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SYNTHESIS OF AMINO DERIVATIVES OF 1,6,8-TRIHYDROXY-3-METHYL-9,10-ANTHRAQUINONE

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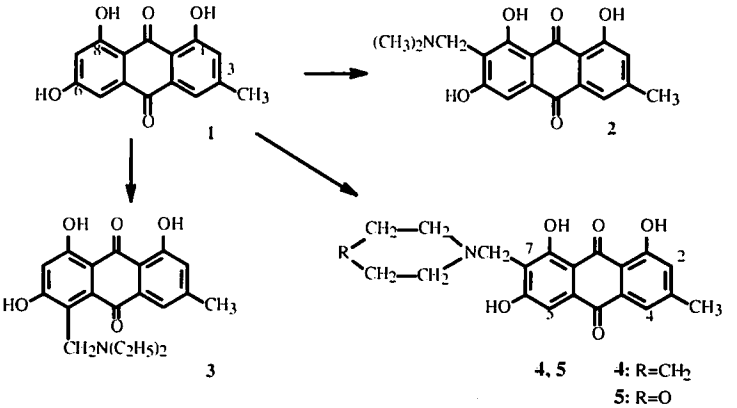
The Mannich synthesis of amino derivatives of 1,6,8-trihydroxy-3-methyl-9,10-anthraquinone isolated from rhamnyl processing wastes is described.

Anthraquinones, in particular, derivatives of isomeric trihydroxyanthraquinones of the emodin group, have been extensively screened for biologically active compounds and medicinal preparations [1, 2]. Thus, diaminoanthraquinones with an aliphatic amino group in the substituent possess antiviral activity and elicit interferon production [3, 4]. Derivatives of hydroxyanthraquinones are recommended as anti-inflammatory and anti-arthritic medicines [5]. Amino and nitro derivatives of chrysophanol and franguloemodin exhibit antitumor activity [6, 7].

Therefore, we synthesized the previously unknown amino derivatives of emodin, 1,6,8-trihydroxy-3-methyl-9,10-anthraquinone (**1**), which is the main component (44.5% content) of the impure product obtained from rhamnyl processing wastes [8, 9].

Emodin (**1**) was isolated from a mixture by column chromatography. It was identified by spectral and elemental analysis and melting point. The Mannich reaction [10, 11] of compound **1** produced the following amino derivatives: 7-dimethylaminomethyl- (**2**), 5-diethylaminomethyl- (**3**), 7-piperidinomethyl- (**4**), and 7-morpholinomethyl-1,6,8-trihydroxy-9,10-anthraquinone (**5**).



The lack of a signal in the PMR for a proton on the seventh C atom in compounds **2**, **4**, and **5** and on the fifth C atom in compound **3** indicates that C_7 (**2**, **4**, and **5**) is substituted with dimethylaminomethyl, piperidinomethyl, and morpholinomethyl groups and that C_5 has a diethylaminomethyl group (**3**). Signals for the CH_2 and $N(CH_3)_2$ protons located on C_7 in compound **2** are situated at δ 3.59 and 2.37 ppm, respectively.

The PMR spectrum of compound **3** contains signals at 3.96, 2.61, and 1.04 ppm, which should be assigned to the CH_2 and $N(CH_2–CH_3)_2$ groups, respectively, on C_5. Signals for the CH_2 protons of the piperdine and morpholine groups of compounds **4** and **5** that are situated *ortho* to the N atom appear at 2.47 and 2.46 ppm, respectively. Signals of the remaining CH_2 protons of the piperidine and morpholine rings have chemical shifts of 1.45 and 3.58 ppm, respectively.

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EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer in mineral oil; UV spectra, on a Specord UV in ethanol; PMR spectra, on a Varian CFT-20 instrument at 80 MHz working frequency and TMS internal standard. Solvents were CCl_4, acetone-D_6, and $CHCl_3$.

Starting compound **1** was isolated from the crude product on a 100-400 μm silica-gel column using diethyl ether:petroleum ether (1:2).

The course of the reaction and the purity of the products was monitored using Silufol UV-254 plates. Elemental analysis of all compounds agreed with that calculated.

1,6,8-Trihydroxy-3-methyl-9,10-anthraquinone (1). mp 254-256°C. IR spectrum (cm^{-1}): 1595, 1632, 1673, 3400. UV spectrum (λ_{max}, nm): 263, 290, 440. $C_{15}H_{10}O_5$.

7-Dimethylaminomethyl-1,6,8-trihydroxy-3-methyl-9,10-anthraquinone (2). Aqueous dimethylamine (1.9 ml, 0.009 moles, 39%) cooled to 0°C was slowly treated with glacial acetic acid (6 ml, 0.104 moles), formalin (1 ml, 0.008 moles, 40%), and compound **1** (0.45 g, 0.002 moles). The reaction mixture was stirred at 20°C for 3 h, treated with water (5 ml), and filtered. The filtrate was treated with stirring dropwise with NaOH (10%) until the pH was 9. The precipitate was filtered off, washed with water, and dried. Yield 0.4 g, 74%, mp 176-178°C. IR spectrum (cm^{-1}): 1370 (C–N<). UV spectrum (λ_{max}, nm): 220, 259, 320, 522-560 (lg ε, 5.61, 5.53, 5.48, 4.78). $C_{18}H_{17}O_5$.

5-Diethylaminomethyl-1,6,8-trihydroxy-3-methyl-9,10-anthraquinone (3). This was prepared analogously to compound **2** using diethylamine. Yield 0.34 g, 63%, mp 185-187°C. IR spectrum (cm^{-1}): 1380 (C–N<). UV spectrum (λ_{max}, nm): 220, 259, 318, 406-430 (lg ε, 3.39, 4.27, 4.27, 4.25, 3.53, 3.73). $C_{20}H_{21}O_5$.

7-Piperidinomethyl-1,6,8-trihydroxy-3-methyl-9,10-anthraquinone (4). Compound **1** (0.45 g, 0.002 moles) was treated with a cooled (0°C) mixture of piperidine (0.56 ml, 0.006 moles), glacial acetic acid (6 ml, 0.104 moles), and formalin (40%, 0.23 g, 0.008 moles). The reaction mixture was stirred at room temperature for 4 h, treated with water (5 ml), and filtered. The filtrate was treated with NaOH (10%) until the pH was 9. The precipitate was filtered off, washed with water, and dried. Yield 0.34 g, 71%, mp 236-238°C. IR spectrum (cm^{-1}): 1380 (C–N<). UV spectrum (λ_{max}, nm): 206, 253, 260, 292 (lg ε, 4.59, 4.83, 4.97, 4.42). $C_{21}H_{21}O_5$.

7-Morpholinomethyl-1,6,8-trihydroxy-3-methyl-9,10-anthraquinone (5). Morpholine (0.6 ml, 0.006 moles) was cooled to 0°C and treated dropwise with formalin (40%, 0.23 g, 0.008 moles) so that the temperature did not rise over 5°C. The mixture was treated with compound **1** (0.45 g, 0.002 moles). The reaction mixture was stirred at room temperature for 1 h, treated with water (10 ml), and filtered. The filtrate was stirred and treated dropwise with NaOH (10%) until the pH was 9. The precipitate was filtered off, washed with water, and dried. Yield 0.35 g, 77%, mp 220-222°C. IR spectrum (cm^{-1}): 1370 (C–N<). UV spectrum (λ_{max}, nm): 207, 254, 260 (lg ε, 4.50, 4.72, 4.45). $C_{20}H_{19}O_6$.

REFERENCES

1. K. C. Murdock and R. G. Bild, *J. Med. Chem.*, **22**, 1024 (1979).
2. Zee-cherg, *J. Med. Chem.*, **21**, 291 (1978).
3. German Pat. No. 3.2702137 (1977); *Chem. Abstr.*, **88**, 37508 (1978).
4. J. R. Broun, *Prog. Med. Chem.*, **15**, 125 (1978).
5. A. Di Marco, *Antibiot. Chemother. (Basel)*, **23**, 216 (1978).
6. U. Weber, ed., *Karsten's Lehrbuch der Pharmakognosie fur Hochschulen*, 6th Ed., Gustav Fischer, Jena (1946).
7. Z. Kabiak, *Farma Polska*, **23**, No. 4, 299 (1967).
8. E. P. Kemertelidze and A. V. Gotsiridze, *Soobshch. Akad. Nauk Gruz. SSR*, **61**, No. 1, 93 (1971).
9. E. P. Kemertelidze and A. V. Gotsiridze, *Khim. Prir. Soedin.*, 519 (1971).
10. F. F. Blicke, *Mannich Reaction*, in: Organic Reactions, Vol. 1, R. Adams, ed., New York (1942) [Russian translation, Mir, Moscow (1948), Vol. 1, p. 399].
11. J. H. Brewster and E. L. Eliel, "Carbon-carbon alkylation of amines and ammonium salts," in: *Organic Reactions*, Vol. VII, R. Adams, ed., John Wiley and Sons, New York (1953).