PREPARATION OF 6,7-ETHYLENEDIOXYCOUMARINS AND THEIR 3-NITRO AND 3-AMINO DERIVATIVES

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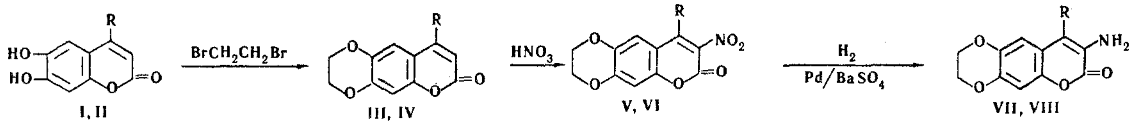
6,7-Ethylenedioxycoumarin and 6,7-ethylenedioxy-4-methylcoumarin have been synthesized by the reaction of esculetin and 4-methylesculetin, respectively, with 1,2-dibromoethane. Their 3-nitro derivatives have been obtained and have been reduced catalytically to the corresponding amines.

It is known that ayapin (6,7-methylenedioxycoumarin) possesses pronounced hemostatic activity [1]. It appeared of interest to us to obtain the next homologs of this substance and to study some of their reactions. With this purpose, starting from esculetin (6,7-dihydroxycoumarin) (I) and 4-methylesculetin (II), we have synthesized the previously undescribed 6,7-ethylenedioxycoumarin (III) and 6,7-ethylenedioxy-4-methylcoumarin (IV). The substances obtained readily underwent nitration, giving monosubstituted products: 6,7-ethylenedioxy-3-nitrocoumarin (V) and 6,7-ethylenedioxy-4-methyl-3-nitrocoumarin (VI). The nitro compounds V and VI were reduced with hydrogen in the presence of $Pd/BaSO_4$ to the corresponding amino derivatives (VII and VIII).



I, III, V, VII R=H; II, IV, VI, VIII R=CH_3

The NH_2 group is present in position 3 of the α-pyrone ring, as is confirmed by the NMR spectrum of the amine VII, in which there are three singlets with an intensity of one proton unit each in the 6-7 ppm region, which must be assigned to the protons in position 4 of the pyrone ring and positions 5 and 8 of the benzene ring, and in the 5.3 ppm region there is a broadened signal with an area of two proton units evidently due to the protons of the NH_2 group. At 4.1 ppm there is an unresolved signal of the four protons of the two methylene groups of the dioxane ring. 6,7-Di(benzyloxy)coumarin (IX) and 6,7-di(benzyloxy)-4-methylcoumarin (X) were also subjected to nitration. The structure of the products obtained as 3-mononitro derivatives (XI and XII) was shown for the case of XII. Debenzylation of the latter (by heating it with a mixture of glacial acetic and concentrated hydrochloric acids) gave the known 4-methyl-3-nitroesculetin (XIII). Its methylation with diazomethane gave the known [2] 6,7-dimethoxy-4-methyl-3-nitrocoumarin (XIV). This method of synthesis may serve for the preparation of compounds of type XIII; the yield of this compound is not given in [2]. The purity of substances III, IV, VI-VIII, and XI was checked by thin-layer chromatography in alumina (activity grade IV, in dichloroethane).

EXPERIMENTAL

6,7-Ethylenedioxy-4-methylcoumarin (IV) and 6,7-Ethylenedioxycoumarin (III). A suspension of 19.2 g (0.01 mole) of II, 41.4 g (0.3 mole)of potassium carbonate, and 37.6 g (0.2 mole) of 1,2-dibromoethane in 150 ml of dry acetone was boiled for 60 h. After approximately equal intervals of time, portions of 18.8 g (0.1

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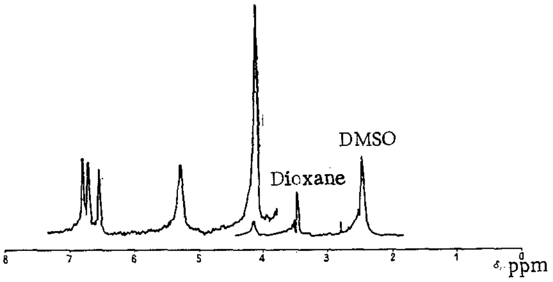

Fig. 1. NMR spectrum of 3-amino-6,7-ethylenedioxycoumarin (VII) (60-MHz instrument, solvent DMSO, standard dioxane).

mole) of dibromoethane and 27.6 g (0.2 mole) of potassium carbonate were added. The solvent was distilled off in vacuum, and the residue was treated with 2 N NaOH, water, and chloroform until two layers had formed. The aqueous layer was extracted several times with chloroform. The combined chloroform solution was washed with water and dried. The solvent was distilled off and the residue was triturated with petroleum ether and filtered, and the residue was washed with petroleum ether, giving 11.4 g (52%) of IV, mp 157.5-157.8°C (from absolute ethanol, dried over P_2O_5 in vacuum at 65°C), R_f 0.66. Found %: C 66.08, 66.07; H 4.66, 4.90. $C_{12}H_{10}O_4$. Calculated %: C 66.04; H 4.62. Compound III was obtained analogously with a yield of 53%, mp 215.5-216°C (from absolute ethanol, dried over P_2O_5 in vacuum at 65°C), R_f 0.55. Found %: C 64.78, 65.02; H 4.01, 3.99. $C_{11}H_8O_4$. Calculated %: C 64.71; H 3.95.

6,7-Ethylenedioxy-4-methyl-3-nitrocoumarin (VI) and 6,7-Ethylenedioxy-3-nitrocoumarin (V). With heating, 2.73 g (0.0125 mole) of IV was dissolved in 40 ml of glacial acetic acid, and the solution was cooled to approximately 50°C and a solution of 2.5 ml of HNO_3 (d 1.507) in 15 ml of CH_3COOH was added dropwise; the suspension that formed after 10 min was stirred for 2 h and was then heated at 70-80°C for 10 min, cooled, and poured into cold water. The precipitate that deposited was filtered off and washed with water, ethanol, and ether (weight 2.95 g) and was crystallized from nitromethane and washed with nitromethane, ethanol, and ether. This gave 2.7 g (82%) of VI as a yellow substance with mp 228°C (decomp., dried over P_2O_5 in vacuum at 65°C), R_f 0.75. Found %: C 54.98, 54.79; H 3.33, 3.42; N 5.09, 5.24. $C_{12}H_9NO_6$. Calculated %: C 54.75; H 3.45; N 5.32. Compound V was obtained analogously (100 ml of CH_3COOH was used for 0.02 mole of III), yield 78%, mp >300°C (decomp., from nitromethane, dried over P_2O_5 in vacuum at 65°C). Found %: C 53.02, 53.10; H 2.75, 2.88; N 5.61, 5.75. $C_{11}H_7NO_6$. Calculated %: C 53.01; H 2.83; N 5.62.

3-Amino-6,7-ethylenedioxy-4-methylcoumarin (VIII) and 3-Amino-6,7-ethylenedioxycoumarin (VII). A suspension of 0.62 g (0.0025 mole) of VI in 50 ml of ethanol was added under the usual conditions to a reduced catalyst from 0.3 g of $PdO/BaSO_4$ in 10 ml of ethanol, and hydrogenation was carried out with stirring until the theoretical amount of hydrogen had been absorbed; then 50 ml of ethanol was added to the reaction mixture and it was heated to the boil and the catalyst was filtered off. The filtrate was evaporated in vacuum until a precipitate appeared; this was redissolved by heating and the solution was left to stand. The precipitate that deposited was filtered off and washed with ethanol and ether to give 0.42 g (72%) of VIII, mp 196.5-197.5°C (decomp., from absolute ethanol, dried over P_2O_5 in vacuum at 65°C), R_f 0.54. Found %: C 61.93, 61.77; H 4.85, 4.89; N 6.20, 6.17. $C_{12}H_{11}NO_4$. Calculated %: C 61.79; H 4.75; N 6.01. Compound VII was obtained analogously, yield 36%, mp 228°C (decomp., from absolute ethanol, dried over P_2O_5 in vacuum at 80°C), R_f 0.49. Found %: C 60.42, 60.41; H 4.30, 4.27; N 6.34, 6.21. $C_{11}H_9NO_4$. Calculated %: C 60.27; H 4.14; N 6.39.

6,7-Di(benzyloxy)-3-nitrocoumarin (XI) and 6,7-Di(benzyloxy)-4-methyl-3-nitrocoumarin (XII). With gentle heating, 1.79 g (0.005 mole) of IX was dissolved in 90 ml of glacial CH_3COOH, the solution was cooled to 20°C, and, with stirring, a solution of 1 ml of HNO_3 (d 1.507) in 3 ml of glacial CH_3COOH was added dropwise, and then the reaction mixture was stirred for 45 min and poured onto ice, and the precipitate was filtered off and washed with water, ethanol, and ether. This gave 1 g (50%) of XI, mp 236°C (decomp., from nitromethane, dried over P_2O_5 in vacuum at 65°C), R_f 0.68. Found %: C 68.29, 68.54; H 4.30, 4.26; N 3.47, 3.49. $C_{23}H_{17}NO_6$. Calculated %: C 68.47; H 4.25; N 3.47. Compound XII was obtained analogously with a yield of 57%, mp 196.5-197.5°C (decomp., from nitromethane, dried over P_2O_5 in vacuum at 65°C), R_f 0.75. Found %: C 69.09, 68.92; H 4.62, 4.66; N 3.49, 3.48. $C_{24}H_{19}NO_6$. Calculated %: C 69.02; H 4.59; N 3.36.

6,7-Dihydroxy-4-methyl-3-nitrocoumarin (XIII) and 6,7-Dimethoxy-4-methyl-3-nitrocoumarin (XIV). A mixture of 3.5 g of XII, 175 ml of glacial CH_3COOH, and 35 ml of concentrated HCl was boiled for 2 h, the solution formed was evaporated, and the residue was treated with water, filtered off, and washed with water to give 1.9 g (96%) of substance XIII, mp 228-229°C (decomp., from aqueous CH_3COOH) [2]. The methylation of XIII with diazomethane in ether yielded XIV, mp 213-214°C (decomp.), giving no depression of the melting point with an authentic sample [2].

LITERATURE CITED

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