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CASE REPORT

Michael reaction in α, β-dihalo-substituted cyclopentenones

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ABSTRACT

It has been established that due to the conjugation effect of 2,5-dichloro-3N,N-dialkylamino-4,4-dimethoxy-5-allyl-(propa-dienyl)cyclopent-2-en-1-ones with various nucleophilic agents (pyridine, tert- butyl anion, secondary and tertiary amines) react violently and lead to the formation of abnormal products.

Keywords: anchimeric; chloroketone; aziridine-aminal; anisochronous; diastereotopicity

Introduction

The reactions of β-ketovinylation in the β-halogenvinylketone series have been studied in detail[1]. At the same time, there is practically no information on such reactions of α, β-dihalogen-substituted vinyl ketones. The presence of additional halogen in the structures of the latter can undoubtedly influence the course of the β-ketovinylation process involving various nucleophiles, since additional stabilization with the α-substituent X of the intermediate carbanions of Michael is possible[2]. In Michael's final adducts, one should expect an effective vinylogical n-d-π overlapping of electron clouds of planar nucleophiles, halogen atoms and CO-groups, which should have a significant effect on the chemical stability of these systems. An experimental check of these assumptions is especially important in the case of cyclopentenones, which are fragmentarily or in camouflaged form the main signatures of chemically unstable bioactive cyclopentane natural compounds (chlorovulons, clavulons, punaglandins, prostaglandins A and J, pentenomycins, dicranenones, sarcomycin, etc.)[3].

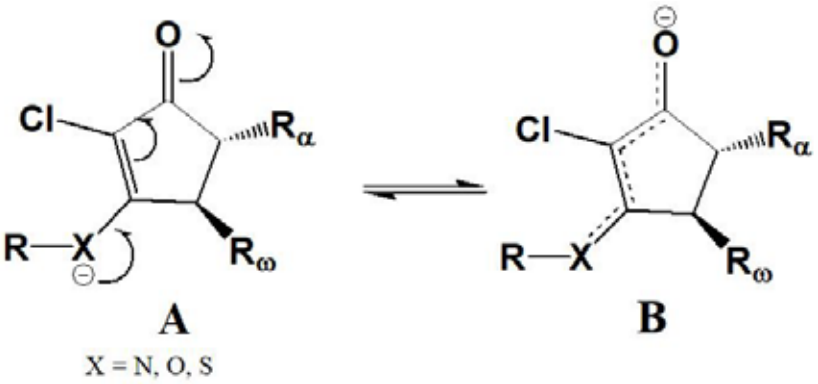
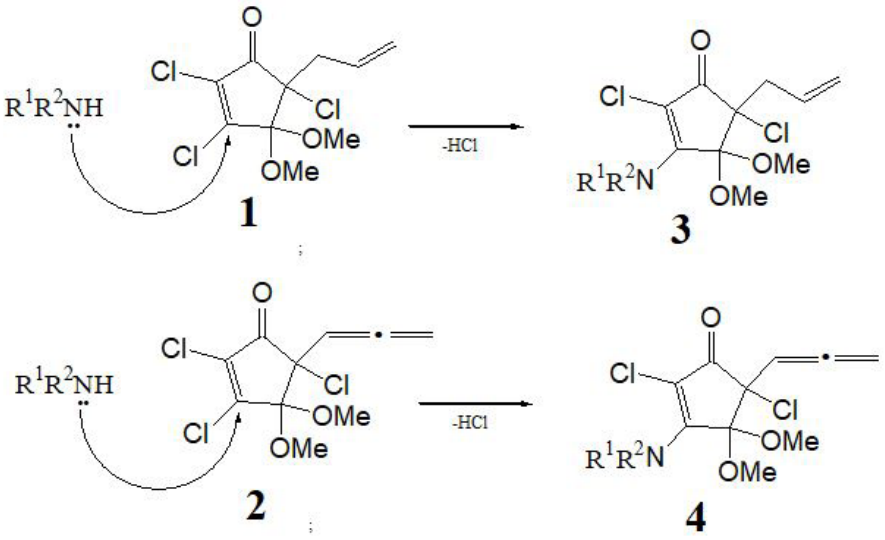


Figure 1: Resonance effect in cyclopentenones

Discussion

In order to reach the precursors of type A compounds, we investigated the reactions of trichloroketones (1, 2) with various kinds of nucleophiles: aliphatic, cyclic, heterocyclic (primary or secondary) amines, as well as methylate, tert-butylate anions. This reaction with amines in alcohol medium at 20 °C proceeds smoothly and regiospecifically at C (3), yielding corresponding aminochloro ketones with high yields (3, 4):



(**a**) $R^1=R^2=Me$; (**b**) $R^1=Me$, $R^2=H$; (**c**) $R^1=H$, $R^2=-CH_2CH_2OH$;
(**e**) $R^1+R^2=-CH_2CH_2OCH_2CH_2-$; (**f**) $R^1+R^2=-(CH_2)_5-$

Figure 2: Reaction of dichlorocyclopentenones with amines

The reaction of chloroketone (1) with the aforementioned nucleophiles in the presence of a three-molar excess of pyridine is anomalous, giving a more polar compound (5). When using instead of the secondary amines of their hydrochlorides, the compound (5) is preferably formed:

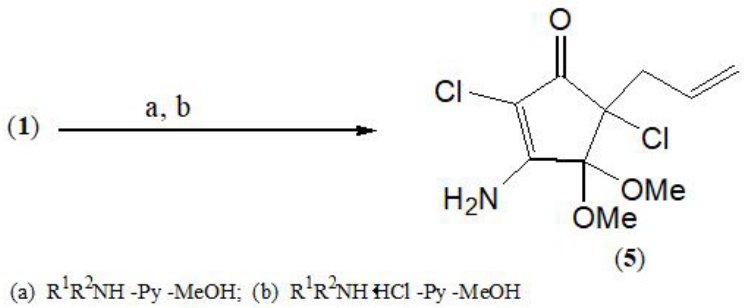


Figure 3: Reaction of chlorocyclopentenone (1) with hydrochlorides of secondary amines

In the absence of the amine, *Py* reacts easily with chloroketone (1), giving a water-soluble ionic complex, colored to brown color. Obviously, the cycle of transformations (1 → 5) takes place with the participation of pyridine and the proposed stepwise reaction route can be depicted as follows:

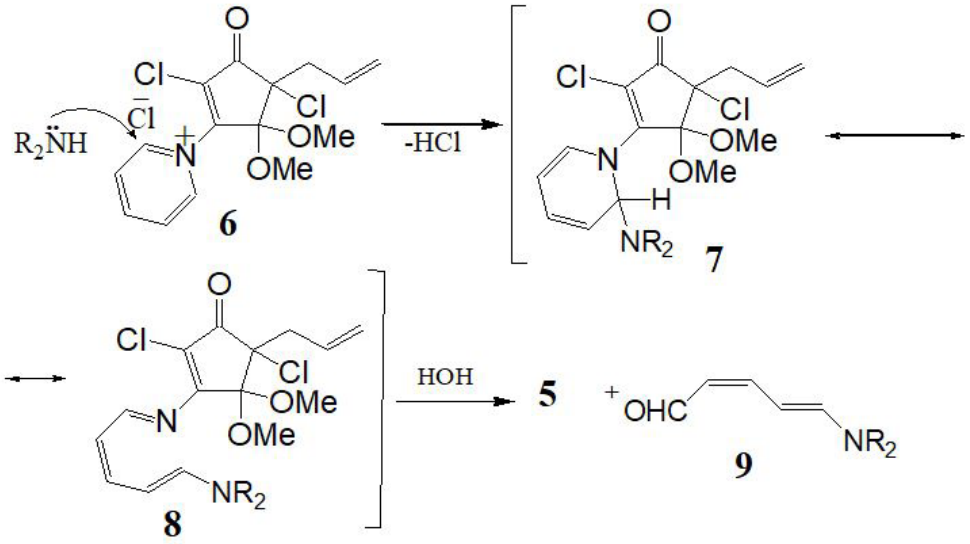


Figure 4: Proposed mechanism of the reaction of chlorocyclopentenone (1) with pyridine

When sterically hindered amines are used in this reaction, N-dienal (10) is formed:

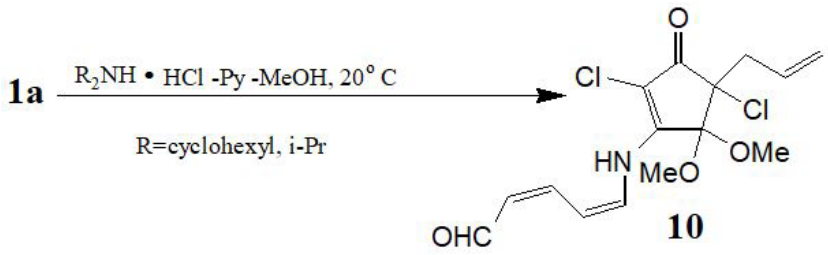


Figure 5: Reaction of chlorocyclopentenone (1a) with hindered amines

An unusual transformation was observed when the ketone (1) was boiled in triethylamine medium containing 1-2 equivalents H_2O. In this case, enamineketones (11) and (12) were obtained in a ratio of 2: 3 with a total yield of 55%. The structure of the compound (12), in addition to the spectroscopic data, is also confirmed by counter synthesis.

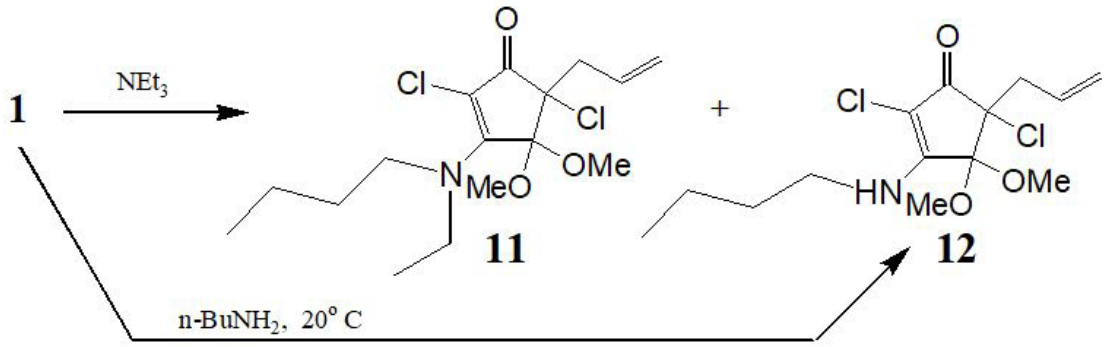


Figure 6: Reaction of chlorocyclopentenone (1) with triethylamine

Unlike the above bases, the reaction of the ketone (1) with tret-butylate anion results in a high yield (90%) of the γ-lactone (13) and the acyclic derivative of enolized 3,4-dioxopentanoic acid (14) in a ratio of 1: 1.4 .

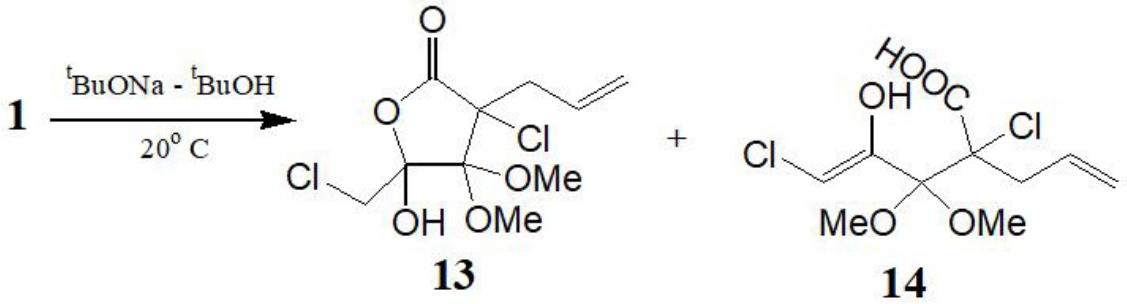


Figure 7: Reaction of chlorocyclopentenone (1) with tert-butylate anion

The probable mechanism of this transformation, we believe, includes the stages of intramolecular retroene fragmentation of the primary replacement adduct (15), the retroaldol splitting of the intermediate 1,3-dione (16), and the intramolecular cyclization of the intermediate (17). The acyclic acid (14) is formed from the tautomer (18) after acidifying the reaction mass.

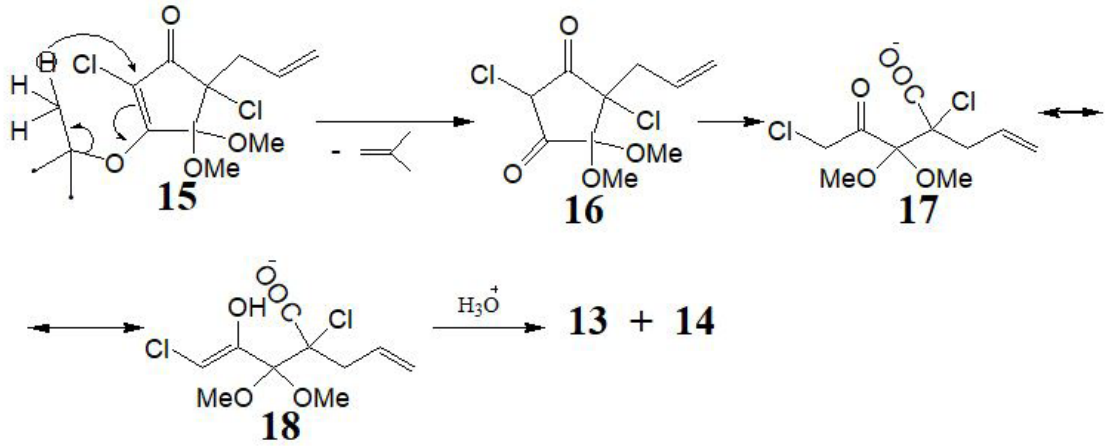


Figure 8: Proposed reaction mechanism of chlorocyclopentenone (1) with tert-butyl anion

Polyfunctional cyclopentane derivatives (1, 2) and (3,4) are hyper-conjugated systems overloaded with heterogeneous substituents, which are of interest primarily to reactivity and chemical transformations. In this case, the unusual hydrolytic stability of the enaminochlorketone fragment in compounds (3,4) is striking. All our attempts to carry out exhaustive hydrolysis of these compounds by the action of mineral acids have not been successful; Only partial hydrolysis of the dimethylacetal group occurred. Such an anomalous hydrolytic stability, to our view, is related to the thermodynamic disadvantage of the hydrolysis stage-the π-π and n-π equilibrium of the chlorine atom at C (2) with a double bond in (3,4), as shown below:

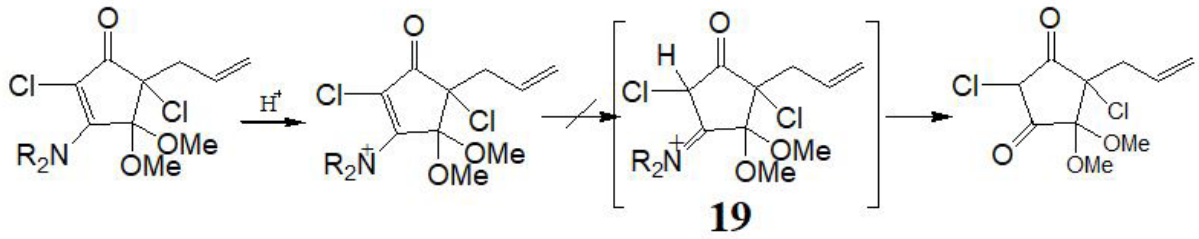
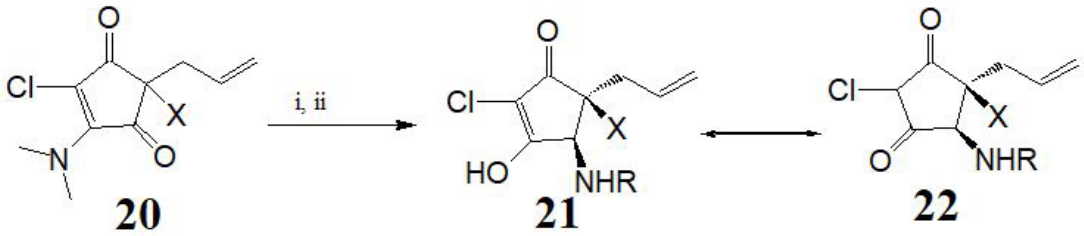


Figure 9: Hydrolytic stability of aminochlorocyclopentenones

At the same time, within the framework of our approach to 13-azaprostanoids on model compounds, it has been possible to develop a simple and convenient way of hydrolysis of the aforementioned fragment of enaminochlor ketone. This became possible due to the selection of the substrate and the realization of the effect of the anchimeric assistance. Thus, the implementation of the standard ketone-imine-amine transition with the participation of the non-conjugated C = O group of enamyochloroketones (20) resulted in a roughly equal ratio (70-90%) to the tautomeric mixture of keto- enols (21) and (22).



(**i**) H_2NR, ms(3A°), MeOH, 20° C; (**ii**) $NaBH_4$, MeOH, -40 °C; X=H, Cl

Figure 10: Anchimeric assistance at the stage of hydrolysis in aminochlorocyclopentenones

The proposed mechanism of the described reaction is undoubtedly connected with the transformations of the expected adducts (23), which in situ are cyclized to the "aziridine-aminal" - intermediates (24), smoothly hydrolyzed then in 1,3-diketone (25).

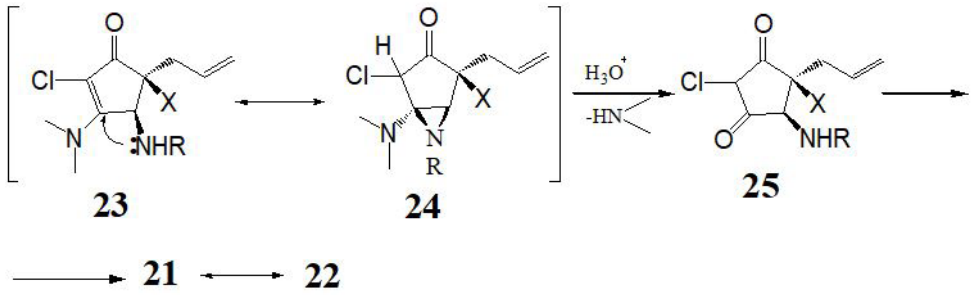


Figure 11: Proposed mechanism of hydrolysis in aminochlorocyclopentenones

Unlike trichloro ketones (1, 2), in enaminechloroketones (3, 4), the vinyl chloride atom is inert both under conditions of reducing dechlorination with zinc and when the C = O group is reduced by sodium borohydride.

Compound (4a) by the action of OsO_4-$NaIO_4$ system is smoothly converted to α, β-unsaturated acid with good yield (28). The corresponding E-isomer is not formed.

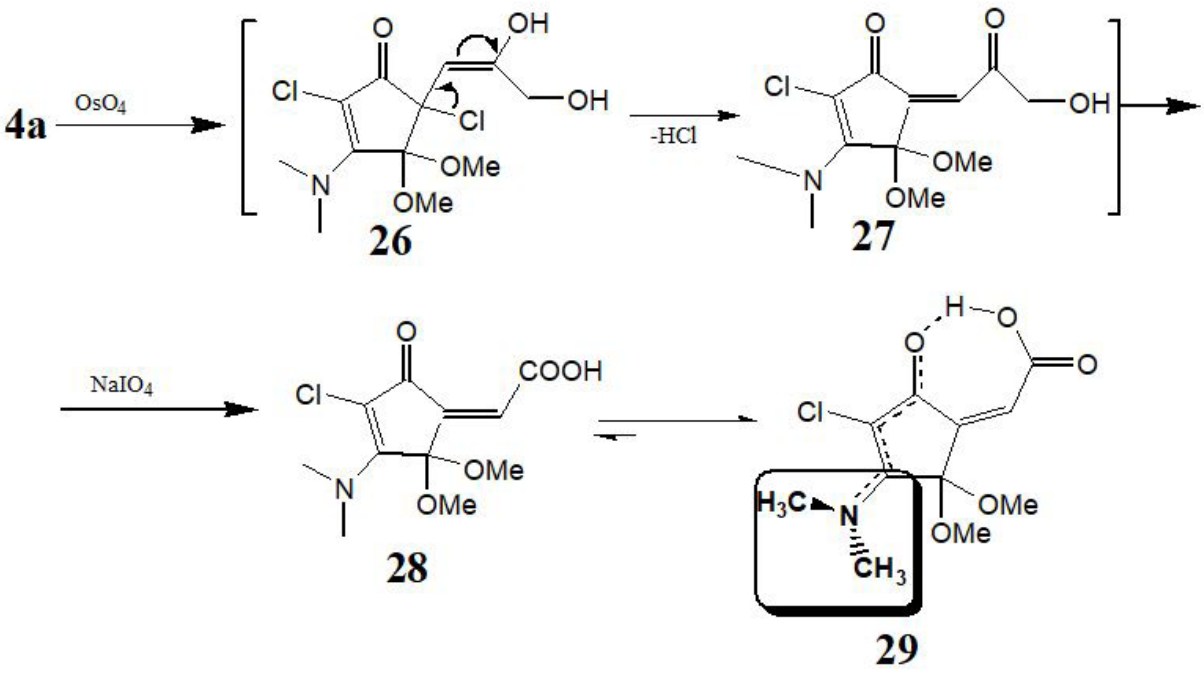


Figure 12: Reaction of aminochloroketone (4a) with OsO_4

Obviously, the mechanism of this transformation includes the stages of the formation of glycol (26), ketol (27), and the splitting of the last period of the anion by a known pathway. According to spectroscopy and X-ray diffraction data, the acid (28) due to the intramolecular hydrogen bond exists exclusively in the conjugated form (29).

Attention is drawn to the spectral characteristics of acids (28). In its NMR spectrum, the proton signal of the COOH group is anomalously weakly polarized ($CDCl_3$, δ15.6 ppm) and the value of δ does not depend on the dilution, which indicates the chelating character of this proton. Interestingly, the N-dimethyl groups are anisochronous (there is no rotamer rotation of the N-dimethyl groups around the ordinary C (1) -N bond) and is resonated as two narrow singlets at δ 3.52 and 3.70 ppm. The di-astereotopy of these groups is also visible in the ^{13}C NMR spectrum (δs 42.45 k and 42.29 k ppm). In the IR spectrum, there is no absorption band in the 3000-3600 cm-1 region, which is characteristic of the OH group, instead, there is an intense broadened absorption band at 1536 cm^{-1} of enolic coupling. These data indicate that the acid (28) exists in the preferred resonance form (29) and is the main reason for the selective formation of cis-acid (28).

Experimental

The IR spectra were taken with a Specord M-80 spectrophotometer in a liquid film and in a suspension in vaseline oil, the absorption frequencies are given in cm^{-1}. The 1H and 13C NMR spectra were recorded on a Bruker AM 300 spectrophotometer operating at 300 and 75 MHz, respectively, the internal standard was TMS, and the solvent was $CDCl_3$. The chemical shifts of ^1H and ^{13}C NMR signals are shown in the scale δ, in parts per million (ppm). The mass spectra were measured on a MX-1303 instrument, and the energy of ionizing electrons was 70 eV. For qualitative analysis of TLC, Silufol UV-254 plates with detection of substances with UV irradiation (λ 254 nm) and iodine were used.

Dichloro-3-N, N-dimethylamino-4,4-dimethoxy-5-allylcyclopent-2-en-1-one (3a)

A solution prepared from 4.89 g of dimethylamine hydrochloride in 70 ml of methanol was added dropwise to a stirred solution of 6.0 g of ketone (1) in 30 ml of methanol at 20 ° C for 1 hour, after which the mixture was stirred for an additional 2 hours. After the reaction (TLC), methanol was evaporated, water added, extracted with chloroform and dried with Na_2SO_4. After chromatography on SiO_2 (eluent-hexane-ethyl acetate, 1: 1), 5.6 g (90%) of product (3a), mp.72-73 ° C, was obtained. IR spectrum (cm^{-1}): 1740 (C = O), 1695 (N-C = CCl-C = O), 1620 (C = C). ^1H NMR ($CDCl_3$, δ, ppm): 2.58 (2H, CH_2, J = 7.0 Hz), 3.13 s (3H, OCH_3), 3.50 s (3H, OCH_3), 3.28 s (6H, N-dimethyl group), 4.67-5.01 m (2H, CH_2 =), 5.30-6.01 m (1H, CH =). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm):

187.84 s (C = O), 159.62 s (C^3), 133.35 d (CH =), 117.23 t (CH_2 =), 106.84 s (C^2), 102.55 s (C^4), 75.15 s (C^5), 52.38 q (OCH_3), 51.55 q (OCH_3), 45.13 t (CH_2), 42.35 q (CH3). Mass spectrum (m / z): 293 [M] $^+$, 258 [M-Cl] $^+$, 262 [M-OCH_3] $^+$, 278 [M-CH_3] +, 266 [M-C_2H_3] $^+$, 226 [M -CO-C_3H_5] $^+$, 222 [M-HCl-Cl] $^+$.

In a similar manner, compound (4a) was obtained.

Dichloro-3-amino-4,4-dimethoxy-5-allylcyclopent-2-en-1-one (5)

A solution of 0.428 g of dimethylamine hydrochloride and 0.415 g of pyridine in 20 ml of methanol was added dropwise to a stirred solution of 0.5 g of ketone (1) and 25 ml of methanol at 20 °C for 0.5 h. The reaction mixture was stirred for 6 hours, methanol was distilled off, water was added, extracted with chloroform and dried with Na_2SO_4. After chromatography on SiO_2, 0.3 g (65%) of compound (5) m.p. 129-131 °C was obtained. IR spectrum (cm^{-1}): 1710 (C = O), 1620 (N-C = CCl-C = O), 1585 (C = C), 3200-3400 (NH_2). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.87 d (2H, CH_2, J = 7.0 Hz), 3.43 s (3H, OCH_3), 3.52 s (3H, OCH_3), 5.05-5.17 m (2H, CH_2 =), 5.55 is widened with. (2H, NH_2), 5.80-6.00 (1H, CH =). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 187.08 s (C = O), 162.15 s (C^3), 132.39 d (CH_2), 119.02 t (CH_2 =), 102.06 s (C^2), 101.67 s (C^4), 75.19 s (C^5), 52.34 q (OCH_3), 52.10 q (OCH_3), 41.16 t (CH_2). Mass spectrum (m / z): 265 [M] $^+$, 234 [M-OCH_3] $^+$, 230 [M-Cl] $^+$, 198 [M-Cl-CH_3OH] $^+$.

The reaction products of the ketone (1) with triethylamine

A mixture of 0.5 g of ketone (1) of 5 ml of triethylamine and 0.5 ml of water was heated under reflux for 8 hours. The reaction mass was distilled on a rotary evaporator and, after diluting the residue with water, it was extracted with chloroform. $CHCl_3$ was evaporated and the product was chromatographed on SiO_2 (eluent-hexane-ethyl acetate, 3: 1). Two products (11) and (12) were obtained.

Dichloro-3- (N-Ethyl-N-butylamino) -4,4-dimethoxy-5-allyl- cyclopent-2-en-1-one (11)

Yield 20%, oily liquid. IR spectrum (cm^{-1}): 1702 (C = O), 1585 (N-C = CCl-C = O). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.96 t (3H, CH_3, J = 7.30 Hz), 1.26 t (3H, CH^3, J = 7.04 Hz), 1.34 m (2H, CH_2), 1.65 m , CH_2), 2.75 d (2H, CH_2, J =7.16 Hz), 3.22 s (3H, OCH_3), 3.58 s (3H, OCH_3), 3.76 m (4H, $2CH_2N$), 5.03-5.09 m (2H, CH_2 =) , 5.70-5.82 m (1H, CH =). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 186.62 s (C = O), 158.31 s (C^3), 132.44 d (C H =), 118.63 t (CH_2 =), 104.85 s (C_4), 102.19 s (CH_2N), 44.83 t (CH_2), 30.99 t (CH_2), 19.94 t (CH_2N), 45.84 t (CH_2N), 44.83 t (CH_2), 30.99 t (CH_2), 19.94 t (CH_2)), 13.95 q (CH_3), 13.87 q (CH_3). Mass spectrum (m / z): 349 [M] $^+$, 314 [M-Cl] $^+$, 334 [M-CH_3] $^+$, 318 [M-OCH_3] $^+$, 278 [M-Cl-HCl] $^+$.

Dichloro-3N-butylamino-4,4-dimethoxy-5-allylcyclopent-2en-1-one (12)

Yield 35%, m.p. 97-98 ° C. IR spectrum (cm^{-1}): 1704 (C = O), 1596 (N-C = CCl-C = O), 3300 (NH). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.98 t (3H, CH_3, J = 7.29 Hz), 1.41 m (2H, CH_2), 1.66 m (2H, CH_2), 2.75 d. (2H, CH_2, J = 7.08 Hz, J = 1.04 Hz), 3.38 s (3H, OCH_3), 3.52 s (3H, OCH_3), 3.75 m (2H, CH_2), 5.04-5.15 m (2H, CH_2 =), 5.73 -5.95 m (1H, CH = and 1 H, NH). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 187.49 s (C = O), 159.76 s (C^3), 132.44 d (C H =), 118.75 t (CH_2), 101.90 s (C^4), 98.01 s (CH_2), 32.91 t (CH_2), 19.74 t (CH_2), 13.70 q (CH_3), 43.95 t (CH_2N), 41.97 t (CH_2). Mass spectrum (m / z): 321 [M] $^+$, 286 [M-Cl] $^+$, 306 [M-CH_3] $^+$, 290 [M-OCH_3]$^+$ 278 [M-C_3H_7] $^{+\cdot}$

Dichloro-4-hydroxy-3,3-dimethoxy-2-allylpentane-4-olide (13)

IR spectrum (cm^{-1}): 1780 (C = O), 1640 (C = C), 3376 (OH). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.98 d. (2H, CH_2-allyl, $J^1 = J^2 = 7$ Hz), 3.56 s (3H, OCH_3), 3.58 s (3H, OCH_3), 4.05 d. (2H, CH_2Cl, $J^1 = J^2 = 12$ Hz), 4.64 broad singlet (1H, OH), 5.14-5.26 m (2H, CH_2 =), 5.91-604 m (1H, CH =). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 168.87 s (C = O), 131.34 (CH =), 119.68 t (CH_2 =), 104.59 s (C^3), 103.66 s (C^4), 72.16 s (C^2), 53.24 q (OCH_3), 53.90 q (OCH_3), 49.31 t (C^5), 40.37 t (CH_2). Mass spectrum (m / z): 284 [M] $^+$, 253 [M-OCH_3] $^+$, 252 [M-CH_3OH] $^+$, 267 [M-OH] $^+$, 235 [M-OCH_3-HOH] $^+$, 231 [M-OH-HCl]$^+$, 217 [M-OCH_3-HCl]$^+$, 207 [M-HCl-C_3H_5]$^+$.

Dichloro-4-hydroxy-3,3-dimethoxy-2-allylpent-4-en-1-oic acid (14)

IR spectrum (cm^{-1}): 1720 (C = O), 1640, 1600 (C = C), 3100-3400 (OH). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.90 d. (2H, CH_2 = allyl, J^1 = J^2 = 7 Hz), 3.55 s (3H, OCH_3), 3.58 s (3H, OCH_3), 5.12-5.25 m (2H, CH_2 =), 5.75-5.90 m (1H, CH =), 6.98 s (1H, HClC =), 9.30 br s. (2H, COOH and OH). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 169.42 (C = O), 131.37 (CH =), 131.33 s (C^4), 126.80 d (ClHC =), 120.29 t (CH_2 =), 104.26 (C^3), 77.86 s (C^2), 53.19 q (OCH_3), 53.04 q (OCH_3), 41.63 t (CH_2). Mass spectrum (m / z): 235 $[M\text{-}OCH_3]^+$, 231 $[M\text{-}Cl]^+$, 169 $[M\text{-}CO_2\text{-}C_4H_5]^+$.

A tautomeric mixture of 2,5-dichloro-3-oxy-4β-N-dodecylamino-5α-allylcyclopent-2-en-1-one (21) and 2,4-dichloro-3-hydroxy-5β-N-dodecylamino-4α-allylcyclopent-2-en-1-one (22)

To a mixture of 1.0 g of ketone (20) and 1.0 g of molecular sieves (3 A°) in 30 ml of absolute methanol under argon was added 1.65 g of dodecylamine and the reaction mass was stirred at 20 °C for 28 h. After the disappearance of the starting compound and the formation of the imine (TLC), the mass was cooled to -40 °C and 0.2 g of $NaBH_4$ was added, stirred for 1 hour, 1 ml of acetone was added (to neutralize unreacted $NaBH_4$). After the usual treatment of the reaction mass (extraction with $CHCl_3$ and evaporation), the residue was chromatographed on SiO_2 (eluent-hexane-ethyl acetate, 1: 2) to give 0.7 g (63%) of compound (21-22). IR spectrum (cm^{-1}): 1600 (CO-CCl = COH), 3100 (NH), 3300-3400 (OH). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.88 t (3H, CH_3, J = 7.0 Hz), 1.26 m (20 H, 10 CH_2), 2.80 d (2H, $CH_2CH = CH_2$, J = 7.5 Hz) 3.70-3.76 m (3H, CH_2N and NH), 4.65 s (1H, H^4), 4.77 s (1H, H^5), 5.16-5.30 m (2H, $CH_2CH = CH_2$), 5.71-5.78 m (1H, $CH_2CH = CH_2$), 6.20 broad singlet (1H, OH). ^{13}C NMR spectrum ($CDCl_3$, δ_c, ppm): 187.93 s (C^1), 185.71 s with (C^1), 165.94 s (C^3), 164.43 s (C^3), 131.53 d (C H =), 131.27 d (CH_2N), 44.13 t (CH_2N), 44.13 t (CH_2N), 44.75 t (CH_2N), 44.13 t (CH_2N), 100.53 s (C^2), 73.70 s (C^5), 71.28 s (C^4), 71.02 d (C^4), 69.39 d (C^5)), 42.36 t ($CH_2CH = CH_2$), 41.12 t ($CH_2CH = CH_2$), (31.92 t, 30.75 t, 29.64 t, 29.37 t, 29.24 t, 26.57 t, 22.72 t) - alkyl chain, 14.17 qu (CH_3).

Chloro-3-N, N-dimethylamino-4,4-dimethoxy-5Z- (carboxymethylidene) cyclopent-2-en-1-one (28)

To a solution of 2.94 g of ketone (4a) in 90 ml of THF, 18 ml of 0.1% OsO4 were added at 20 °C. After the blackening of the reaction mass, a solution of 8.8 g of $NaIO_4$ in 60 ml of water was added thereto within 30 minutes, the mixture was stirred for 2 hours, the precipitate was filtered off, washed with chloroform, the organic portion was separated, treated with saturated NaCl and dried with Na_2SO_4. After passing through a SiO2 layer and evaporating with $CHCl_3$, 2.86 g (86%) of an acid (28) were obtained. Mp.140-141 °C. IR spectrum (cm^{-1}): 1712 (COOH), 1700 (C = O), 1580 ((NC = CCl-C = O), 1536 (= -OH). ^{1}H NMR ($CDCl_3$, δ, ppm):3.30 s (6H, $2CH_3O$), 3.52 s (3H, CH_3N), 3.70 s (3H, CH_3N), 6.10 s (1H, CH =), 15.60 with (1H, COOH) NMR ^{13}C ($CDCl_3$, δ_c, ppm): 181.74 s (C = O), 164.99 s (COOH), 161.96 s (C^3), 138.88 s (C^5), 123.72 d (CH=), 110.06 s (C^2), 103.53 s (C^4), 52.04 q (OCH_3), 42.45 q (CH_3N), 42.29 q (CH_3N). Mass spectrum (m / z): 275 $[M]^+$, 258 $[M\text{-}OH]^+$, 244 $[M\text{-}OCH_3]^+$, 240 $[M\text{-}Cl]^+$.

Conflict of interest statement

There is no conflict with these materials.

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References

1. Nesmeyanov AN (1971) Research in organic chemistry Moscow: Nauka, 530.

2. Tokoroyama, T (2010) Discovery of the Michael Reaction» European Journal of Organic Chemistry 1:2009-16.

3. Timoshchuk O V, Lembryk I S, Kocherga Z R (2018) Prostaglandins are universal bioregulators in the human body (literature review) Zaporozhe Medical Journal 1:121-7.