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REACTION OF DI-, AND TRIALKYL PHOSPHITES WITH ISATINS

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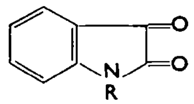
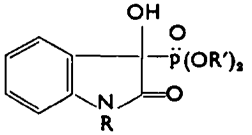
Abstract—Isatins (Ia–c) react with dialkyl phosphites to produce the corresponding dioxindole-3-phosphonic esters (IIa–i). 4:5-Benzocoumaran-2,3-dione (III), the oxygen analogue of 4:5-benzoisatin reacts similarly with diethyl phosphite giving the α-hydroxyphosphonate (IV). Trialkyl phosphites effect the conversion of the isatins (Ia–c) into colourless 2:1-adducts, believed to have structure similar to VII or the corresponding cyclic saturated oxyphosphorane (VIII). The IR and NMR spectra of the adducts are in favour of the proposed structures.

DIALKYL phosphites $(RO)_2P(O)H$ react with aldehydes or ketones[1] to yield dialkyl α-hydroxyphosphonates, and with a number of symmetrical halogenated quinones,[2] and 2-methyl-1,4-naphthaquinone[3] to give mono-dialkoxyphosphinyl derivatives of the corresponding hydroquinone. The scope of this reaction[4] between phosphite esters and suitable carbonyl systems has now been extended to include compounds of possible biological interest.



I

Ia, $R = H$
Ib, $R = CH_3$
Ic, $R = COCH_3$



II

IIa, $R = H$, $R' = CH_3$
IIb, $R = H$, $R' = C_2H_5$
IIc, $R = H$, $R' = C_3H_7$-i
IId, $R = R' = CH_3$
IIe, $R = CH_3$, $R' = C_2H_5$
IIf, $R = CH_3$, $R' = C_3H_7$-i
IIg, $R = COCH_3$, $R' = CH_3$
IIh, $R = COCH_3$, $R' = C_2H_5$
IIi, $R = COCH_3$, $R' = C_3H_7$-i

In isatin (Ia), regarded as the lactam of *o*-aminobenzoylformic acid, both the amide and keto carbonyl functions appear in the reactions of the molecule. Although the α-carbonyl is part of an amide grouping, and as such does not enter into the usual reactions of a ketone function, there are cases in which isatin behaves as an α-dicarbonyl compound, with both groups taking part in a reaction.[5]

We have found that dialkyl phosphites, namely, dimethyl, diethyl and diisopropyl phosphite react with isatin (Ia), N-methylisatin (Ib) and/or N-acetylisatin (Ic) in

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[1] W. F. Barthel, P. A. Giang and S. A. Hall, *J. Amer. Chem. Soc.* **76**, 4186 (1954); F. Ramirez, H. Yamanaka and O. H. Basedow, *Ibid.* **83**, 173 (1961).

[2] E. Diefenbach, G.P. 937 956 (1956); F. Ramirez and S. Dershowitz, *J. Org. Chem.* **22**, 1282 (1957).

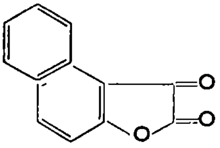
[3] K. J. M. Andrews and F. R. Atherton, *J. Chem. Soc.* 4682 (1960).

[4] A. Mustafa, M. M. Sidky and M. R. Mahran, *Liebegs Ann.* in press.

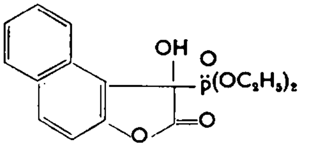
[5] W. C. Sumpter and F. M. Miller, *The Chemistry of Heterocyclic Compounds. A series of Monographs* Edited by A. Weissberger *Heterocyclic Compounds with Indole and Carbazole Systems*, pp. 121–130. Interscience, New York (1954), W. C. Sumpter, *Chem. Revs.* **34**, 393 (1944).

presence or absence of a solvent. In each case only one pure colourless crystalline product was isolated, presumably the corresponding α-hydroxyphosphonate (cf. II). Thus, a phosphorus–carbon bond is established in this reaction with the formation of a 1 : 1-adduct. The reactivity of the C-3 carbonyl group in isatins (Ia–c) towards the action of dialkyl phosphites is in accord with their behaviour towards the action of mercaptans,[6] and active hydrogen containing compounds[7] leading in all cases to dioxindole derivatives.

The similarity of formation of the adducts IIa–i suggests that they are of analogous constitution. In favour of the proposed structure, taking IIe as an example, are the following: (1) Elemental analysis and mol. wt. determination agree with the formula $C_{13}H_{18}NO_6P$. (2) The IR spectrum of IIe in KBr shows bands at 1708 cm^{-1} (5-membered lactam); 1602 cm^{-1} (aromatic band); 1225 cm^{-1} (bonded phosphate $\geqslant P \rightarrow 0$) and 1152 cm^{-1} ($P\text{–}O\text{–}C_2H_5$); in chloroform, absorption bands were at 3530 cm^{-1} (OH, hydrogen bonded); 1720 cm^{-1} (5-membered lactam) and at 1612 cm^{-1} (aromatic band). (3) The NMR spectrum of IIe shows the presence of four aromatic protons as a multiplet at 2·20–3·20 τ, four methylene protons of the ethoxy groups as a quartet (J = 9 c/s) at 5·84 τ, three protons of the N-methyl as a singlet at 6·79 τ and six methyl protons of the ethyl ester residue as a triplet (J = 9 c/s) at 8·68 τ. The signal for the OH-proton is hidden by the last peak of the triplet at 8·68 τ because the intensity decreases on the addition of trifluoroacetic acid. (4) Compound IIe on heating, regenerates N methylisatin and diethyl phosphite. The carbon-phosphorus bond in O,O-dialkyl-α-hydroxyphosphonates is known to cleave easily by the action of heat to regenerate the starting materials.[8]



III



IV

4:5-Benzocoumaran-2,3-dione (III), the oxygen analogue of 4:5-benzoisatin, reacts[9] similarly with diethyl phosphite to form IV. Unlike the parent compound (golden yellow in colour), the adduct IV is colourless. In favour of the proposed strucutre, IV gave the correct analytical results, and its mol. wt. corresponds to the monomeric formula. The IR spectrum in KBr shows a lactone band at 1806–1795 cm^{-1}, and a bonded phosphate $\geqslant P \rightarrow O$ band at 1245 cm^{-1}; in chloroform IV shows absorption at 3540 cm^{-1} (OH, hydrogen bonded) and at 1810 cm^{-1} (5-membered lactone ring). The other bands are too weak to be assigned; no doubt due to the limited solubility of IV in chloroform. Pyrolysis of the adduct IV results in the formation of 4:5-benzocoumaran-2,3-dione (III) and diethyl phosphite.

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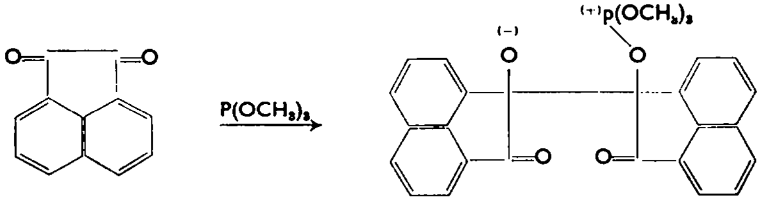
[6] A. Schönberg *et al.*, *Ber. Dtsch. Chem. Ges.* **60**, 2344 (1927).

[7] H. G. Lindwall *et al.*, *J. Amer. Chem. Soc.* **54**, 4739 (1932); **55**, 325 (1933); **56**, 2716 (1934); **57**, 207 (1935); **58**, 1236 (1936); **62**, 171 (1940).

[8] V. S. Abramov, L. P. Semenova and L. G. Semenova, *Dokl. Akad. Nauk, S.S.S.R.* **84**, 281 (1952).

[9] Compare the reactivity of the 3-ketonic group in coumaran-2,3-dione towards the usual carbonyl reagents, R. C. Elderfield, *Heterocyclic Compounds* Vol. II, p. 40. J. Wiley, New York (1951).

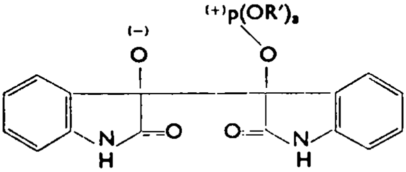
Trialkyl phosphites react with α-diketones, and with *o*-quinones to form 1:1-adducts[10] having a cyclic unsaturated oxyphosphorane structure.[11] On the other hand, acenaphthenequinone (V) gives a 2:1-adduct (VI)[12] on reaction with trimethyl phosphite.



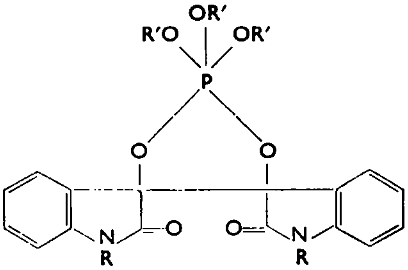
V

VI

The analogy between isatins (Ia–c) and α-dicarbonyl compounds[5] prompted the investigation into their reaction with tertiary phosphite esters. Thus, whereas isatin (Ia), does not react with triphenyl phosphine[13] in boiling benzene, it reacts readily with trialkyl phosphites, e.g., trimethyl, triethyl and/or triisopropyl phosphite at room temperature to yield colourless 2:1-adducts believed to have a structure similar to VII or the corresponding cyclic saturated oxyphosphorane (VIII). This reaction is similar to that between acenaphthenequinone and trimethyl phosphite forming a phosphorus–oxygen bond.[12]



VII, R' = Alkyl

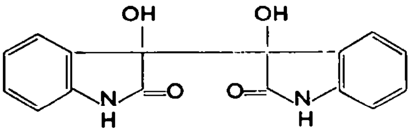


VIII

VIII a, $R = H$, $R' = CH_3$
b, $R = H$, $R' = C_2H_5$
c, $R = H$, $R' = C_3H_7\text{-i}$

d, $R = CH_3$, $R' = CH_3$
e, $R = CH_3$, $R' = C_2H_5$
f, $R = CH_3$, $R' = C_3H_7\text{-i}$

g, $R = COCH_3$, $R' = CH_3$
h, $R = COCH_3$, $R' = C_2H_5$
i, $R = COCH_3$, $R' = C_3H_7\text{-i}$



IX

This is in contrast to the formation of a phosphorus–carbon bond in the case of dialkyl phosphites with isatin and its N-substituted derivatives. In other words, the

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[10] V. A. Kukhtin, *Dokl. Akad. Nauk, S.S.S.R.* 121, 466–9 (1958). *Chem. Abstr.* 53, 1105 (1959); G. H. Birum and J. L. Dever, U.S. Pat. 2961 455 (1960); through *Chem. Abstr.* 55, 8292 (1961).

[11] F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.* 85, 3252 (1963); F. Ramirez, N. Ramanathan and N. B. Desai, *Ibid.* 85, 3465 (1963).

[12] F. Ramirez and N. Ramanathan, *J. Org. Chem.* 26, 3041 (1961).

[13] cf. the ready reaction of triphenyl phosphine with quinones; F. Ramirez and S. Dershowitz, *Chem. & Ind.* 665 (1956); *J. Amer. Chem. Soc.* 78, 5614 (1956).

carbon–carbon condensation is induced by the reducing action of the tertiary phosphite esters on isatin and related derivatives. Similarly, trialkyl phosphites react with N-mehtyl- and N-acetylisatin to yield the corresponding 2:1-adducts (VIIId–i).

The crystalline colourless adducts (VIIIa–i) gave the correct analytical values (cf. Table 1). Mol. wt. determination by the osmometric method indicates the interaction of two molecules of isatin; on the other hand marked decomposition has been observed in camphor (Rast method). Active hydrogen determinations for adducts VIIIa–c illustrate the presence of two active hydrogen atoms. The IR and NMR spectral data reveal that the 2:1-adducts have a cyclic saturated oxyphosphorane structure (compare VIII), in which five oxygen atoms are covalently bound to phosphorus. The IR spectrum of VIIIb, taken as an example, in Nujol shows bands at 3240 cm^{-1} (N–H band); 1755 cm^{-1} (5-membered lactam); 1615 cm^{-1} aromatic band); 1160 cm^{-1} (P–O–C_2H_5); in chloroform there is no marked difference in the spectrum. Information derived from the IR absorption spectra of compounds VIIIb, c and h shows no enolate bands, moreover, the absorption spectra of these compounds lack the C-3 carbonyl band appearing at 1745 cm^{-1} (as a shoulder),* 1785 cm^{-1} (as a shoulder)† and at 1820† cm^{-1} in the parent compounds Ia, Ib and Ic respectively.

The NMR spectrum of the adduct VIIIb shows the presence of 8 aromatic protons as a multiplet at 2·50–3·54 τ in addition to the amide proton as a singlet at 2·02 τ, 6 methylene protons of the ethoxyl groups as a multiplet at 5·57–6·18 τ and 9 methyl protons of the ethyl ester groups as a multiplet at 8·51–8·89 τ. The NMR spectrum of the adduct is compatible with the oxyphosphorane structure VIII and possibly favours it over the open dipolar structure VII. The latter could not be completely excluded and may exist in equilibrium with the cyclic form. Moreover, the ready formation of isatyde (IX) from VIIIb upon treatment with zinc and acetic acid in alcohol may be taken in favour of the proposed structure.

EXPERIMENTAL

All m.ps are uncorrected. The trialkyl phosphites were purified by treatment with Na followed by fractional distillation. Moisture and O_2 must be avoided in making and handling the adducts. The IR spectra were taken in a Perkin–Elmer 137 spectrophotometer. The NMR spectra were run on a Varian A-60 spectrometer, in $CDCl_3$ solution, using tetramethylsilane as internal standard.

Dialkyl phosphite adducts (IIa–i and IV). A mixture of the keto compound (0·01 mole) an dialkyl phosphite[14] (0·012 mole) in dry benzene (25 ml) was refluxed under N_2 for 12 hr. After removal of the volatile materials under red. press., the oily residue was washed several times with pet. ether (b.p. 40–60°). The solid product, thus obtained, was crystallized from an appropriate solvent. Similar results were obtained by carrying out the same reaction in acetonitrile or in absence of solvent. Yields, physical and analytical data are given in Table 1.

Thermal decomposition of the adduct IIe. Compound IIe (1 g) was heated (bath temp 100°; 1 hr) under red. press. (5 mm) in an apparatus similar to that employed for vacuum distillation (using a Liebeg condenser) but without a capillary tube, the receiver being immersed in an ice-salt mixture. The reaction vessel was left to cool and small amounts of EtOH added. The crystals which separated were crystallized from EtOH and proved to be N-methylisatin[15] (m.p., mixed m.p.) and the indophenine

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* In Nujol.

† In KBr

[14] For the preparation of dimethyl, diethyl and diisopropyl phosphite, see, H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.* 380 (1945); B. A. Arbuzov, V. S. Vinogradova, Izvestiya *Akad. Nauk. S.S.S.R.* o. kh. n. 617 (1947); *Dokl. Akad. Nauk S.S.S.R.* **55**, 31 (1947).

[15] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).

TABLE 1. ADDUCTS FROM THE REACTION OF DI-, AND TRIALKYL PHOSPHITES WITH ISATIN AND ITS ANALOGOUS COMPOUNDS

Adducts	Yield %	M.P.	Found (%)*					Formula	Required %				
			C	H	N	P	Mol. wt.†		C	H	N	P	Mol. wt.
IIa	72	182–184°[a]	46·54	4·77	5·38	11·97	—	$C_{10}H_{12}NO_5P$	46·70	4·70	5·44	12·04	257·19
IIb	85	161–162°[b]	50·36	5·45	5·07	10·9	280	$C_{12}H_{16}NO_5P$	50·52	5·65	4·91	10·86	285·24
IIc	80	158–160°[b]	53·39	6·33	4·58	10·06	—	$C_{14}H_{20}NO_5P$	53·67	6·43	4·47	9·88	313·30
IId[e]	75	184–186°[c]	48·61	5·09	5·19	11·37	—	$C_{11}H_{14}NO_5P$	48·71	5·20	5·16	11·42	271·22
IIe	62	125–127°[d]	52·06	6·06	—	10·21	311	$C_{13}H_{18}NO_5P$	52·17	6·06	4·68	10·35	299·27
IIf	70	132–133°[d]	54·94	6·70	4·29	9·37	—	$C_{15}H_{22}NO_5P$	55·04	6·77	4·28	9·46	327·32
IIg	80	173–175°[b]	47·95	4·86	4·72	10·16	—	$C_{12}H_{14}NO_6P$	48·16	4·71	4·68	10·35	299·23
IIh	82	145–147°[d]	51·30	5·64	4·26	9·50	—	$C_{14}H_{18}NO_6P$	51·37	5·54	4·28	9·46	327·28
IIi	69	140–142°[d]	53·99	6·16	3·89	8·76	—	$C_{16}H_{22}NO_6P$	54·08	6·24	3·94	8·71	355·34
IV	60	154–156°[b]	57·28	5·16	—	9·31	330	$C_{16}H_{17}O_6P$	57·14	5·09	—	9·21	336·29
VIIIa	92	122–124°[b]	54·68	4·61	6·39	7·34	—	$C_{19}H_{19}N_2O_7P$	54·54	4·57	6·69	7·40	418·35
VIIIb[f]	90	115–117°[b]	57·44	5·57	5·86	6·59	474	$C_{22}H_{25}N_2O_7P$	57·38	5·47	6·08	6·72	460·43
VIIIc	90	103–105°[d]	59·55	6·24	5·51	5·86	514	$C_{25}H_{31}N_2O_7P$	59·75	6·21	5·57	6·16	502·51
VIIId	50	145–147°[d]	56·34	5·09	6·42	6·76	458	$C_{21}H_{23}N_2O_7P$	56·50	5·19	6·27	6·93	446.41
VIIIe	62	138–140°[d]	58·89	5·90	6·00	6·02	—	$C_{24}H_{29}N_2O_7P$	59·01	5·98	5·73	6·13	488·49
VIIIf	60	143–145°[d]	61·25	6·45	5·30	6·09	517	$C_{27}H_{35}N_2O_7P$	61·12	6·64	5·28	5·83	530·57
VIIIg	65	143–145°[b]	54·75	4·41	5·67	6·13	503	$C_{23}H_{23}N_2O_9P$	54·98	4·61	5·57	6·16	502·43
VIIIh[g]	62	125–127°[d]	57·34	5·30	5·22	5·86	525	$C_{26}H_{29}N_2O_9P$	57·34	5·37	5·14	5·68	544·51
VIIIi	50	158–160°[d]	59·34	6·04	4·66	5·21	578	$C_{29}H_{35}N_2O_9P$	59·37	6·01	4·77	5·28	586·59

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* Microanalysis has been carried out in "Mikroanalytisches Laboratorium 'Beller' Gottingen, W. Germany".

† Mol. wt. has been determined by the osmometric method in $CHCl_3$.

[a] Crystallized from EtOH–benzene.

[b] Xylene was used as solvent for crystallization.

[c] Crystallized from $CHCl_3$/pet. ether (b.p. 40–60°).

[d] Solvent of crystallization was benzene–pet. ether (b.p. 40–60°).

[e] OCH_3 group, Found 22·56; Required 22·88.

[f] Active hydrogen, Found 0·48; Required 0·43; OC_2H_5 group, Found 29·03; Required 29·35.

[g] OC_2H_5 group, Found 25·02; Required 24·82.

reaction[16] upon treatment with thiophene and sulphuric acid. Drops were formed in the receiver and the violet colour reaction recently described[17] for dialky phosphites with 3,5-dinitrobenzoic acid in presence of alkali was obtained.

Pyrolysis of adduct IV. Similar thermal decomposition (bath temp 200°) of this compound under red. press. (5 mm) for 2 hr afforded III[18] (identified by m.p. and mixed m.p.). Diethyl phosphite was detected in the receiver as in the case of IIe.

Trialkyl phosphite adducts (VIIIa–i). Trialkyl phosphite[19] (0·012 mole) was added to a cooled suspension of the keto-derivative (0·01 mole) in dry benzene (30 ml) under N_2 with stirring. The reaction mixture was kept at room temp for 8 hr then filtered off (in case of Ia) otherwise, treated with pet. ether (b.p. 40–60°). The solid product so obtained was crystallized from the appropriate solvent (cf. Table 1). The solid adducts, almost colourless in colour, are quite stable when kept under dry N_2 or in a vacuum in a cool place (ice-chest). They are extremely sensitive to moisture, air and heat.

Attempted reaction of isatin (Ia) *with triphenyl phosphine.* A mixture of isatin (1·4 g), triphenyl phosphine (2·6 g) and dry benzene (25 ml) was boiled under reflux for 12 hr in a N_2 atmosphere. After cooling, the resulting precipitate was collected and proved to be unchanged isatin (1·3 g) by m.p. and mixed m.p. From the filtrate, triphenyl phosphine[20] was recovered unchanged (m.p. and mixed m.p.) in an almost quantitative yield.

Action of zinc and acetic acid on VIIIc. Compound VIIIc (2 g) dissolved in a mixture of absolute EtOH (60 ml) and glacial acetic acid (5 ml) was treated portionwise under good stirring with Zn powder (4 g) during ½ hr. After removing of the inorganic material by filtration, water (ca. 50 ml) was added to the filtrate and the mixture kept for 48 hr. The precipitate obtained was washed with water and crystallized from EtOH to give IX (ca. 0·4 g). A mixed m.p. with authentic isatyde (IX)[21] was not depressed.

Acknowledgment—We are grateful to Dr. H. Reinshagen of Institut für Organische Chemie der Technischen Hochschule, Darstadt, W. Germany for valuable instruction in IR and NMR spectroscopy.

[16] V. Meyer, *Ber. Dtsch. Chem. Ges.* **16**, 1465, 2973 (1883).

[17] B. C. Saunders and B. P. Stark, *Tetrahedron* **4**, 197 (1958).

[18] K. Fries and R. Frellstedt, *Ber. Dtsch. Chem. Ges.* **54**, 719 (1921).

[19] For the preparation of trimethyl, triethyl and triisopropyl phosphite, see B. A. Arbuzov and K. V. Nikonov, *Zh. Obsh. Khim.* **17**, 2139 (1947).

[20] J. Dodonow and H. Medox, *Ber. Dtsch. Chem. Ges.* **61**, 907 (1928).

[21] G. Heller, *Ber. Dtsch. Chem. Ges.* **37**, 938 (1904).