STRUCTURES OF BROMO-SUBSTITUTED PYRONE-4-CARBOXYLIC ACIDS OBTAINED BY DIRECT BROMINATION

G. A. Khutornenko, S. G. Rozenberg, and A. E. Vasil'ev

UDC 547.812.5.7

Ethyl esters of mono- and dibromocomanic acid were obtained by direct bromination, and the corresponding acids were obtained from the esters by acid hydrolysis. The structures of the compounds obtained and of the previously synthesized bromo-substituted comanic acid were established, and it was proved that the attack of bromine is directed to the 5-C and 3-C atoms; attack takes place first at the more nucleophilic 5-C center, after which the 3-C atom undergoes attack.

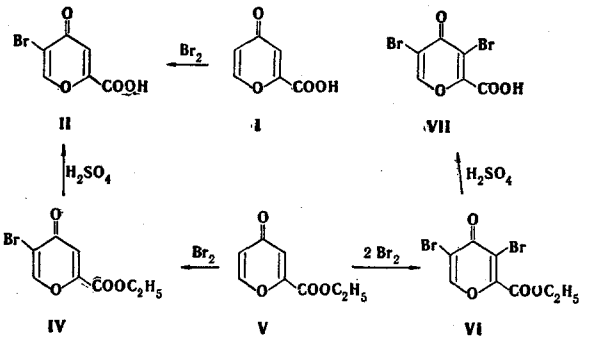
Little study has been devoted to the bromination of pyrone-4-carboxylic acids that do not contain a hydroxyl group. According to [1], chelidonic and comanic acids and their esters do not undergo bromination. Later we were able to carry out the direct bromination of comanic acid (I) in aqueous dioxane [2], but we were unable to determine the position of the bromine atom in the resulting bromocomanic acid. In a continuation of this research, we have now established the structure of the bromocomanic acid as 5-bromo-4-pyrone-2-carboxylic acid (II). According to the results of paper chromatography, a mixed-melting-point determination, and the IR and PMR spectra, acid II is identical to the substance with a proved structure obtained via the scheme diethyl acetonedioxalate (III) → diethyl bromochelidonate → monoethyl bromochelidonate → ethyl 5-bromocomanate (IV) → 5-bromocomanic acid (II), in which the starting aliphatic ester III [3] was subjected to bromination. Analysis of the PMR spectra on the basis of the chemical shifts of the ring protons showed that the spectrum of acid II in $(CD_3)_2SO$ contains two singlets of equal intensity that correspond to the 6-H (8.86 ppm) and 3-H (7.0 ppm) protons.

By reaction of ethyl comanate (V) with bromine in chloroform or in 50% aqueous dioxane we were able to obtain ethyl 5-bromocomanate (IV) (ethyl 5-bromo-4-pyrone-2-carboxylate) and ethyl 3,5-dibromocomanate (VI) (ethyl 3,5-dibromo-4-pyrone-2-carboxylate). Bromination of ester V at room temperature with slow addition of bromine leads to a mixture of esters IV and VI [80 and 20%, respectively, according to the results of gas-liquid chromatography (GLC)]. Starting V and esters IV and VI are detected in the reaction products when the reaction is carried out at 10-12°C or the reaction time is shortened. We were unable to select experimental conditions for the preparation of ester IV as the only reaction product. The latter was isolated from a mixture with dibromo ester VI by preparative thin-layer chromatography (TLC) on a plate with a fixed layer of silica gel. Bromination of ester V in 50% aqueous dioxane but with 2 moles of bromine at 20-25°C leads to ester VI.

The individuality, compositions, and structures of esters IV and VI were proved by elementary analysis, the TLC data, and the absence of a melting point depression for mixtures with esters IV and VI obtained by the method in [2, 4] (ester IV was synthesized by bromination of diester III and workup as indicated above, while ester VI was obtained from the same diester III through diethyl dibromochelidonate and subsequent treatment as in the synthesis of ester IV). The molecular ions in the mass spectra of esters IV and VI were in agreement with the expected molecular ions. The PMR spectra of esters IV and VI served as a substantial confirmation of their structures. The signal at 8.06 ppm in the PMR spectrum of ester IV (in CCl_4) was assigned to the 6-H proton, the signal at 6.96 ppm was assigned to the 3-H proton, and the triplet at 1.4 ppm and the quartet at 4.4 ppm were assigned to the ethyl group. The spectrum of ester VI in $(CD_3)_2CO$ contains a signal of the 6-H proton at 8.7 ppm and a triplet at 1.4 ppm and a quartet at 4.5 ppm due to the protons of the ethyl group.

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 901-903, July, 1978. Original article submitted July 11, 1977.

0009-3122/78/1407-0725$07.50



The PMR spectra of esters IV and VI synthesized by different methods are identical. When esters IV and VI were heated in concentrated sulfuric acid, they were converted to 5-bromocomanic acid (II) and 3,5-dibromocomanic acid (VII). Acids II and VII were identical (with respect to the results of mixed-melting-point determinations and the IR and PMR spectra) to the corresponding acids synthesized [2, 3] from diester III. In addition, acids II obtained by hydrolysis of ester IV and direct bromination of acid I were identical.

It follows from the above data that attack of bromine in 4-pyrone-2-carboxylic acid and its ester, as in unsubstituted 4-pyrone and 2,6-dimethyl-4-pyrone [1], is directed to the 5-C and 3-C atoms; attack takes place first at the more nucleophilic 5-C center, after which the 3-C atom undergoes attack.

The authors thank V. A. Zagorevskii for his interest in this research and for his valuable recommendations.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian-112 chromatographic mass spectrometer. Silufol UV-254 plates (Czechoslovakian Socialist Republic) and acetone–benzene (1 : 20) were used for TLC of esters IV and VI. Chromatography of acids II and VII was carried out on Leningrad IB paper in n-butanol–water–acetic acid (2 : 2 : 1). The spots were detected in UV light during chromatography. The neutralization equivalents were determined by titration with 0.1 N NaOH with respect to methyl red.

Ethyl 5-Bromocomanate (IV). A) A solution of 6.4 g (40 mmole) of bromine in 7 ml of glacial acetic acid was added in the course of 10 h to a solution of 6.72 g (40 mmole) of ester V in 67 ml of chloroform. The next day the solution was washed with water (three 5-ml portions) and 10% NH_4OH until the chloroform layer was slightly alkaline, after which it was washed with water to neutrality and subjected to vacuum evaporation. The oily residue was recrystallized from 50% alcohol to give 4.55 g of a product with mp 74-76°C. According to the TLC data, the product was a mixture of monobromo ester IV (R_f 0.44) and dibromo ester VI (R_f 0.55). Ester IV was isolated by preparative TLC on glass plates with a fixed layer of silica gel (L 5/40, Czechoslovakian Socialist Republic) in the same solvent systems as in the case of analytical TLC of these compounds. The pure product had mp 94-97°C (from 50% alcohol). Found: C 38.8; H 3.1; Br 32.3%; M^+ 247. Calculated: C 38.9; H 2.8; Br 32.4%; M^+ 247. IR spectrum: 1754 ($COOC_2H_6$), 1650 (C=O), 1610 cm^{-1} (C=C).

B) A solution of 3.2 g (20 mmole) of bromine in 3 ml of glacial acetic acid was added to a solution of 3.36 g (20 mmole) of ester V in 60 ml of 50% aqueous dioxane, after which the solvent was removed by distillation, and the residue was recrystallized from 50% alcohol to give 2.56 g of a product with mp 74-76°C. According to the GLC data, the product was similar to the compound obtained by method A and contained ~80% ester IV and 20% ester VI.

Ethyl 3,5-Dibromocomanate (VI). A 3.2-g (20 mmole) sample of bromine was added at 20-25°C in the course of 7 h to a solution of 1.68 g (10 mmole) of ester V in 32 ml of 50% aqueous dioxane. The next day the reaction mixture was subjected to vacuum evaporation, and the residue was recrystallized from 50% alcohol to give 1.78 g (55%) of a product with mp 114-116°C and R_f 0.54. Found: C 29.3; H 1.5; Br 49.3%; M^+ 326. $C_8H_5Br_2O_4$. Calculated: C 29.4; H 1.8; Br 49.1%; M^+ 326. IR spectrum: 1739 ($COOC_2H_5$), 1645 (C=O), 1600 cm^{-1} (C=C).

5-Bromocomanic Acid (II). A solution of 3.5 g of ester IV in 5 ml of concentrated H_2SO_4 was heated at 100°C for 5 h, after which it was cooled and poured over ice. The aqueous mixture was saturated with NaCl and allowed to stand overnight. The resulting precipitate was separated, washed with ice water and chloro-

form, dried, and recrystallized from water to give 1.65 g (53%) of a product with mp 253-254°C (dec., in a sealed capillary) and R_f 0.70. Found:C 32.8; H 1.6; Br 36.5%; neutralization equivalent 218; M^+ 219. $C_6H_3BrO_4$. Calculated: C 32.9; H 1.4; Br 36.5%; neutralization equivalent 219; M^+ 219. IR spectrum: 2450-2570 (OH from COOH), 1731 (C=O from COOH), 1623 (C=O), 1600, 1555 cm^{-1} (C=C).

3,5-Dibromocomanic Acid (VII). This acid was similarly obtained from 1.5 g of ester VI in 2.3 ml of concentrated H_2SO_4. Recrystallization of the crude product from anhydrous alcohol gave 1 g (70%) of a product with mp 219-220°C (dec., in a sealed capillary) and R_f 0.66. Found: C 24.0; H 0.9; Br 54.0%; neutralization equivalent 296; M^+ 298. $C_6H_2Br_2O_4$. Calculated: C 24.2; H 0.7; Br 53.7%; neutralization equivalent 298; M^+ 298. IR spectrum: 2400-2570 (OH from COOH), 1730 (C=O from COOH), 1605-1580 cm^{-1} (C=O from C=C).

LITERATURE CITED

1. F. Feist and E. Baum, Ber., 38, 3562 (1905).
2. G. A. Garkusha and G. A. Khutornenko, Khim. Geterotsikl. Soedin., No. 3, 341 (1966).
3. G. A. Garkusha and G. A. Khutornenko, Zh. Obshch. Khim., 33, 3579 (1963).
4. G. A. Garkusha, G. A. Khutornenko, and N. A. Kurakina, Zh. Org. Khim., 3, 1699 (1967).

BENZOXAZOLE IN THE HETARYLATION REACTION*

A. K. Sheinkman, T. V. Stupnikova, V. I. Zherebchenko, L. A. Rybenko, and N. A. Klyuev

UDC 547.759'787.3

N-Acylbenzoxazolium salts formed in situ in the reaction of benzoxazole with acylating agents react with indoles with opening of the oxazole ring to give tri(3-indolyl)methanes. Hetarylation products are formed in the reaction of N-acylbenzoxazolium salts in situ with oxindole and pyrazolone.

Up until now hetarylation with N-acyl heteroaromatic cationic salts in situ has been extended only to two types of azoles – imidazoles [2] and perimidine [3]. Pyrazoles could not be used in this reaction. In the present research we decided to investigate the behavior of benzoxazole under the conditions of the hetarylation reaction [4] upon reaction with nucleophilic aromatic and heteroaromatic compounds in the presence of acylating agents.

We found that N,N'-dialkylanilines do not undergo hetarylation in the case of the reaction of benzoxazole with N,N'-dialkylanilines in the presence of acylating agents in an inert solvent; however, the oxazole ring in the intermediately formed N-acylbenzoxazolium salt I opens to give N-acyl-o-aminophenols II, and the unchanged N,N'-dialkylanilines are recovered in quantitative yield. However, in the case of the reaction with indoles under similar conditions tri(3-indolyl)methanes (V) are formed in addition to II, regardless of the nature of the acyl halide used. When the reaction is carried out in acetic anhydride, V undergoes partial acylation to give bis(1-acyl-3-indolyl)(3-indolyl)methane (Vd). The formation of V can be represented as the result of succesive addition of indole molecules to the intermediately formed N-acylbenzoxazolium cations of I and III and the existence of intermediate IV in equilibrium with open form IVa and successive alkylation of a gramine fragment of a third molecule of indole, which leads to final products V. Similar processes have also been previously noted for N,N'-diacylbenzimidazolium salts [5].

We also were unable to introduce the benzoxazole residue into the indole ring by means of protic benzoxazole salts formed in the reaction of o-aminophenol and tri(3-indolyl)methane with indole.

*See [1] for our preliminary communication.

Donetsk State University, Donetsk 340055. Dnepropetrovsk Engineering-Construction Institute, Dnepropetrovsk 320092.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 904-908, July, 1978. Original article submitted June 23, 1977.