How to Cite: Salkeyeva, L.K., Pevzner, L.M., Vojtíšek, P., Minayeva, Ye.V. (2024). On the Bromination of Diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate: the True Structure of the Halbig's Product. *Eurasian Journal of Chemistry, 29, 1(113),* 14-23. https://doi.org/10.31489/2959-0663/1-24-4

Article

Received: 14 November 2023| Revised: 23 January 2024|
Accepted: 10 February 2024 | Published online: 22 February 2024

UDC 547:794.3

https://doi.org/10.31489/2959-0663/1-24-4

Lyazat K. Salkeyeva[1], Leonid M. Pevzner[2], Pavel Vojtíšek[3], Yelena V. Minayeva[1*]

[1]*Department of Organic Chemistry and Polymers, Karaganda Buketov University, Karaganda, Kazakhstan;*
[2]*Department of Organic Chemistry, Saint-Petersburg State Technological Institute (Technical University), St. Petersburg, Russia;*
[3]*Department of Chemistry, Faculty of Science, Jan Evangelista Purkyně University in Ústí nad Labem, Ústí nad Labem, Czech Republic*
*(*Corresponding author's e-mail: yelenaminayeva@yandex.ru)*

On the Bromination of Diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate: the True Structure of the Halbig's Product

Pyrrole and its derivatives have attracted the attention of researchers as promising objects of practical importance in various areas of human life. Focusing on Knorr pyrrole as the most readily available pyrrole derivative, our objective was to obtain its bromo derivatives, containing an allyl bromine atom followed by phosphorylation reactions. The reaction involving bromination was carried out with 2 mol of N-bromosuccinimide per 1 mol of Knorr pyrrole **1** in carbon tetrachloride. This reaction was initiated with azobis(isobutyronitrile) and carried out at a boiling point. In acetic acid, the bromination reaction was carried out at a temperature of 38–45°C with a molar ratio of Knorr pyrrole to bromine of 1:4 and another reaction was carried out at 40–50°C with a molar ratio of Knorr pyrrole to bromine of 1:5. The bromination reaction was also performed in chloroform at 27–30°C in the presence of catalytic amounts of aluminum chloride. The same crystalline product was obtained in all cases. X-ray diffraction analysis revealed that the single crystal structure is diethyl 5-(dibromomethyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3,4-dicarboxylate **5** with two bromine atoms. This composition is identical to that of the Halbig product. It was found that the bromination of Knorr pyrrole **1** occurs stepwise with excess N-bromosuccinimide and bromine, resulting in the unsaturated lactam **5**, commonly known as Halbig's product. The true structure of product **5** was determined.

Keywords: Knorr pyrrole, α-methylpyrroles, bromination, the Halbig's product, bromo derivatives, Diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate, phosphorylation, reaction mechanism.

Introduction

Pyrrole and its derivatives remain a significant focus of researchers due to their role in providing new bioactive compounds. Some of them are crucial in various life processes [1]. Many pyrrole derivatives have shown diverse biological activities [2–12]. Knorr pyrrole, also known as diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate, is among the most commonly available pyrrole derivatives. There are additional studies regarding the phosphorylation of pyrrole and Knorr pyrrole [13]. The bromination reactions of derivatives of pyrrole followed by phosphorylation are unquestionably fascinating in the field of pyrrole chemistry [14].

The side-chain bromination of α-methylpyrroles has been well-known [15, 16]. At a pyrrole: bromine molar ratio of 1.06:1, the bromination reaction of Knorr pyrrole with molecular bromine in acetic acid, at 45 °C, produced 2-bromomethyl-4-methylpyrrole-3,5-dicarboxylic acid diethyl ester **2** in 42 % yield [15–20]. Likewise, using N-bromosuccinimide in carbon tetrachloride, in the presence of benzoyl peroxide at reflux, resulted in the same product in 47% yield [21]. The reaction scheme is displayed in Figure 1.

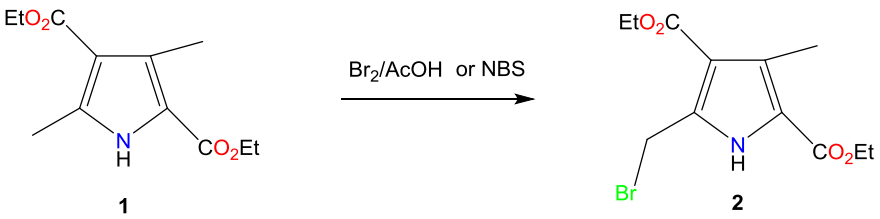
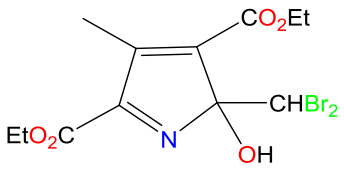


Figure 1. The formation of 2-bromomethyl-4-methylpyrrole-3,5-dicarboxylic acid diethyl ester **2**

Simultaneously, Halbig P. and Walach B. [17] observed the extraction of a crystalized substance upon cooling the reaction mixture of Knorr pyrrole with excess of bromine in acetic acid at 45–50 °C. After multiple washes with acetic acid, a compound with a melting point of 130-131 °C and a composition of $C_{12}H_{15}Br_2NO_5$ was obtained.

Treibs A. and Bader H. [21] obtained a compound with identical properties by brominating Knorr pyrrole in a blend of acetic acid and petroleum ether (1:1). Once the reaction mixture had been evaporated and the substance obtained had been recrystallized from dilute acetic acid and then from ethanol, a vibration band at 2.92 μ ($CHCl_3$) was detected in the compound's IR spectrum [21]. Following the reaction of α-unsubstituted pyrrole carboxylic acid esters with bromine, structure **3** was assigned to this substance [17], which was not disputed subsequently. The substance was referred to as the Halbig's product in the literature (Fig. 2).

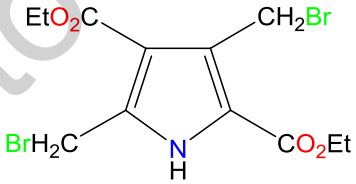


3

Figure 2. The structural formula of the Halbig's product [17, 21]

Later, Angelini et al. [19] conducted a ^1H NMR spectroscopic study on the crude bromination products. The study revealed the formation of α-dibromomethyl derivatives as byproducts. These byproducts were not observed in detectable amounts when the molar ratio of Br_2 to pyrrole was ≤0.5. However, they were the only reaction product formed when the molar ratio of Br_2 to pyrrole was ≥2 and the reaction was allowed to go to completion. α-Dibromomethylpyrroles were obtained as red oils that are sensitive to moisture. They were characterized by a singlet (1H) at approximately δ 6.5 ppm ($CHBr_2$) in the NMR spectrum. Additionally, they were converted into the corresponding aldehydes.

The aim of this study was to investigate the potential of obtaining 3,5-bis(bromomethyl) derivative **4** (Fig. 3) via the bromination of Knorr pyrrole as a starting compound for subsequent phosphorylation reactions.



4

Figure 3. Structural formula of diethyl 3,5-bis(bromomethyl)-1H-pyrrole-2,4-dicarboxylate **4**

Experimental

Material and Instrumentation

All chemicals were of analytical grade and procured from Sigma-Aldrich suppliers without the need for further purification. Reactions underwent monitoring via thin layer chromatography (TLC) on F 254 silica gel coated plates from Merck. Bruker 400 and 600 MHz spectrometers were used to record the ^1H and ^{13}C NMR spectra in $CDCl_3$ along with TMS functioning as the internal standard. Mass spectra were taken using a Shimadzu mass spectrometer. IR spectra were taken with a Thermo Scientific Nicolet 6700 FTIR spectrometer (Madison, WI, USA). The melting point was determined using a Buchi Melting point M-560 instrument.

Diffraction experiments for **1** and **5** were performed on a Bruker D8 VENTURE Kappa Duo PHOTON100 by IμS micro-focus sealed tube either with MoKα (λ= 0.71073) radiation at a temperature of 120(2) K for **5,** or CuKα (λ = 1.54178) for **1**at a temperature of 150(2) K.

The structures were solved by direct methods [22] and refined by the full matrix F^2-based least squares method [23]. Hydrogen atoms on carbon were fixed into idealized positions (riding model) and assigned temperature factors either $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$ (pivot atom) for methyl moiety, the hydrogen atoms in –N-H moiety were found on difference Fourier maps and refined under rigid body assumption with assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom).

Synthesis Section

General procedure for bromination of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole with NBS:

3.1 g (0.013 mol) of Knorr pyrrole, 5.02 g (0.028 mol) of NBS, 0.23 g of AIBN as an initiator and 70 ml of CCl_4 were added into a three-neck flask equipped with a mechanical stirrer, a thermometer and a reflux condenser. The reaction mixture was heated until boiling occurs at around 60 °C, due to the activation of the initiator. The reaction mixture was heated and stirred at a temperature of 77-78 °C for a duration of 3 hours. Upon completion of the reaction (with monitoring via TLC), the succinimide formed was removed by decantation from the still hot mixture. The residue was then left alone for 24 hours before the solvent was distilled off using a rotary evaporator. The remaining residue gradually crystallized over time. To obtain the final product, the crystallized residue was dissolved in benzene whilst being heated and subsequently precipitated using hexane. The overall yield of the product was 63 %.

Bromination of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole with bromine in acetic acid:

3g (0.012 mol) of Knorr pyrrole dissolved in 7.8ml of CH_3COOH was brominated with 7.2 g (0.045 mol) of bromine in 1.2 ml of glacial acetic acid. The temperature during bromination was maintained at 38–45 °C. The starting pyrrole instantly dissolved when bromine in acetic acid was added and a slight exo-effect was observed. The reaction mixture was kept at a temperature of 38–45 °C for 4 hours and after that it was left overnight. The reaction mixture was diluted using chloroform, extracted with cold water twice, and then twice with a saturated solution of sodium carbonate, followed by water, then with a saturated solution of sodium sulfite, and again with water. When treated with sodium sulfite, the solution lost its colour. The extract was dried over sodium sulfate for two hours, and then chloroform was distilled off. The remaining substance was crystallized from hexane with a product yield 33 %.

Bromination of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole with bromine in acetic acid under low heat:

3 g (0.012 mol) of 2,4-dimethyl-3,5-dicarboethoxypyrrole were heated gently in 45 ml of glacial acetic acid. Then, 9.6 g (0.06 mol) of bromine were added at 40–50 °C.The reaction mixture was kept at a temperature of 40–50 °C for 4 hours. The reaction mass did not form crystals when left to stand for 24 hours. The reaction mixture was then cooled to 0 °C, and after thawing at room temperature, a small amount of the precipitated crystals were dissolved. The reaction mixture was poured onto ice and transferred to a separatory funnel. Chloroform was used for extraction, which was carried out thrice. This was then extracted twice with ice water followed by a one-time extraction with a saturated solution of sodium sulfite. Further, it was washed once with water and left to dry over sodium sulfate for 20 hours in a dark place. The yield of the crude product was 30 %. The oily residue was crystallised in hexane, then dissolved in benzene. The crystals precipitated from the solvent mixture and were subsequently recrystallised from benzene.

Bromination of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole in the presence of $AlCl_3$ as a catalyst:

3 g (0.012 mol) of 2,4-dimethyl-3,5-dicarboethoxypyrrole were placed in a three-necked flask, followed by the addition of 30 ml of chloroform and 0.25 grams of $AlCl_3$ as a catalyst. The mixture was stirred vigorously, and a slight exothermic effect of +6 °C (21–27 °C) was observed. Subsequently, a solution of bromine in chloroform (25 ml of chloroform and 7.2 g (0.045 mol) of bromine) was prepared. The bromine solution was slowly added dropwise, leading to discoloration, and an exothermic effect of +3 °C (27–30 °C) was observed. After the addition of bromine, the temperature of the reaction mixture decreased to 26-27 °C before stabilizing at 25 °C. The mixture was stirred for 4-5 hours before being poured onto ice and extracted with chloroform. The extracted mixture was then washed sequentially with cold water, sodium sulfite and water, and sodium carbonate. Following this, it was dried with calcium chloride and the chloroform extract was filtered off from the calcium chloride before being distilled off. The oily residue was crystallized and the resulting product had a yield of 30 %. After recrystallisation from a mixture of benzene and hexane, the product was found to be soluble in benzene, methanol, chloroform, ethyl acetate, and acetone but had poor solubility in hexane.

Diethyl 5-(dibromomethyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3,4-dicarboxylate (5):

IR spectrum, ν, cm^{-1}: 3057 (N-H), 1711 (COOR), 1752 C=O, 1625 (C=C), 675 (C-Br).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.15–7.09 (m, 1H), 7.04–6.98 (m, 1H), 6.88 (d, J = 2.1 Hz, 1H), 4.45 (t, J = 7.4 Hz, 1H), 3.54 (t, J = 6.6 Hz, 2H), 2.25–2.17 (m, 2H), 1.63–1.54 (m, 2H), 1.48–1.37 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.61, 127.10, 121.71, 121.57, 120.13, 119.58, 118.98, 111.20, 62.91, 62.78, 35.61, 32.80, 24.46 ppm; HRMS (ESI): m/z calcd for $[C_{13}H_{16}NO]$ + ($[M+H]^+$) 202.2686, found 202.2651.

Results and Discussion

In light of the findings presented in [13, 14] concerning the phosphorylation of dibrominated Knorr pyrrole, an extensive search was conducted to acquire precise methods for obtaining dibromo derivative **4**. Unfortunately, no viable approaches were discovered in the literature, with the exception of the synthesis procedure for **2** [15, 16]. Consequently, we proceeded to evaluate the subsequent protocols:

– The reaction of two mols of N-bromosuccinimide per one mol of Knorr pyrrole in refluxing carbon tetrachloride with traces of azobis (isobutyronitrile) for initiation.

– The reaction of Knorr pyrrole with excess of bromine (ratio from 1:4 to 1:5) in acetic acid at 40–50 °C.

– The reaction of Knorr pyrrole and excess of bromine in chloroform at 27–30°C in the presence of catalytic amounts of aluminum chloride.

The identical workup was utilised in both previous instances: extracting the reaction mixture in chloroform, washing with an aqueous sodium bicarbonate solution, reducing discoloured bromine residuals with an aqueous sodium sulfite solution, drying the organic phase with sodium sulfite, and recrystallising the solute from benzene or a benzene-hexane mixture. After removing the formed succinimide by filtration, the resulting filtrate was evaporated before reprecipitating the crystal mass with the addition of hexane to a hot solution in benzene.

All three methods for bromination referred to above were partly optimised (refer to Experimental section), but they only produced maximum yields of about 30–60%. To make matters worse, the resulting product was not compound **4**. In each instance, the same crystalline product with a melting point of 132-133 °C was produced.

The ^{1}H NMR spectrum in deuterochloroform displays a singlet at 1.66 ppm (3H), a singlet at 7.58 ppm (1H) and a broad singlet at 8.40 ppm (1H, NH), along with two ethyl group signals from ester radicals. Upon comparison with the Knorr pyrrole spectrum, one methyl group signal vanishes, while the other group's signal shifts by 0.9 ppm to a stronger field. In this instance, it appears that the signal belongs to the region typical of methyl groups attached to the sp^3-hybridized carbon atom. The signal of the ethyl radical from one of the ester groups bears the same structure as that of Knorr pyrrole. However, both methyl and methylene protons resonate in a somewhat stronger field. On the other hand, the signal from the methylene protons of the second ester group is divided into four quartets with coupling constants of 7.2 Hz at 4.14, 4.17, 4.20, and 4.24 ppm. The signals have an intensity ratio of 1:3:3:1, showing that the oxymethylene group is in a complicated steric situation. It is clear that four stable conformers produce distinguishable signals.

Comparison of the ^{13}C NMR spectra of Knorr pyrrole and the resulting product indicates that the carbonyl group signal in the β-position of the pyrrole ring and in one of the carbonyl groups in the product are similar (161.79 and 161.69 ppm, respectively). Conversely, the second carbonyl group signal in the product shifts to 174.88 ppm, falling in the ester group region characterized by the sp^3-hybridized carbon atom. A correlation between the proton and carbon signals of the methyl group (δ 1.66 ppm, δC 18.70 ppm), the carbonyl group, and the carbon nucleus at 26.39 ppm was established. Additionally, there is a correlation between the proton signal of this methyl group and the carbon nucleus signal at 109.25 ppm, where the latter lacks protons. Finally, a correlation has been observed between the protons of the methyl group and the carbon nucleus at 150.24 ppm.

The proton signal at 7.58 ppm corresponds with the signals of the carbon nuclei at 57.87 ppm, 167.00 ppm, and 150.24 ppm. Assuming we accept the assignment of the signals of the dibromomethyl group [19], it becomes evident that this structural fragment is situated at a double bond. Furthermore, analysis of the ^{1}H and ^{13}C NMR spectra of Knorr pyrrole and the resulting product shows that the NH group is preserved during bromination. However, the heteroaromatic system of the pyrrole is disrupted, leaving only a singular C=C double bond in the molecule.

Furthermore, we grew a crystal suitable for X-ray analysis, which revealed the crystal's structure to be of **5** with two bromine atoms. The crystal was found to be identical in composition to Halbig's product (Fig. 4).

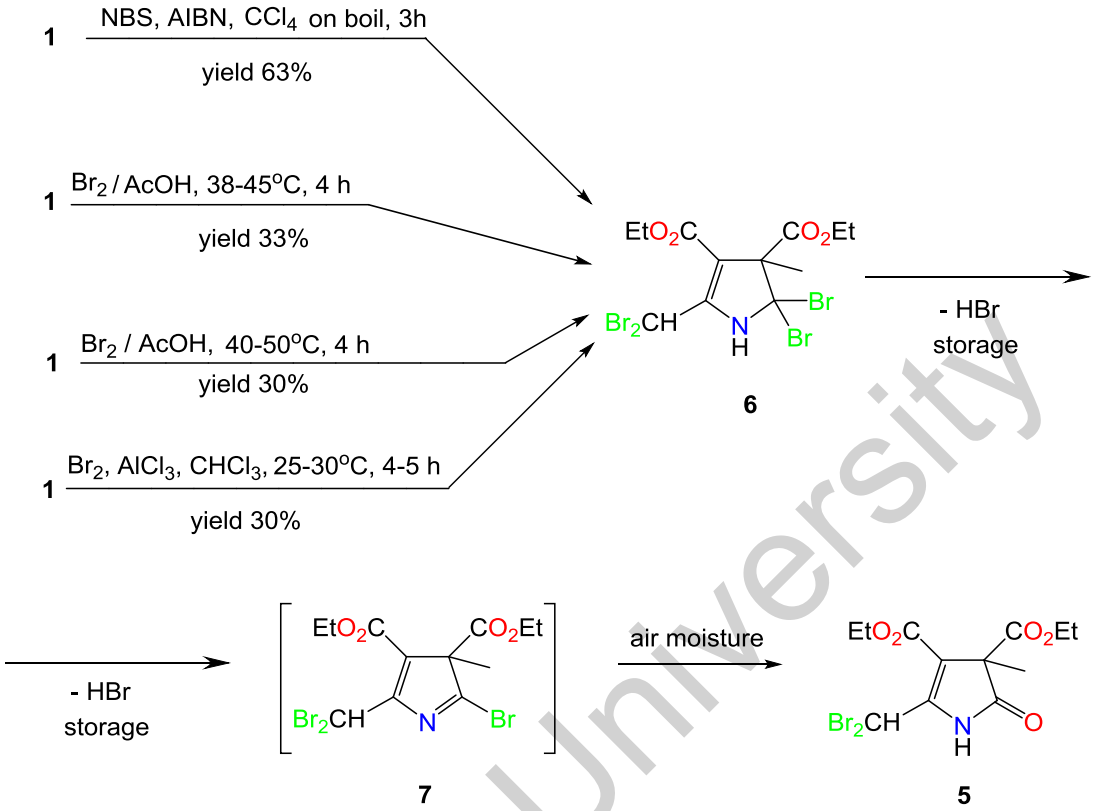


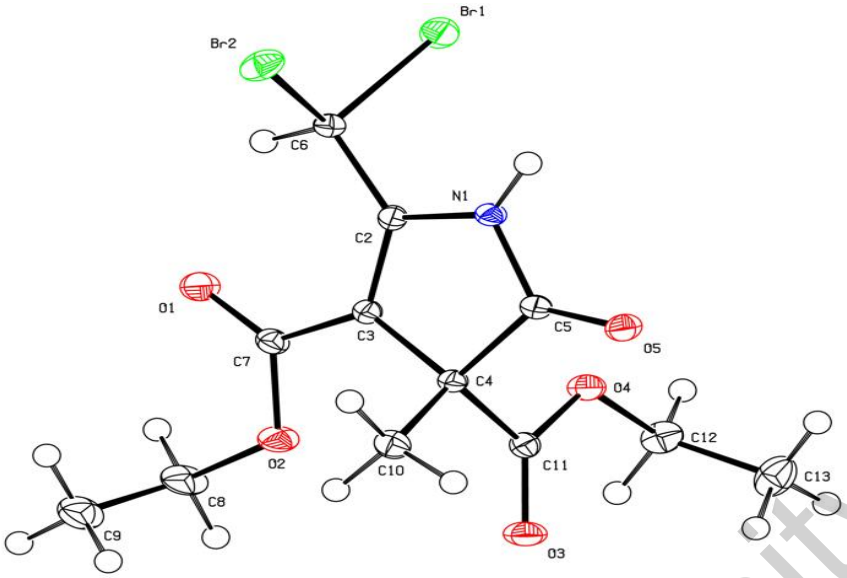
Figure 4. General synthesis scheme of diethyl 5-(dibromomethyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3,4-dicarboxylate (**5**)

The crystal structure of compound **5** consists of neutral molecules. Two of them are always connected by two intermolecular hydrogen bonds. The first is between the nitrogen atom N1 and oxygen atom O5 of the neighboring molecule, and the second one is between O5 and N1 of the same neighboring molecule, forming centrosymmetric pairs. The distance N1 … O5 is 2.811(2) Å and the angle at the H atom is 176.9°. The values of the distances between the bonds in the ring are expected. The shortest one is 1.352(2) Å formally corresponds to the double bond C2–C3, the single bonds C3–C4 and C4–C5 (1.518(1) Å and 1.539(2) Å, respectively) are the longest ones.

The bond distances N1–C2 and N1–C5 are in the expected range. The geometry of dibromomethyl group (C6–Br1 = 1.943(1) Å, C6–Br2 = 1.942(1) Å and the angle at C6 is 109.05(4)° and again the normal range.

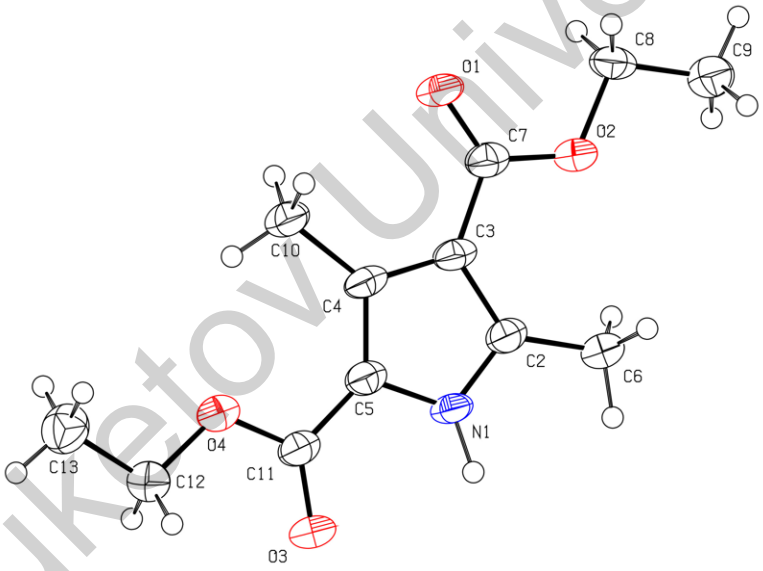
However, the order of the substituents on the pyrrole ring is very interesting. Starting from the atom N1, we found dibromo-substituent at C1, ester substituent at C2, another ester substituent together with a methyl group at C3 and O= substituent at C5 (Fig. 5). So, the ester groups are located on adjacent atoms C3, C4. But we started from compound **1,** where the ester substituents are localized on positions 3 and 5 starting from nitrogen atom N1. The structure is shown in Figure 6.

The crystal structure of compound **1** consists of neutral planar molecules. They are connected in endless chains by one medium strong H-bond. Each molecule participates in two identical (due to symmetry) H-bonds. The N1 atom acts as a hydrogen donor and the O1oxygen atom as a hydrogen acceptor. The distance of N1 … O1 is 2.898(x) Å and the angle at the H-atom is 158.0°. Values of the bond distances in the ring are in the range 1.34–1.42 Å. This is the range typical of aromatic pyrroles. Substitution pattern is methyl at C1, ester group at C3, methyl at C4 and ester group at C5 (Fig. 6).



The default probability in Ortep is 60 %

Figure 5.Crystal structural of diethyl 5-(dibromomethyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3,4-dicarboxylate (**5**)



The default probability in Ortep is 60 %

Figure 6. Crystal structural of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole

The basic crystallographic data, measurement and refinement details for compounds **5** and **1** are presented in Table.

T a b l e

Crystallographic data and details of refinements for compounds 5 and 1

Compound	**5**	**1**
CCDC no.	2239489	2239477
Empirical formula	$C_{12}H_{15}Br_2NO_5$	$C_{12}H_{17}NO_4$
Formula mass, g mol^{-1}	413.07	239.26
Crystal system	Triclinic	orthorhombic
Space group	P-1 (no. 2)	Fdd2 (no. 43)
a, Å	6.0558(4)	28.4442(15)

Continuation of Table

Compound	5	1
b, Å	10.1493(5)	38.959(2)
c, Å	12.8464(8)	4.4053(3)
α, deg	81.251(2)	90
β, deg	76.753(2)	90
γ, deg	81.216(2)	90
Z	2	16
V, Å^3	753.89(8)	4881.8(5)
Temperature, K	120(2)	150(2)
$D_{(calcd)}$, g cm^{-3}	1.820	1.302
μ(Mo-Ka), mm^{-1}	5.393	---
μ(Cu-Ka), mm^{-1}	---	0.812
F(000)	408	2048
θ_{min}-θ_{max}, deg	2.46 – 30.00	3.85 – 72.28
Reflections collected	20153	16538
No. of unique data	4362	2419
R_{int}	0.0253	0.1214
Obs.refl.ns [I> 2σ(I)]	4069	1876
Parameters refined	184	158
R1, wR2 (all data)[a, b]	0.0201;0.0437	0.0835; 0.1657
Residuals, e Å^{-3}	-0.517; 0.684	-0.215; 0.187

[a] w = 1/[σ2(Fo2)+(0.0559P)2],

[b] w = 1/[σ2(Fo2) + (0.0623P)2 + 0.2235P], where P = (Fo2 + 2Fc2) /3.

The X-ray structural analysis data were deposited in the form of CIF files at the Cambridge Crystallographic Data Center (deposit CCDC no.2239489 for compound **5** and no. 2239477 for compound **1**).

Thus, the above information enables us to present the following sequence of reactions. Bromide **2** reacts with an excess of bromine or bromosuccinimide to form dibromomethyl derivative **8**. Based on the given principles, the improved version is: subsequently, the bromine cation attacks position 2 of the pyrrole ring of the product, resulting in the formation of a σ-complex. During this attack or simultaneously, the ester group is transferred to position 3. Since the reaction with N-bromosuccinimide and bromine leads to the same outcome, we can conclude that:

a) the medium becomes polar enough to cause heterolytic cleavage of the N-Br bond with the formation of the bromine cation due to the presence of succinimide and the significant NH-acidity of the pyrrole derivatives in the reaction mixture;

or b) the process can take place viaboth ionic and radical pathways with the formation of the same end-product.

In this instance, the final step involves stabilising the reorganised cation, resulting in compound **6**. The compound was obtained in every case when mild conditions were used to treat the reaction mixture. The NMR spectroscopic data accurately describes compound **6**'s structure. It is expected that product **6** will easily cleave hydrogen bromide and convert into tribromide **7**, which has a structure of a cyclic, unsaturated imidoyl bromide. Accordingly, it should react with compounds containing hydroxyl groups (including moisture in the air) to transition to unsaturated lactam **5**, of which the crystal was analyzed by XRD.

The methods for synthesising Halbig's product were discussed in detail previously. The data presented illustrates that the reaction was conducted at high temperatures, with the product washed using hydroxyl-containing substances before being recrystallised from them. Consequently, lactam **5** was the only feasible product under the given conditions. Figure 7 depicts the proposed transformation scheme and mechanism.

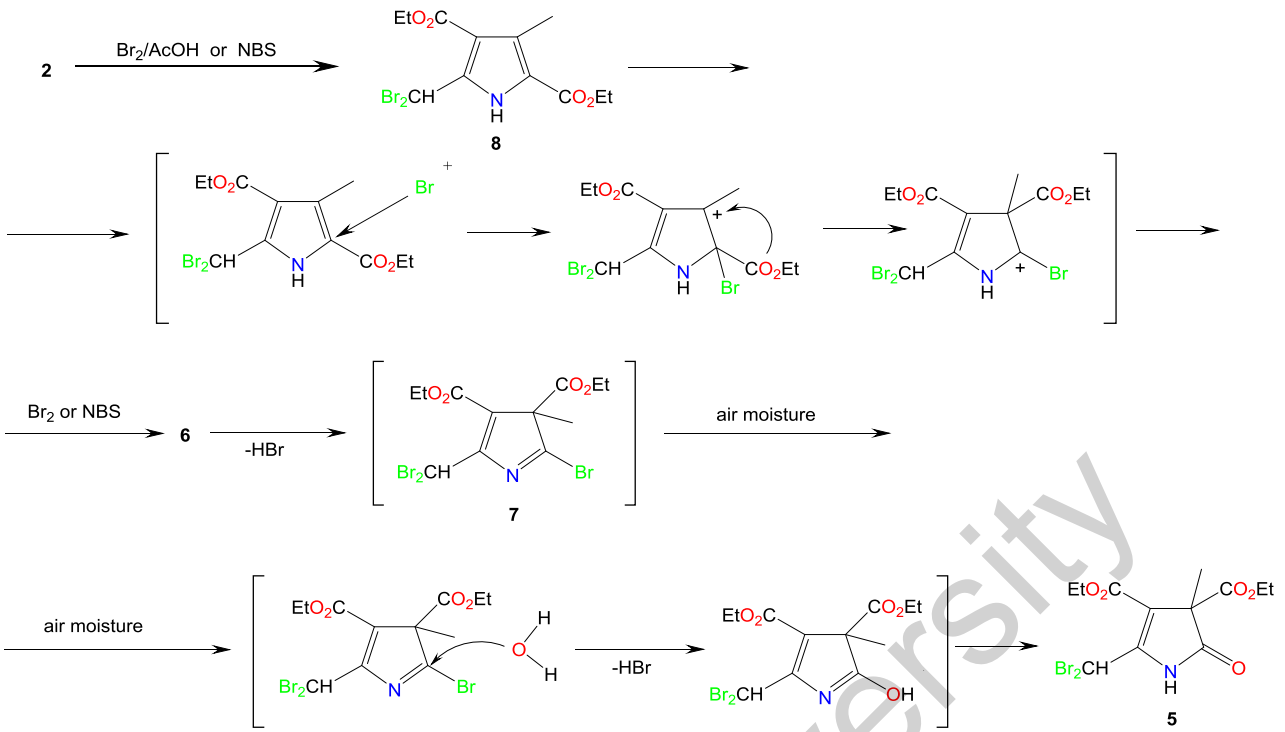


Figure 7. The transformations chain and the proposed mechanism of compound **5** formation

It was discovered that the bromination process of Knorr pyrrole follows a stepwise progression, when carried out with an excess of N-bromosuccinimide or bromine. The methyl group at position 5 is targeted first with the addition of two bromine atoms. Then, the ensuing attack of the bromine cation (or bromine radical) occurs at position 2 of the pyrrole ring, which causes the ester group to transfer to position 3 and disrupts aromaticity of the system. Finally, the integration of one more bromine atom into the molecule stabilises the structure, resulting in the formation of a 2,3-dihydropyrrole derivative. In the presence of bases and substances containing hydroxyl groups, the latter undergoes successive transformations into cyclic imidoyl bromide and ultimately unsaturated lactam **5**. This compound is known as Halbig's product and its true structure was established by our team.

Conclusions

In conclusion, the effort to produce a dibromo derivative of Knorr pyrrole where bromine atoms occupy both allyl positions was not successful, even with the outcomes presented in [13, 14]. The bromination reaction was carried out using 2 mol of N-bromosuccinimide per 1 mol of Knorr pyrrole **1** in carbon tetrachloride by boiling and initiating with azobis(isobutyronitrile), in acetic acid at 40–50 °C at a molar ratio of Knorr pyrrole **1**: bromine 1:5 and at a temperature of 38–45 °C at a molar ratio of Knorr pyrrole **1**: bromine 1:4 and in chloroform at 27–30 °C in the presence of catalytic amounts of aluminum chloride. While all three bromination methods were partially optimized, the yields obtained were limited to 30–63 %. In all instances, we obtained the same crystalline product with a melting point of 132-133 °C. We confirmed the compound's structure of diethyl 5-(dibromomethyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3,4-dicarboxylate **5**, with two bromine atoms, through our analysis of ^{1}H and ^{13}C NMR-spectroscopy, mass-spectrometry and X-ray diffraction. This compound is identical in composition to the Halbig's product. These findings demonstrate the lack of systematic research on the β-bromomethylpyrroles' preparation.

*Author Information**

**The authors' names are presented in the following order: First Name, Middle Name and Last Name*

Lyazat Karishovna Salkeyeva — Doctor of Chemical Sciences, Professor, Department of Organic Chemistry and Polymers, Karaganda Buketov University, Universitetskaya str., 28, 100024, Karaganda, Kazakhstan; e-mail: lsalkeeva@mail.ru; https://orcid.org/0000-0003-4207-916X

Leonid Markovich Pevzner — Candidate of Chemical Sciences, Senior Researcher, Department of Organic Chemistry, Saint Petersburg State Technological Institute (Technical University), Moskovsky prospect, 26, 190013, Saint Petersburg, Russian Federation; e-mail: pevzner_lm@list.ru; https://orcid.org/0000-0002-1678-2524

Pavel Vojtíšek — Associate Professor RNDr., CSc. Jan Evangelista Purkyně University in Ústí nad Labem, Department of Chemistry, Faculty of Science, Pasteurova 3632/15, Ústí nad Labem, 400 96, Czech Republic; e-mail: pavojt@natur.cuni.cz; https://orcid.org/0000-0002-4685-9238

Yelena Viktorovna Minayeva (*corresponding author*) — Candidate of Chemical Sciences, Associate Professor, Department of Organic Chemistry and Polymers, Karaganda Buketov University, 100024, Karaganda, Kazakhstan; e-mail: yelenaminayeva@yandex.ru; https://orcid.org/0000-0001-9382-5965

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Lyazat Karishovna Salkeyeva** conceptualization, methodology, data curation, writing-review & editing, supervision; **Leonid Markovich Pevzner** resources, investigation,methodology, data curation, formal analysis, visualization, validation, writing-original draft; **Pavel Vojtíšek** investigation, resources, data curation, formal analysis, writing-original draft; **Yelena Viktorovna Minayeva** investigation, validation, writing-original draft, writing-review & editing.

Conflicts of Interest

The authors declare no conflict of interest.

References

1 Ivan, B.-C., Barbuceanu, S.-F., Hotnog, C.M., Anghel, A.I., Ancuceanu, R.V., Mihaila, M.A., Brasoveanu, L.I., Shova, S., Draghici, C., Olaru, O.T., Nitulescu, G.M., Dinu, M., & Dumitrascu, F. (2022). New Pyrrole Derivatives as Promising Biological Agents: Design, Synthesis, Characterization. In *Silico, and Cytotoxicity Evaluation.Int. J. Mol. Sci.*, 23, 8854. https://doi.org/10.3390/ijms23168854

2 Jeelan Basha, N., Basavarajaiah, S.M., & Shyamsunder, K. (2022). Therapeutic potential of pyrrole and pyrrolidine analogs: An update. *Mol. Divers.*, 1–23. https://doi.org/10.1007/s11030-022-10387-8

3 Mateev, E., Georgieva, M., & Zlatkov, A. (2022). Pyrrole as an Important Scaffold of Anticancer Drugs: Recent Advances. *J. Pharm. Pharm. Sci.*, *25*, 24–40. https://doi.org/10.18433/jpps32417

4 Azad, I., Jafri, A., Khan, T., Akhter, Y., Arshad, M., Hassan, F., Ahmad, N., Khan, A.R., & Nasibullah, M. (2019). Evaluation of pyrrole-2,3-dicarboxylate derivatives: Synthesis, DFT analysis, molecular docking, virtual screening and in vitro anti-hepatic cancer study. *J. Mol. Struct.*, *1176*, 314–334. https://doi.org/10.1016/j.molstruc.2018.08.049

5 Imperatore, C., Scuotto, M., Valadan, M., Rivieccio, E., Saide, A., Russo, A., Altucci, C., Menna, M., Ramunno, A., Mayol, L.,Russo G., & Varra M. Photo-control of cancer cell growth by benzodiazo N-substituted pyrrole derivatives. *J. Photochem. Photobiol. A Chem.* (2019), *377*, 109–118. https://doi.org/10.1016/j.jphotochem.2019.03.042

6 Rashmi, K.C., Harsha Raj, M., Paul, M., Girish, K.S., Salimath, B.P., & Aparna, H.S. (2019). A new pyrrole based small molecule from Tinosporacordifoliainduces apoptosis in MDA-MB-231 breast cancer cells via ROS mediated mitochondrial damage and restoration of p53 activity. *Chem.-Biol. Interact.*, *299*, 120–130. https://doi.org/10.1016/j.cbi.2018.12.005

7 Khalilpour, A., & Asghari, S. (2018). Synthesis, characterization and evaluation of cytotoxic and antioxidant activities of dihydropyrimidone substituted pyrrole derivatives. *Med. Chem. Res.*, *27*, 15–22. https://doi.org/10.1007/s00044-017-2041-4

8 Sowmya, P.V., Poojary, B., Kumar, V., Vishwanatha, U., & Shetty, P. (2017). Fluorinated pyrrole incorporated 2-thiazolyl hydrazone motifs: A new class of antimicrobial and anti tuberculosis agents. *Arch. Pharmacal Res.*, 1–21. https://doi.org/10.1007s12272-017-0967-1

9 Jung, E.K., Leung, E., & Barker, D. (2016). Synthesis and biological activity of pyrrole analogues of combretastatin A-4. *Bioorganic Med. Chem. Lett.*, *26*, 3001–3005. https://doi.org/10.1016/j.bmcl.2016.05.026

10 Carvalho, R.C.C., Martins, W.A., Silva, T.P., Kaiser, C.R., Bastos, M.M., Pinheiro, L.C.S., Krettli, A.U., &Boechat, N. (2016). New pentasubstituted pyrrole hybrid atorvastatin-quinoline derivatives with antiplasmodial activity. *Bioorg. Med. Chem. Lett.*, *26*, 1881–1884. https://doi.org/10.1016/j.bmcl.2016.03.027

11 Sarg, M.T., Koraa, M.M., Bayoumi, A.H., & Gilil, S.M.A.E. (2015). Synthesis of Pyrroles and Condensed Pyrroles as Anti-Inflammatory Agents with Multiple Activities and Their Molecular Docking Study. *Open J. Med. Chem.*, *05*, 49–96. https://doi.org/10.4236/ojmc.2015.54005

12 Battilocchio, C., Poce, G., Alfonso, S., Porretta, G.C., Consalvi, S., Sautebin, L., Pace, S., Rossi, A., Ghelardini, C., Di Cesare Mannelli, L.D.C., Schenone, S.,Giordani, A., Francesco, L.D., Patrignani, P., & Biava, M. (2013). A class of pyrrole deriva-

tives endowed with analgesic/anti-inflammatory activity. *Bioorganic Med. Chem.*, *21*, 3695–3701. https://doi.org/10.1016/j.bmc.2013.04.031

13 Gurevich, P.A., & Yaroshevskaya, V.A. (2000). Phosphorus-containing Derivatives of Indole and Pyrrole. (Review). *Chem. Heterocycl. Compd.*, *36*, 1361–1401. https://doi.org/10.1023/A:1017562111215

14 Gurevich, P.A., Moskva, V.V., & Kiselev, V.V. (1993). Uspekhi nauki i tekhnolohii. Orhanicheskaia khimiia [Advances of Science and Technology. Organic Chemistry]. VINITI, Moscow, *30*, 3[in Russian].

15 Fischer, H., & Scheyer, H. (1923). Einwirkung von Brom auf substituierte Pyrrole und Synthese in α-Stellung bromierter Dipyrrylmethen-Farbstoffe. *Justus Liebigs Annalen der Chemie*, *434*(1), 237–251.

16 Fischer, H., & Ort, G. (1937). Chemistry of Pyrrole [Russian translation]. *ONTI, Leningrad*, 122.

17 Halbig, P., & Walach, B. (1927). *Justus Liebigs Annalen der Chemie*, *457*, 245.

18 Kutscher, W., & Klamerth, O. (1950). *Hoppe-Seyler'sZeitschrift fur Physiologische Chemie*, *286*, 191.

19 Angelini, G., Giancaspro, C., Illuminati, G., & Sleiter, G. (1980). Electrophilic heteroaromatic reactions. 3[1]. The α-side-chain bromination of some polysubstitutedα-methylpyrroles in the dark. Evidence for the formation of intermediate σ adducts.*J. Org. Chem.*, 45, 10, 1786–1790. https://doi.org/10.1021/jo01298a009

20 Byun, Y., & Lightner, D.A. (1991). Synthesis and properties of a bilirubin analog with propionic acid groups replaced by carboxyl. *Journal of Heterocyclic Chemistry*, *28*(7), 1683–1692. Portico. https://doi.org/10.1002/jhet.5570280707

21 Treibs, A., & Bader, H. (1959**)**. *Justus Liebigs Annalen der Chemie*, *627*, 182.

22 Sheldrick, G.M. (2014). SHELXT-2014. Program for Crystal Structure Solution from Diffraction Data. *University of Göttingen: Göttingen.*

23 Sheldrick, G. M. (2015). Crystal structure refinement with SHELXL. *Acta Crystallographica Section C: Structural Chemistry*, *71*(1), 3–8. https://doi.org/10.1107/S2053229614024218