CONDENSATION OF HYDROXYCOUMARINS WITH CHLORAL

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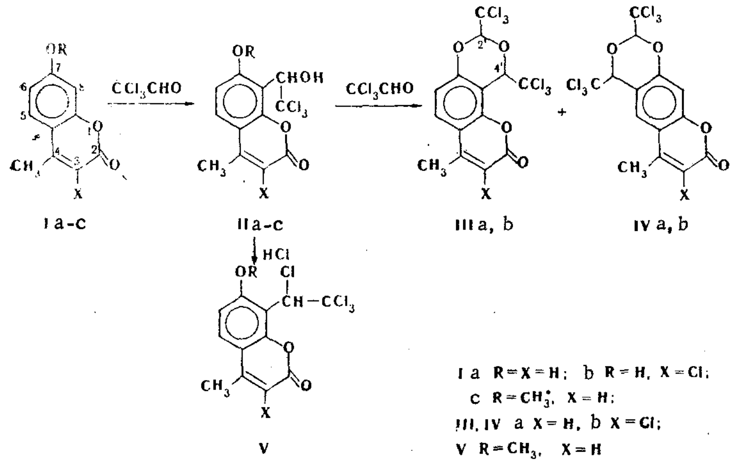
Derivatives of a new class of 1,3-dioxanocoumarins – 4-methyl-(2',4'-bistrichloromethyl)-7,8-coumarinodioxane and 3-chloro-4-methyl-(2',4'-bistrichloromethyl)-7,8-coumarinodioxane, respectively – were synthesized by condensation of 4-methyl- and 3-chloro-4-methyl-7-hydroxycoumarin with chloral in concentrated sulfuric acid. 8-(1,2,2,-2-Tetrachloroethyl)-7-hydroxycoumarin was obtained under similar conditions from 4-methyl-7-hydroxycoumarin methyl ether and chloral.

It is known that the condensation of hydroxycoumarins with chloral may proceed with the formation of different products, depending on the condensing agents and the position and character of the hydroxyl group. Thus, condensation of 4-hydroxycoumarin with chloral hydrate (molar ratio 1:1) in acetic acid gives 3-(α-hydroxytrichloroethyl)-4-hydroxycoumarin [1], i.e., typical aldol condensation occurs in this case without participation of the hydroxyl group of the lactone ring; however, when the molar ratio is 2:1, symmetrical 3,3'-trichloroalkylidenebis(4-hydroxycoumarin) is formed [2]. At the same time, we have established that the condensation of 4-hydroxycoumarin in concentrated sulfuric acid (instead of acetic acid) does not take place at all. However, we have shown that if the reaction of chloral in sulfuric acid is carried out with phenolic coumarins, particularly with 4-methyl-7-hydroxycoumarin (Ia) or 3-chloro-4-methyl-7-hydroxycourmain (Ib), one observes cycloaddition of two molecules of chloral to the phenolic hydroxyl group to give alkali-insoluble trichloromethyl derivatives of coumarino-1,3-dioxane (III, IV), and their ratio depends on the structures of starting coumarins Ia,b. Thus, 4-methyl-(2',4'-bistrichloromethyl)-7,8-coumarinodioxane (IIIa) was obtained as the major product from 4-methyl-7-hydroxycoumarin (Ia), and 4-methyl(2',4'-(bistrichloromethyl)-6,7-coumarinodioxane (IVa) was obtained as a side product (~5% yield). However, a mixture of 60% 3-chloro-4-methyl-(2,4-bistrichloromethyl)-7,8-coumarinodioxane (IIIb) and 40% 3-chloro-4-methyl-(2,4-bistrichloromethyl)-6,7-coumarinodioxane (IVb) was obtained in the condensation of 3-chloro-4-methyl-7-hydroxycoumarin (Ib).



I a R=X=H; b R=H, X=Cl;
c $R=CH_3^*$, X=H;
III, IV a X=H, b X=Cl;
V $R=CH_3$, X=H

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The structures of III and IV were proved by means of PMR spectroscopy and mass spectrometry. A molecular ion peak (M^+) with m/e 450 and intense fragments* with m/e 415 ($M^+ - Cl$), 380 ($M^+ - 2\ Cl$), 345 ($M^+ - 3\ Cl$), 333 ($M^+ - CCl_3$), 305 ($M^+ - CCl_3 - CO$), 269 ($M^+ - CCl_3 - CO - HCl$), 234 ($M^+ - CCl_3 - CO - HCl - Cl$), and 199 ($M^+ - CCl_3 - CO - HCl - 2\ Cl$), which are characteristic for coumarino derivatives [3, 4], were observed in the mass spectrum of coumarinodioxane IIIa. The mass spectrum of coumarinodioxane IVa does not differ fundamentally from the mass spectrum of IIIa. Thus, the mass spectral data constitute evidence for the participation of two chloral molecules and the 7-hydroxy group of coumarin Ia in the condensation to give two products (IIIa and IVa) of the linear and angular types, which differ with respect to the orientation of the dioxane ring, as was ascertained in a study of the PMR spectra.

Two doublets with J = 8.6 Hz and chemical shifts (δ) of 7.14 and 7.86 ppm are observed in the PMR spectrum of coumarin IIIa; this indicates the presence of two ortho protons, i.e., IIIa is 4-methyl-(2',4'-bistrichloromethyl)-7,8-coumarinodioxane. The presence in the PMR spectrum of coumarin IVa of two singlets with chemical shifts of 7.03 and 8.09 ppm, which are characteristic for protons in the para position, attests to location of the dioxane ring at $C_{(6)}$ and $C_{(7)}$. We were unable to separate the mixture of coumarinodioxanes IIIb and IVb; molecular ion M^+ with m/e 484 and fragments with m/e 366 ($M^+ - H - CCl_3$), 338 (366 − CO), 304 (366 − CO − HCl), 268 (366 − CO − 2HCl), and 205 ($366 - CCl_3 - COO$) were observed in their mass spectrum; this also constitutes evidence for participation of two chloral molecules in the condensation. The PMR spectrum of a mixture of IIIb and IVb contains two doublets with J = 8 Hz and chemical shifts of 7.16 and 7.88 ppm and two singlets at 7.06 and 8.12 ppm, the intensity ratio of which is 60 : 40.

Chloral reacts in a different manner with 4-methyl-7-hydroxycoumarin methyl ether (Ic), in which the phenolic hydroxyl group is blocked. In this case, only one molecule of chloral reacts to give 8-(1,2,2,2-tetrachloroethyl)-7-methoxycoumarin (V). The mechanism of this reaction is apparently similar to the mechanism of the reaction of strictly phenols with chlorals [5], i.e., 8-(α-hydroxytrichloroethyl)-7-hydroxycoumarins (IIa-c) or 6-(α-hydroxytrichloroethyl)-7-hydroxycoumarins, the quantitative ratio of which is determined by the electron density distribution at $C_{(6)}$ and $C_{(8)}$ of starting coumarins Ia-c, are formed initially. The results that we obtained constitute evidence for the presence of high electron density on $C_{(8)}$ for coumarins Ia,c and equalization of the electron density on $C_{(6)}$ and $C_{(8)}$ for coumarin Ib.

The formation of tetrachlorocoumarin V takes place through chlorination of the alcoholic hydroxyl group in IIc by the HCl usually present in a mixture of chloral with concentrated sulfuric acid [6].

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 spectrometer. The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a Varian HA 100 spectrometer; the chemical shifts (δ, ppm) are presented relative to the internal standard – tetramethylsilane.

4-Methyl-(2',4'-bistrichloromethyl)-7,8-coumarinodioxane (IIIa). A 17.6-g (0.1 mole) sample of Ia and 33.0 g (0.2 mole) of chloral hydrate were dissolved in 300 ml of concentrated H_2SO_4, and the mixture was held at 20-25° for 48 h. The sulfuric acid solution was filtered through a glass filter to remove a certain amount of waxy trimer (α-parachloral) formed during the reaction, and the filtrate was poured over crushed ice. The resulting precipitate was washed successively with water and 5% sodium hydroxide solution to remove the unchanged 4-methyl-7-hydroxycoumarin (~2 g). The water-washed coumarinodioxane IIIa was dried to give 28.5 g (73.8%) (on the amount of converted hydroxycoumarin Ia) of a product with mp 178-183°. Recrystallization from alcohol gave a product with mp 194-195°. PMR spectrum: 2.45 (3H, d†, J ≈ 1 Hz) $4\text{-}CH_3$, 5.42 (1 H, s) 4'-CH, 6.24 (1H, s) 2'-CH, 6.25 (1H, d, J ~ 1 Hz) 3-CH, 7.14 (1H, d, J = 8.6 Hz) 6-CH, 7.86 (1H, d, J = 8.6 Hz) 5-CH. Found: Cl 47.4%. $C_{14}H_8O_4Cl_6$. Calculated: Cl 47.0%.

Workup of the mother liquor yielded 1.8 g (~5%) of coumarinodioxane IVa with mp 208-209°. PMR spectrum: 2.43 (3H, d, J ≈ 1 Hz) $4\text{-}CH_3$, 5.36 (1H, s) 2'-CH, 6.23 (2H, broad s) 4'-CH and 3 -CH, 7.03 (1H, s) 8-CH, 8.09 (1H, s) 5-CH. Found: Cl 46.7; 46.9%. $C_{14}H_8O_4Cl_6$. Calculated: Cl 47.0%.

3-Chloro-4-methyl-(2',4'-bistrichloromethyl)-7,8-Coumarinodioxane (IIIb) and 3-Chloro-4-methyl-(2',4'-bistrichloromethyl)-6,7-coumarinodioxane (IVb). Coumarinodioxanes IIIb and IVb were obtained

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*Here and subsequently, in all of the spectra the configuration of the fragments containing chlorine was in agreement with the calculated amount of chlorine.

† Here and subsequently, s is singlet and d is doublet.

under similar conditions from 21.0 g (0.1 mole) of Ib and 33.03 g (0.1 mole) of chloral hydrate. The yield of product with mp 192-193° (from alcohol) was 34.5 g (71%). PMR spectrum: 2.54, 2.58 4-CH_3, 5.36, 5.58 2'-CH (IVb), and 4'-CH (for IIIb), 6.22 2'-CH (IIIb) and 4'CH (IVb), 7.06 8-CH (IVb), 8.12 5-CH (IVb), 7.16 (d, J=8 Hz) 6-CH (IIIb), 7.88 (d, J=8 Hz) 5-CH (IIIb). Found: Cl 51.0%. $C_{13}H_7O_4Cl_7$. Calculated: Cl 51.0%.

8-(1,2,2,2-Tetrachloroethyl)-7-methoxycoumarin (V). Under similar conditions V was obtained from 18.0 g (0.1 mole) of hydroxycoumarin Ic and 33.0 g (0.1 mole) of chloral hydrate. The yield of product with mp 157-158° (from alcohol) was 9.6 g (28%). Mass spectrum: M^+ 354, fragments with m/e 236 ($M^+ - CCl_3 -$ H), 189 (236 − CCl) 161 (189 − CO). PMR spectrum: 2.33 (3H, d, $J \approx 1$ Hz) 4-CH_3, 3.80 (3H) OCH_3, 6.07 (1H, d, $J \approx 1$ Hz) 3-CH, 6.73 (1H) $CH - CCl_3$, 6.81 (1H, d, J=8.0 Hz) 6-CH, 7.42 (1H, d, J=8 Hz) 5-CH. Found: Cl 39.4%. $C_{13}H_{10}O_3Cl_4$. Calculated: Cl 40.0%.

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