CHLORINATION OF N-TRITYLPROLINE METHYL ESTER

F. D. Polyak, A. V. Eremeev,
M. P. Gavars, A. P. Gaukhman,
and I. B. Mazheika

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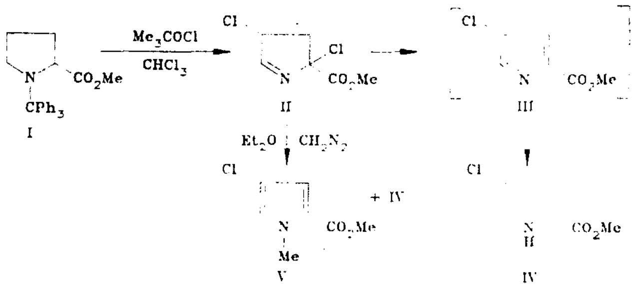
The reaction of N-tritylproline methyl ester with tert-butyl hypochlorite gave 2,4-dichloro-2-methoxycarbonyl-5-pyrroline, which is readily converted to 2-methoxycarbonyl-4-chloropyrrole. The intermediate products were identified by chromatographic mass spectrometry when the reaction was carried out at low temperatures.

It is known that the reaction of methyl N-tritylaziridine-2-carboxylate with tert-butyl hypochlorite led to the formation of methyl N-chloroaziridine-2-carboxylate [1]. To establish the general character of the detritylation of N-trityl derivatives of cyclic amino acids under the influence of tert-butyl hypochlorite we investigated its reaction with N-tritylproline methyl ester (I). When we carried out the reaction of ester I with tert-butyl hypochlorite in chloroform at room temperature, we isolated a single (according to GLC and TLC data) reaction product, to which we assigned structure II. Its PMR spectrum contains, in addition to the singlet of an OMe group, three groups of signals, which can be ascribed to the protons of the $-CH-CH-CH_2-$ fragment of the five-membered ring on the basis of the integral intensity (1:1:2) and the multiplicity. The weak-field shift of the 5-H proton (7.65 ppm) can be explained by the presence in the II molecule of a $CH{=}N$ fragment. A molecular-ion peak is not observed in the mass spectrum of this compound; isotope peaks with an intensity that indicates the presence of two chlorine atoms in these fragments accompany the peaks of fragment ions with m/z 164, 136, 109. Since the molecular mass of ester II is 195, the indicated peaks can be ascribed to $(M - OCH_3)^+$, $(M - COOCH_3)^+$, and $(M - COOCH_3 - HCN)^+$ fragments. Thus the set of PMR and mass spectrometric data indicates that the product of the reaction of pyrrolidine I with tert-butyl hypochlorite is 2,4-dichloro-2-methoxycarbonyl-5-pyrroline (II). This compound is unstable and after 3 days undergoes quantitative conversion to 2-methoxycarbonyl-4-chloropyrrole (IV); this follows unambiguously from its PMR and mass spectra.



Two doublets ($^4J_{HH}$ = 1.0 Hz) that are characteristic for the protons of disubstituted pyrroles [2] and a broad signal of the proton of an NH group are observed in the PMR spectrum. The mass spectrum of IV contains peaks of molecular ions at 159 and 161 (3:1) and of all of the characteristic fragments of the molecule (Table 1). Pyrroline II evidently loses a molecule of HCl, thereby undergoing conversion to ester III, after the isomerization of which pyrrole IV is formed. To confirm the structure of ester II we carried out its reaction with diazomethane, in which we observed the formation of two compounds, which were isolated by preparative gas chromatography. They proved to be pyrrole IV and its N-methyl derivative V. Dehydrochlorination of II evidently occurs under the influence of diazomethane*; this is

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*The dehydrochlorination of N-acetyl-α-chloroglycine methyl ester under the influence of diazomethane is known [3].

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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TABLE 1. Characteristic Ions in the Mass Spectra of II, IV, VII, VIII, and IX

Compound	m/z (I, % of the maximum peak)*							
	$M^{+\cdot}$	$(M-OCH_3)^+$	$(M-COOCH_3)^+$	$(M-COOCH_3-HCN)^+$	$(CH_2)_2COOCH_3^+$	$COOCH_3^+$	$(M-Cl)^+$	$(M-HCl)^{+\cdot}$
II	195 (0)	164 (1)	136 (9)	109 (7)	99 (100)	59 (21)	160 (1)	159 (5)
IV	159 (54)	128† (51)	100‡ (9)	73 (20)	99 (8)	59 (2)	—	—
VII	127** (3)	96 (3)	68 (100)	41 (52)	99 (6)	59 (15)	—	—
VIII	161 (1)	130 (3)	102 (26)	75 (26)	99 (100)	59 (24)	126 (22)	125 (19)
IX	161 (0)	130 (4)	102 (41)	75 (18)	99 (100)	59 (26)	126 (14)	195 (15)

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*The ions containing ^{35}Cl are presented.

†$(M - CH_3OH)^{+\cdot}$ ion at 127 (100).

‡$(M - COOCH_3 - HCl)^+$ ion at 64 (24).

**$(M - H)^+$ ion at 126 (36).

followed, after the conversion of intermediate III to ester IV, partial N-methylation of the latter.

The conversion of starting pyrrolidine I to pyrroline II is undoubtedly a multistep process. In order to ascertain the intermediates the reaction of ester I with tert-butyl hypochlorite was carried out at low temperatures (−50°C, −30°C, 0°C); monitoring by GLC was carried out for 2 h. Because of their extreme instability the intermediates could not be isolated either by high-vacuum distillation or by preparative GLC, and the analysis of the intermediates was therefore carried out by chromatographic mass spectrometry.

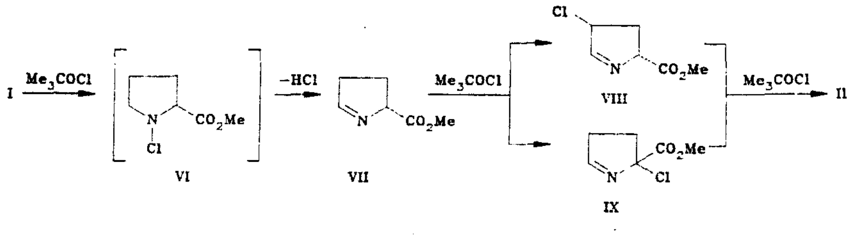
At −50°C in the reaction mixture we detected one substance, the molecular mass (M = 127) and the character of the fragmentation (see above) of which constitute evidence for the presence of 2-methoxycarbonylpyrroline (VII), which is evidently formed as a result of the dehydrochlorination of 2-methoxycarbonyl-1-chloropyrrolidine.

At −30°C we detected four substances in the reaction mixture; the mass spectra of these substances correspond to pyrrolines II and VII and two isomers with M = 161 (one Cl atom).

At 0°C pyrroline II and one of the isomers with M = 161 are present in the reaction medium.

On the basis of the structure of pyrroline II it may be assumed that the dehydrochlorination of N-chloroproline methyl ester (VI) leads to 2-methoxycarbonyl-5-pyrroline (VII), which under the influence of tert-butyl hypochlorite undergoes chlorination in the 2 and 4 positions (a process of the allyl substitution type) to form the intermediate monochloro-substituted pyrrolines VIII and IX with M = 161.

The mass spectra of II and VII-IX are characterized by low stability of the molecular ion (2.7-0% of the maximum ion). The fragmentation of the molecular ions is characterized by two general processes: detachment of $CH_3O^\cdot$ and $COOCH_3^\cdot$ radicals with the subsequent elimination of a molecule of HCN (Table 1).



In addition, the molecular ions of II, VIII, and IX eliminate a $Cl^{\bullet}$ radical, and detachment of $H^{\bullet}$ with the subsequent ejection of a molecule of HCN is observed in the mass spectrum of VII.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were obtained with a Bruker WH-90 spectrometer (90 MHz) with TMS as the internal standard. The chromatographic mass spectra were obtained with a Kratos MS-25 spectrometer (ionizing voltage 70 eV, OV-101 packed column). Analytical gas chromatography was carried out with a Chrom-5 chromatograph, while preparative chromatography was carried out with a Pye-Unicam-105 chromatograph with SE-30 (10%) applied to Chromosorb WAW 100-102 mesh as the stationary phase and a flame-ionization detector.

2,4-Dichloro-2-methoxycarbonyl-5-pyrroline (II). A 0.54-g (5 mmole) sample of tert-butyl hypochlorite was added at 15°C to a solution of 1.86 g (5 mmole) of ester I in 50 ml of chloroform, after which the mixture was maintained for 24 h at room temperature, during which the starting ester vanished completely from the reaction medium (according to TLC data). The residue remaining after removal of the solvent was distilled under a high vacuum (10^{-2} mm) at a bath temperature of 40°C. The yield was 0.3 g (31%).* PMR spectrum: 2.99 and 3.07 (2H, two q, AB, $^2J_{33}$ = 14.4, $^3J_{34}$ = 7.0 Hz, 3-H_2); 3.82 (3H, s, CH_3), 4.91 (1H, two t, $^3J_{45}$ = 3.0, $^3J_{43}$ = 7.0 Hz, 4-H), 7.65 ppm (1H, d, $^3J_{54}$ = 3.0 Hz, 5-H).

2-Methoxycarbonyl-4-chloropyrrole (IV). A solution of 0.2 g (1 mmole) of pyrroline II in 2 ml of chloroform was maintained for 3 days at room temperature, after which the solvent was removed in vacuo, leaving a colorless oily substance. The yield was 0.5 g (96%).* PMR spectrum: 3.88 (3H, s, CH_3), 6.70 and 6.90 (2H, two dd, $^4J_{35}$ = 1.0, $^3J_{51}$ and $^4J_{13}$ = 2.6 and 2.35 Hz, 3-H and 5-H), 9.38 ppm (1H, broad s, 1-H).

Reaction of 2,4-Dichloro-2-methoxycarbonyl-5-pyrroline (II) with Diazomethane. An ether solution of diazomethane was added at 0°C to a solution of 0.55 g (3 mmole) of pyrroline II in 10 ml of ether until a persistent yellow coloration developed. The reaction mixture was then maintained for 2 days at room temperature, as a result of which two reaction products developed in the solution. After removal of the solvent, they were isolated by preparative gas chromatography. Pyrrole IV and 1-methyl-2-methoxycarbonyl-4-chloropyrrole (V) were obtained. PMR spectrum: 3.81 (3H, s, N-CH_3), 3.89 (3H, s, O-CH_3), 6.72 and 6.81 ppm (2H, two d, $^4J_{35}$ = 1.5 Hz, 3-H and 5-H). Found: C 48.5; H 4.7; N 8.0%. $C_7H_8ClNO_2$. Calculated: C 48.4; H 4.6; N 8.1%.

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*A satisfactory elementary analysis was not obtained because of the insufficient stability of the compound.