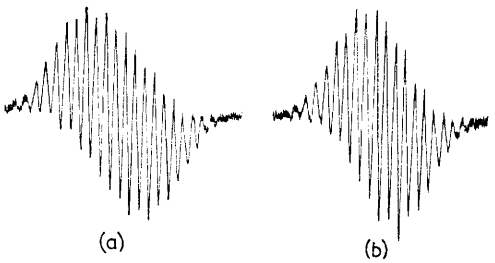
937. *Derivatives of 4-(Dihydroxyphosphinyloxy)phenyldiphenylmethane and a Related Free Radical*

By C. W. F. McClare and F. Wild

Some of the biological actions of *X*-rays can be increased by the presence of oxygen or of nitric oxide, and it has been suggested [1,2] that this is partly due to their paramagnetic character. It was decided therefore, as part of an investigation into possible radiosensitisers,[1] to synthesise a water-soluble free radical, which might thereby have some clinical value. During the attempted synthesis of the disodium salt of 4-(dihydroxyphosphinyloxy)-α,α-diphenylbenzyl, a previously unreported triphenylmethyl radical and a novel phosphorylation have been discovered and are here reported.

All practicable routes to the above free radical were through 4-(dihydroxyphosphinyloxy)phenyldiphenylmethane. The phosphate moiety had to be protected, and acetylation was chosen since the acetyl group could subsequently be removed in mild alkali. The acetyl derivative reacted with *N*-bromosuccinimide to give a labile oil, which could not be crystallised, and which readily developed a deep red colour owing to the formation of diphenylquinomethane. The properties of this oil were consistent with its main constituent's being the expected 4-(diacetoxyphosphinyloxy)phenyldiphenylbromomethane. Thus in



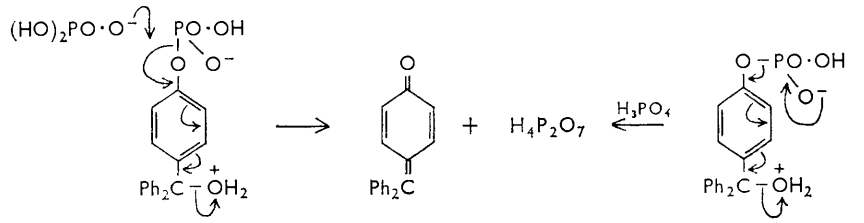
E.p.r. spectra of (*a*) triphenylmethyl, (*b*) reaction-product.

solution in benzene it reacted with silver powder to give a solution which absorbed oxygen, and which gave an electron paramagnetic resonance (e.p.r.) spectrum, due presumably to the free radical 4-(diacetoxyphosphinyloxy)-αα-diphenylbenzyl, in an inert atmosphere. This spectrum, which could only be obtained at low resolution, has two lines fewer than that of triphenylmethyl, as would qualitatively be expected of a triphenylmethyl with one less *para* hydrogen atom, and it is compared in the Figure with a low-resolution spectrum of triphenylmethyl.

The decomposition of the bromination product into diphenylquinomethane is also consistent with the structure formulated and, since it appeared to have analogies with the oxidative hydrolysis of quinol monophosphate,[3] its possible phosphorylating action was investigated. After removing the acetyl groups by hydrolysis (which would also be expected to hydrolyse the bromo-group to hydroxyl) we treated the product with phosphate ions in acid solution. Under these conditions a precipitate of diphenylquinomethane formed and pyrophosphate ions, together with traces of polyphosphate, were detectable in the supernatant solution. The mechanism of this reaction probably involves a protonation of the α-hydroxyl group, followed either by attack by orthophosphate ion or by unimolecular elimination of the phosphate moiety as the hypothetical metaphosphate ion.[4] However the kinetics of this reaction have not been investigated.

Thus, although complete characterisation of the bromo-compound or of the free radical was not effected, these properties are consistent with the formulation given.

[1] Mitchell, "Studies in Radiotherapeutics," Blackwell, London, 1960, p. 160.
[2] Powers, Webb, and Ehret, *Radiation Research, Suppl.* 2, "Bioenergetics," p. 115; Mason, *ibid.*, p. 455.
[3] Clark, Hutchinson, Kirby, and Todd, *J.*, 1961, 715.
[4] Butcher and Westheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 2420.



Experimental.—**4-(*Dihydroxyphosphinyloxy*)*phenyldiphenylmethane.*** 4-Hydroxyphenyldiphenylmethane [5] (m. p. 110°) (38 g., 0·15 mol.) was mixed with 1 equiv. of potassium hydroxide (8·25 g.) in methanol (100 c.c.), the mixture evaporated, and thoroughly dried. Dibenzyl phosphorochloridate [6] (0·16 mol.) was prepared from dibenzyl phosphite [7] (43 g., 0·16 mol.) and *N*-chlorosuccinimide (21·9 g., 0·16 mol.) in dry chloroform (300 c.c.). This solution was filtered into the above phenoxide and stirred, with cooling for 2 hr., and then overnight at room temperature. The resulting homogeneous solution was washed with aqueous alkali, dilute acid, and water (twice) and dried (Na_2SO_4). An uncrystallisable oil (80 g.) was obtained on evaporation, a portion (30 g.) of which was dissolved in rectified spirit (100 c.c.) and refluxed for 1 hr. with 5% palladium–charcoal (1 g.). The filtered solution was then diluted with water (10 c.c.) and hydrogenated with a palladium oxide catalyst. The hydrogenation was usually complete in 6 hr., although in some preparations an inhibition (probably due to traces of dibenzyl phosphite) was observed. The filtered solution was then evaporated and dried azeotropically with toluene. On standing the resulting oil in toluene, it crystallised and could be recrystallised from toluene as lustrous plates (13 g., 65%) of **4-(*dihydroxyphosphinyloxy*)*phenyldiphenylmethane***, m. p. 172° (Found: C, 67·2; H, 4·6%; Equiv., 359·2 and 170·5. $C_{19}H_{17}O_4P$ requires C, 67·0; H, 5·0%; Equiv., 340·2 and 170·1).

Acetylation and reaction with N-*bromosuccinimide.* A portion (*ca.* 3 g.) of the 4-(dihydroxyphosphinyloxy)phenyldiphenylmethane was dissolved in ethanol (5 c.c.) and 5% ethanolic sodium hydroxide added until the solution became alkaline. After leaving at −20° overnight crystals were precipitated, which were separated, washed with ethanol (50 c.c.), and dissolved in water (5 c.c.). On treating the solution with a small excess of aqueous silver nitrate, a white precipitate formed which was separated, washed with water, and dried at 80° and finally *in vacuo*. The silver salt was covered with dry ether in a sintered-glass filter and freshly-distilled acetyl chloride was added in small portions. The reaction was rapid and, after brief stirring, the solution was filtered into a dry flask. The residue was washed with more acetyl chloride and the combined filtrates (20 c.c.) evaporated to dryness *in vacuo* at room temperature, to give a yellow, labile oil. The product contained a trace of acid which interfered with the subsequent reaction and was effectively removed by treating it, in benzene, with sodium wire. Evaporation of the benzene left a light yellow oil, which would not crystallise, but reacted with water to give 4-(dihydroxyphosphinyloxy)phenyldiphenylmethane in high yield (m. p. 172°, undepressed on admixture with authentic sample). A portion of the oil (0·86 g., 2·0 mmole) was refluxed with *N*-bromosuccinimide in dry benzene (10 c.c.) for 1 hr. to give an orange solution, together with a precipitate of succinimide. The filtered solution was evaporated at low temperature *in vacuo* to give an orange oil, which would not crystallise.

Properties of the bromination product. (*a*) On heating the oil its colour deepened considerably and, by taking the spectrum of a benzene solution of the product, this was found to be due to the development of a peak at 380 mμ. Diphenylquinomethane in benzene has a peak at 370 mμ, and it was assumed that the displacement to lower frequency was due to the presence of bromodiphenylquinomethanes formed also during the bromination. (*b*) In concentrated sulphuric acid hydrogen bromide was evolved and the intense yellow, characteristic of trityl cations, developed. (*c*) A solution of the oil (1·0 g.) in benzene (50 c.c.) was equilibrated with oxygen in a gas-burette, before tipping mercury (*ca.* 1 g.) into it from a side-arm. On being shaken, the solution absorbed 10 c.c. of oxygen. This is 45% (±10%) of the volume calculated for complete reaction. (*d*) A 5% solution of the oil in dry benzene in a Pyrex tube (2 mm. bore and 20 cm. long) was frozen in liquid nitrogen and silver powder was added. The air in the tube was replaced with nitrogen and the tube sealed rapidly whilst being evacuated. The tube was then shaken

[5] Van Alphven, *Rec. Trav. chim.*, 1927, **46**, 799.
[6] Kenner, Todd, and Weymouth, *J.*, 1952, 3678.
[7] Atherton, Openshaw, and Todd, *J.*, 1945, 384.

at room temperature for 1 hr. No colour-change could be detected, but in a Varian 100 kc./sec. electron paramagnetic resonance spectrometer a signal with a *g*-value of 2·0 could be detected. This is shown in the Figure. In some experiments very little signal could be detected, but the cause of this was not understood.

The formation of pyrophosphate. A portion of the bromination-product was dissolved in dilute aqueous sodium hydroxide to give a light yellow solution, from which a yellow uncrystallisable oil was obtained on evaporation. A portion of the solution was treated with enough monosodium orthophosphate (AnalaR, free from pyrophosphate) to make it acid. A yellow precipitate developed slowly and after 1 hr. a few drops of 1 : 1 hydrochloric acid were added. A little of the clear supernatant solution was then spotted on Whatman No. 3 paper and, after allowing it to dry at room temperature, it was developed with methanol–formic acid–water (80 : 15 : 5 v/v/v). The paper was then dried, and treated with molybdate reagent, whereupon a small blue spot, which was behind the orthophosphate spot and ran parallel with a marker of pyrophosphate, was observed, as well as some slower trace spots probably due to polyphosphates. Another portion of the solution gave a yellow-orange precipitate with acid which was subjected to thin-layer chromatography on silica-gel. This revealed the presence of several yellow compounds, one of which had the same R_F (with benzene–glacial acetic acid 10 : 1 v/v) as diphenylquinomethane. The compound was extracted from the silica-gel and its spectrum recorded in concentrated AnalaR sulphuric acid. This was identical with that of authentic diphenylquinomethane. The other yellow products showed similar spectra in sulphuric acid, and were probably bromodiphenylquinomethanes.

A Medical Research Council grant (for C. W. F. McC.) is gratefully acknowledged.

Department of Radiotherapeutics, The University, Cambridge.

[Present address (C. W. F. McC.): Department of Biophysics, King's College, 26—29 Drury Lane, London W.C.2.] [*Received, June 20th,* 1963.]