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COMPLEX COMPOUNDS BASED ON A COLCHICINE DERIVATIVE

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Complex compounds based on deacetyl-10-ethanolamino-10-demethoxycolchicine with Co, Mn, and Fe chlorides have been obtained, and their radiomodifying and antitumoral properties have been investigated.

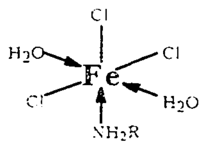
The cytotoxic and radiomodifying properties of colchicine have aroused interest in the creation of less toxic analogs with properties superior to the activity of the initial alkaloid. It is also known that the search for active drugs among coordination compounds of the transition metals not infrequently leads to the desired results [1].

As a ligand we have taken a colchicine derivative – deacetyl-10-ethanolamino-10-demethoxycolchicine (**1**), which contains a primary amino group. Compound (**1**) possesses a lower toxicity than colchicine and higher radiomodifying and antitumoral activities than the initial alkaloid [2]. The synthesis of complexes of (**1**) with Co, Mn, and Fe chlorides was conducted in nonaqueous media: in isopropyl alcohol for $CoCl_2$ and $MnCl_2$ and in diethyl ether for $FeCl_3$, with the formation of compounds (**2**), (**3**), and (**4**), respectively. A derivatographic and IR-spectral investigation has been made of the reaction products and they have been analyzed for their metal ion contents by a complexonometric method [3]. Nitrogen was determined by the micro Dumas method, and Cl ions by potentiometric titration with a silver chloride electrode [4].

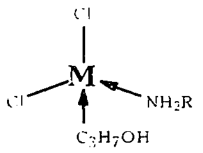
A comparison of the IR spectra of the initial (**1**) and of the coordination compounds showed a sharp decrease in the intensity of the 3400-3440 cm^{-1} band and also a change in the region of deformation vibrations of the HH bond in the spectrum of (**1**), the frequency of the vibrations of which changed from 1590 cm^{-1} to 1600 cm^{-1} in the cobalt compound (**2**), to 1620 cm^{-1} in the manganese compound (**3**), and to 1625 cm^{-1} in the iron compound (**4**). The information obtained permits the conclusion that in all three complexes the nitrogen atom of the primary amino group of (**1**) participated in coordination, since it possesses a greater donor capacity than the other substituents. The IR spectra of the complexes also showed an intense band at 670-690 cm^{-1} corresponding to the Cl^- ion.

The derivatographic results showed that when the coordination compounds that had been obtained were heated (to 85-100°C) solvated solvent molecules were eliminated, with a weak endo effect. Breakdown of the Cu compound was observed in the 230-260°C region, loss of mass being accompanied by oxidation of the reaction products by atmospheric oxygen. The complex with Mn underwent decomposition starting from 260°C and continuing to 500°C, while the Fe compound decomposed at 360°C and above.

Complex compound (**2**) was represented by a tetrahedral structure in which two of the coordinates around the Co^{2+} ion were occupied by Cl^- ions, the third by the nitrogen atom of the primary amino group of (**1**), and the fourth by a molecule of isopropyl alcohol. Consequently, only one molecule of the ligand was bound to the central Co atom, as was confirmed by the results of the quantitative determination of nitrogen and metal.



(4)



where M = Co^{2+} (2)
or Mn^{2+} (3)
NH_2R = (1)

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According to its IR spectrum, its derivatogram, and the quantitative determination of nitrogen and metal, compound (3) had an analogous structure.

From the results of analysis for Fe^{3+} (trigonometrically) and nitrogen (Dumas method), the product of the interaction of (1) with $FeCl_3$ corresponded to the formula $C_{21}H_{26}N_2O_5 \cdot FeCl_3 \cdot 2H_2O$, and it may be represented by structure (4).

The substances obtained were investigated for radiomodifying (complexes (2) and (3)) and antitumoral (complex (4)) activities. It was established that all the complex compounds were less toxic than colchicine, but only compound (4) possessed a lower toxicity than (1). The radiosensitizing activity of complex (3) was more pronounced than that of colchicine but was lower than that of (1). Compound (2) exhibited no such activity. The antitumoral activity of the iron complex, investigated on two tumoral strains – sarcoma 45 and sarcoma M-1 –, was higher than that of colchicine, and on strain M-1 it was greater than that of (1).

Thus, of the three complex compounds obtained from (1) only the Fe-containing compound exhibited a lower toxicity and a more pronounced antitumoral activity than (1) on the tumoral strain of sarcoma M-1.

EXPERIMENTAL

IR spectra were taken on a UR-20 double-beam spectrophotometer in the 3700-750 cm^{-1} range in potassium bromide tablets, and derivatograms were obtained on an instrument using the Paulik–Paulik–Erdey system (Hungary).

The metal chlorides and solvents were used after additional purification. The compositions of the hydrated Co and Mn salts were determined by a gravimetric method. Compound (1) was obtained from colchicine as described in [2].

(1)[Deacetyl-10-ethanolamino-10-demethoxycolchicine]·$CoCl_2 \cdot C_3H_8O$ (2). For the synthesis we took $3 \cdot 10^{-4}$ mole (0.0714 g) of kh.ch [chemically pure] grade cobalt chloride that had been twice recrystallized from double-distilled water and $1 \cdot 10^{-3}$ mole (0.386 g) of (1). The components were dissolved in the minimum amounts of isopropyl alcohol and were mixed. The reaction was conducted at room temperature. The green precipitate that deposited was washed three times with isopropyl alcohol. The yield amounted to 0.133 g (65% calculated on the initial cobalt chloride hexahydrate). The substance was dried at 45-50°C. It was bright green and readily soluble in water. Found %: N 5.20, Co 10.30. Calculated %: N 5.00, Co 10.52. $C_{24}H_{34}N_2O_6Cl_2Co$.

Compound (1)·$MnCl_2 \cdot C_3H_8O$ (3) was synthesized similarly, but in absolute isopropyl alcohol. The synthesis was complicated by the hygroscopicity of the final product. The components were mixed in a ratio of $MnCl_2 \cdot 4H_2O$ to (1) of 1:3 [sic] – $1 \cdot 10^{-3}$ mole of $MnCl_2 \cdot 4H_2O$ (0.198 g) and $2 \cdot 10^{-3}$ mole of (1) (0.772 g). The composition of the product obtained corresponded to a 1:1 ratio of the components, as was found from the results of analysis for nitrogen and manganese. The excess of (1) was washed out with isopropyl alcohol. The yield of complex (3) was 0.431 g (67% calculated on the initial manganese chloride tetrahydrate). Yellow substance, mp 206°C, readily soluble in water. Found %: N 4.98, Mn 9.51. Calculated %: N 5.04, Mn 9.87. $C_{24}H_{34}N_2O_6Cl_2Mn$.

Compound (1)·$FeCl_3 \cdot 2H_20$ (4). Anhydrous ferric chloride was prepared from hydrogen-reduced iron in a current of dry chlorine by a known procedure [3]. Then a saturated solution of 10^{-3} mole (0.270 g) of $FeCl_3 \cdot 6H_2O$ in diethyl ether was made, and to it was gradually added 1.16 g ($3 \cdot 10^{-3}$ mole) of (1) until some undissolved part of it remained in the vessel. The mixture was then kept for two days with constant stirring. The ether-insoluble (1) passed into solution as it bound with the ferric chloride.

The solution was evaporated, and the dark brown substance that deposited was dissolved in hot isopropyl alcohol. After cooling, the solution deposited a product still containing a certain amount of ferric chloride, in which this salt is readily soluble. Such fractional crystallization was carried out four times. The yield was 0.234 g (40%, calculated on the initial ferric chloride hexahydrate). Substance (4) was readily soluble in water, mp 355°C. Found %: N 4.94, Fe 9.24. Calculated %: N 4.79, Fe 9.55. $C_{21}H_{30}N_2O_7Cl_3Fe$.

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