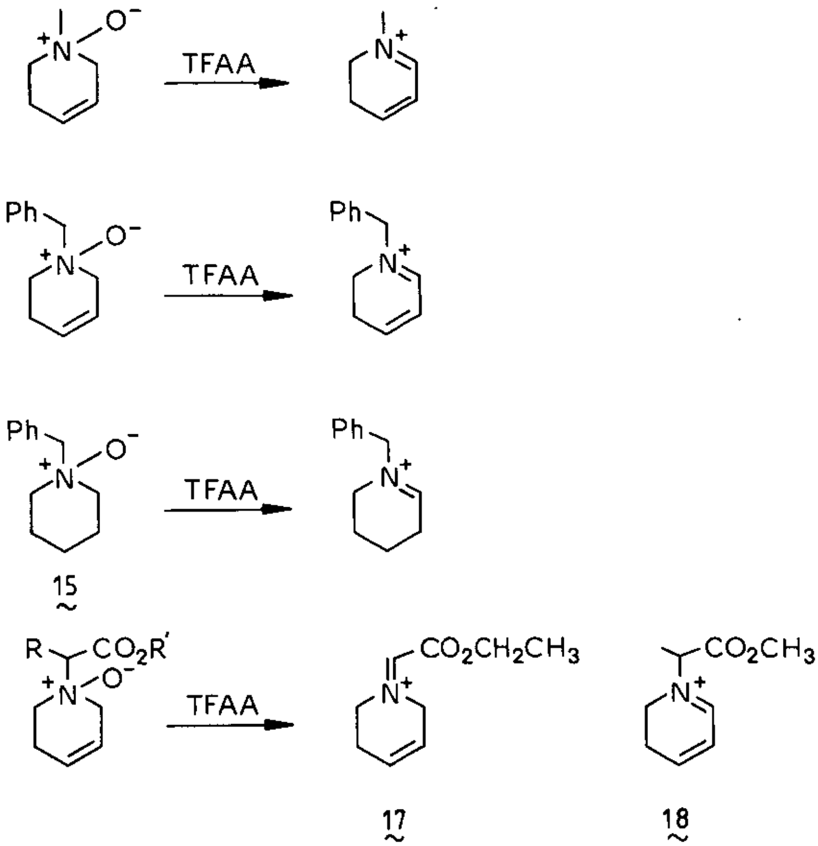
ii) a fragmentation reaction, in which the C-C bond adjacent to the C-N bond is cleaved. Examples of this mode abound in the literature, mainly in connection with the biomimetic syntheses of indole alkaloids.[21]

The factors controlling the course of the modified Polonovski reaction, i.e. elimination vs. fragmentation, can be summarized as follows:

i) in the case of elimination, the most acidic proton α to the nitrogen is abstracted. It has not been explicitly studied whether the deprotonation occurs under kinetic or thermodynamic conditions but it seems that at least with trifluoroacetic anhydride as the acylating reagent, it is the thermodynamically most acidic proton that is cleaved. Thus the following reactions are observed (Equations 2, 3, 4, 5):

Chevolot et al.[22] did in fact claim to have produced the iminium ion 17 from 16a. However, we have shown[23] that the propionic acid derivative 16b did lead to the endocyclic iminium ion 18. Furthermore, observation that the N-benzylpiperidine N-oxide 15 forms the endocyclic iminium species,[24] is also in contradiction with the explanation of the French group.

Gartner[16] has also observed that, with acetic anhydride as acylating reagent, the course of the reaction on cyclohexyldimethylamine N-oxide is temperature-dependent: at low temperatures (-70°C) only kinetic deprotonation (20) is observed, whereas higher temperatures (+80°C) lead to a



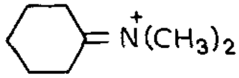
16a R = H, R' = CH_2CH_3
16b R = CH_3, R' = CH_3

Equations 2, 3, 4, 5

statistical 6:1 mixture of 20 and the thermodynamic product 19.

ii) in the case of fragmentation, the C-C bond to be cleaved must be antiperiplanar to the N-O bond.[20] This reasoning is based on a consideration of the reaction in the light of Grob's rules[25] for heteroatomic fragmentation reactions. A dextrous manifestation of this requirement was observed and exploited in the biomimetic synthesis of vinblastine-type alkaloids by Potier's group.[20]

The question of cis/trans-disposition of the N-O bond and the C-H or C-C bond to be cleaved has received scanty experimental consideration. Although previously considered to proceed by cis-elimination,[26] LaLonde et al.[27] showed that in fact a trans-elimination took place in the Polonovski reaction. Thus, treatment of nupharidine 21 with acetic anhydride led, probably via the corresponding iminium ion (note the orientation of the elimination with respect to the furyl



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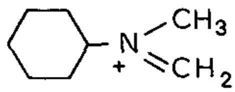

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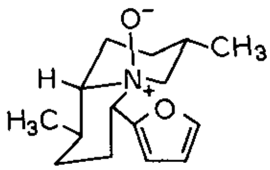

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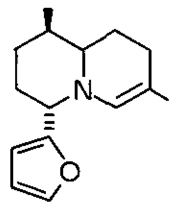

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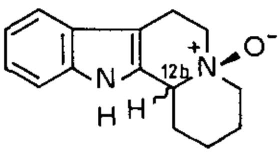
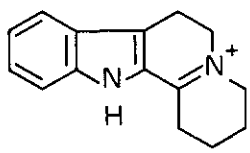


23a 12bβH
23b 12bαH



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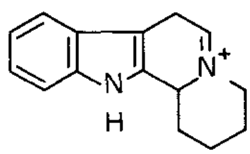

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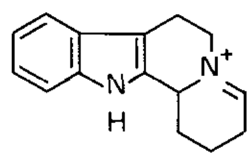

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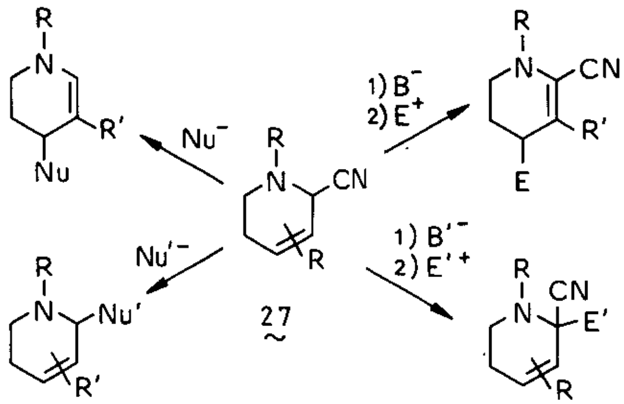
Chart 2

substituent!), to the enamine 22. With appropriately deuterated starting material they were able to verify that the proton abstracted is in fact anti-periplanar to the N-O bond.

Recently, Nakagawa et al.[28] have studied the stereochemical requirements for the generation of an iminium ion from cyclic amine N-oxide. As starting materials, they used the cis and trans-indoloquinolizidines 23a and 23b. In the case of the cis-N-oxide 23a, either the strong acid present (CF_3COOH) could facilitate the isomerization of 25 or 26 to 24, or partial cis-elimination in $(CF_3CO)_2O/CF_3CO_2H$ could lead directly to 24. Furthermore, the authors state that "treatment of either 23a or 23b with $(CF_3CO)_2O$ in methylene chloride at room temperature afforded 24 in 50 % yield". Somewhat surprisingly, they end up concluding "that the reactions proceed probably by trans-elimination".[28]

An important extension of the modified Polonovski reaction of sundry synthetic applications is the cyanotrapping method.[23,29] In this method, the iminium ion 6, generated by means of the modified Polonovski reaction, is converted to the α-aminonitrile 27 simply by treatment of the reaction mixture with an aqueous solution of KCN. The α-aminonitrile 27 is itself an extremely versatile synthetic intermediate permitting both nucleophilic and electrophilic reactions to be conducted on the compound (some of the reactions are depicted in Scheme 5).



Scheme 5

Already prior to the unsaturated aminonitriles 27, the saturated aminonitriles of the type 28 have established their versatility as synthetic intermediates: the carbon atom α to the nitrogen being easily transformable to either nucleophilic or electrophilic at will, this functional unit provides easy access to a masked carbonyl equivalent or an iminium ion (through loss of cyanide ion). The functionality has also been shown to be dehydrocyanated to the corresponding enamine or decyanated reductively to the amine.[30]

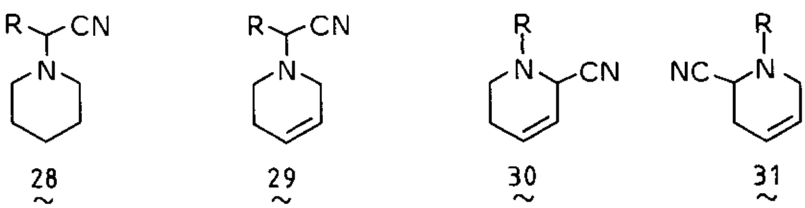


Chart 3

In the piperidine series, we have shown[23] that all three regioisomeric α-aminonitriles 29, 30 and 31 can be selectively prepared [23,31] from the same starting material in short, high-yield syntheses thus giving access to a wide array of variously substituted piperidine synthons. We have also shown that the unsaturated aminonitriles of the type 27 are best alkylated at the 4-position using silyl enol ethers as nucleophiles and employing mild Lewis acid catalysis conditions.[32]

II SYNTHETIC APPLICATIONS

Some synthetic applications of the Polonovski reaction have been reviewed[18,33] but because of the limited scope or availability of these accounts, a more extensive and up-to-date review is presented below. The examples will be presented mainly in pictorial language, as flow charts.

As one can easily anticipate, most of the applications come from alkaloid chemistry. Thus, this chapter is divided in sections dealing with steroid alkaloids, indole alkaloids, simple piperidine derived alkaloids (including some frog toxins and adaline type alkaloids), benzodiazepines and finally other applications of more general interest. A special section is devoted to the synthetic transformations towards the important class of anti-tumor alkaloids of the vinblastine type.

II-1 Steroid alkaloids

The modified Polonovski reaction was first introduced to synthesis in connection with studies concerning steroid alkaloid transformations.[34] Typically, N-methyldihydroparavallarine 32 was oxidatively deaminated to the corresponding 3-oxo compound. Also stereoselective hydroxylation at C-5 could be conducted on Δ^5 steroidal 3α or 3β amides 33a or 33b.

II-2 Indole alkaloids

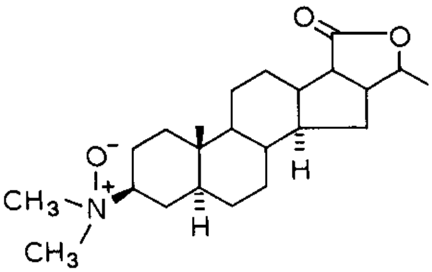
An unexpected fragmentation observed in the modified Polonovski reaction of 3 β-N,N-dimethylamino-Δ^5-androstene N-oxide led Ahond et al.[35] to study the fate of N,N-dimethyltryptamine N-oxide under similar reaction conditions. The fragmentation found its applications in a partial synthesis of ervatamine-type alkaloids 36 from those of vobasine type (dregamine, 34). The original idea presented by the French group[35] had to await until Scott et al.[36] in 1978 realized a transformation of stemmademine 37 to vallesamine 38.

Hugel et al.[37] observed a novel rearrangement of 1,2-dehydroaspidospermine N-oxide under the modified Polonovski reaction conditions.

dl-18,19-Dihydroantirhine 39 was synthesized by Chevolot et al.[38] in a straightforward manner.

Δ^{14}-Vincine 40 has been converted to craspidospermine 41.[22,39]

Using a somewhat altered strategy, the French group devised a total synthesis of the anti-tumor alkaloid ellipticine 43.[40] The strategy consisting of six steps and giving a total yield of 18 % is presented in Scheme 6.



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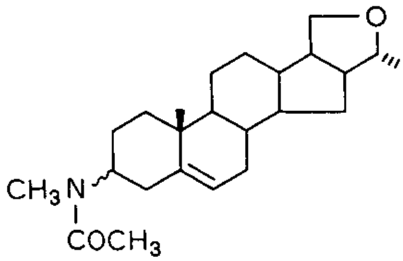
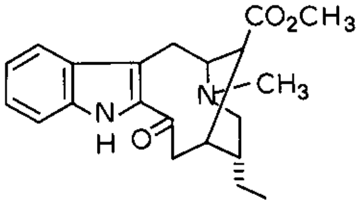


33a 3α

33b 3β



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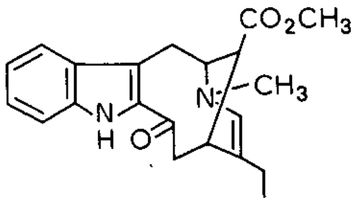

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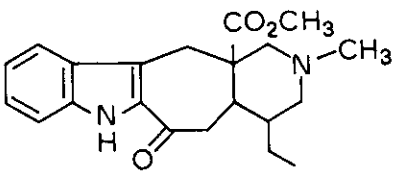

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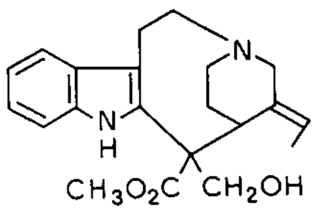

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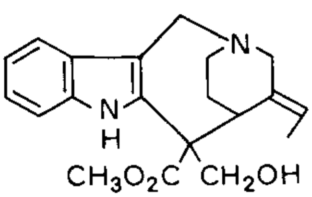

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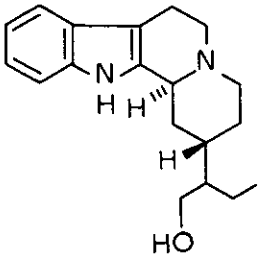
Chart 4



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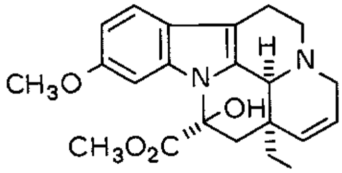

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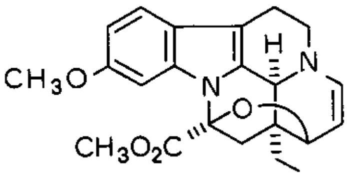

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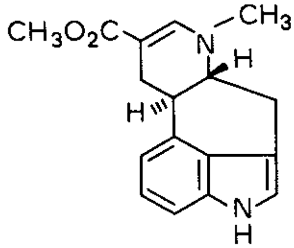

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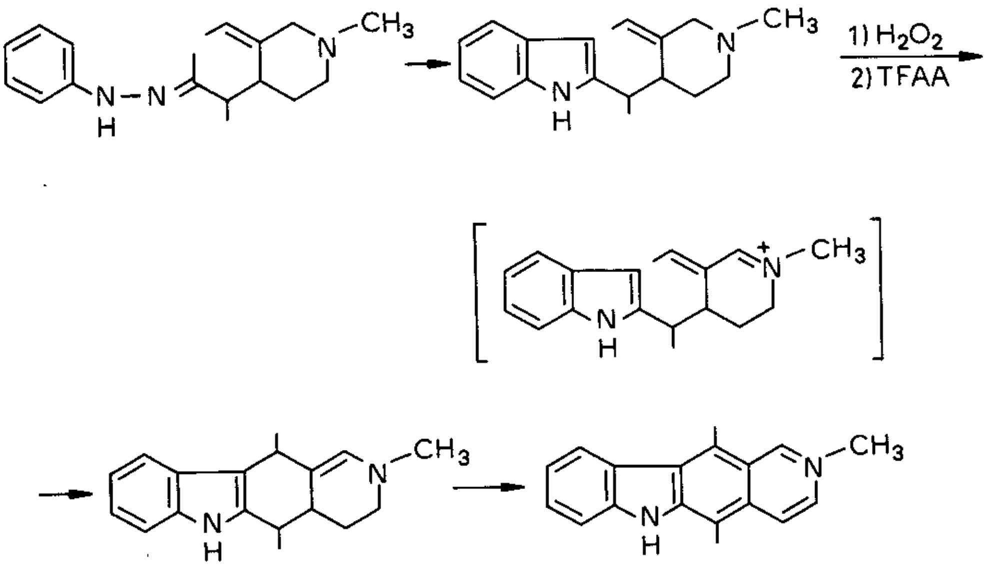
Chart 5



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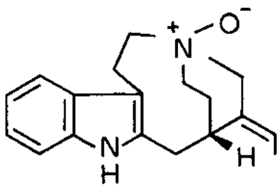
Scheme 6

Mangeney[41] has converted dregamine 34 to Δ^{20}-dregamine 35 with acetic anhydride or acetyl chloride, in contrast to the modified Polonovski reaction of 34 with trifluoroacetic anhydride or trifluoroacetyl acetate, where 20-epiervatamine 36 was formed.

Δ^{7}-Lysergic acid derivatives 42 are conveniently prepared in a one-pot reaction from 9,10-dihydrolysergic acid methyl ester in fair yield.[42]

Takano et al.[43] have devised a new entry to the Strychnos alkaloids. Interestingly, treatment of the unsaturated amine oxide 44 with trifluoroacetic anhydride led to the isolation of only the Strychnos framework 45. The formation of the alternative aspidospermatidine skeleton 46 could not be observed.



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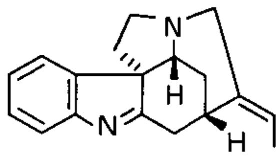

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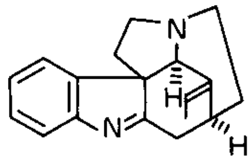

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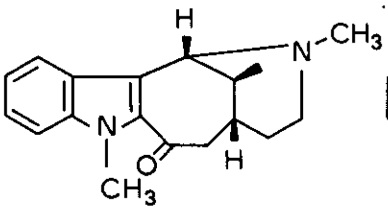

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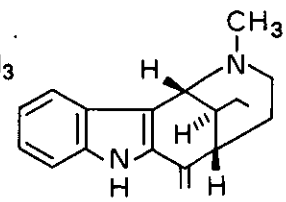

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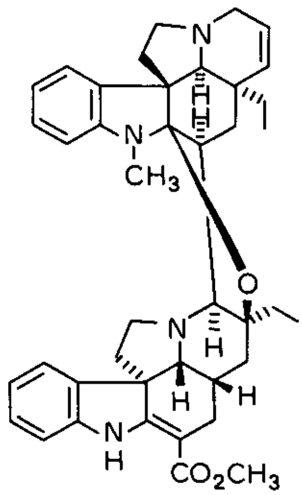

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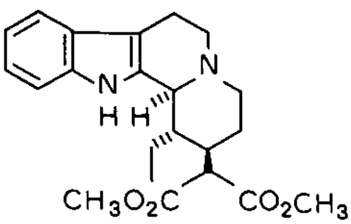

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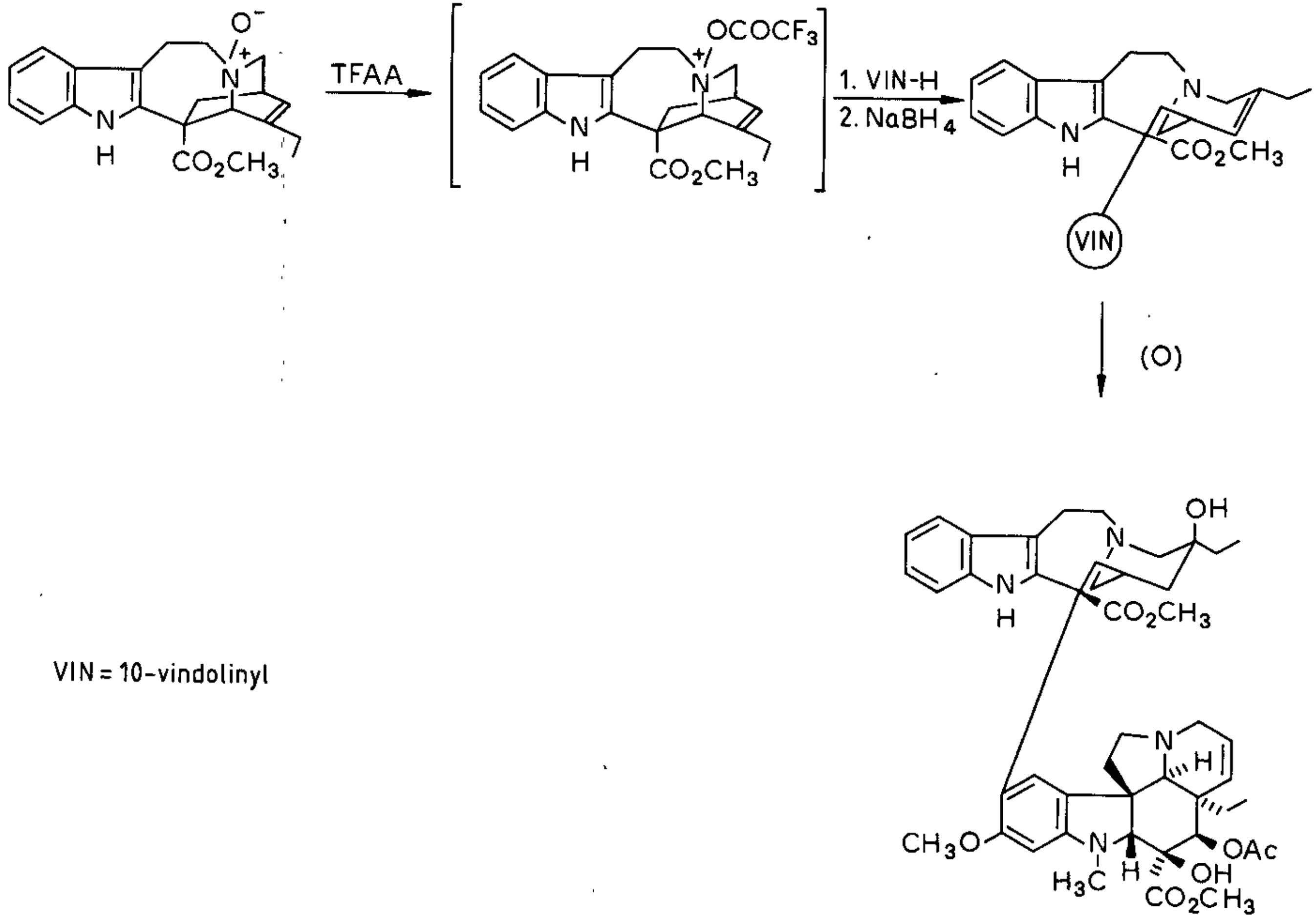
Chart 6



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VIN = 10-vindolinyl

Scheme 7

Recently, the French group has presented a synthesis of the ervitsine type compound 47[44a], a total synthesis of (±)-20-epiuleine 48[44b], a synthetic approach to the novel dimeric ervafoline series 49[44c,d] and a synthetic approach to the "inside" Corynanthe alkaloids 50[44e], all strategies employing the α-aminonitrile synthon generated by means of the modified Polonovski reaction.

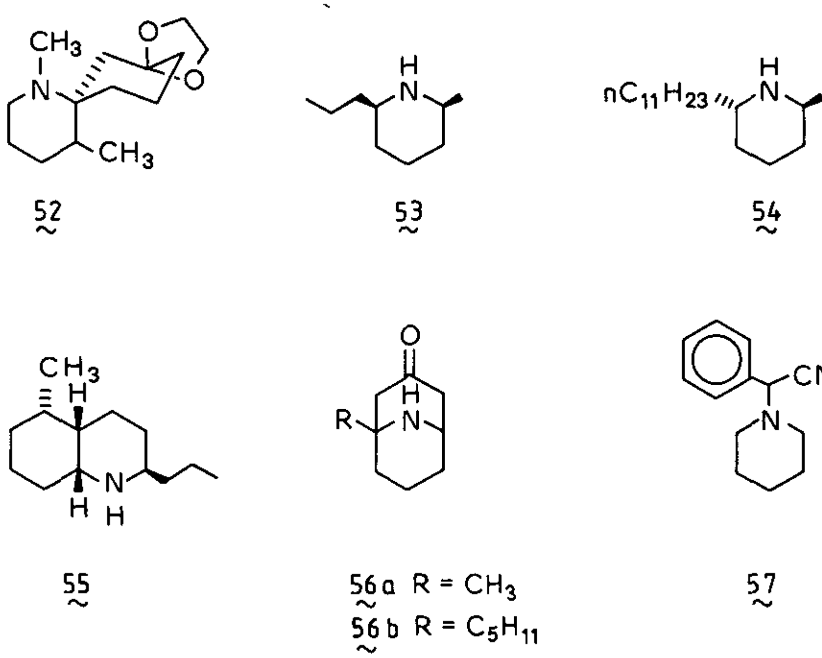
II-3 Vinblastine type alkaloids

The partial synthesis of the anti-tumor alkaloids of vinblastine-type was first realized by Potier et al.[45] in 1975. This important body of alkaloids soon had several research groups working on it: those of Potier[46], Kutney[47], Ban[48] and Atta-ur-Rahman[49].Since two fine reviews by Potier[46] have been devoted to the subject we shall leave it to present the synthesis of vinblastine 51 itself in Scheme 7.

II-4 Piperidine analogues

The α-aminonitrile approach has led to strikingly many synthetic applications. Thus, a 2-spiro-substituted piperidine model 52 of the frog toxin histrionicotoxin 3 was synthesized using this approach.[50]

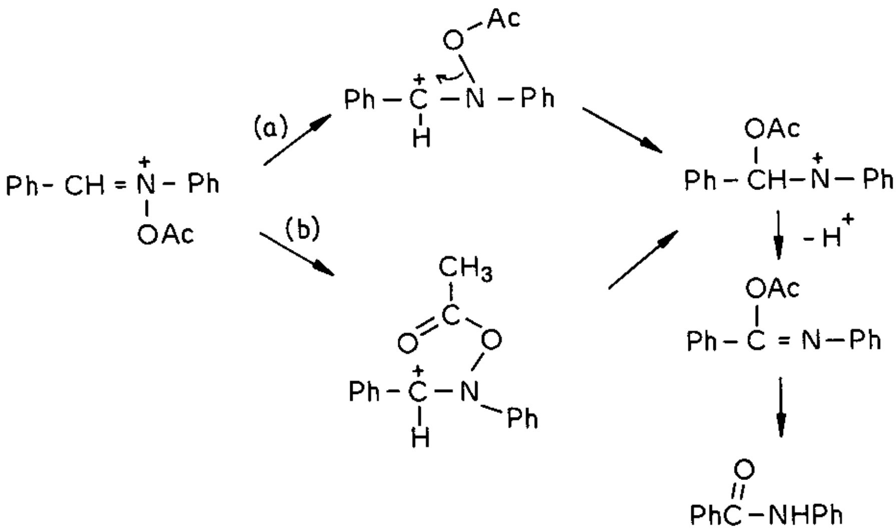
Also the 2,6-dialkylpiperidines (±)-dihydropinidine 53 and (±)-selenopsin A 54[51], the poison-dart frog toxin gephyrotoxin model 55[52] and the ladybug alkaloids 56a and 56b of the adaline series have recently fallen to synthesis by this methodology.[53] The modified Polonovski reaction approach has also been employed by us in the synthesis of deoxygirgensonine 57.[23] The achievements of the French group have recently been reviewed by Husson.[54]



52 53 54

55 56a $R = CH_3$ 56b $R = C_5H_{11}$ 57

Chart 7



Scheme 8

II-5 Benzodiazepines

Since the Polonovski reaction of benzodiazepine N-oxides very closely resembles that of α,N-diphenylnitrone it is worthwhile to notice that, according to Oae et al.,[12] the rearrangement occurs via the competing bridged model (path a) and the cyclic migration model presented by Hanama et al. (path b) (Scheme 8).[55] Of the two paths, the bridged model seems to be the favored one and the rearrangement of the acetoxy group has been suggested to be the rate-determing step.

The Hoffmann-La Roche[56] group has used the Polonovski reaction conditions to transform 1,4-benzodiazepine 4-oxide 58 to pyrrolo[2,1-c]-1,4-benzodiazepine 59.

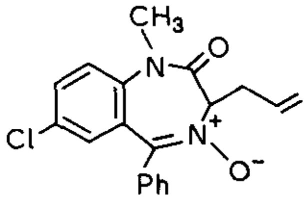
II-6 Other applications

One of the earliest applications of the Polonovski reaction was the synthesis of N-alkylpyrroles from the corresponding Δ^3-pyrrolidine N-oxides.[57]

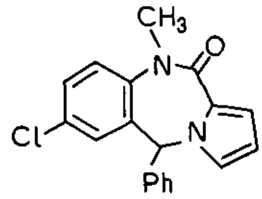
A Z-ethylidene double bond at the 3-position in piperidines can be inverted to the natural E-configuration by means of the modified Polonovski reaction (e.g. 60 to 61).[58]

Wenkert et al.[59] have suggested use of the modified Polonovski reaction for epimerisation of C-3 in geissoschizine. This approach gives highly improved yields over those of the previously employed oxidation-reduction sequence.

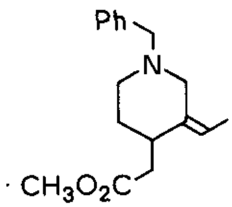
When the N-oxides of 62a and 62b were subjected to the modified Polonovski reaction followed by aqueous KCN treatment, two regioisomeric α-aminonitriles were obtained.[60] Compound 62a with equatorial methyl group at C-4 furnished expectedly the endocyclic α-aminonitrile 63, whereas 62b, where the endocyclic iminium ion formation is blocked by the axial 4-methyl group, was transformed to the 3-cyanomethyl benzazocine 64.



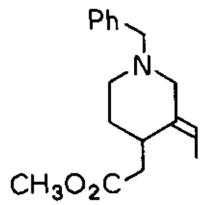
58



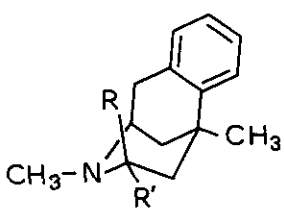
59

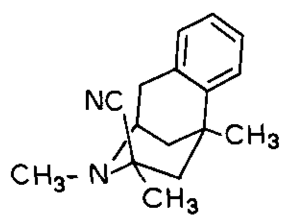


60

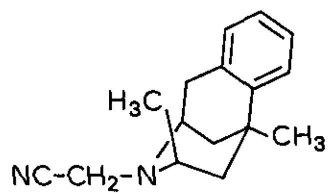


61





63



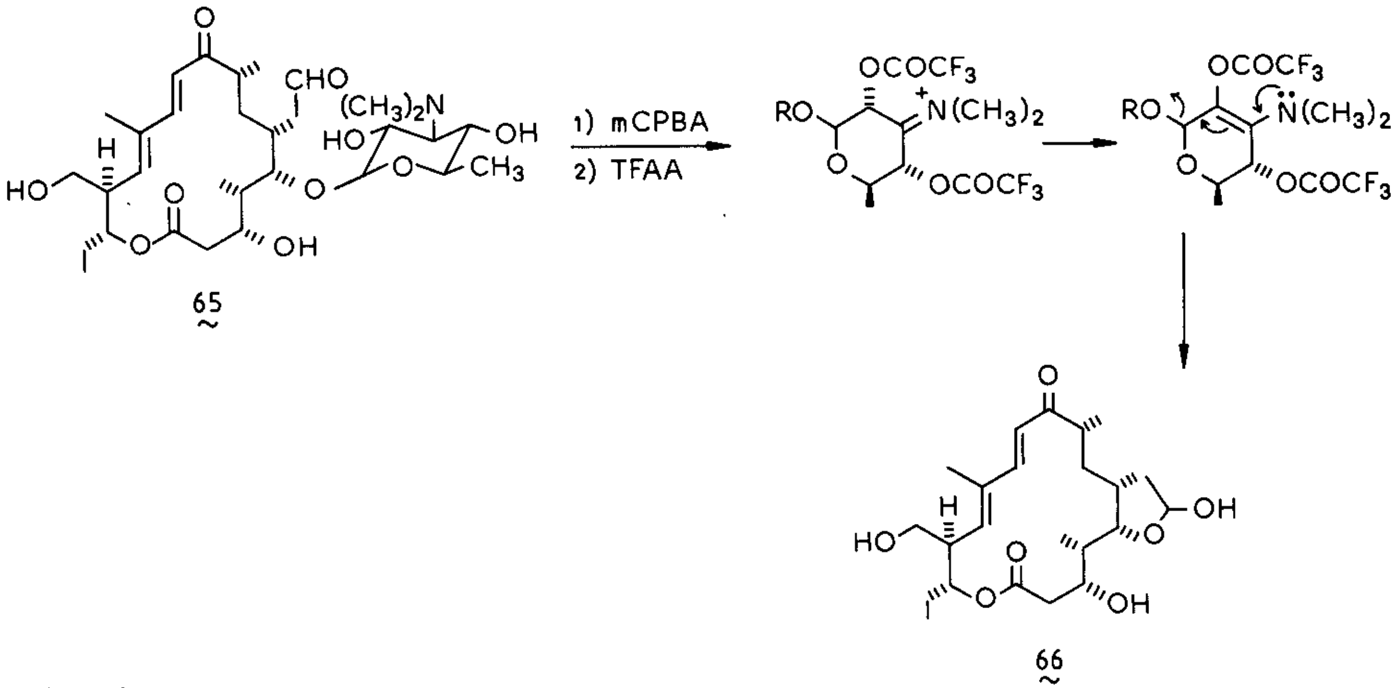
64

62a R = H; R′ = CH_3

62b R = CH_3; R′ = H

Chart 8

An ingenious but neglected use of the modified Polonovski reaction comes from an area rather distant to alkaloid chemistry, viz. that of macrolide antibiotics! The amino sugar moieties have thus been cleaved under conditions mild enough not to destroy the aglycone.[61] The example chosen here is a very recent one from the degradation of O-mycaminosyltylonolide 65 to tylonolide 66 (Scheme 9).[62]



Scheme 9

III CONCLUSIONS

A trisubstituted nitrogen atom is an essential feature of alkaloids, alkaloid analogues and synthetic intermediates on the way to alkaloidal compounds. With the Polonovski reaction and its recent modifications the functionality is amenable to a plethora of useful synthetic transformations. As the examples in this Review show, alkaloid synthesis has already gained from the applications of this reaction. And as we have shown, its usefulness has spread beyond the area of alkaloid chemistry, inter alia to the important field of macrolide chemistry.

The mechanistic basis of the modified Polonovski reaction, and the variables governing its regiochemical outcome, are at present sufficiently well understood so that the reaction can be included in the chemical arsenal of the synthetician working in natural products field.

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