QUATERNARY DIHYDROPYRROLIZINES*

A. KLÁSEK[a], P. SEDMERA[b] and F. ŠANTAVÝ[a]

[a] *Chemical Institute, Medical Faculty, Palacký University, 775 15 Olomouc,*
[b] *Institute of Microbiology, Czechoslovak Academy of Sciences, 142 20 Prague*

Received May 28th, 1974

The structure *II* is assigned to the quaternary dihydropyrrolizine derivative which arises by reaction of clivorine (*I*) with acetic anhydride. Attempts have been made to prepare dihydropyrrolizine analogs from other pyrrolizidine alkaloids of othonecine type.

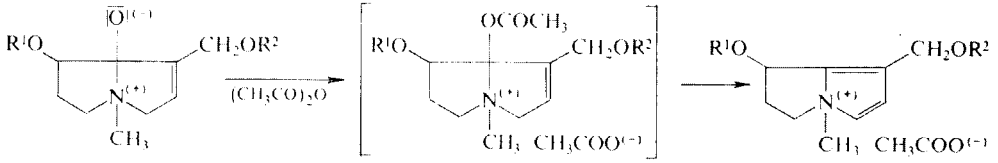
In one of our previous papers[1], we have described the reaction of the pyrrolizidine alkaloid clivorine with acetic anhydride in pyridine which gives rise to a substance designated as acetylclivorine. Since the structure of clivorine (*I*) is now definitely known[2] and has been confirmed by X-ray analysis[2,3], we have studied the structure of acetylclivorine.

A follow-up of the course of the reaction of clivorine (*I*) with acetic anhydride in pyridine by thin-layer chromatography showed that, at room temperature, only trace amounts of acetylclivorine are obtained; the main portion is formed on heating during evaporation of the reaction mixture. Acetylclivorine can also be prepared by reaction of clivorine (*I*) with acetic anhydride in a solution of benzene or chloroform on boiling and, in the presence of pyridine, respectively. Amorphous acetylclivorine is a very unstable substance[1] which polymerizes when trace amounts of acids are present. This instability is obviously caused by an incomplete removal of traces of acetic anhydride and acetic acid. Acetylclivorine is stable in crystalline state and gives a deep violet colour reaction with the Ehrlich reagent.

Mattocks[4] reported that dehydrogenation of unsaturated pyrrolizidine alkaloids or dehydration of their N-oxides affords dihydropyrrolizines. Later on, those dihydropyrrolizines were prepared[5–13] in pure state from a series of unsaturated pyrrolizidine alkaloids and studied in detail. They are very unstable substances which easily polymerize even in slightly acidic media; they were also found[11,14] native in plants. The toxic effect of pyrrolizidine alkaloids is explained by their conversion to dihydropyrrolizines with a high alkyiation ability to —OH and —SH substances. All the dihydropyrrolizines give a deep blue up to violet colour reaction with the Ehrlich reagent.

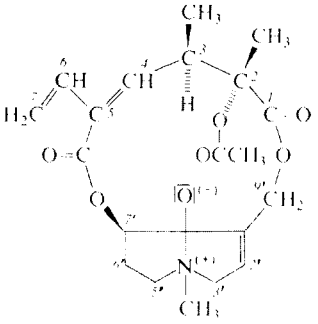
* Part XXII in the series Pyrrolizidine Alkaloids; Part XXI: This Journal *38*, 2658 (1973).

** Presented at the Days of Organic Chemistry, Liblice near Prague, May 6—8th, 1974.

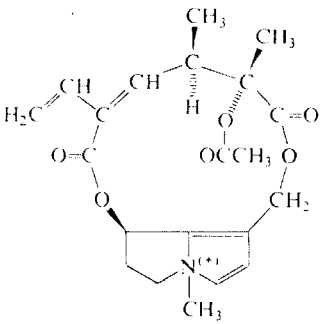


SCHEME 1

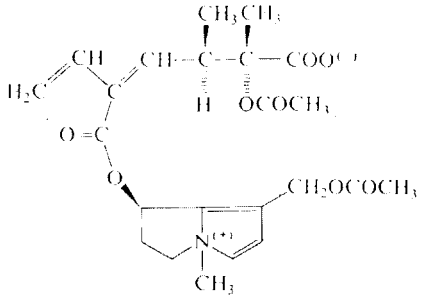
Some of the properties of acetylclivorine, identical with those of dihydropyrrolizines, have led us to the assumption that acetylclivorine is also a dihydropyrrolizine derivative which arises on dehydration of the othonecine moiety of the alkaloid (Scheme 1). A comparison of the PMR spectra of clivorine (*I*) with those of its acetylation product *II* (Table I) shows that the acetylderivative contains three additional protons in the region of δ 4·00–6·00 p.p.m. The signal of one aliphatic methylene group



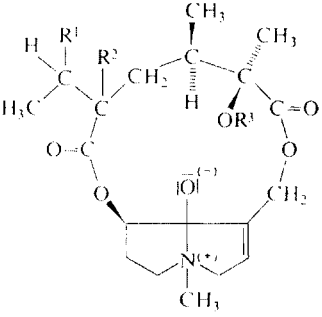
I



II



III



IV, $R^1 + R^2 = cis\ \Delta^{5,6}$, $R^3 = H$
V, $R^1 + R^2 = -O-$, $R^3 = H$
VI, $R^1 + R^2 = -O-$, $R^3 = CH_3CO$

is absent in its spectrum. Two of the mentioned protons, located at 4·13 p.p.m., are assigned to the protons of the methylene group at $C_{(5')}$ on the basis of their coupling to the aliphatic protons at 2·13 p.p.m. which are further coupled to a multiplet of a proton of the —OCH— type ($H_{(7')}$). The topological interpretation of the sequence of vicinal couplings leads to the identification of all the protons of the acidic moiety of the molecule and the—CH_2— group ($C_{(9')}$). The latter group gives two doublets at 4·26 and 5·03 p.p.m. (J = 11·5 Hz). Long-range coupling of one of them to the low-field member of another AB-system (6·48 and 6·00 p.p.m., J_{AB} = 3·0 Hz) localizes the latter protons in the vicinity of the $C_{(9')}$ atom. The coupling constant 3 Hz and the chemical shifts of the two protons are consistent with the parameters of pyrrol and the protons $H_{(2')}$ and $H_{(3')}$ of dihydropyrrolizines[12,14]. The presence of two double bonds in the A-ring of the base is also in good agreement with the downfield shift (1·59 p.p.m.) of the N—CH_3 signal, caused by the increasing positive charge of the nitrogen atom [15] and the downfield shifts of the signals $H_{(9')}$ and $H_{(5')}$. A comparison of the value $\Delta H_{(9')}$ of acetylclivorine with the literary data[12] implies the macrocyclic arrangement *II* which does not, however, quite preclude the acyclic form *III*. The quaternary nature of acetylclivorine was confirmed by reaction with silver oxide.

Stirring of the chloroform solution of acetylclivorine with an anex in the Cl^- cycle has yielded a very labile amorphous substance whose PMR spectrum exhibits only one acetyl signal; the other chemical shift values undergo only small changes (Table I). This finding shows that acetylclivorine is a macrocyclic quaternary substance – dehydroclivorinium acetate *II* – which on reaction with the anex exchanges the anion.

Clivorine (*I*) also yields the dihydropyrrolizine derivative by reaction with benzoic anhydride, which was demonstrated by thin-layer chromatography. However, the product was not isolated because of the difficulty to remove the benzoic anhydride and benzoic acid from the reaction mixture. Analogous reactions were also observed in other alkaloids of the othonecine type, *i.e.* in senkirkine (*IV*), othosenine (*V*), and florosenine (*VI*). In all these cases, thin-layer chromatography confirmed the formation of dihydropyrrolizines on the basis of the characteristic reaction with the Ehrlich reagent. However, if compared with clivorine (*I*), the yield gave only a small quantity of the product which could not be isolated. A prolongation of the time of reaction or an increase in temperature led to the formation of polymeric substances.

EXPERIMENTAL

The melting points have been determined on a Kofler block and are uncorrected. Preparative column chromatography was carried out on alumina (activity II, Reanal), thin-layer chromatography on silica gel G (Merck) using the solvent system benzene–ethyl acetate–diethylamine (7 : 2 : 1), detection by spraying with the Dragendorff and the Ehrlich reagent. The solutions of all the substances in organic solvents were dried over anhydrous sodium sulphate. The PMR

Collection Czechoslov. Chem. Commun. [Vol. 40] [1975]

TABLE I

A comparison of the PMR Data of Clivorine (*I*), Dehydroclivorinium Acetate (*II*) and Dehydroclivorinium Chloride (*II*.Cl)

Compound	$H_{(3)}$	$H_{(4)}$	$H_{(6)}$	$H_{(7u)}$	$H_{(7d)}$	$C_{(2)}$—CH_3	$C_{(3)}$—CH_3	$OCOCH_3$	$H_{(2')}$
I[a]	2·84 dq	5·40 dd	6·28 q	5·01 d	5·16 d	1·51 s	1·17 d	2·06 s	6·00 d
II[a]	3·03 dq	5·33 dd	6·32 q	5·10 d	5·23 d	1·48 s	1·10 d	1·98 s 2·05 s	6·05 d
II.Cl	3·03 dq	5·42 dd	6·33 q	5·17 d	5·22 d	1·47 s	1·10 d	1·98 s	6·07 d

Compound	$H_{(3'u)}$	$H_{(3'd)}$	$H_{(5')}$	$H_{(6')}$	$H_{(7')}$	$H_{(9'u)}$	$H_{(9'd)}$	N—CH_3
I[a]	0·18 m	3·42 m	2·4—3·0 m	1·9—2·4 m	5·18 q	4·26 d	5·03 d	2·04 s
II[a]	6·48 d		4·13 m	2·20 m	6·00 q	4·45 d	5·50 d	3·63 s
II.Cl	6·53 d		3·88 m	2·20 m	6·00 q	4·43 d	5·50 d	3·68 s

[a] For the values of the coupling constants see ref.[1].

spectra were measured on a Varian HA-100 and a Varian T-60 using tetramethylsilane as an internal standard in deuteriochloroform, the chemical shifts are given in δ-scale.

Preparation of Dehydroclivorinium Acetate *II*

A) By using the procedure according to ref.[1], 400 mg of clivorine (*I*) yielded 180 mg of the substance *II*, m.p. 122—123°C (ether–light petroleum). For the PMR data see Table I.

B) A solution of 100 mg of clivorine (*I*) in a mixture of 2·5 ml of acetic anhydride and 2 ml of pyridine was refluxed for 10 min. After evaporation *in vacuo*, the residue was extracted with ether, the ether extract was passed through a 2 cm column of Al_2O_3, and evaporated. On thin-layer chromatography, the residue afforded trace amounts of clivorine (hR_F 36) besides the substance *II* (hR_F 88, after spraying with the Ehrlich reagent a deep violet colour reaction). Crystallization from ether–light petroleum gave 35 mg of *II*, m.p. 121—122°C.

C) To a solution of 200 mg of clivorine (*I*) in 40 ml of benzene, acetic anhydride (2 ml) was added and the mixture heated at reflux for 2 h. The solution was shaken with moist sodium bicarbonate, filtered and evaporated *in vacuo*. Thin-layer chromatography showed that the residue contained the initial substance *I* and the product *II* in the ratio of c. 1 : 1. The mixture was chromatographed on a column of Al_2O_3, elution with benzene gave 65 mg of *II*, m.p. 122—123°C.

D) By a similar procedure as sub *C*, except that benzene was replaced by chloroform, 200 mg of clivorine (*I*) gave 80 mg of *II*, m.p. 121—122°C.

E) To a solution of 200 mg of clivorine in 40 ml of chloroform, 0·1 ml of pyridine and 0·3 ml of acetic anhydride were added and the mixture heated at reflux for 3 h. Work-up of the mixture as described sub *C*) afforded 75 mg of *II*, m.p. 122—123°C.

Conversion of the substance II *into a quaternary chloride*: The solution of 100 mg of the substance *II* in 10 ml of chloroform was stirred for 2 h with 150 mg of Amberlite IRA 401 in a Cl^- cycle. Filtration and evaporation gave an amorphous chloride which polymerized within 4 h. For the PMR spectrum of the chloride see Table I.

Reaction of Clivorine (*I*) and Othosenine (*V*) with Benzoic Anhydride

To a solution of 50 mg of the substance in 10 ml of benzene, 20 mg of benzoic anhydride were added and the mixture heated at reflux for 4 h. Thin-layer chromatography gave in both cases mixtures of the initial substance with the dihydropyrrolizine derivative; in the case of clivorine (*I*), the main substance of the mixture was the dihydropyrrolizine derivative which, in the case of othosenine (*V*), was present only in traces. Isolation by preparative chromatography was unsuccessful.

Attempt to Dehydrate Senkirkine (*IV*), Othosenine (*V*) and Florosenine (*VI*)

To a solution of 35 mg of the substance in 0·5 ml of pyridine, 2 ml of acetic anhydride were added and the mixture left standing for 2 days at room temperature. Thin-layer chromatography did not reveal the presence of any dihydropyrrolizines. The mixture was heated for 15 min at 100°C. Thin-layer chromatography revealed the presence of a small quantity of Ehrlich-positive substances in the mixture which, however, could not be isolated by preparative chromatography.

REFERENCES

1. Klásek A., Sedmera P., Šantavý F.: This Journal *35*, 956 (1970).
2. Birnbaum K. B., Klásek A., Sedmera P., Snatzke G., Johnson L. F., Šantavý F.: Tetrahedron Lett. *1971*, 3421.
3. Birnbaum K. B.: Acta Cryst. *B28*, 2825 (1972).
4. Mattocks A. R.: Anal. Chem. *39*, 443 (1967).
5. Mattocks A. R.: Nature *217*, 723 (1968).
6. Mattocks A. R.: Nature *219*, 480 (1968).
7. Mattocks A. R.: Anal. Chem. *40*, 1749 (1968).
8. Mattocks A. R.: J. Chem. Soc. (C) *1968*, 225.
9. Mattocks A. R.: J. Chem. Soc. (C) *1969*, 1155.
10. Culvenor C. C. J., Edgar J. A., Smith L. W., Tweedale H. J.: Tetrahedron Lett. *1969*, 3599.
11. Culvenor C. C. J., Smith L. W.: Tetrahedron Lett. *1969*, 3603.
12. Culvenor C. C. J., Edgar J. A., Smith L. W., Tweedale H. J.: Australian J. Chem. *23*, 1853 (1970).
13. Culvenor C. C. J., Edgar J. A., Smith L. W., Tweedale H. J.: Australian J. Chem. *23*, 1869 (1970).
14. Borges de Castillo J., España de Aguirre A. G.: Tetrahedron Lett. *1970*, 1219.
15. Ma J. C. N., Warnhoff E. W.: Can. J. Chem. *43*, 1849 (1965).

Translated by I. Bartošová.