STERIC EFFECTS IN THE IODOMETHYLATION OF SPATIAL ISOMERS OF MATRIDINE

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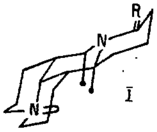
In spite of the fact that the stereoisomeric matridine (I) and allomatridine (II) are constructed of two trans-quinolizidine fragments, the first of them forms a monomethiodide and the second a dimethiodide [1]. This is due, in all probability, to steric effects connected with the specific arrangement in space of the atoms of each isomer.

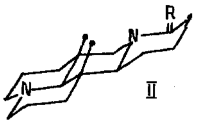
Consequently, a study of the iodomethylation reaction in relation to the other known isomers of matridine – sophoridane (III) and isosophoridane (IV) – is of definite interest.

We performed iodomethylation by adding drop by drop a solution of methyl iodide to an acetone solution of one of the bases (II-IV) at the boil. The course of the reaction after the addition of every two drops was checked by TLC [Al_2O_3, acetone–ethanol (20 : 5)].

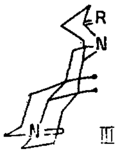
In the case of compounds (II) and (III), when the initial base is still present in the reaction mixture only the monomethiodide is formed. The monomethiodides obtained in this way are identical with the N_1-monomethiodides of (II) and (III), respectively [2] (mp, R_f, IR spectrum). As soon as all the initial base has been converted into the monomethiodide, the dimethiodide is formed. Consequently, the nitrogen atoms of (II) and (III) are methylated successively, and while the formation of the monomethiodide from the base takes place readily that of the dimethiodide from the monomethiodide takes place with considerably more difficulty.



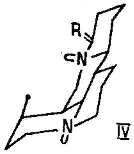
I



II



III



IV

I–IV $R=H_2$
(I IV)a $R=O$

On considering Dreiding models of the molecules of (II) and (III) it can be seen that a methyl group attached either to N_1 or to N_{16} undergoes no spatial hindrance whatever, and this explains the production of these two isomers of the mono- and dimethiodide derivatives, even though their N_{16} atoms are present in different quinolizidine systems [in (II) both nitrogen atoms are in a trans quinolizidine system, and in (III) N_1 is in a trans system and N_{16} in a cis system].

In matridine (I), the methyl group attached to N_1 would interact with the H_a's at C_{17} and C_{11} (butane interaction), and the possible inversion at the nitrogen atom would lead to a still more hindered configuration. This apparently explains the inertness of N_1 of matridine in the iodomethylation reaction.

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So far as concerns (IV), the approach of the reagent to N_1 is not hindered, while a methyl group attached to N_{16} must interact with H_a at C_4 and the possible inversion at the nitrogen atom must lead to the unfavorable boat form of ring C where the N-methyl group should be of the "bayonet" type. Consequently, isosophoridane (IV) gives only the N_1 monomethiodide even with an excess of methyl iodide. Consequently in this case, only the nitrogen of the cis nucleus methylates.

It can be seen from an analysis of the results obtained that in these reactions it is not the basicity of the nitrogen that has the primary importance but steric effects due to the general geometry of the molecule, and that in the iodomethylation reaction only that nitrogen atom of a rigidly fixed heterocyclic molecule will participate for which a methyl group, after attachment to it, will not undergo nonbound skew interactions; in the opposite case, there will "be no room" between the surrounding atoms. It may be assumed that all the matridine isomers of the cis series will form only N_1-monomethiodides.

Interesting results were obtained in the thermolysis of the methiodides of (II-IV) and of (Ia-IVa). Thin-layer chromatography [Al_2O_3, acetone–ethanol (20 : 5)] and paper chromatography [isobutanol–HCl –H_2O (100 : 20 : 20)] of the thermolysis products showed that in all cases demethylation took place to the extent of 40-60%. On rapid sublimation, the monomethiodides, for example, sophoridine monomethiodide and sophoridane N_1-monomethiodide, gave the demethylated bases (IIIa) and (III), respectively, and sophoridane dimethiodide gave the N_1-monomethiodide. With more prolonged heating (2-5 min) the dimethiodides are converted completely into the demethylated bases.

In the thermolysis of allomatridine monomethiodide, there is a partial formation of the dimethiodide, which can be explained by the iodomethylation of the second nitrogen atom of the monomethiodide by the methyl iodide obtained as a result of thermolysis.

EXPERIMENTAL

Preparation of the Mono- and Dimethiodides. At the boil, a solution of 0.6 ml (0.00962 M) of methyl iodide in 5 ml of acetone was added drop by drop to a solution of 1 g (0.00427 M) of allomatridine, sophoridane, or isosophoridane until the initial compound could no longer be detected in the reaction mixture by chromatography. As soon as none of the initial base remained in the reaction mixture (determined chromatographically), it was separated into two portions. The corresponding monomethiodides were obtained from the first portion after the elimination of the solvent (Table 1).

The remaining amount of the acetone solution of methyl iodide was added to the second portion of the reaction mixture. The crystals that formed were washed with acetone and recrystallized from ethanol (see Table 1). The iodine contents in the mono- and dimethiodides determined by titration corresponded to the calculated figures.

TABLE 1. Results of the Thermolysis of the Methiodides of the Compounds Studied

Substances subjected to thermolysis	R_f	Temperature, °C of melting	Temperature, °C of thermolysis	Products obtained *
Allomatrine methiodide	0,44	295	310	II a
Allomatridine monomethiodide	0,41	235	265	II, dimethiodide of (II)
Allomatridine dimethiodide	0,31	290	310	II, Monomethiodide of (II)
Matridine methiodide	0,45	237	255	I
Sophoridine methiodide	0,38	238	260	III a
Sophoridane monomethiodide	0,34	234	255	III
Sophoridane dimethiodide	0,28	305	325	III, Monomethiodide of (III)
Isosophoridine methiodide	0,43	317	325	IV a
Isosophoridane methiodide	0,37	235	255	IV

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*In all cases a certain amount of the initial methiodide was present in the reaction products.

The thermolysis of the methiodides was performed in open tubes. A tube with 0.1 g of the appropriate methiodide was kept for 1-2 min in Wood's metal previously heated to 15-20° C above the melting point of the sample.

After metling, sublimation took place without decomposition (charring). The contents of the tube were dissolved in ethanol and chromatographed (see Table 1).

SUMMARY

1. Only that nitrogen atom of a heterocyclic molecule can take part in the iodomethylation reaction for which a methyl group, after addition to it, undergoes no steric hindrance.

2. The rapid thermolysis of the methiodides of the isomers studied leads to partial demethylation without the decomposition of the molecule of the base itself.

LITERATURE CITED

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