Tetrahedron Vol. 27, pp. 985 to 990. Pergamon Press 1971. Printed in Great Britain

A NOVEL RING ENLARGEMENT: THE CYCLIC EXPANSION OF 2-DICHLOROMETHYL-2H-PYRROLES*

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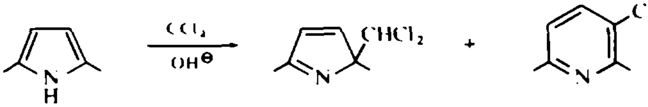
(*Received in the UK* 29 *June* 1970; *received in revised form* 22 *September* 1970; *accepted for publication* 16 *October* 1970)

Abstract—Substituted 2-dichloromethyl-2H-pyrroles, when treated with strong bases under appropriate conditions, undergo ring enlargement giving substituted 3-chloropyridines.

The data collected on different substrates and reagents indicate the carbenoid nature of intermediate.

α-α DIALKYL PYRROLES react in protic media with dichlorocarbene generated under basic conditions giving 2,5-dialkyl-2-dichloromethyl-2H-pyrroles (Plancher's pyrrolenines) and 2,6-dialkyl-3-chloropyridines.[1, 2]



Previous workers claimed that 2-dichloromethyl-2H-pyrroles are converted into β-chloropyridines by ethanolic sodium ethoxide or aqueous alkali;[1] they concluded that this transformation occurs also in the reaction mixture, and the 2H-pyrroles are intermediate products of the reaction mentioned above. This statement was proved in this laboratory to be incorrect;[2] and recently a different group reached the same conclusion.[3]

In fact, Plancher's pyrrolenines react with sodium methoxide in refluxing methanol affording a substituted pyridine, but different from a β-chloropyridine:[3, 4] however, unlike indole derivatives (3-dichloromethyl-3H-indoles are not transformed into 3-chloroquinolines[5]), the dichloromethyl-2H-pyrroles give actually the corresponding β-chloropyridines on treatment with sodium methoxide at high temperature, or with a stronger base such as BuLi in appropriate conditions.

A preliminary report on this subject has been published;[6] a more detailed study is the subject of the present work.

RESULTS

Three different pyrrolenines, (I), (II), (III), prepared according to the methods described[2, 7] have been subjected to the reaction with BuLi and sodium methoxide under several conditions

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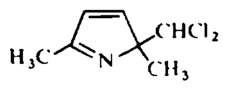
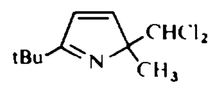
* This paper can be considered as part III of the series—Transformation of Plancher's pyrrolenines by reaction with bases. Part II: *Gazz. Chim. Ital.* 97, 685 (1967)



I



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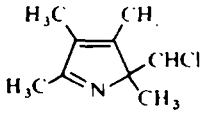

III

Compound I, treated with a slight excess of BuLi in ether at 0°, gives a complex mixture, in which abundant tars are present; by chromatography on silica gel, the 2,6 dimethyl-3-chloro-pyridine (IV) was isolated (yield: 25%). A second, less polar substance, probably an alcohol (appropriate IR absorptions) was not further investigated. The reaction does not occur at low temperatures: at − 40° C the pyrrolenine was recovered unchanged.

The pyrrolenine (I), treated with sodium methoxide (1:1·5 mole ratio) at 220–240° in toluene (sealed tube), gives a mixture which, examined by gas–liquid chromatography (GLC), does not contain any appreciable amount of pyridine (IV). The starting compound is absent from the reaction mixture, and several unidentified products are present.

The pyrrolenine (II) appears less reactive than (I) towards BuLi: at 0° a large amount of starting compound was unchanged. By carrying out the reaction at 20° and by subsequent chromatographic separation of the reaction mixture, the 2-methyl-6-t-butyl-3-chloropyridine (V) was isolated as the only product, in a yield of 37%. An examination of the traces, carried out with a combination* of GLC and MS showed that no other products with mass 183 (that of β-chloropyridine (V)) were present (by analogy with the behaviour of the pyrrolenine (III) a small amount of an isomeric α-chloropyridine was expected: see below).

The pyrrolenine (II) was treated with sodium methoxide in toluene, under the same conditions as previously described. A GLC analysis showed that the pyridine (V) was formed with 38% yield and that 20% of the starting compound was unchanged. The same reaction, carried out in methanol at the same temperature, gives a mixture containing a large amount of starting compound, nevertheless the β-chloropyridine (V) was formed with a yield of 5%.

The pyrrolenine (III) gives the most interesting reaction mixture with BuLi; free from tars it contains four products and the starting compound, all separable by column chromatography on silica gel. The less polar of them turned violet very quickly in the air: it was not further investigated. The product which was eluted subsequently, purified by distillation, has a composition corresponding to the molecular formula $C_9H_{12}NCl$. UV and IR spectra are consistent with a pyridine structure (see Table 1). The NMR spectrum compared with that of 3-chloro-2,4,5,6 tetramethyl-pyridine (VI) permitted the identification of this new pyridine, which is 2-chloro-3,4,5,6-tetramethyl-pyridine (VII). In the NMR spectrum only four signals of equal intensity are present: hence it is a tetramethyl-chloropyridine, and cannot be the isomeric pyridine (VIII), because in this instance, methyl group are equivalent in pairs and should give only two signals. The yield is about 10%.

Subsequent fractions contained the expected pyridine (VI) (yield: 46%).

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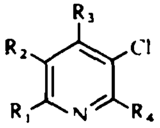
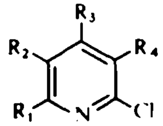
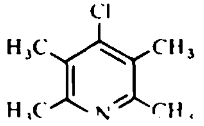
* An ATLAS CH7 combined with a gas-chromatograph was used. We are very grateful to the staff of the Varian-MAT research laboratories, Bremen, for these determinations



IV: $R_1 = R_4 = CH_3$
$R_2 = R_3 = H$
V: R_1 = t-butyl
$R_2 = R_3 = H$
$R_4 = CH_3$
VI: $R_1 = R_2 = R_3 = R_4 = CH_3$



VII: $R_1 = R_2 =$
$= R_3 = R_4 = CH_3$



VIII

Elution with a more polar solvent gave some fractions containing the starting compound (III). A very polar substance was finally eluted, whose properties and structure are under investigation.

The pyrrolenine (III), treated with sodium methoxide in toluene gives the corresponding pyridine (VI) with an 18% yield (GLC analysis) and the isomeric pyridine (VII) in very small yield (0·3%). The starting compound was no longer present in the reaction mixture, which contained some other unidentified products. By carrying out the reaction in methanol, after 2 hours the starting compound was consumed, but no β-chloropyridine (VI) could be detected: other unidentified products, with higher retention time, were present.

DISCUSSION

A comparison between the reactions undergone by the three different substrates allows the following conclusions.

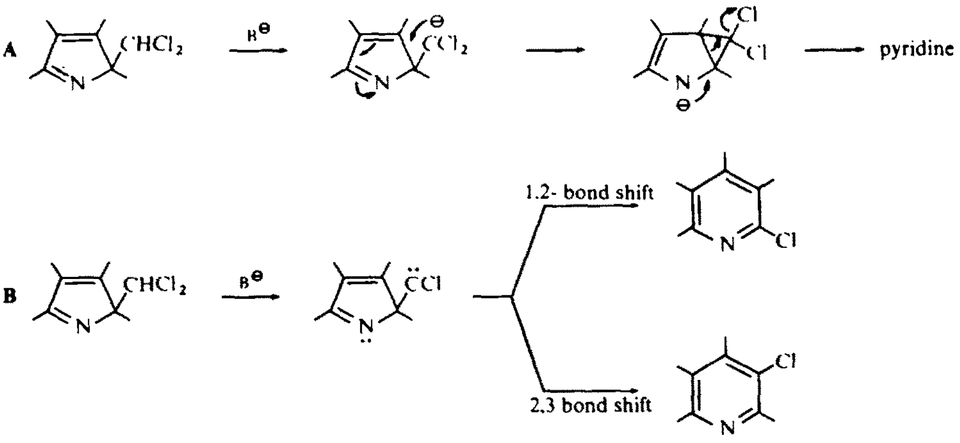
The 5-Me substituted 2-dichloromethyl-2H-pyrroles react with bases, under a variety of conditions, giving complex mixtures: whereas the 5-t-Bu substituted pyrrolenine, in an aprotic medium, undergoes mainly cyclic expansion. Clearly, the presence of removable hydrogens[7] in the side chain permits side reactions, which are suppressed when the hydrogens are absent. Even in methanol cyclic expansion occurs with the t-butyl substituted compound, whereas different reactions are

TABLE 1. SPECTROSCOPIC DATA OF THE PYRIDINES (VII) AND (VI)

	2-chloro-3,4,5,6-tetramethyl-pyridine (VII)				3-chloro-2,4,5,6-tetramethyl-pyridine (VI)			
UV Spectra	λ_{max} 273 mμ (ε = 4000; in 95% EtOH)				λ_{max} 274 mμ (ε = 4400: in 95% EtOH)			
IR Spectra	ν_{max} 1583; 1552; 1260; 1218; 1027; 955; 866; 755 (liquid film) cm^{-1}				ν_{max} 1575; 1555; 1175; 1010; 978; 778 (in nujol) cm^{-1}			
	δ (ppm from TMS)	multiplicity	no. of protons	Assignments	δ (ppm from TMS)	multiplicity	no. of protons	Assignments
NMR Spectra	2·12	s	3	CH_3—C^5	2·12	s	3	CH_3—C^5
	2·17	s	3	CH_3—C^4	2·28	s	3	CH_3—C^4
	2·23	s	3	CH_3—C^3	2·38	s	3	CH_3—C^6
	2·34	s	3	CH_3—C^6	2·48	s	3	CH_3—C^2

predominant in these conditions when the 5-substituent is a methyl.[3, 4] Hence, the base induced cyclic expansion is a general reaction of 2-dichloromethyl-2H-pyrroles although concurrent pathways are operative.

On the mechanism of the cyclic expansion reaction* considered here, two hypotheses seem to be attractive: a nucleophilic attack in the 3-position of the formed carbanion followed by the collapse of the bicyclic anion (**A**), or a simpler path, involving a carbene intermediate (**B**).



In our opinion, a mechanism like **B**, *via* the formation of a carbene generated by α-elimination, which has been previously observed,[8] seems to be consistent with all the experiments described so far. Let us consider first the reactions promoted by MeONa.

The MeONa induced D–H exchange of the dichloromethyl group, which occurs at the temperature of refluxing MeOD,† makes the formation of the carbanion probable (path **A**, first step) under these conditions:[9] however, cyclic expansion occurs only at higher temperatures (see behaviour of pyrrolenine (II)). In an aprotic medium (toluene), a temperature > 200° is necessary to promote the reaction. Therefore, the cyclic expansion takes place with MeONa in both protic or aprotic media, but an elevated temperature appears to be necessary. In terms of scheme **A**, this could mean that the second step (internal nucleophilic attack) is too slow at moderate temperatures.

But it seems reasonable to assume that the loss of $Cl^{\ominus}$ would be fast at high temperature, and hence path **B** would be operative: this is supported by the fact that the loss of $Cl^{\ominus}$ is the rate-determining step of the hydrolysis of chloroform.[10]

When the BuLi reagent is used, the reagent takes place at temperatures ranging from 0° to 20°; this is in good agreement with the well-known easy α-eliminations induced by this reagent.[11] At −40° the reaction does not occur: the Li-derivative could be stable in these conditions, as the isolation of $LiCHCl_2$ at − 100° is reported.[12]

* It is reasonable to assume that the reaction pathway is the same also with different reagents: in this respect the identification of the α-chloropyridine formed from pyrrolenine (III) by using BuLi or MeONa is significant.

† R. Nicoletti and M. L. Forcellese, unpublished experiments

Dealing now with the reaction products, the presence of an α-chloro-substituted pyridine in the reaction mixtures from III is hard to understand on the basis of path **A**; however, according to path **B**, the formation of such a compound is easy to justify, considering that the cyclic expansion—which could be concerted with the LiCl elimination—can occur by the shift of 1,2 bond (forming 2-chloropyridines) or by the 2,3-bond shift (forming the 3-chloro isomers).

It is worth noting that these reactions in which 2- and 3-chloropyridines are produced, parallel the reaction between pyrrole and chloroform in the gas-phase: in this instance both types of pyridines are formed.[13]

The meaning of the observed cyclic expansion of Plancher's pyrrolenines deserves a further comment. 3-chloropyridines and 2-dichloromethyl-2H-pyrroles are both products of the reaction between pyrroles and dichlorocarbene in several protic solvents under basic conditions: it was reasonable to assume that one was a transformation product of the other. This idea must be definitely ruled out. Although the cyclic expansion can occur under severe conditions (high temperatures or bases stronger than alkoxides), since the reaction on pyrroles occurs in conditions similar to those of the Reimer–Tiemann reaction (*i.e.* in alcohol–water mixtures at moderate temperatures) one can exclude the dichloromethyl-2H-pyrroles from being intermediates in the formation of 3-chloropyridines.

EXPERIMENTAL

NMR spectra were recorded on a Varian A-60 in CCl_4 with TMS ($\delta = 0$) as internal standard. IR spectra were determined on Perkin–Elmer 257, UV spectra on Perkin–Elmer 137. GLC analyses have been carried out with a Perkin–Elmer 800 (flame ionization detector), while quantitative GLC determination used a Carlo Erba Fractovap GV instrument (flame ionization detector). In both cases, N_2 was used as carrier.

Silica gel refers to silica 140–230 Mesh, treated with HCl, washed with water and dried. Light petroleum refers to Petroleum ether 40–70 (Carlo Erba P.) C,H,N analyses were carried out with a Technicon CHN analyser.

*2-Dichloromethyl-*2H*-pyrroles with n-BuLi.* The appropriate pyrrolenine, dissolved in anhydrous Et_2O, was treated, under a stream of N_2 and stirring, with an ethereal solution of n-BuLi (1 : 1·2 mole ratio), freshly prepared and titrated, according the procedure reported.[14] The concentration of the reagent ranged between 0·7 and 1 M. Temp was maintained at 0° (ice bath) in the case of I, at 20° in other cases (water bath). The dropping of the reagent lasted approximately 30 mins and the stirring is continued for 1 h longer. The reaction mixture was then treated with water, the ethereal solution dried over Na_2SO_4, and the solvent removed under reduced pressure.

Separation of the reaction mixture of I *with n*-BuLi. Compound I (0·67 g) in Et_2O (20 ml) treated with the appropriate amount of n-BuLi as previously described, gave a residue (0·62 g) which appeared as a complex mixture on TLC (Silica gel, light petroleum EtOAc 6:4 as eluent, I_2 as developer). By chromatography on Silica gel (40 g), eluting with a mixture of light petroleum EtOAc 95:5, 35 fractions (100 ml each) were collected. The fourth fraction gave a residue (0·04 g), as a colourless oil: it is N-free and shows in the IR absorption bands at 3610 and 1135 cm^{-1} (solvent CCl_4).

Fractions 5–18 gave a residue 0·15 g (yield 25%) of IV, identified by its NMR spectrum: bands at 2·43 (3H, CH_3—C_6); 2·54 (3H, CH_3 C_2); 7·12 δ (2H, AB system, $J = 8$ c/s, β, γ hydrogens). The picrate melted at 137–139° (sintering from 130°) alone or in mixture with an authentic sample. Fractions 23–33 contained 0·07 g of the starting material.

Separation of the reaction mixture of II *with n*-BuLi. Pyrrolenine II (1·57 g) in Et_2O (30 ml), treated with n-BuLi reagent, afforded a mixture (1·37 g) which showed four spots on TLC (Silica gel, benzene-Et_2O 8:2, I_2 as developer), one of them corresponding to the starting material.

By chromatography on Silica gel (150 g), and eluting with benzene-Et_2O 95:5, 30 fractions (50 ml each) were collected. Fractions 1–5 contained the V (0·46 g: 37% yield) identified by its NMR spectrum: bands at 1·30 (9H, t-Bu); 2·54 (3H, CH_3); 7·17 δ (2H, AB system, $J = 8$ c/s, β, γ hydrogens). IR spectrum was superimposable on that of an authentic sample.

Fraction 6 give a residue (0·1 g), which showed as a mixture on GLC (SE 30 12%, supported on "Celite" containing 2% KOH: programmed temp between 120° and 160°, rate 8·3 degrees/min.). An examination by mass spectrometer of the effluent peaks showed that none of the substances has molecular peak corresponding to m/e 183. Fractions 20–25 gave as residue 0·1 g of the starting material. No other substances could be eluted from the column.

Separation of the reaction mixture of III *with n*-BuLi. III (1 g) in anhydrous Et_2O (25 ml), treated with n-BuLi gives a residue (0·95 g) which showed on TLC (silica-gel, benzene–Et_2O 8:2, iodine as developer) as a mixture of four products, plus the starting compound.

By chromatography on silica-gel (20 g) with benzene-Et_2O 95:5 as eluent, 10 fractions (50 ml each) were collected. Fractions 1–2 gave an oily residue (0·1 g) which turned violet in the air: it was not further investigated. Evaporation to dryness of fractions 3–4 and 5–9 gave two substances (A and B) (0·09 and 0·385 g respectively). Compound A is a low melting solid, which was distilled at 120–130°/5 mm Hg. Spectroscopic data (see Table I) are consistent with the structure VII. Yield: 10%. (Found: C, 64·0; H, 7·37, N, 8·23. $C_9H_{12}NCl$ requires C, 63·7; H, 7·13; N, 8·26%). Compound B crystallizes on standing; it is a low melting solid, and can be purified by sublimation at reduced pressure. IR and NMR spectra are superimposable on those of an authentic sample of VI (see Table I). Yield: 46%.

Subsequent elution with benzene-Et_2O 7:3 gave 0·07 g of the starting material (fractions 18–23) and 0·16 g of an oil (b.p. 150–160°/20 mm Hg), now under investigation.

2-*Dichloromethyl*-2H-*pyrroles with* NaOMe *in toluene*. Into three small Carius tubes, I, II and III (0·1 g of each) were introduced along with an excess of dry NaOMe (1:1·5 mole ratio), and toluene (1 ml). The tubes were sealed, and then heated in an oil bath at 220–240° for 4 h. The brown mixture in each tube was then treated with water, extracted with Et_2O, and the soln dried over Na_2SO_4. Most of the solvent was removed *in vacuo*, an exactly weighted amount of 2,5-lutidine was added, and the mixture brought to 2·5 ml with toluene. The resulting solns were examined on GLC (Carbowax 20 M column, $t = 160$ or 190°), by comparing them with standard solns prepared with known amounts of the appropriate pyrrolenine, β-chloropyridine and 2,5-lutidine. The composition of the reaction mixtures were computed by measuring peak areas.

2-*Dichloromethyl*-2H-*pyrroles with* NaOMe *in* MeOH. Pyrrolenines II and III, dissolved in MeOH, were treated with NaOMe in the same conditions as previously described. The reaction mixtures, after the usual working up, were examined by GLC in the same way.

In a different run, after 2h at the same temp, the reaction mixture of pyrrolenine was examined in order to test for the disappearance of the starting material.

Acknowledgements—We are indebted to Italian CNR for financial support

REFERENCES

[1] G. Plancher and U. Ponti, *Rend. Accad. Lincei* **18** (II), 469 (1909); G. Plancher and T. Zambonini, *Ibid.* **22** (II), 712 (1913)

[2] R. Nicoletti and M. L. Forcellese, *Gazz. Chim. Ital.* **95**, 83 (1965)

[3] R. L. Jones and C. W. Rees, *J. Chem. Soc.* (C) 2255 (1969)

[4] C. W. Rees and S. E. Smithen, *Proc. Chem. Soc.* 217 (1964); R. Nicoletti and M. L. Forcellese, *Tetrahedron Letters*, 153 (1965); R. Nicoletti and M. L. Forcellese, *Gazz. Chim. Ital.* **97**, 148 (1967)

[5] C. W. Rees and C. E. Smithen, *J. Chem. Soc.* 928 (1964)

[6] R. Nicoletti and M. L. Forcellese, *Tetrahedron Letters* 3033 (1965)

[7] R. Nicoletti, M. L. Forcellese and C. Germani, *Gazz. Chim. Ital.* **97**, 685 (1967)

[8] G. L. Closs and V. N. Rao, *J. Am. Chem. Soc.* **88**, 4116 (1966)

[9] R. Nicoletti, M. L. Forcellese and C. Germani, *loc. cit.*, see p. 686 footnote 5

[10] H. Hine, *J. Am. Chem. Soc.* **72**, 2438 (1950)

[11] See W. Kirmse, *Carbene Chemistry*, chap. 8, p. 188, *et ref. cit.* Academic Press, New York (1964)

[12] G. Köbrich, K. Flory and W. Drischel, *Angew. Chem.* Int. Edit. **3**, 513 (1964)

[13] H. L. Rice and T. E. Londergan, *J. Am. Chem. Soc.* **77**, 4678 (1955)

[14] H. Gilman, J. A. Beel, C. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *J. Am. Chem. Soc.* **71**, 1499 (1949)