ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2012, *57*(2), 95-99

HYDROACRIDINES. Part 31.[1] SATURATED AMINE OXIDES. Part 9.[2]

STUDY OF A PROCEDURE FOR *N*-DEMETHYLATION OF SATURATED AZAHETEROCYCLIC TERTIARY *N*-METHYLAMINES *VIA* THEIR *N*-OXIDES

Francisc POTMISCHIL,[a]* Claudiu DOBRINESCU,[a] Alina NICOLESCU[b] and Călin DELEANU[c]

[a] Department of Organic Chemistry, Biochemistry and Catalysis, University of Bucharest, 4-12 Regina Elisabeta Blvd., RO-030018 Bucharest-1, Roumania
[b] "Petru Poni" Institute of Macromolecular Chemistry, Group of Biospectroscopy, 41A Aleea Grigore Ghica, RO-6600 Iaşi, Roumania
[c] National NMR Laboratory, "C. D. Nenițescu" Institute of Organic Chemistry, 202B Spl. Independenței, RO-060023 Bucharest-15, Roumania

Received March 21, 2011

The oxidative *N*-demethylation of the *N*-epimeric *N*-oxides of four stereoisomeric *N*-methyl-tetradecahydroacridines, with K_2CrO_4, was performed with yields varying within 39-85%. The course and yield of the reaction is clearly influenced by the geometry of the tricyclic carbon framework of the parent amine, whereas the configuration of the *N*-methyl group (axial or equatorial) has no obvious influence upon yields.

INTRODUCTION

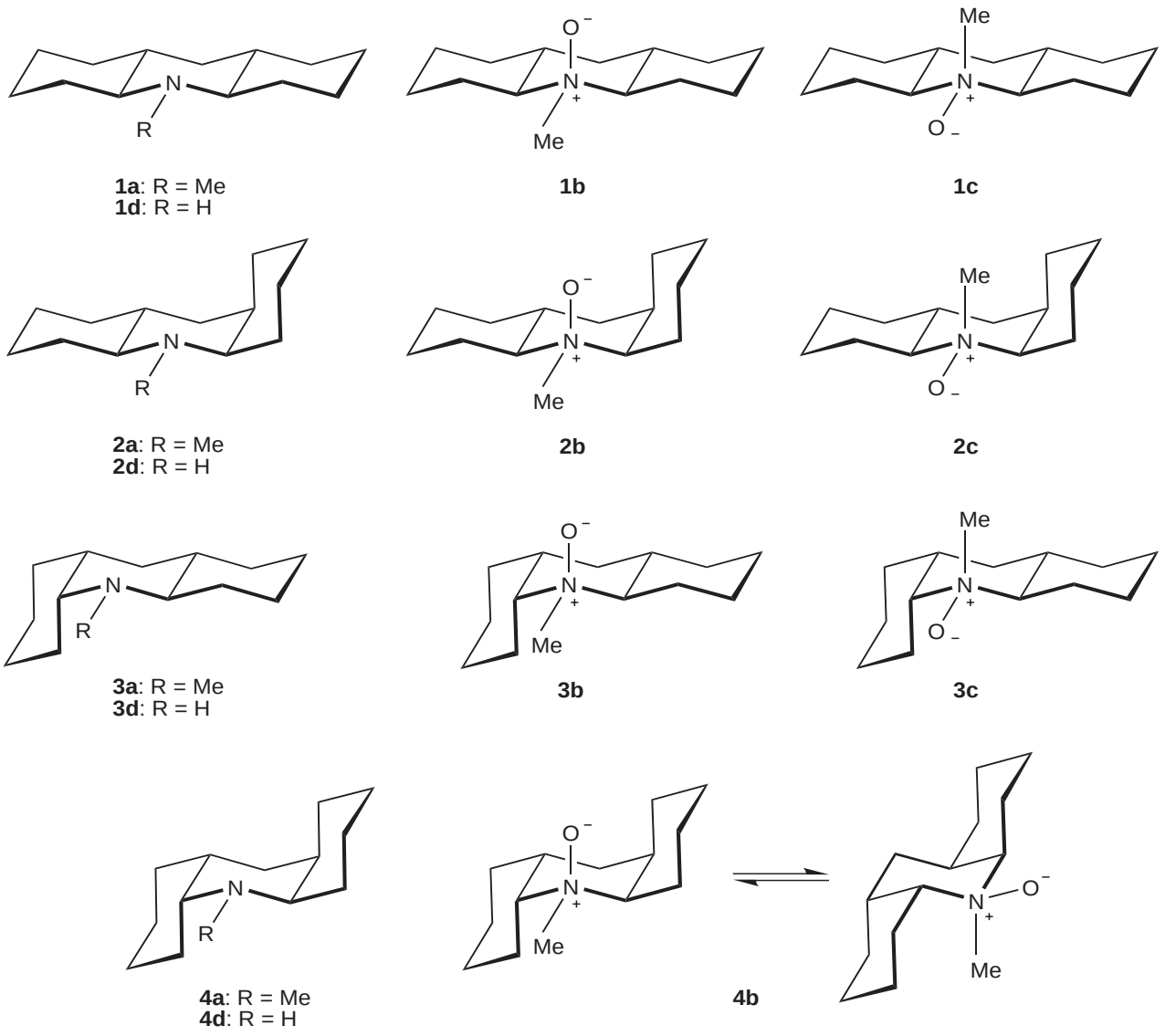
N-Demethylation is a chemical transformation of major importance in drug synthesis, and a variety of methods for the *N*-demethylation of tertiary *N*-methylamines have been studied and reported in the literature.[3] An important category of *N*-demethylation reactions are those conducted *via* the *N*-oxides of the amines, which comprise the classical Polonovski reaction[3,4] and numerous "nonclassical variants" of the Polonovski reaction.[5-17] Oxidation of codeine-*N*-oxide with K_2CrO_4 has been reported, nearly a century ago, to provide nor-codeine in about 24% yield.[18] However, it has been found that, under the same treatment, the *N*-oxides of strychnine and brucine underwent no N—C bond cleavage, but yielded pseudostrychnine and pseudobrucine, respectively,[19] and since, oxidation with K_2CrO_4 has not been further investigated as a method for *N*-demethylation of *N*-oxides.

None of the *N*-demethylation procedures mentioned above[3-18] proved to have general applicability, as the yields considerably depend on the molecular structure of the amines, and, thus, for each amine has to be chosen or developed a specific, most appropriate procedure. Therefore, in our opinion, the reaction of *N*-oxides with K_2CrO_4 deserves more detailed investigations, in order to assess its utility in organic synthesis. Thus, in this study we have performed a series of experiments for the *N*-demethylations of (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-methylacridine (**1a**) to (4aα,8aβ, 9aβ,10aα)-tetradecahydroacridine (**1d**), *via* (4aα,8aβ, 9aβ,10β,10aα)-tetradecahydro-10-methylacridine-10-oxide (**1b**) and *via* (4aα,8aβ,9aβ,10α,10aα)-tetradecahydro- 10-methylacridine-10-oxide (**1c**); of (4aα, 8aα,9aβ,10aα)-tetradecahydro-10-methylacridine **2a**) to (4aα,8aα,9aβ,10aα)-tetradecahydroacridine (**2d**), *via* (4aα,8aα,9aβ,10β,10aα)-tetradecahydro-10-methylacridine-10-oxide (**2b**) and *via* (4aα, 8aα,9aβ,10α,10aα)-tetradecahydro-10-methylacridine-

* Corresponding author: potmisch@yahoo.com

10-oxide (**2c**); of (4aα,8aα,9aα,10aβ)-tetradecahydro-10-methylacridine (**3a**) to (4aα,8aα,9aα,10aβ)-tetradecahydroacridine (**3d**), *via* (4aα,8aα,9aα,10α,10aβ)-tetradecahydro-10-methylacridine-10-oxide (**3b**), and of (4aα,8aβ,9aα,10aβ)-tetradecahydro-10-methylacridine (**4a**) to (4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (**4d**), *via* (4aα,8aβ,9aα,10α,10aβ)-tetradecahydro-10-methylacridine-10-oxide (**4b**); **3c** was not included in the study, because it could not be isolated free of **3b** (for the structural formulae of the compounds, see Scheme 1).

The *N*-oxides utilized in these experiments are very well suited as model-compounds, owing to the following facts: (i) besides the aminoxide group, they possess no other functionalities that could alter the course of the reaction; (ii) the various steric structures of their carbon frameworks allowed to determinate whether, and in which manner, the stereochemistry of the carbon framework influences the course of the reaction; (iii) the *N*-epimeric pairs of *N*-oxides **1b-1c**, and **2b-2c**, respectively, allowed to observe whether, and to what extent, the steric orientation of the N—CH_3 group (axial or equatorial) influences the yield of the *N*-demethylation.



Scheme 1 – Structural formulae of compounds **1a-4a**, **1b-4b**, **1c-3c**, and **1d-4d**.

RESULTS AND DISCUSSION

On *N*-oxidation by 30% H_2O_2, the *N*-methylamines **1a**, **2a**, and **3a** yielded mixtures of the *N*-epimeric *N*-oxide pairs **1b** + **1c**,[20] **2b** + **2c**,[21] and **3b** + **3c**,[22] respectively, in quantitative or near quantitative yields. Because of its all-*cis* fused structure, the tricyclic ring system of compounds **4** is conformationally mobile, and so, the *N*-epimeric *N*-oxides resulted from **4a** undergo rapid conformational interconversion, behaving themselves as a single compound (**4b**)[2] (see Scheme 1). The *N*-demethylation experiments were performed on the *N*-oxides **1b**, **1c**, **2b**, **2c**, **3b** and **4b** in a pure state, separated as reported earlier.[20-22] The reactions of *N*-oxides with K_2CrO_4 were basically conducted under the same conditions as used by Diels and Fischer[18] for codeine *N*-oxide (see experimental section), affording the secondary amines **1d**-**4d** in 39-85% yields. The results are summarized in Table 1.

Inspection of Table 1 shows that substrates **1b** and **1c**, possessing two *trans* junctions next to the *N*-oxide functionality, afford the highest yields (80-85%) in the corresponding secondary amine, free of any by-product. The *N*-oxides containing one *trans* and one *cis* junction (**2b**, **2c** and **3b**) give somewhat diminished yields (about 72%) in secondary amine, contaminated with the corresponding tertiary *N*-methylamine. The *N*-oxide **4b,** with no *trans*, but two *cis* junctions, gives the lowest yield (39%) in secondary amine, also contaminated with the corresponding tertiary *N*-methylamine. From the data of Table 1 further emerges that the steric orientation of the *N*-methyl group (or of the oxygen atom) in the *N*-oxide has no obvious influence upon the course and yield of the *N*-demethylation reaction. Prolongation of the reaction time from 3 hours to 6 hours, generally produces no enhancement of yields.

The identity and purity of **1d** resulted by the *N*-demethylations of **1b** and **1c**, were proved by ^{13}C NMR spectroscopy. The identities and quantitative ratios of **2d**:**2a** and **3d**:**3a**, in the product mixtures resulted by the *N*-demethylations of **2b**, **2c**, and **3b**, respectively, were determined by quantitative ^{13}C NMR spectroscopy, and the identities additionally confirmed by ^{15}N NMR spectra of the mixtures. Because of the conformational mobility of the compounds with all-*cis* junctions, ^{13}C NMR spectroscopy was inappropriate for compounds **4a**, **b**, **d** (extremely broad signals), and thus, the identities and ratio of **4d**:**4a**, resulted by *N*-demethylation of **4b**, were determined by GC-MS.

It is hard to suggest a reaction mechanism able to explain all these results. So far it is only known that the *N*-methyl group is eliminated as formaldehyde.[18] The data presented in Table 1 show that *N*-oxides containing only *trans* junctions next to the aminoxide group (**1b**, **1c**) undergo only the *N*-demethylation reaction, in which the $N^+—O^-$ oxygen atom is most probably involved in an intramolecular process. The occurrence of **2a**, **3a** and **4a** among the reaction products of **2b**, **2c**, **3b** and **4b**, respectively, proves that the *N*-oxides possessing at least one *cis* junction next to the aminoxide group can undergo, instead of *N*-demethylation, also another reaction (a loss or donation of oxygen), in which the $N^+—O^-$ oxygen atom obviously should be involved in an intermolecular oxidation process. (The participation of aliphatic amine oxides as oxidants in various organic reactions is already well documented![4]) To make sure the *N*-deoxygenations were not simple thermal decompositions, we heated aqueous solutions of **2b** and **4b**, in the absence of K_2CrO_4, for 12 h on the boiling water bath, and in both instances the pure, unchanged *N*-oxide was recovered entirely (see the experimental section).

Table 1

Results of the oxidative degradations of amine oxides **1b**, **1c**, **2b**, **2c**, **3b** and **4b**, by K_2CrO_4 in H_2O solution, at 95-100 °C

Substrate	Reaction time (h)	Reaction products (yields, %)
1b	6	**1d** (81)[a]
1c	3	**1d** (85)[a]
	6	**1d** (85)[a]
2b	3	**2d** (84)[b] + **2a** (15)[b]
2c	3	**2d** (72)[b] + **2a** (11)[b]
	6	**2d** (72)[b] + **2a** (11)[b]
3b	3	**3d** (72)[b] + **3a** (2)[b]
	6	**3d** (72)[b] + **3a** (2)[b]
4b	6	**4d** (39)[b] + **4a** (9)[b,c]

[a] Sole product, resulted in a pure state
[b] Products not isolated from the mixture
[c] Additional six unidentified by-products were detected (see experimental)

It could be interesting to note that, qualitatively, the geometry of the carbon framework of the tertiary amines seems to influence the yields of *N*-demethylations *via* the *N*-oxides in a similar manner as those of *N*-demethylations *via* the *N*-nitrosamines. However, quantitatively, the yields *via* the *N*-oxides are higher: on *N*-nitrosative *N*-demethylation, **1a** gave **1d** in a yield of nearly 76%,[23] and **4a** gave **4d** in a yield of only 6.7%.[24]

EXPERIMENTAL

NMR Spectra

The NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer operating at 400.13 MHz (^{1}H), 100.62 MHz (^{13}C) and 40.54 MHz (^{15}N), equipped with a 5mm multinuclear inverse detection *z*-gradient probe head. Typically, 60 mg of sample were dissolved in 1 mL $CDCl_3$ (Aldrich), and 0.7 mL of the solution transferred into a 5mm Norell 507 NMR tube, and the measurements performed at 27°C. The ^{13}C NMR spectra were measured using parameter sets according to the standard Bruker software. The ^{15}N chemical shifts were measured with respect to external nitromethane and reported in ppm downfield from liquid ammonia (δ = 0.0 ppm) corresponding to δ = –381.8 ppm relative to nitromethane. Positive chemical shifts refer deshielding. The ^{15}N chemical shifts were obtained as projections from the 2D indirectly detected ^{1}H,^{15}N-HMBC spectra, employing a standard pulse sequence[25] in the version with *z*-gradients,[26] as delivered by Bruker, with TopSpin 1.3 PL4 spectrometer control and processing software. The HMBC sequence was optimized for 95 Hz direct, and 3-7 Hz long range ^{1}H-^{15}N couplings, and the following parameters were used: 3.130/31.682 Hz (F_2/F_1) digital FID resolution, 2048×128 ($F_2\times F_1$) matrix size, 6410/4005 Hz (F_2/F_1) spectral widths, with overall 0.008/0.78 (F_2/F_1) ppm/data point resolution, 8 scans, 16 dummy scans, 1.5 s relaxation delay, and 70.0 : 30.0 : 50.1% gradient ratio.

GC-Mass Spectra

GC-MS were performed using a Fisons Instruments GC-8000 gas chromatograph coupled to a Fisons Instruments MD-800 quadrupole mass spectrometer operated in the EI mode (70 eV), with a source temperature of 200 °C, interface temperature of 300 °C, injection temperature of 300 °C, carrier gas He. The instrument was operated with a scan speed of 1 scan/s, from 30 to 600 a.m.u.

Syntheses

*(4aα,8aβ,9aβ,10aα)-tetradecahydroacridine (***1d***) from (4aα,8aβ,9aβ,10β,10aα)-tetradecahydro-10-methylacridine-10-oxide (***1b***).*

To a solution of **1b** (0.5 g, 2 mmol) in 5 mL of H_2O, was added 1 mL of aqueous 10% K_2CrO_4 solution (containing 0.6 mmol of K_2CrO_4), and the mixture was heated for 6 h on the boiling water bath. (After approx. 1h of heating, the mixture troubled because of the appearance of an oily product and a greenish-grey precipitate). On cooling, the oily product solidified. The mixture was extracted with 3×15 mL of ether, the combined etheric extracts dried over anh. K_2CO_3 and the ether evaporated, to afford 0.35 g (81%) of pure **1d**. The ^{13}C NMR spectrum of this product was identical with the spectrum of an authentic sample of **1d**,[27] with no traces of any by-product signals.

*(4aα,8aβ,9aβ,10aα)-Tetradecahydroacridine (***1d***) from (4aα,8aβ,9aβ,10α,10aα)-tetradecahydro-10-methylacridine-10-oxide (***1c***).*

From **1c** (0.5 g, 2 mmol), following the procedure described above, 0.367 g (yield 85%) of pure **1d** was obtained, indifferent whether the reaction time was of 6 or 3 h. The reaction product was again identified by ^{13}C NMR spectroscopy.

*(4aα,8aα,9aβ,10aα)-tetradecahydroacridine (***2d***) from (4aα,8aα,9aβ,10β,10aα)-tetradecahydro-10-methylacridine-10-oxide (***2b***).*

With **2b** (0.5 g, 2 mmol) the same procedure was applied as described for **1b** (except the reaction time was only 3 h), and 0.424 g of a mixture was obtained. The quantitative ^{13}C NMR spectrum of the mixture showed a set of 13 intense (approx. 85%) signals with chemical shifts matching those of an authentic sample of **2d**[27] (yield 84%), and a set of 14 weak (approx. 15%) signals with chemical shifts matching those of an authentic sample of **2a**[28] (yield 15%). In addition, the ^{1}H,^{15}N-HMBC spectrum of the mixture showed a cross-peak at 57.0 ppm, matching the ^{15}N chemical shift of an authentic sample of **2d** (found: 57.6 ppm), and another one at 47.6 ppm, corresponding to authentic **2a** (Ref.[2]: 47.4 ppm).

When, in a separate test run, **2b** dissolved in distilled water was heated for 12 h on the boiling water bath, in the absence of K_2CrO_4, then pure **2b** was entirely recovered.

*(4aα,8aα,9aβ,10aα)-tetradecahydroacridine (***2d***) from (4aα,8aα,9aβ,10α,10aα)-tetradecahydro-10-methylacridine-10-oxide (***2c***).*

On following the procedure described for **1b**, from **2c** (0.5 g, 2 mmol) resulted 0.368 g of a mixture of approx. 85% **2d** (yield 72%) and 15% **2a** (yield 11%), indifferent whether the reaction time was of 6 or 3 h. The identification and quantitative evaluation of **2d** and **2a** in the mixture were performed by hand of the ^{13}C and ^{1}H,^{15}N-HMBC NMR spectra, as described above for **2b**.

*(4aα,8aα,9aα,10aβ)-tetradecahydroacridine (***3d***) from (4aα,8aα,9aα,10α,10aβ)-tetradecahydro-10-methylacridine-10-oxide (***3b***).*

By the procedure described for **1b**, from **3b** (0.5 g, 2 mmol) resulted 0.328 g of a mixture of approx. 95% **3d** (yield 72%) and 5% **3a** (yield 2%), indifferent whether the reaction time was of 6 or 3 h. The ^{13}C NMR spectrum of the mixture showed a set of 13 intense (approx. 95%) signals with chemical shifts matching those of an authentic sample of **3d**,[27] and a set of 14 weak (approx. 5%) signals matching the chemical shifts of an authentic sample of **3a**.[29] The ^{1}H,^{15}N-HMBC spectrum of the mixture showed a cross-peak at 66.2 ppm, matching the ^{15}N chemical shift of an authentic sample of **3d** (found: 66.9 ppm), and another one at 48.7 ppm, compatible with the ^{15}N chemical shift of authentic **3a** (Ref.[2]: 50.9 ppm).

*(4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (***4d***) from (4aα,8aβ,9aα,10α,10aβ)-tetradecahydro-10-methylacridine-10-oxide (***4b***).*

According to the procedure described for **1b**, from **4b** (0.5 g, 2 mmol) resulted 0.335 g of a products mixture. Examination by GC-MS revealed that the mixture was formed of 52% **4d** (yield 39%), 12% **4a** (yield 9%), and six additional compounds in concentrations varying from 2.5% to 14.5%, which could not be identified.

When, in a separate test run, **4b** was heated together with the K_2CrO_4 solution at only 60 °C, then after 4 h no sign of reaction could be observed. When, in another test run, **4b** dissolved in distilled water was heated for 12 h on the boiling water bath, in the absence of K_2CrO_4, then pure **4b** was entirely recovered.

CONCLUSIONS

Although in the literature have been reported a quite large number of procedures for the *N*-demethylation of tertiary amines (particularly of alkaloids), thus far none of them proved to have general applicability. As the yields considerably depend on the structure of the amines, for each particular amine must be chosen or worked out the most appropriate procedure. The *N*-demethylation procedure studied in this paper is inappropriate for, e.g., opiate alkaloids, but affords very good yields (72-85%) when applied to saturated polycyclic *N*-methylamines with stable conformations. It requires only cheap reagents and solvents, and working temperatures that do not exceed 100° C. During the reaction, the toxic Cr^{6+} ion is largely reduced to much less toxic Cr^{3+}, which can be precipitated with lime, and removed from the wastewater as $Cr(OH)_3$.

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