REACTIONS OF NATURAL ANTHRAQUINONE PIGMENTS
1. Nitrogen-Containing Derivatives of Chrysophanic Acid

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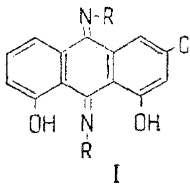
Chrysophanic acid (4, 5-dihydroxy-2-methylanthraquinone) has been isolated from the roots of Rumex tianschanicum (T'ien Shan dock), which is widely distributed in Zailiiskii Alatau and is used as a tanning agent in the leather industry. The chemical substances present in the roots of this plant have been studied thoroughly [1, 2]. In particular, they include from 1 to 2% of hydroxymethylanthraquinones (emodin, chrysophanol, physcion, etc). The method of isolation and identification of the hydroxymethylanthraquinones is simple. In contrast to the benzene, chloroform, and alcohol-benzene extractions previously proposed in [3, 4], we used kerosene as solvent. It extracts the anthraquinone substances more selectively and does not reduce the tannide content (the amount of tannides before extraction of the pigments was 22.6% and after kerosene extraction 22.4%).

The anthraquinone derivatives were extracted from the kerosene extract by successive treatment with aqueous solutions of sodium carbonate and alkali.

We have studied the kinetics and the mechanism of the catalytic hydrogenation of chrysophanic acid on Raney Ni, PdO_2, and Pd/C in the liquid phase [5]. The hydrogenated product was similar to chrysarobin.

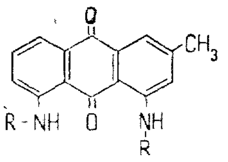
Emodin, chrysophanic acid, mixtures of them, and the reduced product were tested for their healing action on dermatitides in the Kazakh Scientific Research Institute for Dermatology and Venerealogy and clinically in the Alma Ata venereal disease clinic. In view of this, great interest is attached to the testing of other compounds of the same type, particularly nitrogen-containing derivatives. For this reason, we have made an attempt to introduce N-containing groups into the molecule of chrysophanic acid.

We have obtained the oxime (Ia), hydrazone (Ib), osazone (Ic), the amino derivative (IIa), the ethylamino derivative (IIb), the benzoylamino derivative (IIc), and the anilide of chrysophanic acid (IId):



I

Ia R = OH
Ib R = NH_2
Ic R = NHC_6H_5



II

IIa R = H
IIb R = C_2H_5
IIc R = COC_6H_5
IId R = C_6H_5

Experimental

For all compounds, the elementary analysis was determined, exhaustive acetylation with acetic anhydride in the presence of powdered sodium acetate for 6-8 hr at the boiling point of the solvent was carried out, the number of active hydrogen atoms was determined by the Tschugaeff-Zerewitinoff method using pyridine as the solvent, and the UV spectrum (in n-hexane and ethanol) and the IR spectrum were recorded by the usual methods [6, 7].

4, 5-Diamino-2-methylanthraquinone (IIa). A solution of 2.45 g (0.01 mole) of chrysophanic acid in 25 ml of concentrated aqueous ammonia was treated with 0.52 g of ferric ammonium alum, and 0.26 g (0.005 mole) of ammonium chloride. The mixture was held in a stainless-steel autoclave, with stirring, at 60-70° for 12 hr. The reaction mixture was cooled and the precipitate was filtered off. The cherry-red solution was acidified to neutrality with 0.1 N hydrochloric acid. The unchanged substances were filtered off, and the mother liquor was repeatedly extracted with ether. The ethereal solution was dried with sodium sulfate and the solvent was distilled off in a current of nitrogen. The residue was recrystallized from alcohol and carbon tetrachloride. This gave 2.14 g of IIa (84.3%), mp 258-260° (from CCl_4). Found, %: C 72, 71.96; H 4.98, 5.11; N 11.4, 11.2; H_{act} 1.51, 1.57. Calculated for $C_{15}H_{12}O_2N_2$, %: C 71.43; H 4.82; N 11.1; H_{act} 1.58.

Tetra-acetyl derivative, mp 190-192°. UV spectrum of IIa: λ_{max} (n-hexane) 224, 268, 410 mμ (lg ε 3.94, 4.10, 3.38). Found, %: $COCH_3$ 41.2, 39. Calculated for $C_{23}H_{20}O_6N_2$, %: $COCH_3$ 40.0.

Compound IIa was diazotized and coupled with β-naphthol. The reaction products were subjected to paper chromatography with petroleum ether saturated with methanol as the solvent.

4, 5-Dihydroxy-2-methyl-9, 10-dioxime [of anthraquinone] (Ia). A solution of 2.54 g of chrysophanic acid and

1.65 g (0.05 mole) of hydroxylamine in alcohol was heated under reflux for 8 hr. After the end of the reaction, the alcohol was distilled off under vacuum. The residue was recrystallized from benzene and dioxane. This gave 2 g of Ia (70.4%) with mp 117-121°. When the dioxime was acetylated, only two hydrogen atoms reacted. Rearrangement or the formation of an additional ring apparently takes place in an acid medium. Found, %: N 9.3, 9.47; H_{act} 1.47, 1.52. Calculated for $C_{15}H_{12}O_4N_2$, %: N 9.85; H_{act} 1.4.

Dieacetyl derivative mp 96-98° (from alcohol). UV spectrum of Ia: λ_{max} (n-hexane) 226, 256, 286, 430 mμ (lg ε 4.30, 4.15, 3.96, and 3.92). Found, %: $COCH_3$ 24.2, 24.0. Calculated for $C_{19}H_{16}O_6N_2$, %: $COCH_3$ 23.37.

4, 5-Dihydroxy-2-methyl-9, 10-dihydrazone [of anthraquinone] (Ib). A solution of 2.54 g of chrysophanic acid and 3.2 g (0.1 mole) of hydrazine hydrate in dioxane was treated with 0.56 g (0.01 mole) of caustic potash. The reaction was carried out for 14 hr at the boiling point of the solvent. The mixture was cooled and the precipitate was filtered off. The dioxane was distilled off in a current of nitrogen. The residue was recrystallized from alcohol and then from carbon tetrachloride. This gave 2.83 g of Ib (90.27%), mp 95-97°, (from CCl_4). Found, %: N 18.6, 18.2; H_{act} 2.01, 2.25. Calculated for $C_{15}H_{14}O_2N_4$, %: N 19.85; H_{act} 2.1.

Acetyl derivative of Ib, mp 143-146°. UV spectrum of Ib: λ_{max} (n-hexane) 256, 276, 286, 430 mμ (lg ε 4.00, 3.77, 3.75, 3.75). Found, %: $COCH_3$ 47.6, 47.37. Calculated for $C_{27}H_{26}O_8N_4$, %: $COCH_3$ 48.3.

4, 5-Dihydroxy-2-methyl-9, 10-diphenylhydrazone [of anthraquinone] (Ic). 2.54 g (0.01 mole) of chrysophanic acid and 2.16 g (0.02 mole) of phenylhydrazine hydrate were dissolved in in absolute alcohol (70 ml). The reaction lasted 10.5 hr in the presence of 0.02 g of iron turnings and 0.02 g of ferrous chloride. The mixture was filtered, the alcohol was distilled off, and the residue was treated with ether. The ethereal solution was distilled, and the residue was crystallized from benzene and petroleum ether. This gave 3.16 g of Ic (82.7%), mp 132-134°. Found, %: N 11.38, 11.46; H_{act} 0.90, 0.93. Calculated for $C_{27}H_{22}O_2N_4$, %: N 11.48; H_{act} 0.92.

UV spectrum of Ic: λ_{max} 226, 256, 287, 430 mμ (lg ε 3.98, 3.88, 3.73, 3.92). Found, %: $COCH_3$ 30.2, 30.42. Calculated for $C_{35}H_{30}O_6N_4$, %: $COCH_3$ 31.7.

4, 5-Diethylamino-2-methylanthraquinone (IIb). A mixture of 0.254 g (0.001 mole) of chrysophanic acid and 20 ml of a saturated alcoholic solution of ethylamine was heated at 70° for 5 hr and was left to stand for 12 hr. The excess of ethylamine and the alcohol were distilled off under vacuum. The residue was dried over P_2O_5 and recrystallized from ethyl acetate. Yield 67.2% (2.07 g), mp 106-108°. Found, %: N 9.01, 9.1; H_{act} 0.6, 0.62. Calculated for $C_{19}H_{20}O_2N_2$, %: N 9.3; H_{act} 0.65.

Acetyl derivative of IIb, mp 82-84°. Found, %: $COCH_3$ 21.3, 21.35. Calculated for $C_{23}H_{24}O_4N_2$, %: $COCH_3$ 21.9.

4, 5-Dibenzoylamino-2-methylanthraquinone (IIc). 0.252 g (0.001 mole) of 4, 5-diamino-2-methylanthraquinone was treated with 0.35 g (0.0025 mole) of benzoyl chloride, and the mixture was dissolved in 10 ml of pyridine; to this solution, 0.445 g (0.0015 mole) of potassium carbonate was added, and the mixture was heated at 90-100° in a flask with a magnetic stirrer for 3.5 hr. The mixture was cooled, and the precipitate was filtered off. The excess of benzoyl chloride was removed with ether, and the pyridine was then distilled off. The residue was acidified with hydrochloric acid to a weakly acid reaction to congo red. The upper layer was separated off and shaken with ether. A microcrystalline precipitate was deposited. The ether was distilled off and the residue was recrystallized from alcohol. This gave 3.2 g of IIc (69.4%), mp 146-148°. Found, %: N 2.15, 2.32; H_{act} 0.45, 0.44. Calculated for $C_{29}H_{20}O_4N_2$, %: N 2.5; H_{act} 0.43.

Anilide of chrysophanic acid (IId) [4, 5-Di-(phenylamino)-2-methylanthraquinone]. A solution of 0.254 g (0.001 mole) of chrysophanic acid in the minimum amount of alcohol (7 ml) and 0.225 g of freshly-distilled aniline was heated for 10 hours at 70° in a flask with a magnetic stirrer in the presence of zinc chloride catalyst. At the end of the reaction, the solid matter was filtered off and the alcohol was distilled off under vacuum. The residue was treated by the method of O. M. Cherntsov and N. S. Drozdov (for "neozone D") [8]. This gave 2.5 g of (IId) (62%), mp 274-286° (from alcohol). Found, %: N 7.1, 7.15; H_{act} 0.5, 0.51. Calculated for $C_{27}H_{20}O_2N_2$, %: N 6.9; H_{act} 0.49.

The acetyl derivative of IId, mp 184-187°. Found, %: $COCH_3$ 17.35, 17.47. Calculated for $C_{31}H_{24}O_4N_2$, %: $COCH_3$ 17.5.

Summary

By condensing chrysophanic acid with nitrogen-containing substances, derivatives substituted at the carbonyl and hydroxyl-group positions have been obtained. Substance IIa possess antitumor activity.

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