SYNTHESIS OF 3-(β-DIALKYLAMINOETHYL)-4-METHYL-7-HYDROXYCOUMARIN

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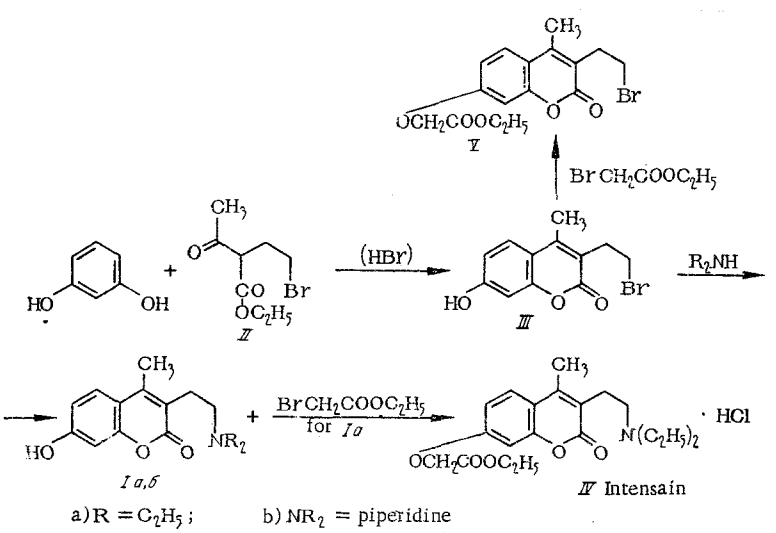
The majority of the well-known coumarins belongs to 7-hydroxy-coumarin derivatives. Such compounds are of interest for pharmacological tests, especially in the field of stimulants for the central nervous system and drugs with coronary-vasodilator activity. For example, chlorohydrate 3-(β-diethylaminoethyl)-4-methyl-7-ethoxycarbonylmethoxycoumarin (Intensain) has found a practical application as a coronary-vasodilator preparation. The last phase in the synthesis of coronary-vasodilator preparations of this type was described in [1]: the action of bromoacetate in methylethylketone on 3-(ω-dialkylaminoalkyl)-4-methyl (or phenyl)-7-hydroxycoumarins in the presence of potassium carbonate. No experimental data are given in this work [1] for methods of preparing coumarins. From the available data it is impossible to establish how efficient the process is of preparing Intensain and its analogs. Considering the specific properties of 3-(ω-dialkylaminoalkyl)-4-methyl-7-hydroxycoumarins as internal salts, it can be assumed that the isolation of the compounds listed above from the sulfuric acid medium, in which the Pechmann reaction is carried out, is not a fairly convenient process. We have proposed another method for preparing 3-β-dialkylaminoethyl-4-methyl-7-hydroxycoumarins by using compounds Ia and Ib. The method involves the Pechmann reaction of resorcinol with α-(β-bromoethyl)-acetoacetic ester (II) to yield 3-(β-bromoethyl)-4-methyl-7-hydroxycoumarin (III) which is treated with secondary amines. Hydroxyaminocoumarin (Ia), according to method [1] in a reaction with bromoacetate in methylethylketone in the presence of potassium carbonate yielded Intensain (IV). The initial ester II was synthesized by us in two stages: first, 1,2-dibromoethane in a reaction with the ester of acetoacetic acid in methylethylketone in the presence of potassium carbonate gave α, α-(dimethyleno)acetoacetic ester, which when treated with hydrogen bromide in glacial acetic acid yielded II. Apart from the ester, an isomeric 2-methyl-3-ethoxycarbonyl-4,5-dihydrofuran was obtained which, according to our observations, when treated with hydrogen bromide was transformed into II and because of this it was unnecessary to separate one from the other. Ester II can be used in the Pechmann condensation as a crude reaction product. A solution of hydrogen bromide in glacial acetic acid was used as a condensing agent in the synthesis of coumarin III. The reaction of hydroxycoumarin III with bromoacetate yielded ethoxycarbonylmethoxy derivative (V) which can be used for the synthesis of substituted coumarins of the IV type or the appropriate amides:



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EXPERIMENTAL

3-(β-Bromoethyl)-4-methyl-7-hydroxycoumarin (III). The reaction of 260 g (2 moles) of acetoacetic ester and 92 g (1 g-atom) of sodium in 2 liters of absolute alcohol with 188 g (2 moles) of 1,2-dibromoethane for 10 h gave a mixture of α,α-(dimethyleno)acetoacetic ester and 2-methyl-3-ethoxycarbonyl-4,5-dihydrofuran [2], which can be separated from acetoacetic ester by distillation at 63-73° (5 mm). The same ester mixture can be obtained by carrying out the acetoacetic ester reaction with dibromoethane in boiling methylethylketone in the presence of potassium carbonate for 30 h. Yield of mixture 65-70 g (20-22%) and 150-158 g (48-50%), respectively. The isomer mixture, 156 g (1 mole), was mixed with 550 g (1.1 mole) of 16% HBr solution in glacial acetic acid and to the resultant solution was added in portions 110 g (1 mole) of resorcinol with external cooling with water. The reaction mixture was stirred to yield a solution which was kept at room (or somewhat lower) temperature for 1-2 days. The precipitate III was filtered, washed with water, dried, and recrystallized from alcohol. The acetoacetic filtrate was heated for 10 min at 80-100°, cooled, poured into water, and the precipitate III was also crystallized from alcohol. The total yield was 180-190 g (30-33%, based on acetoacetic ester), mp 174-175°. Found %: C 50.94, 51.25; H 3.90, 4.12; Br 28.28, 27.99. $C_{12}H_{11}BrO_3$. Calculated %: C 50.91; H 3.91; Br 28.23.

3-(β-Diethylaminoethyl)-4-methyl-7-hydroxycoumarin (Ia). After boiling a mixture of 14.15 g (0.05 mole) of III and 50 g (0.4 mole) of diethylamine in 70 ml of absolute alcohol for 1.5 h, the solvent and the diethylamine excess were distilled off in vacuo on a boiling water bath. The residue was dissolved in 50 ml of concentrated ammonia, the solution filtered, extracted with chloroform (4 × 50 ml), the extract evaporated to dryness, the residue dissolved in 20 ml of absolute alcohol, and an excess of an alcoholic solution of hydrogen chloride was used to precipitate the chlorohydrate Ia; yield 7.07 g (46.9%), mp 260-261° (from alcohol, saturated with HCl). Found %: C 61.51, 61.52; H 7.13, 7.26; N 4.10, 4.15. $C_{16}H_{21}NO_3 \cdot HCl$. Calculated %: C 61.63; H 7.11; N 4.49.

3-(β-Diethylaminoethyl)-4-methylethoxycarbonylmethoxycoumarin (IV). To 3.12 g (0.01 mole) of Ia, 40 ml of methylethylketone, and 2.76 g (0.02 mole) of potassium carbonate was added dropwise 1.67 g (0.01 mole) of ethyl bromoacetate with stirring and refluxing for 1 h and then the mixture was refluxed for 9 h. The volatile substances were distilled off in vacuo and the residue extracted with ether (3 × 40 ml). The ether extract was washed 3 times with 2N NaOH solution, dried with magnesium sulfate, and chlorohydrate IV was precipitated by passing through hydrogen chloride. Yield 2.14 g (54%), mp 153-154° (from alcohol, precipitated with ether). According to literature data: mp 154-156°. Found %: C 59.84, 59.71; H 7.03, 7.08; N 3.44, 3.69; Cl 8.87, 8.69. $C_{20}H_{27}NO_5 \cdot HCl$. Calculated %: C 60.37; H 7.09; N 3.52; Cl 8.91.

3-(β-Piperodylethyl)-4-methyl-7-hydroxycoumarin (Ib). Similar to the synthesis of Ia, bromide II and piperidine gave Ib, yield 45%, mp 236-237° (from alcohol). Found %: C 70.99, 70.72; H 7.42, 7.35; N 4.94, 4.87. $C_{17}H_{21}NO_3$. Calculated %: C 71.06; H 7.37; N 4.87.

Chlorohydrate. Yield 87%, mp 259-261°. Found %: C 62.80, 62.75; H 7.10, 7.18; N 4.22, 4.29; Cl 10.74, 10.62. $C_{17}H_{21}NO_3 \cdot HCl$. Calculated %: C 63.05; H 6.85; N 4.33; Cl 10.95.

3-(β-Bromoethyl)-4-methyl-7-ethoxycarbonylmethoxycoumarin (V). Similar to the last stage in the synthesis of IV, 0.1 mole of bromide III and 0.1 mole of bromoacetate gave V, yield 58%, mp 119-120° (from ethyl acetate). Found %: Br 21.65, 21.64. $C_{16}H_{17}BrO_5$. Calculated %: Br 21.65.

LITERATURE CITED

1. Belgian Patent No. 621,327, 1962; Chem. Abstr. 59, No. 114438 (1963).
2. P. C. Freer and W. H. Perkin, J. Chem. Soc., 51, 822, 833 (1887).