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NEW ANTIVIRAL DRUG FLORENAL'

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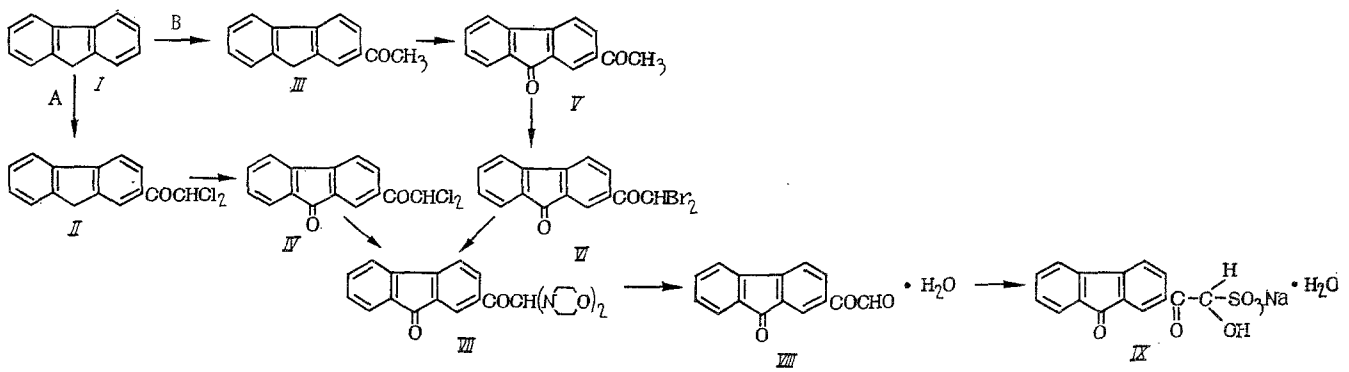
Florenal' — a new antiviral drug — is the bisulfite derivative of fluorenon-2-ylglyoxal [1]. Florenal' possesses a high antiviral activity in relation to the influenza virus (type A, strain PR8) *in vitro* and in experiments on chick embryos, to herpes simplex virus in the model of experimental herpetic keratitis of rabbits, and to the adenovirus in cell culture [1-2]. In a clinical study of the therapeutic action of florenal' at ophthalmologic, dermatologic, and stomatologic medical institutes, its effectiveness has been shown in the treatment of viral diseases of the eyes: herpetic keratitis and adenovirus keratoconjunctivitis [3, 4]; viral diseases of the skin: in vascular acute and recurring herpes simplex and flat and common warts; and also of viral diseases of the mucous membrane of the oral cavity — acute herpetic stomatitis and recurring aphthous stomatitis [5]. Medicinal forms of florenal' with a prolonged action have been developed [6]. Florenal' has been recommended by the Pharmacological Committee at the Ministry of Health of the USSR for local application in the treatment of viral diseases of the eyes, skin, and mucus membrane of the mouth.

Florenal' was first obtained by the sodium bisulfite treatment of the hemiacetal of fluorenon-2-ylgyloxal, prepared by the oxidation of 2-acetylfluorenone with selenium dioxide [7]. However, this method is of limited application because of the high toxicity of selenium dioxide and the low quality and low yield of the fluorenon-2-ylglyoxal. We have proposed a method of obtaining florenal' which has permitted the use of selenium dioxide to be avoided [1, 10]. As the initial raw material in the synthesis of florenal' we used fluorene.



Fluorene (I) was acylated in the presence of ammonium chloride with dichloroacetyl chloride (variant A) or acetic anhydride (variant B); this gave the previously unknown 2-(dichloroacetyl)fluorene (II) [1] and 2-acetylfluorene (III) [8]. The acylation of I with dichloroacetyl chloride can be performed only in the presence of phosphoryl chloride. Chlorobenzene is used as solvent in both cases. Compounds II and III were oxidized with sodium dichromate in acetic acid at 85-90°C, which gave 2-(dichloroacetyl)fluorenone (IV) and 2-acetylfluorenone (V) [9]. The light-catalyzed bromination of V gave 2-(dibromoacetyl)-

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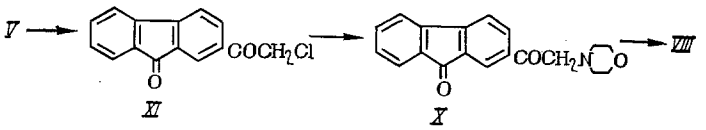
fluorenone (VI) [1, 11]. When both IV and VI were heated with an excess of morpholine, 2-(dimorpholinoacetyl)fluorenone (VII) was obtained. The hydrolysis of VII with mineral acids formed fluorenon-2-ylglyoxal (VIII) with a yield close to quantitative. The reaction of VIII with a solution of sodium bisulfite gave a 92% yield of the bisulfite derivative IX [1]. To obtain a pharmacopoeial florenal' preparation, the bisulfite derivative IX was hydrolyzed with 40% sulfuric acid at 95°C for 6 h. This led to the isolation of purified compound VIII, which was again treated with sodium bisulfite. The yield of florenal' in its synthesis by variant A was 45% and by variant B 41.5%, calculated on the fluorene. Variant B is proposed as the basis of an industrial method of obtaining florenal'.

We have also studied the synthesis of fluorenon-2-ylglyoxyl by the oxidation of 2-(morpholinoacetyl)fluorenone (X) with salts of bivalent mercury using a method described recently for the synthesis of other bicarbonyl compounds [11]. The morpholine derivative X is formed from 2-(chloroacetyl)fluorenone (XI), which we obtained by the chlorination of 2-acetylfluorenone (V).



However, the florenal' formed by the oxidation of the monomorpholino derivative X was of low quality and, after purification, was obtained in low yield.

Florenal' is an odorless yellow or yellowish green crystalline powder with a bitter taste. It is sparingly soluble in water and practically insoluble in 96% ethanol. It is soluble in 85% formic acid. It is stable on storage.

EXPERIMENTAL

The IR spectra were taken in paraffin oil on a UR-10 recording spectrograph. The UV spectra were taken in ethanol on an EPS-3 recording spectrometer.

2-Acetylfluorene (III). To a solution of 664 g of I in 11,310 ml of freshly distilled chlorobenzene was added 1072 g of anhydrous aluminum chloride and to the resulting mixture 420 ml of acetic anhydride was added dropwise with stirring at such a rate that the temperature in the reaction mixture did not exceed 48-52°C. Then the reaction mixture was kept under the same conditions for an hour and was cooled to room temperature, and the complex formed was decomposed with 2 liters of water and 3 liters of 3.5% hydrochloric acid. Then the chlorobenzene layer was separated off and the chlorobenzene was distilled off in vacuum at 50-55°C (100 ml); the residue was recrystallized. The yield of III was 880 g (91.2%), mp 129-131°C (from ethanol) [8].

2-(Dichloroacetyl)fluorene (II). A solution of 50.5 g of I in 225 ml of chlorobenzene was treated with 24 ml of phosphoryl chloride and 85 g of anhydrous aluminum chloride and then, at 10-15°C, gradually and with vigorous stirring 42.5 g of dichloroacetyl chloride was added dropwise. The reaction mixture obtained in this way was heated at 30-40°C for an hour. The substance was isolated under the conditions of the preceding experiment. The yield of II was 68.7%, mp 136-137.5°C (from glacial acetic acid). Found, %: C 64.77; H 3.41; Cl 25.20. $C_{15}H_{10}Cl_2O$. Calculated, %: C 65.01; H 3.64; Cl 25.58.

2-Acetylfluorenone (V). At 85-90°C with stirring, 3700 g of sodium dichromate was added over 40-50 min to a solution of 880 g of compound III in 11,600 ml of acetic acid, and the reaction mixture was kept at the same temperature for 4 h. Then the mixture was cooled to 65°C and 7 liters of acetic acid was distilled off at 50-55°C (100 mm), and 16 liters of water heated to 60°C was added to the residue. The suspension so formed was stirred for 20 min and was cooled to 20°C. The precipitate was filtered off and was washed with 2% sulfuric acid until a colorless aqueous solution had been formed and with water until there was no acid reaction. The moist precipitate was stirred with 400 ml of 42% caustic soda solution and 4700 ml of water at 85-90°C for 30 min. Then the precipitate was filtered off and washed with water. The yield of V was 600 g (74%), mp 156-157°C (from benzene) [9].

2-(Dichloroacetyl)fluorenone (IV). This compound was obtained under the conditions for the synthesis of compound V. The experiment was performed with 33.2 g of compound II, 332 ml of acetic acid, and 125 g of sodium dichromate. The yield of IV was 24.0 g (69%), mp 193-195°C (from glacial acetic acid). Found, %: C 62.13; H 2.90; Cl 24.53. $C_{15}H_8Cl_2O$. Calculated, %: C 61.98; H 2.77; Cl 24.35.

2-(Dibromoacetyl)fluorenone (VI). A suspension of 530 g of compound V in 7100 ml of chloroform was stirred at 45°C until the solid had dissolved and then 890 g of bromine in 2100 ml of chloroform was added dropwise over 3.5 h at 45-50°C with illumination (150-W lamp). Then the reaction mixture was kept under the same conditions for 3.5 h and was cooled to 20°C. The precipitate was filtered off, washed with chloroform, and dried at 40°C. The yield of VI was 805 g (86%), mp 211-212°C (from glacial acetic acid). Found, %: C 47.12; H 2.20; Br 41.99. $C_{15}H_8Br_2O_2$. Calculated, %: C 47.41; H 2.13; Br 42.04.

2-(Chloroacetyl)fluorenone (XI). A boiling solution of 11.1 g of compound V in 200 ml of chloroform was treated dropwise with a solution of 7.1 g of chlorine in 50 ml of chloroform, and then the reaction mixture was boiled until the evolution of hydrogen chloride ceased and was cooled to 20°C. The precipitate that deposited was filtered off. Yield of IX 9.4 g (73.5%), 216-218.5°C (from glacial acetic acid). Found, %: C 70.38; H 3.65; Cl 13.64. $C_{15}H_9ClO_2$. Calculated, %: C 70.17; H 3.54; Cl 13.82.

2-(Dimorpholinoacetyl)fluorenone (VII). a) Synthesis from Compound VI. At 20°C with stirring, 805 g of compound VI was added in portions to 2400 ml of morpholine at such a rate that the temperature of the reaction mixture did not rise above 50°C (1 h). Then the reaction mixture was kept at 50°C for 3.5 h and at 5°C for 1 h, 1600 ml of methanol was added, the mixture was stirred for 15 min, and the precipitate was filtered off. The moist product was additionally stirred with 900 ml methanol, and the precipitate was filtered off. The yield of VII was 710 g (85%), mp 138-140°C (decomp., from dioxane). Found, %: C 70.34; H 5.91; N 7.02. $C_{23}H_{24}N_2O_4$. Calculated, %: C 70.39; H 6.17; N 7.14.

b) Synthesis from Compound IV. The reaction was performed under the conditions of experiment a), using 4.75 g of compound IV and 24 ml of morpholine. The yield of VII was 5.45 g (87%), mp 138.5-140°C (decomp., from dioxane).

2-(Morpholinoacetyl)fluorenone (X). Compound X was obtained under the conditions of the synthesis of VII using 5.1 g of compound IX and 63 g of morpholine. The yield of X was 5.45 g (88%), mp 154-156°C (decomp., from dioxane). Found, %: C 74.00; H 5.43; N 4.30. $C_{19}H_{17}NO_3$. Calculated, %: C 74.25; H 5.55; N 4.56.

Fluorenon-2-ylglyoxyal Hydrate (VIII). a) Synthesis from Compound VII. A suspension of 700 g of VII and 2800 ml of water was stirred at 20°C for 20-25 min, and then 2700 ml of 20% sulfuric acid was added in drops at such a rate that the temperature of the reaction mixture did not exceed 55-60°C. After the addition of the whole amount of sulfuric acid, the reaction mixture was stirred at 55-60°C for 30 min, cooled to 20°C, and kept for 3 h. The precipitate was filtered off, washed with water until the acid reaction had disappeared, and was dried at 80°C. The yield of VIII was 430 g (96%), mp 198-200°C (decomp., from glacial acetic acid). Found, %: C 71.14; H 3.81. $C_{15}H_{10}O_4$. Calculated, %: C 70.86; H 3.97. UV spectrum [λ_{max}^{nm} (log ε)]: 277 (4.3251), 394 (2.9868). IR spectrum: ν_{OH} 330,* ν_{CO} 1610, 1670, 1715 cm^{-1}.

b) Synthesis from Compound X. At 20°C, a solution of cupric acetate in 37 ml of 5% acetic acid was added to a solution of 2.8 g of X in 200 ml of 10% acetic acid, and the reaction mixture was stirred with protection from the light for 4.5 h. The precipitate of VIII that deposited under these conditions was filtered off. The yield of technical VIII was 2.3 g (100%). Compound VIII was purified by preparing its hemiacetal and repeatedly recrystallizing the latter from ethanol. The yield of the hemiacetal of fluorenon-2-ylglyoxal was 0.4 g (19% calculated on the compound XI), mp 126-128°C (decomp., from ethanol) [8].

Florenal' (IX). A solution of 440 g of VIII in 8650 ml of 60% ethanol was stirred, heated, and boiled for 30 min. This formed a solution which was then cooled to 70°C, treated with activated carbon (20 g), boiled for few minutes, and filtered. To the filtrate was added 400 ml of a 50% solution of sodium bisulfite and the reaction mixture was stirred for 10 min and cooled to 20°C. The suspension formed was kept at 20°C for 2 h. The precipitate was filtered off and washed with 96% ethanol and acetone. The yield of IX was 570 g (92.5%). Found, %: C 50.43; H 3.16; S 8.86. $C_{15}H_{11}NaO_7$. Calculated, %: C 50.28; H 3.10; S 8.95. IR spectrum: ν_{CO} 1610, 1650, 1710 cm^{-1}.

To obtain a pharmacopoeial preparation of IX, 570 g of florenal' was dissolved in 5700 ml of water at 80°C, the solution was treated with activated carbon, and the mixture was kept at 80°C for 10 min and was then filtered hot; the filtrate was treated with 1140 ml of

*As in Russian original, possibly 3300 — Consultants Bureau.

40% sulfuric acid, the mixture was heated to 95°C and kept at this temperature for 6 h, and was then cooled to 20°C and the resulting precipitate was filtered off. The yield of VIII was 355 g, mp 193-195°C (decomp.). On treatment with sodium bisulfite under the conditions described above, 355 g of VIII gave 560 g (91.8%) of pharmacopoeial florenal'.

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PROPERTIES OF DAUCARINE AS A MATERIAL FOR DRYING

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The dewatering and drying of extracts in the production of drugs from plant raw material is an important technological operation which largely determines the quality and yield of the finished product. It is known that extractive substances consist of various chemical compounds many of which decompose at a comparatively low temperature. In the existing technology of dewatering by evaporation and drying in vacuum shelf drying chests, the loss of extractive substances amounts to about 50% and the process is accompanied by an appreciable resinification of the product. This explains the interest of various workers in new methods of dehydrating extracts characterized by their short-time nature and reliability of the regulation of the drying process.

We give the results of experimental investigations of some properties of daucarine obtained in the development of a spray apparatus for drying daucarine extracts. The apparatus has been introduced into the Khar'kov Zdorov'e Trudyashchimsya pharmaceutical chemicals factory.

A knowledge of the characteristics given below is necessary to choose the drying conditions and those of the storage of the finished product. One of the main advantages of spray drying is the insignificant time of contact of the material being dried with the drying agent. However, powder that had settled on the walls undergoes the prolonged action of heat, which may lead to overheating and to a change in heat-labile materials. We have per-

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