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CHEMISTRY OF THE HETEROANALOGS OF ISOFLAVONES
21.* 1-BENZIMIDAZOLE ANALOGS OF ISOFLAVONES

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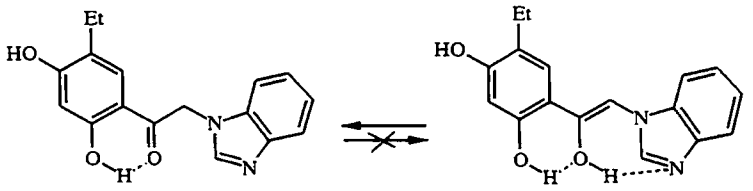
3-(1-Benzimidazolyl)chromones were obtained by the reaction of α-(1-benzimidazolyl)-2,4-dihydroxy-5-ethylacetophenone with trifluoroacetic anhydride and acetic formic anhydride.

While continuing investigations into the series of benzazole analogs of isoflavones and taking account of the high physiological activity of 3-heterylchromones containing a C–N bond between the chromone ring and the nitrogen-containing heterocycle, we undertook the synthesis of 3-(1-benzimidazolyl)chromones.

From saturated heterocycles, such as morpholine, pyrrolidine, piperidine, 1-methylpiperazine, and 3-halogenochromones, the corresponding 3-heteroarylchromones were obtained [2-4]. The reaction of 3-bromochromones with imidazole led to Michael addition of the imidazole to the chromone with the formation of 2-(1-imidazolyl)-3-bromo-2,3-dihydrochromone, which was converted into 2-(1-imidazolyl)chromone as a result of subsequent dehydrobromination [5]. 3-(1-Imidazolyl)chromones were obtained as a result of the cyclization of substituted α-bromo-2-hydroxyacetophenones with an excess of imidazole in DMFA solution [5-10]. 3-(1-Tetrazolyl)flavone was obtained from 3-aminoflavone, triethyl orthoformate, and sodium azide [11]. With furans, the pyrrole derivatives of flavone were obtained [12].



I

The starting compound for the synthesis of 3-(1-benzimidazolyl)chromones in the present work was α-(1-benzimidazolyl)-2,4-dihydroxy-5-ethylacetophenone (I), obtained by the condensation of 4-ethylresorcinol and 1-benzimidazolylacetonitrile under modified conditions of the Hoesch reaction. The ketone (I) is a colorless high-melting compound, soluble in solutions of alkalis and acids, and gives a green color with an alcohol solution of ferric chloride. However, unlike similar compounds [1, 13] with a C–C bond between the α-methylene unit and the benzazole ring, this ketone exists exclusively in the ketone form. In its PMR spectrum, recorded in DMSO-d_6, one-proton singlets for the 2-OH and 4-OH groups were found at 11.48 and 10.75 ppm respectively, and the two-proton singlet of the α-methylene unit was found at 5.89 ppm. The absence of keto–enol tautomerism can be explained by the impossibility of the formation of an intramolecular hydrogen bond between the enolic hydroxyl and the benzimidazole residue of the ketone (I) and also by the absence of conjugation between the enolic part and the heterocycle.

The reaction of the ketone (I) with trifluoroacetic anhydride in pyridine in the cold gave 2-trifluoromethylchromone (II). The Venkataraman method was unsuitable for the production of 3-(1-benzimidazolyl)chromone (III). No changes occurred

*For Communication 20, see [1].

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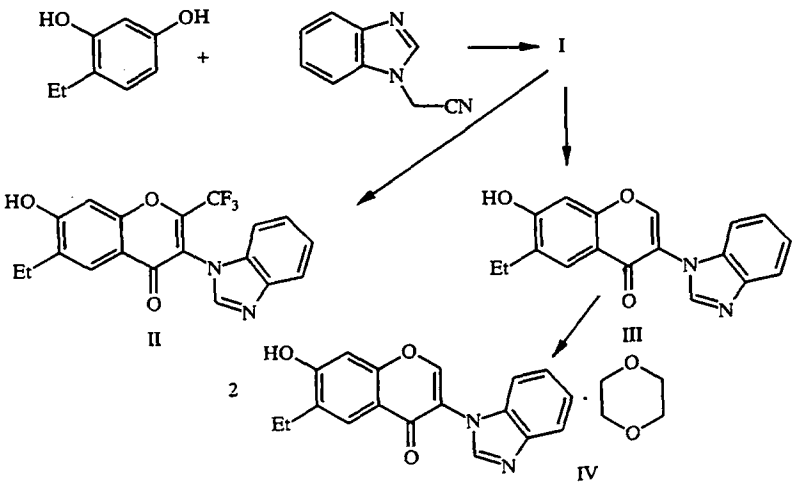
when the reaction mixture was heated for the first six hours, and further heating led to resinification. Acetic formic anhydride in triethylamine was used for the cyclization of the ketone (I). This indicates a decrease in the activity of the α-methylene group compared with the isomeric α-(2-benzazolyl)acetophenones that we synthesized earlier [1, 13]. However, after crystallization of compound (III) from dioxane, compound (IV), which is as confirmed by elemental analysis a 2:1 adduct of the chromone (III) with dioxane, was obtained. In the PMR spectrum of the obtained chromone (IV), a four-proton singlet which did not disappear after prolonged drying under vacuum was found at 3.56 ppm.

Thus, the 3-(1-benzimidazolyl)chromones (II-IV) were produced by the cyclization of α-(1-benzimidazolyl)-2,4-dihydroxy-5-ethylacetophenone.



EXPERIMENTAL

The reactions and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates. Mixtures of chloroform and methanol (9:1, 95:5) were used as eluant. The ^1H and ^{19}F NMR spectra were measured at 100 MHz in DMSO-d_6 on a Bruker WP 100SY instrument.

α-(1-Benzimidazolyl)-2,4-dihydroxy-5-ethylacetophenone (I). A stream of dry hydrogen chloride was passed into a mixture of 16 g (102 mmole) of 1-benzimidazolylacetonitrile and 15.5 g (112 mmole) of 4-ethylresorcinol in 50 ml of boron trifluoride etherate for 10-12 h with stirring and heating to 60°C. The reaction mixture was left overnight and was then added with stirring to 500 ml of water that had been heated to 80°C. The mixture was boiled for 1.5-2 h and made alkaline to pH 6-7 with ammonia, and the precipitate was filtered off. The residue was then reprecipitated from the alkaline solution and crystallized from dimethylformamide. The yield was 18.1 g (60%); mp 311-313°C. Found %: N 9.50. $C_{17}H_{16}N_2O_3$. Calculated %: N 9.45. PMR spectrum (δ, ppm): Protons of phenol part, 11.48 s, 2-OH; 6.44 s, 3-H; 10.75 s, 4-OH; 1.17 t, 2.55 q, 5-CH_2CH_3; 7.74 s, 6-H; 5.89 s, α-CH_2; protons of benzimidazole, 8.20 s, 2-H; 7.65 m, 4-, 7-H; 7.47 m, 5-, 6-H.

2-Trifluoromethyl-3-(1-benzimidazolyl)-6-ethyl-7-hydroxychromone (II). To a suspension of 1.8 g (6 mmole) of the ketone (I) in 10 ml of dry pyridine, while cooling with ice we added dropwise 3.4 ml (24 mmole) of trifluoroacetic anhydride. The mixture was stirred and cooled for 10 min and left overnight. The reaction mixture was poured onto ice, and the crystals were filtered off and recrystallized from absolute methanol. The yield was 1.64 g (75%); mp 284-286°C. Found %: N 7.40. $C_{19}H_{13}F_3N_2O_3$. Calculated %: N 7.49. PMR spectrum (δ, ppm): Protons of chromone ring, 7.84 s, 5-H; 2.68 q, 1.18 t, 5-CH_2CH_3; 11.43 s, 7-OH; 7.08 s, 8-H; protons of benzimidazole, 8.23 s, 2-H; 7.76, 7.49 m, 4-, 7-H; 7.27 m, 5-, 6-H. ^{19}F NMR spectrum: 9.59 ppm (2-CF_3) with reference to trifluoroacetic acid.

3-(1-Benzimidazolyl)-6-ethyl-7-hydroxychromone (III) and 3-(1-Benzimidazolyl)-6-ethyl-7-hydroxychromone, Complex with Dioxane (IV). To a mixture of 7.4 g (25 mmole) of the ketone (I) and 1.5 ml of acetic formic anhydride, while cooling with ice and salt, we added 1.05 ml of triethylamine and then over 20 min a further 10.5 ml of triethylamine so that the temperature of the reaction mixture did not rise above 0°C. The reaction mixture was stirred and cooled for 1 h, and a further 4 ml of acetic formic anhydride and 6 ml of triethylamine were then added. The mixture was then kept for a further

1 h at 0°C and 15 min at 80-100°C and poured onto ice. The crystals were filtered, washed with alcohol, and dried. The yield was 6.5 g (85%). Compound (IV) was obtained after crystallization from dioxane; mp 303-305°C. Found %: N 8.33. $C_{40}H_{36}N_4O_8$. Calculated %: N 8.38. The chromone (IV) was dissolved in DMFA, the solvent was evaporated to two thirds of the volume on a rotary evaporator, and the chromone (III) was precipitated with isopropyl alcohol; mp 274-275°C. Found %: N 9.16. $C_{18}H_{14}N_2O_3$. Calculated %: N 9.15. PMR spectrum (δ, ppm): Protons of chromone ring, 8.86 s, 2-H; 7.86 s, 5-H; 2.66 q, 1.18 t, 5-CH_2CH_3; 11.12 s, 7-OH; 7.02 s, 8-H; protons of benzimidazole, 8.29 s, 2-H; 7.76 m, 4-, 7-H; 7.31 m, 5-, 6-H.

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