

DIBENZO-18-CROWN-6 MODIFIED WITH KOJIC ACID FRAGMENTS

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Diazonium salts were prepared by diazotization of 4'-amino-, 4',4''-, and 4',5''-diaminodibenzo-18-crown-6. Their coupling products with kojic acid (5-hydroxy-2-hydroxymethyl- γ -pyrone) were synthesized for the first time: 4'-(6-aza-5-hydroxy-2-hydroxymethyl- γ -pyronyl)-, 4',4''-di-(6-aza-5-hydroxy-2-hydroxymethyl- γ -pyronyl)-, and 4',5''-di-(6-aza-5-hydroxy-2-hydroxymethyl- γ -pyronyl)-dibenzo-18-crown-6.

Key words: dibenzo-18-crown-6, kojic acid, azo-coupling.

In continuation of our research on the modification of dibenzo-18-crown-6 (DB18C6) with natural compounds [1-5], we synthesized several new heterocyclic derivatives by coupling kojic acid (5-hydroxy-2-hydroxymethyl- γ -pyrone) with 4'-(DB18C6-yl)-diazonium chloride and 4',4''- and 4',5''-di-(DB18C6-yl)-diazonium dichlorides.

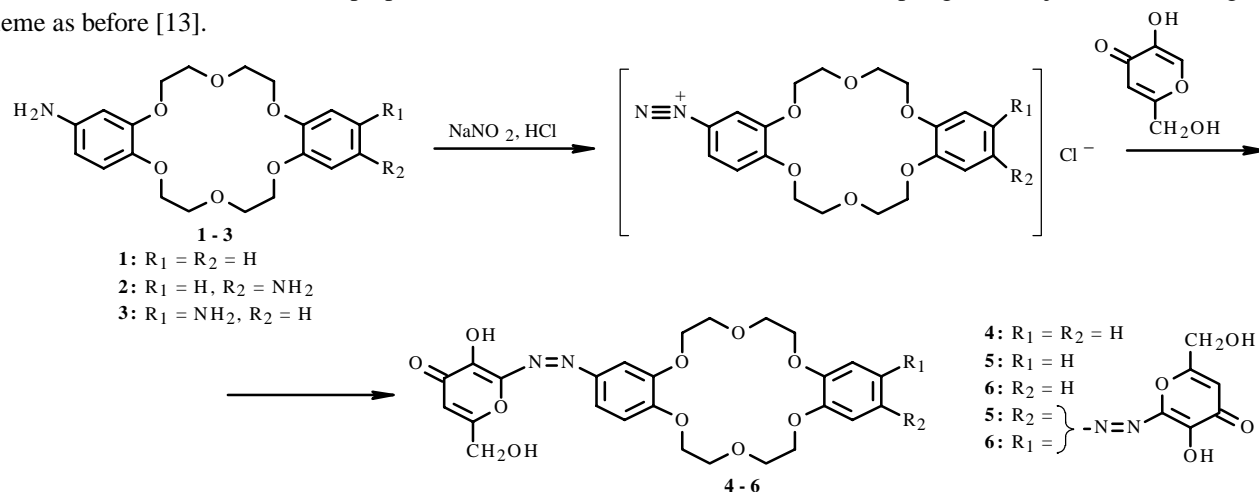
Kojic acid is a natural heterocyclic compound produced by many species of the genus *Aspergillus*, certain species of *Penicillium*, and certain acetic-acid bacteria [6].

The prepared derivatives were potential double ionophores, i.e., capable of binding cations of alkaline and alkaline-earth elements (through the macrocyclic portion) [7] and cations of *d*-transition metals (through the kojic acid portion) [8, 9].

The synthons for preparing the products were 4'-nitro- and 4',4''- and 4',5''-dinitro-DB18C6 [10], which were reduced to 4'-amino- (**1**) and 4',4''- and 4',5''-diamino-DB18C6 (**2** and **3**) according to the literature [11].

Kojic acid is known to undergo electrophilic substitution (halogenation, alkylation, azo-coupling) at the 6-position [12].

The diazonium salts were prepared from amines **1-3** and underwent azo-coupling with kojic acid according to the scheme as before [13].



The structures of the products were determined by PMR and IR spectra.

The PMR spectra of **4**, **5**, and **6** gave multiplets for the aromatic protons of DB18C6 and the aromatic proton in the 3-position of kojic acid at 6.98-6.66 ppm (**4**) and 6.95-6.75 ppm (**5** and **6**). The macrocycle protons appeared as two multiplets at 4.10-3.90 ppm (α -OCH₂) and 3.90-3.62 ppm (β -OCH₂) (**4**) and at 4.20-4.02 ppm (α -OCH₂) and 3.95-3.80 ppm (β -OCH₂) (**5** and **6**). The kojic-acid methylene protons appeared as a singlet at 3.40 ppm (**4**) and 3.45 ppm (**5** and **6**); the OH proton, at 1.24 ppm (**4**) and 1.15 ppm (**5** and **6**).

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The IR spectra of the products contained bands characteristic of kojic-acid OH stretching vibrations (3470 cm^{-1}), N=N asymmetric stretching vibrations (1510 cm^{-1}), and vibrations of the 1,2,4-substituted aromatic ring of DB18C6 (870 and 810 cm^{-1}).

EXPERIMENTAL

PMR spectra were recorded on an XL-100 spectrometer (Varian) at working frequency 100 MHz in DMSO solutions with HMDS internal standard.

4'-Nitro and 4',4''- and 4',5''-dinitro-DB18C6 were prepared as before [10]; 4'-amino-DB18C6, according to the literature [11] by reduction of 4'-nitro-DB18C6 with hydrazine hydrate over Raney nickel in dioxane. Yield 74%, mp $142\text{--}144^{\circ}\text{C}$.

PMR spectrum (δ , ppm, J/Hz): 6.85 (4H, m, ArH-3'', 4'', 5'', 6''), 6.57 (1H, d, J = 8.7, ArH-5'), 6.23 (1H, d, J = 2.5, ArH-3'), 6.02 (1H, d, ArH-6'), 4.12-3.92 (8H, m, $\alpha\text{-OCH}_2$), 3.90-3.57 (8H, m, $\beta\text{-OCH}_2$), 2.45 (2H, s, NH_2).

4',4''-Diamino-DB18C6 was prepared by reduction of the corresponding dinitro derivative as before [11]. Yield 68%, mp $173\text{--}176^{\circ}\text{C}$, lit. [11] mp $177\text{--}178^{\circ}\text{C}$. 4',5''-Diamino-DB18C6 was prepared analogously. Yield 49%, mp $198\text{--}200^{\circ}\text{C}$, lit. [11] mp $198\text{--}201^{\circ}\text{C}$.

General Method for Preparing of Compound 4-6. a) Diazotization of 1, 2, 3. The appropriate amine (0.80 mmol) was dissolved in water (5-10 mL) acidified with HCl (34%, 2.20 or 4.40 mmol). The solution was cooled on an ice bath to 0°C and treated with NaNO_2 (0.80 mmol or 1.60 mmol). The resulting solution was used without purification in the azo-coupling reaction.

b) Azo-Coupling with Kojic Acid. A solution of the appropriate diazonium salt was cooled on an ice bath to 0°C , treated dropwise with a solution of sodium kojate (0.80 mmol for **4** or 1.60 mmol for **5** and **6**) in water (5 or 10 mL), stirred for 3 h at $<5^{\circ}\text{C}$, decomposed with cold water (10 mL), and treated dropwise with ammonia in water until the pH was 8-9. The resulting precipitate was filtered off and washed with cold water.

Yield of **4**, 74%, mp 126°C (dec.). PMR spectrum (δ , ppm): 6.98-6.66 (8H, m, ArH-3', 5', 6', 3'', 4'', 5'', 6'' + kojic-acid H-3), 4.10-3.90 (8H, m, $\alpha\text{-OCH}_2$), 3.90-3.62 (8H, m, $\beta\text{-OCH}_2$), 3.40 (2H, s, CH_2OH), 1.24 (1H, s, CH_2OH).

IR spectrum (λ , cm^{-1}): 3470 (ν_s OH), 1510 (ν_{as} N=N), 870 and 810 (δ_{CC} , 1,2,4-substituted aromatic ring).

Yield of **5**, 66%, mp 129°C (dec.). PMR spectrum (δ , ppm): 6.95-6.75 (8H, m, ArH-3', 5', 6', 3'', 5'', 6'' + kojic-acid 2H-3), 4.20-4.02 (8H, m, $\alpha\text{-OCH}_2$), 3.95-3.80 (8H, m, $\beta\text{-OCH}_2$), 3.45 (4H, s, CH_2OH), 1.15 (1H, s, CH_2OH).

Yield of **6**, 69%, mp 133°C (dec.). The PMR spectrum was analogous to that described above.

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