Chemistry of Natural Compounds, Vol. 30, No. 2, 1994

PHOSPHORYLATION OF EMODIN

L. N. Pribytkova and M. S. Erzhanova

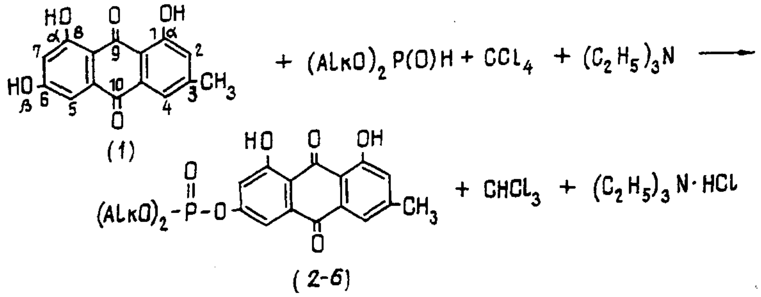
UDC 547.673.6:546.185

A convenient method has been developed for the interaction of dialkyl phosphites with 1,6,8-trihydroxy-3-methylanthraquinone (emodin) under the conditions of the Todd–Atherton reaction. It has been shown that the α-hydroxy groups of emodin are not phosphorylated at an equimolar ratio of emodin and dialkyl phosphite. The phosphorylation of 7-bromo-1,6,8-trihydroxy-3-methylanthraquinone with potassium dialkyl phosphorothioates has been studied. The reaction takes place at the sulfur atom, with the formation of of the product of S-alkylation.

Information on phosphorylation reactions in the hydroxyanthraquinone series is extremely limited. The study of the properties of phosphorus-containing hydroxyanthraquinones is of considerable interest, since compounds have been found among them that possess a high biological activity [1]. Depending on their structure, i.e., on the position and nature of the phosphorus-containing fragment, the phosphorylated anthraquinones investigated possess insecticidal, growth-regulating, or antitumoral activity [2].

Previously [1], phosphates of chrysophanol have been obtained by its interaction with dialkyl phosphorochloridites, which are formed by the interaction of dialkyl phosphites with carbon tetrachloride and a tertiary amine. It is known that if, in addition to the components mentioned, another nucleophilic compound is added to the reaction mixture, the reaction product is the corresponding phosphate [3, 4]. This reaction, discovered and introduced into the arsenal of organophosphorus synthesis by A. R. Todd and F. R. Atherton, has great preparative advantages and is widely used at the present time.

We are the first to have used the conditions of the Todd–Atherton reaction for hydroxyanthraquinones — in the interaction of 1,6,8-trihydroxy-3-methylanthraquinone (emodin) with dialkyl phosphites, the general scheme of the reaction being given below:



Alk=CH_3 (2); C_2H_5 (3); n-C_3H_7 (4); i-C_3H_7 (5); n-C_4H_9 (6)

Since the initial emodin (1) is insoluble in carbon tetrachloride, which is the donor of a chlorine atom in the formation of dialkyl phosphorchloridates under the conditions of the Todd–Atherton reaction, we used isopropyl alcohol as the solvent. After the reactants had been mixed, a characteristic red coloration of the reaction mixture appeared, which changed after some time to yellow-green, and then to brown. It is assumed [4] that this change in the color of the reaction mixture is probably connected with with the formation of an intermediate quasi-phosphonium compound. Under the given conditions, with an equimolar ratio of (1) and the dialkyl phosphite, the α-hydroxy groups in positions 1 and 8 were not phosphorylated, which can be explained by their involvement in intramolecular hydrogen bonds [5].

Al-Farabi Kazakh State National University, Almaty. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 212-216, March-April, 1994. Original article submitted July 28, 1993.

0009-3130/94/3002-0193$12.50 ©1995 Plenum Publishing Corporation

TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

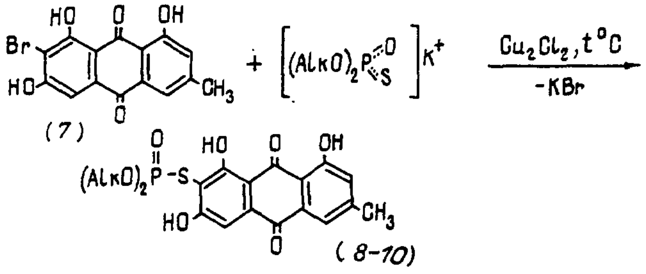
Compound No.	Empirical formula	IR, ν, cm^{-1} (KBr)			^{31}P, ppm in DMFA	PMR, δ, ppm, in DMFA
		P—O—C	P=O	C=O		
2	$C_{17}H_{15}O_8P$	1050, 1090	1265	1620	−4.83	2.43 s (Ar-CH_3); 3.73 d (OCH_3); 6.48 s (H-7); 7.12 d (H-2); 7.22 s (H-5); 7.48 d (H-4); 11.8 s, 12.00 s (OH)
3	$C_{19}H_{19}O_8P$	1000, 1020	1270	1625, 1685	−7.10	1.27 t (CH_3); 2.43 s (Ar-CH_3); 4.25 m (OCH_2); 6.47 s (H-7); 7.10 d (H-2); 7.22 s (H-5); 7.53 d (H-4); 11.95 s, 12.00 s (OH)
4	$C_{21}H_{23}O_8P$	1000, 1050	1270	1625, 1670	−7.00	0.88 t (CH_3); 1.61 m (CH_2); 2.42 s (Ar-CH_3); 4.10 m (OCH_2); 6.50 s (H-7); 7.13 d (H-2); 7.22 s (H-5); 7.49 d (H-4); 11.80 s, 12.00 s (OH)
5	$C_{21}H_{23}O_8P$	950, 1015	1280	1620, 1670	−7.09	1.23 d (CH_3); 2.44 s (Ar-CH_3); 4.41 m (OCH); 6.60 s (H-7); 7.11 d (H-2); 7.22 s (H-5); 7.51 d (H-4); 11.85 s, 12.00 s (OH)
6	$C_{23}H_{27}O_8P$	1020, 1050	1260	1623, 1670	−6.62	0.88 t (CH_3); 1.32 m ($2CH_2$); 2.47 s (Ar-CH_3); 3.88 m (OCH_2); 6.59 s (H-7); 7.12 d (H-2); 7.23 s (H-5); 7.49 d (H-4); 11.92 s, 12.32 s (OH)
8	$C_{17}H_{15}O_8PS$	1015, 1050	1285	1625		2.43 s (Ar-CH_3); 3.73 d (OCH_3); 7.05 d (H-2); 7.38 s (H-5); 7.45 d (H-4)
9	$C_{21}H_{23}O_8PS$	1005, 1030	1270	1620, 1665		1.07 t (CH_3); 1.56 m (CH_2); 2.45 s (Ar-CH_3); 4.89 m (OCH_2); 7.04 d (H-2); 7.34 s (H-5); 7.47 d (H-4)
10	$C_{23}H_{27}O_8PS$	1000, 1055	1270	1620, 1670		1.09 t (CH_3); 1.59 m ($2CH_2$); 2.44 s (Ar-CH_3); 4.99 m (OCH_2); 7.07 d (H-2); 7.39 s (H-5); 7.46 d (H-4)

The emodin phosphates obtained were identified on the basis of elementary analyses and IR, PMR, and ^{31}P NMR spectra (Table 1). The ^{31}P NMR spectra of compounds (**2**)-(**6**) each showed one signal, with a chemical shift in the interval from −7.10 to −4.83 ppm [6]. The phosphorylation of (**1**) at the hydroxy group in position 6, alone, could also be shown by the PMR spectra of the phosphates, which contained signals of the protons of chelate hydroxy groups in the 11.8-12.35 ppm region that are characteristic for α-OH groups, while signals characteristic for free β-OH groups, with chemical shifts in the region of 10 ppm, were absent [7].

The IR spectra of the compounds obtained contained intense absorption bands in the 1260-1280 cm^{-1} region, due to the stretching vibrations of the phosphoroso group (P=O), and at 950-1090 cm^{-1}, corresponding to vibrations of the P—O—C system; there were no bands at 3390 cm^{-1}, corresponding to a β-OH group [7].

We also studied the reaction of 7-bromo-1,6,8-trihydroxy-3-methylanthraquinone (7) with potassium dialkyl phosphorothioates. This reaction was of both theoretical and practical interest, since among readily accessible salts of dialkyl phosphorothioates there are effective preparations, such as Systox (demeton), which is used in agriculture [8]. Furthermore, the study of this reaction would enrich our ideas on characteristics of the chemical behavior of ambident ions. This is because it is known that a dual reactivity in realation to electrophilic reagents in alkylation and acylation reactions is possible for salts of monothio acids of pentavalent phosphorus, the anions of which are mesomeric, i.e., are constructed in the manner of thion-thiol ambident triads. Thus, it has been shown in a number of studies that the alkylation of salts of dialkyl phosphorothioates with alkyl halides usually takes place at the sulfur atom [9, 10], although in individual cases the products of O-alkylation have been observed [11, 12].

The interaction of compound (7) with potassium O,O-dialkyl phosphorothioates was conducted in absolute dioxane in the presence of Cu_2Cl_2, since the reaction did not take place in the absence of a catalyst; raising the temperature to 100-105°C considerably increased the yield of desired products (to 81%); a general scheme of the reaction is given below:



Alk = CH_3 (8); n-C_3H_7 (9); n-C_4H_9 (10)

The apperance in the IR spectra of compounds (8)-10) (see Table 1) of intense bands in the 1270-1285 cm^{-1} region that were undoubtedly connected with the stretching vibrations of the P=O group, showed that the compounds obtained had the thiol structure, i.e., the reaction of emodin bromide with potassium dialkyl phosphorothioates took place at the sulfur atom as the more nucleophilic (polarized) end of the ambident triad, with the formation of the product of S-acylation. In the IR spectra of all the emodin phosphorothioates obtained bands were observed at 1000-1055 cm^{-1}, which may be assigned to P—O—C bonds, while absorption bands of a C—Br bond were absent.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR instrument, and PMR and ^{31}P NMR spectra on a Bruker MCL-400 spectrometer. Dialkyl phosphites were obtained by the procedure of [13], and dioxane dibromide as in [14]. The course of the reactions and the purity of the products were monitored with the aid of TLC on Silufol UV-254 plates in the chloroform—ether (1:1) system. The elemental analyses of all the compounds corresponded to the calculated figures.

6-Dimethoxyphosphinyloxy-1,8-dihydroxy-3-methylanthraquinone (2). A solution of 1.35 g ($5\cdot10^{-3}$ mole) of (1) in 80 ml of isopropyl alcohol was treated with 7.3 ml ($7.5\cdot10^{-2}$ mole) of CCl_4 and 0.7 ml ($5\cdot10^{-3}$ mole) of $(C_2H_5)_3N$. The reaction mixture was cooled to 0-5°C and gradually, dropwise, with stirring in an atmosphere of nitrogen, 1.8 g ($1.65\cdot10^{-2}$ mole) of dimethyl phosphite was added. Then the temperature was gradually raised to that of the room and was kept there until the end of the reaction (14 h). The mixture was filtered, and the mother solution was evaporated to small volume in water-pump vacuum. The concentrated solution was precipitated with HCl-acidified water, and the precipitate, containing product (2) and unchanged (1), was filtered off, washed with water to neutrality, and dried. To eliminate the (1), the reaction product was washed with ether and then with acetone until the washings were no longer colored. This gave 1.39 g (74%) of product (2), mp 271-273°C (DMSO).

6-Diethoxyphosphinyloxy-1,8-dihydroxy-3-methylanthraquinone (3). This was obtained in a similar way to (2) from 1.35 g ($5\cdot10^{-3}$ mole) of (1) in 80 ml of isopropyl alcohol, 7.3 ml ($7.5\cdot10^{-2}$ mole) of CCl_4, 0.7 ml ($5\cdot10^{-3}$ mole) of $(C_2H_5)_3N$, and 2.3 g ($1.65\cdot10^{-2}$ mole) of diethyl phosphite. Yield of (3) 1.58 g (78%), mp 281-282°C (DMSO).

6-Dipropoxyphosphinyloxy-1,8-dihydroxy-3-methylanthraquinone (4). This was obtained in a similar way to (2) from 1.35 g ($5\cdot10^{-3}$ mole) of (1) in 80 ml of isopropyl alcohol, 7.3 ml ($7.5\cdot10^{-2}$ mole) of CCl_4, 0.7 ml ($5\cdot10^{-3}$ mole) of $(C_2H_5)_3N$, and 2.7 g ($1.65\cdot10^{-2}$ mole) of dipropyl phosphite. Yield of (4) 1.67 g (77%), mp 289°C (decomp.) (DMSO).

6-Diisopropoxyphosphinyloxy-1,8-dihydroxy-3-methylanthraquinone (5). This was obtained in a similar way to (2) from 1.35 g ($5 \cdot 10^{-3}$ mole) of (1) in 80 ml of isopropyl alcohol, 7.3 ml ($7.5 \cdot 10^{-2}$ mole) of CCl_4, 0.7 ml ($5 \cdot 10^{-3}$ mole) of $(C_2H_5)_3N$, and 2.7 g ($1.65 \cdot 10^{-2}$ mole) of diisopropyl phosphite. Yield of (5) 1.94 g (85%), mp 295°C (decomp.) (DMSO).

6-Dibutoxyphosphinyloxy-1,8-dihydroxy-3-methylanthraquinone (6). This was obtained in a similar way to (2) from 1.35 g ($5 \cdot 10^{-3}$ mole) of (1) in 80 ml of isopropyl alcohol, 7.3 ml ($7.5 \cdot 10^{-2}$ mole) of CCl_4, 0.7 ml ($5 \cdot 10^{-3}$ mole) of $(C_2H_5)_3N$, and 3.5 g ($1.65 \cdot 10^{-2}$ mole) of dibutyl phosphite. Yield of (6) 1.84 g (85%), mp 303°C (decomp.).

7-Bromo-1,6,8-trihydroxy-3-methylanthraquinone (7). With stirring at 5°C, 0.125 g ($5 \cdot 10^{-4}$ mole) of dioxane dibromide was addd to a solution of 0.135 g ($5 \cdot 10^{-4}$ mole) of emodin in 50 ml of abs. ethyl ether. The precipiate of (7) that deposited was filtered off, washed with ether, and recrystallized from acetone. Yield 0.127 g (94%), R_f 0.66 (chloroform—acetone (9:1)), mp 262-264°C.

O,O-Dimethyl S-(1,6,8-Trihydroxy-3-methylanthraquinon-7-yl) Phosphorothioate (8). A solution of 0.9 g ($5 \cdot 10^{-3}$ mole) of potassium O,O-dimethyl phosphorothioate in 20 ml of abs. dioxane was added dropwise to 1.75 g ($5 \cdot 10^{-3}$ mole) of (7) and 0.5 g (5.10^{-3} mole) of Cu_2Cl_2 in 100 ml of abs. dioxane. The reaction mixture was heated to the boil for 12 h. After cooling, the precipitate that had deposited was filtered off, and the mother solution was concentrated and was treated with HCl-acidified water. The new precipitate that deposited was filtered off and combined with the first precipitate. The combined material was washed with saturated aqueous NH_4Cl solution until copper ions had been completely eliminated, and it was then washed with water and dried. The unchanged (7) was eliminated by treating the substance with a 3:1 mixture of acetone and dioxane. This gave 1.41 g (69%) of product (8), m,p 235-238°C (DMSO).

O,O-Dipropyl S-(1,6,8-Trihydroxy-3-methylanthraquinon-7-yl) Phosphorothioate (9). A solution of 1.2 g ($5 \cdot 10^{-3}$ mole) of potassium O,O-dipropyl phosphorothioate in 20 ml of dioxane was added dropwise to 1.75 g ($5 \cdot 10^{-3}$ mole) of (7) and 0.5 g (5.10^{-3} mole of Cu_2Cl_2 in 100 ml of abs. dioxane. The mixture was heated at the boil for 15 h, and, after working up as described for (8), 1.84 g (79%) of product (9) was obtained, with mp 252°C (decomp.) (DMSO).

O,O-Dibutyl S-(1,6,8-Trihydroxy-3-methylanthraquinon-7-yl) Phosphorothioate (10). A solution of 1.5 g ($5 \cdot 10^{-3}$ mole) of potassium O,O-dibutyl phosphorothioate in 20 ml of dioxane was added dropwise to 1.75 g ($5 \cdot 10^{-3}$ mole) of (7) and 0.5 g (5.10^{-3} mole) of Cu_2Cl_2 in 100 ml of abs. dioxane. The mixture was heated at the boil for 20 h, and, after working up as described for (8), 1.85 g (75%) of the phosphorothioate (10) was obtained, with mp 268°C (decomp.) (DMSO).

REFERENCES

1. S. S. Suleimanova, The Phosphorylation of Natural 4,5-Dihydroxy-2-methylanthraquinone (chrysophanol) and its Derivatives [in Russian], Author's absract of dissertaion ... Candidate of Chemical Sciences, Alma-Ata (n.d.).
2 R. A. Muzychkina, The Chemical Modification of Certain Hydroxyanthraquinones. A Search for Biologically Active Compounds [in Russian], Author's abstract of dissertation ... Doctor of Chemical Sciences.
3. F. R. Atherton, H. T. Howard, and A. R. Todd, J. Chem. Soc., 1106 (1948).
4. D. Purdela and R. Vilceanu, Chimia Compusilor Organici ai Fosorului si ai Acilizor Lui [The Chemistry of Organic Phosphorus Compounds and Their Acid Derivatives], Bucharest, Acad. Republicii Socialiste Romania [in Romanian], (1965) [Russian translation, Khimiya, Mocow (1972), p. 381].
5. M. V. Gorelik, The Chemistry of the Anthraquinones and their Derivatives [in Russian], Khimiya, Moscow (1983), p. 78.
6. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, NMR Spectroscopy in Organic Chemistry [in Russian], Leningrad (1983), p. 47.
7. V. A. Stikhin, A. I. Ban'kovskii, nd A. I. Borodin, The Search for and Chemical Study of Biologically Active Substances [in Russian], Izd-vo VILR, Moscow (1973), p. 110.
8. É. E. Nifant'ev, The Chemistry of Phosphorus Compounds [in Russian], Izd-vo MGU, Moscow (1972) p. 67.
9. P. S. Pishchimuka, Zh. Russ. Khim. Obshchestva, **44**, 1406 (1912).
10. M. I. Kabachnik and T. A. Mastryukova, Zh. Obshch. Khim., **25**, 1924 (1955).
11. N. I. Mel'nikov, Ya. A. Mandel'baum, and V. I. Lomakin, Zh. Obshch. Khim., **28**, 476 (1958).
12. M. I. Kabachnik, T. A. Mastryukova, N. P. Rodionova, and E. N. Popov, Zh. Obshch. Khim., **26**, 120 (1956).
13. E. N. Tsvetkov and M. I. Kabachnik, "The preparation of dialkyl phosphites," in: Reaktsii i Metody Isledovaniya Organicheskikh Soedinenii, **13**, 307 (1964).
14. L. A. Yanovskaya, A. P. Terent'ev, and L. I. Belen'kii, Zh. Obshch. Khim., **22**, 1594 (1952).