Triphenylphosphonium-Alloxan Betaines

*William E. Adams and Ned D. Heindel**

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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Alloxan and 1,3-dimethylalloxan react with triarylphosphines to generate zwitterionic adducts involving the phosphorus and the C-5 carbonyl oxygen atoms of alloxan. The adducts, unlike alloxan, did not induce permanent hyperglycemia but one analog did effect a transient rise in blood glucose.

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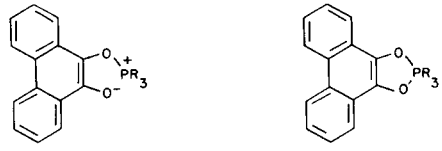
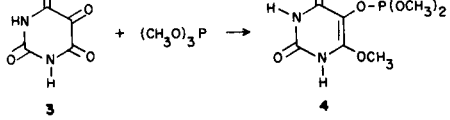
The reaction of *p*-quinoid compounds with triphenylphosphine has been a fruitful area for structural and mechanistic studies (1,2,3). Phenanthraquinone has been shown to react with triphenyl phosphite (4) or with triphenylphosphine (5) to generate 1:1 adducts variously



1 R = $-OC_6H_5$ (4) R = $-C_6H_5$ (5) **2**

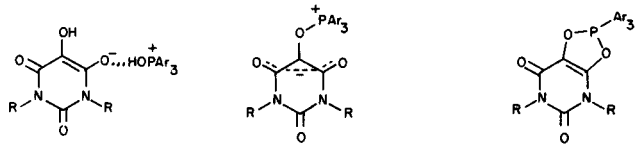
formulated as zwitterions (**1**) or as 1,3,2-dioxaphospholenes (**2**) with the latter formulation generally preferred. A vicinal carbonyl heterocycle, alloxan, has been reacted with trimethyl phosphite to yield 5-hydroxy-6-methoxyuracil 5-dimethylphosphate (**4**) but no studies have appeared on the alloxan-triarylphosphine reaction (6).



3 **4**

Our previous studies in hyper- and hypoglycemic compounds with potential for pancreatic uptake as candidate radiopharmaceuticals (7,8,9), have encouraged our interest in alloxan derivatives with pendant aryl rings as a vehicle for attachment of radioiodine. Alloxan is known to induce frank diabetes by *beta*-cell degranulation (10) and autoradiographic studies of rat pancreata have shown a higher concentration of C-14 alloxan in the islet cells than in the acinar tissue (11). If incorporation of triarylphosphines into the alloxan nucleus yielded compounds with pancreatic effects, the radioiodinated analogs might be useful *beta*-cell tumor imaging agents.

Alloxan or 1,3-dimethylalloxan reacted readily with triarylphosphines in refluxing ethanol to product 69 to 98% yields of 1:1 adducts for which several formulations would find precedent as plausible structural assignments. A redox process between the triarylphosphine and the



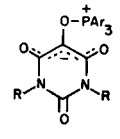
5 **6** **7**

alloxan hydrate could yield a 5-hydroxybarbituric acid-triphenylphosphine oxide salt (**5**). Such a structure would involve the acid's most acidic hydrogen (12) in a proton bridge with the oxide, such as has been suggested for sulfonamide N-H and the phenolic O-H hydrogen atoms, with phosphine oxides (3,13). Intense P-O stretching absorptions (at 1190-1160 cm^{-1}) in the 1:1 adducts obtained herein might be cited as support for such salt-like compounds, but the elemental analysis eliminated that formulation since all of the adducts analyzed for one less molecule of water. A 2,2,2-triaryl-1,3,2-dioxaphospholene (**7**) remains a possibility as does a phosphonium betaine (**6**).

The 1,3,2-dioxaphospholene structure, however, requires a nonequivalence for the methyl signals in the pmr of 1,3-dimethylalloxan adducts since the two *N*-methyl moieties would lie in different environments. A single sharp resonance for these *N*-methyl groups at δ 3.19 and δ 3.15 in adducts of 1,3-dimethylalloxan with triphenylphosphine and tri-*o*-tolylphosphine, respectively, would appear to exclude the ring structure from serious consideration.

Table I

Carbonyl Frequencies of Betaines



Compound	Ar	R	C=O (cm^{-1})
6a	C_6H_5	H	1675, 1650, 1600
6b	p-$CH_3C_6H_4$	H	1690, 1660, 1590
6c	p-$CH_3OC_6H_4$	H	1695, 1655, 1590
6d	m-$CH_3C_6H_4$	H	1655, 1610, 1590
6e	C_6H_5	CH_3	1680, and 1630-1600
6f	p-$CH_3C_6H_4$	CH_3	1690, and 1625-1585

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Table II

Spectral Literature Models Supporting a Betaine Rather Than a Phospholene Structure for Alloxan-Triarylphosphine Adducts

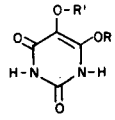
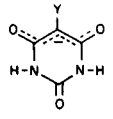
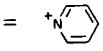
Compound	Substituents	C=O (Cm^{-1})	Literature References
	R′ = H, R = H	1710, 1650, 1630	14
	R′ = $PO(OCH_3)_2$, R = CH_3	1715, 1681, 1658	6
	R′ = $PO(OCH_3)_2$, R = H	1730, 1667, 1618	6
8	R′ = $CHPhPO(OCH_3)_2$, R = CH_3	1750, 1670, 1620	16
	Y = $\dot{I}Ph$	1712, 1590	17
	Y = 	1708, 1585, 1562	17
	Y = $^{+}S(CH_3)_2$	1713, 1592	18
9	Y = $CHPh\overset{+}{P}(OCH_3)_3$	1695, 1578	16

Table III

Triarylphosphine-Alloxan Adducts

Compound	Yield	M.p. °C	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
6a	98%	200-201°	$C_{22}H_{17}N_2O_4P$	65.34	4.24	6.93	65.11	4.24	6.93
6b	90%	189-190	$C_{25}H_{23}N_2O_4P \cdot \frac{1}{2}H_2O$	65.93	5.31	6.15	66.21	5.21	6.03
6c	95%	183-184	$C_{25}H_{23}N_2O_7P \cdot \frac{1}{4}H_2O$	60.18	4.75	5.61	59.97	4.53	5.62
6d	69%	180-181	$C_{25}H_{23}N_2O_4P$	67.26	5.19	6.27	66.98	5.23	6.21
6e	71% (a)	150-151	$C_{24}H_{21}N_2O_4P \cdot \frac{1}{2}H_2O$	65.30	5.02	6.35	65.60	4.98	6.48
6f	77% (b)	140-141	$C_{27}H_{27}N_2O_4P$	68.34	5.74	5.91	68.64	5.76	5.87

(a) This reaction was carried out in chloroform; the product isolated by precipitation with petroleum ether (60-110°). (b) This reaction was carried out in benzene; the product precipitated upon concentration to reduced volume and cooling.

Additional support for the betaine structure can be found in an analysis of the C=O stretching absorptions in the infrared. Alloxan hydrate (1740 and 1695 cm^{-1}), alloxan anhydride (1760, 1695 cm^{-1}), and 1,3-dimethylalloxan (1765, and 1690 cm^{-1}) all displayed carbonyl stretch modes at higher energy than these adducts of triarylphosphines which possessed strong absorptions between 1695 and 1590 cm^{-1} (Table I). Such a shift to lower energies in the adducts would be consistent with a lowered bond order for the C=O as expected in the delocalized betaine anion or similarly in the extensively conjugated 1,3,2-dioxaphospholenes. A reasonable structural approximation of the dioxaphospholenes (**7**) would be the barbituric acid analogs (**8**) (Table II). Similarly, models for the proposed phosphonium betaine structure (**6**) would be the dipolar barbituric acid derivatives (**9**) prepared by Russian investigators. The observed spectra for our adducts displayed their major C=O absorption modes at considerably lower frequencies than the oxybarbituric acid models and in closer agreement to the dipolar barbituryl analogs.

There is an obvious steric inhibition to formation of the phosphonium betaines. The presence of *ortho*-methyl groups in the phosphine (*i.e.*, tri-*o*-tolylphosphine) apparently prevented adduct formation with alloxan because no betaine was detectable even upon prolonged contact. Similarly, the 1,3-dimethylalloxan gave lower yields with triphenyl and tri-*p*-tolylphosphine (than did alloxan) and gave no adduct at all on attempted condensation with tri-(*p*-methoxyphenyl)phosphine and tri-(*m*-tolylphenyl)phosphine. Alloxan, either as its hydrate in refluxing ethanol or as its anhydride in ethanol or in anhydrous tetrahydrofuran, gave the identical adducts in comparable yields from the triarylphosphines. Although the uv spectra of alloxan and alloxan hydrate were somewhat different upon instantaneous recording after dissolution in ethanol,

they rapidly equilibrated to the same spectrum, a spectrum characteristic of 5-ethoxy-5-hydroxybarbituric acid. The latter compound was isolated in 70% yield by agitation of magnesium sulfate with an ethanol solution of alloxan hydrate. Any, or all, of the pyrimidine derivatives (alloxan, alloxan hydrate, or 5-ethoxy-5-hydroxybarbituric acid) would be plausible precursors of the betaine adducts under the reaction conditions employed with triarylphosphines.

Unlike alloxan, which rearranges at physiological *p*H (*ca.* 7.4) *via* a benzilic acid-like pathway to alloxanic acid (15), the adducts (**6a-f**) were stable to base, although labile to aqueous acid. Acid treatment gave an excellent conversion to alloxantin. Compounds **6a** and **6e** were evaluated for effects upon blood glucose in a fasted rat model described in a previous publication (9). At 50 mg./kg. s.c., **6a** evidenced a 25% transient rise in blood glucose level above control at 2 hours postdosing. No such effect was detected with **6e** at 50 mg./kg. i.p. Neither **6a** nor **6e** induced any permanent glycosuria at 24-48 hours after treatment, indicating that unlike alloxan, these compounds are not *beta*-cytotoxins (19).

EXPERIMENTAL

All melting points were obtained in capillaries on a Mel-Temp Apparatus and are reported uncorrected. Infrared spectra were measured as 1-2% potassium bromide discs on a Perkin Elmer 257 or on a Beckman IR-33. The ^{1}H nmr spectra were determined on a Hitachi Perkin-Elmer R-20A spectrometer with TMS as an internal standard. Uv spectra were recorded on a Perkin-Elmer 402 spectrometer. The microanalyses were performed by Robertson Laboratories, Florham Park, N.J.

Alloxan Anhydride.

Sublimation at 0.5 torr and 220° of commercial alloxan hydrate produced a dense yellow crystalline sublimate of the anhydrous material, m.p. 256-257° dec [lit. (20) m.p. 256° dec.].

1,3-Dimethylalloxan.

Oxidation of amulinic acid with concentrated nitric acid according to the method of Blitz (20) and Fischer (21) gave a 93% yield of the product, m.p. 260-261° dec [lit. (21) m.p. 252-255° dec.].

Preparation of Alloxan and 1,3-Dimethylalloxan Adducts of Triarylphosphines.

A solution prepared from 10 ml. of absolute ethanol and an equimolar amount of the triarylphosphine and the alloxan hydrate (1.0 mmole each) was refluxed with stirring for 1-2 hours. Crystals began to appear shortly after commencement of heating and mere chilling of the reaction mixture precipitated analytically pure material. Deviations from this procedure are indicated on Table III along with yields and physical properties. The ^{1}H nmr spectrum of **6e** in deuteriochloroform displayed a sharp methyl singlet, integrating for 6 protons, at δ 3.19. A similar resonance appears at δ 3.15 in **6f**.

5-Ethoxy-5-Hydroxybarbituric Acid.

A suspension of 1.0 g. of magnesium sulfate, 5.0 g. of alloxan hydrate and 100 ml. of ethanol was refluxed with stirring for 12 hours, cooled, filtered, and evaporated to a reduced volume to precipitate 4.12 g. (70%) of the ethoxyhydroxybarbituric acid, m.p. 135-145° foaming and shrinking, 254-255° dec [lit. (20) m.p. 125-235°, foaming, 252-254° dec.]: nmr (DMSO-d_6): δ 11.33 (s, br, 2, N-*H*), 7.40 (s, 1, O*H*), 3.56 (q, 2, -OCH_2-CH$_3$), (J = 7.2 Hz) and 1.06 ppm (t, 3, -OCH$_2$CH_3, J = 7.2 Hz).

Stability Studies on **6a**.

A vigorously agitated mixture of 100 ml. of aqueous sodium hydroxide (*p*H 7.4), 25 ml. of chloroform and 2.00 g. of **6a** was maintained at ambient temperature for 40 hours. Filtration and washing of the solid with 30 ml. of chloroform and 30 ml. ethanol gave 1.84 g. (92%) of unchanged **6a**, identified by m.p. and spectral comparison with the authentic material.

An aqueous suspension of 2.00 g. (4.95 mmoles) of **6a**, 1.96 g. (9.90 mmoles) of *p*-toluenesulfonic acid monohyrate and 20 ml. of water was stirred at reflux for 2.5 hours, concentrated *in vacuo*, cooled and filtered to yield 0.62 g. (78%) of alloxantin, m.p. 237-239° dec [lit. (14) m.p. 235° dec.]. The infrared spectrum of the isolated material agreed with that published for alloxantin (14).

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