Reactions of Lead Tetra-acetate. Part XVI.[1] The Oxidation of Monoacylhydrazines

By **J. B. Aylward** and **R. O. C. Norman,*** Department of Chemistry, The University of York, Heslington, York

Five aroylhydrazines have been oxidised by lead tetra-acetate, usually at room temperature, to give, after hydrolysis, high yields of the corresponding aroic acids. A study of the reaction of benzhydrazide under various conditions has provided evidence that reaction occurs by way of the aroyldi-imide, and this can be diverted in part to give benzaldehyde and thence, by further reactions, 2,5-diphenyloxadiazole. When the hydrazide is in considerable excess, it can trap an intermediate in the oxidation to give *NN'*-dibenzoylhydrazine. The oxidation of benzhydrazide by mercuric acetate occurs in a similar manner, although not under such mild conditions.

MONOACYLHYDRAZINES are susceptible to oxidation by a variety of reagents. In some conditions the corresponding *NN'*-diacylhydrazine is formed, as with iodine[2] or 1 equivalent of either sulphur monochloride[3] or *N*-bromosuccinimide.[4] In other conditions, other types of product can be obtained: for example, oxidation

---

[1] Part XV, R. O. C. Norman and C. B. Thomas, *J. Chem. Soc.* (*B*), 1968, 994.

[2] T. Curtius, *J. prakt. Chem.*, 1894, **50**, 281.

[3] P. Hopes and L. A. Wiles, *J. Chem. Soc.*, 1964, 5837.

[4] Y. Wolman, P. M. Gallop, A. Patchornik, and A. Berger, *J. Amer. Chem. Soc.*, 1962, **84**, 1889.

with chlorine in the presence of hydrogen chloride,[5] or with 2 equivalents of sulphur monochloride,[3] gives the carboxylic acid chloride; oxidation with potassium ferricyanide[6,7] or sodium metaperiodate[7] in ammonia solution gives the aldehyde; and oxidation with 2 equivalents of *N*-bromosuccinimide gives the carboxylic acid.[4] The fact that the last reagent converts the γ-hydrazide of glutamic acid quantitatively into pyrrolidone-5-carboxylic acid shows that an intermediate in the oxidation has acylating power, and this property has been utilised in the synthesis of several dipeptides by carrying out the oxidation of monoacylhydrazines in the presence of amino-acids.[4] We have now studied the oxidation of five aroylhydrazines with lead tetra-acetate.

When benzhydrazide was added slowly to 2·5 mol. of lead tetra-acetate in benzene at room temperature, the evolution of nitrogen began at once and ceased within 2 min. of the final addition. After hydrolytic work-up, benzoic acid was isolated in 90% yield, and there was gas-chromatographic evidence for the formation of a small quantity of benzophenone. The 4-chloro-, 4-methyl-, and 4-methoxy-derivatives of benzhydrazide behaved similarly, giving the corresponding acids in high yield (Table). However, with the 4-nitro-derivative the evolution of nitrogen was barely perceptible at room temperature; reaction was therefore conducted at 60° and was complete in *ca.* 2 hr.

Benzhydrazide also reacted rapidly, and gave benzoic acid in high yield, in methylene dichloride, methanol, or anisole. There was gas-chromatographic evidence for the formation of small quantities of 4-methoxybenzophenone in anisole and of methyl benzoate in methanol; in contrast, the major product isolated from reaction of 4-nitrobenzhydrazide in methanol was the corresponding methyl ester.

When 1·25 mol. of lead tetra-acetate was added during 30 min. to benzhydrazide, in either acetic acid or benzene, both *NN'*-dibenzoylhydrazine and tribenzoylhydrazine were isolated in significant yield and the yield of benzoic acid was considerably reduced. The results are collected in the Table.

Mechanism of Oxidation.—When the reaction product from the oxidation of benzhydrazide with 2·5 mol. of lead tetra-acetate in benzene was analysed by gas chromatography before hydrolytic work-up, peaks corresponding to both acetic and benzoic anhydride were detected; both were absent from the chromatograph after hydrolysis. Since the mixed anhydride $PhCO{\cdot}OAc$ would be expected readily to disproportionate to the two symmetrical anhydrides,[8] it is probable that either the mixed anhydride or benzoic anhydride is the oxidation product; according to the discussion below, the former is the more likely. We infer also that anhydrides are formed from the other aroylhydrazines.

Products from the oxidation of aroylhydrazines ($ArCO{\cdot}NH{\cdot}NH_2$) by lead tetra-acetate at room temperature (except where stated)

Ar	$Pb(OAc)_4$ (mol.)	Solvent	Products (%)[a]	
			$ArCO_2H$	Others
Ph	2·5	PhH	90	Ph_2CO (0·6)
$4\text{-}Cl{\cdot}C_6H_4$	2·5	PhH	86	—
$4\text{-}Me{\cdot}C_6H_4$	2·5	PhH	93	—
$4\text{-}MeO{\cdot}C_6H_4$	2·5	PhH	86	—
$4\text{-}O_2N{\cdot}C_6H_4$	2·5	PhH[b]	89	—
Ph	2·5	CH_2Cl_2	91	—
Ph	2·5	MeOH	82	$PhCO_2Me$ (4)
Ph	2·5	PhOMe	83	$4\text{-}MeO{\cdot}C_6H_4{\cdot}COPh$ (2)
$4\text{-}O_2N{\cdot}C_6H_4$	2·5	MeOH[b]	7	$4\text{-}O_2N{\cdot}C_6H_4{\cdot}CO_2Me$ (88)
Ph	1·25	HOAc[c]	30	$PhCO{\cdot}NH{\cdot}NH{\cdot}COPh$ (13) $(PhCO)_2N{\cdot}NH{\cdot}COPh$ (6)
Ph	1·25	PhH[c]	25	$PhCO{\cdot}NH{\cdot}NH{\cdot}COPh$ (20) $(PhCO)_2N{\cdot}NH{\cdot}COPh$ (6)

[a] Based on aroylhydrazine. [b] At 60°. [c] Lead tetra-acetate was added slowly to the hydrazine.

The oxidation of *NN'*-diacylhydrazines with lead tetra-acetate gives the corresponding diacyldi-imides,[9,10] and likewise *N*-benzoyl-*N'*-phenylhydrazine gives benzoylphenyldi-imide.[9] The first stage in the oxidation of monoacylhydrazines should occur similarly, to give the acyldi-imides (2). Analogy with the behaviour of other basic nitrogen compounds towards lead tetra-acetate suggests that this should be a two-step reaction in which the unsubstituted, more strongly nucleophilic nitrogen atom of the hydrazine displaces an acetate group from the oxidant to give the organolead(IV) intermediate (1) which then undergoes elimination.[11,12] This view is in accord with the facts that monoacylhydrazines are oxidised under milder conditions than are *NN'*-diacylhydrazines[9,10] (in which the nucleophilic displacement must be brought about by a nitrogen atom whose nucleophilic activity is decreased by the conjugated carbonyl group), and that 4-nitrobenzhydrazide requires more vigorous conditions for oxidation than the other acylhydrazines we studied.

A reaction of the type (1) ⟶ (2) presumably occurs also in the McFadyen–Stevens procedure for the conversion of aroylhydrazines, through their *N'*-benzenesulphonyl derivatives, into aldehydes, the group SO_2Ph replacing $Pb(OAc)_3$ as the electronegative leaving group.[13,14] In this case, the formation of (2) is followed by base-catalysed elimination of a proton and loss of nitrogen to give $ArCO^-$ and thence the aldehyde,[14] whereas with lead tetra-acetate further oxidation evi-

---

[5] L. A. Carpino, *J. Amer. Chem. Soc.*, 1957, **79**, 96.

[6] L. Kalb and O. Gross, *Ber.*, 1926, **59**, 727.

[7] H. N. Wingfield, W. R. Harlan, and H. R. Hanmer, *J. Amer. Chem. Soc.*, 1952, **74**, 5796.

[8] C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 1960, 3070; R. E. Dunbar and F. G. Garven, *J. Amer. Chem. Soc.*, 1955, **77**, 4161.

[9] S. G. Cohen and J. Nicholson, *J. Org. Chem.*, 1965, **30**, 1162.

[10] R. A. Clement, *J. Org. Chem.*, 1960, **25**, 1724.

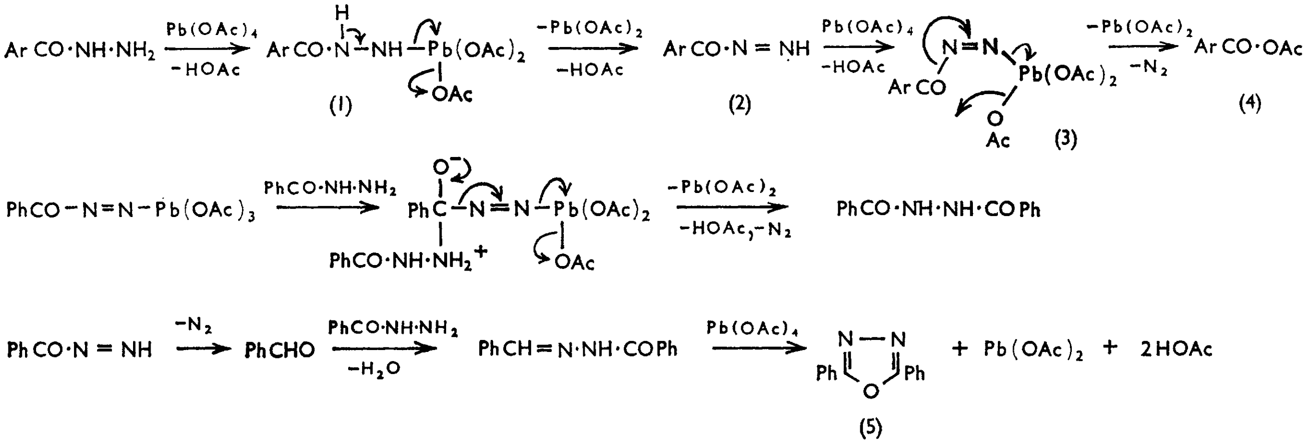
[11] W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1966, 1536.

[12] M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1967, 735.

[13] J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 1936, 584.

[14] D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.*, 1963, **85**, 1108.

dently occurs preferentially. In order to reduce the probability of further oxidation of the expected di-imide, we carried out the oxidation of benzhydrazide in methylene dichloride by adding the lead tetra-acetate solution during 6 hr., with very dilute solutions of both oxidant and benzhydrazide. This resulted in the formation of *NN'*-dibenzoylhydrazine (58%) (which is also formed when the oxidant is added more rapidly; see below) together with benzaldehyde (1%) and 2,5-diphenyloxadiazole (5) (3%); the oxadiazole is known to be formed by the oxidation of benzaldehyde benzoylhydrazone under these conditions,[15] and we found that benzaldehyde and benzhydrazide form this hydrazone under the conditions of the oxidation. This result is consistent with the mediation of the acyldi-imide, and moreover, when the reaction was carried out in the presence of triethylamine, the yield of the oxadiazole was increased to 9%, consistent with the formation of benzaldehyde by base-catalysed elimination from the acyldi-imide (2; Ar = Ph).



Oxidation of the acyldi-imide (2) should occur by way of the organolead(IV) species (3). Because of the tendency of organolead(IV) compounds to cleave heterolytically with the formation of lead diacetate and acetate ion, together with, in this case, the potential driving force available from the formation of the nitrogen molecule from the azo-group, the intermediate (3) is likely to undergo heterolysis readily. Three reaction paths appear to be available: unimolecular heterolysis to give the aroyl cation, ArCO$^+$; bimolecular heterolysis, in which a nucleophile displaces nitrogen from the carbonyl group through its addition to that group; and an intramolecular reaction to give the mixed anhydride, as in the Scheme. The first possibility can be discounted because the aroyl cation should be a highly reactive species which should give a predominance of the corresponding methyl ester when generated in methanol solution, whereas benzhydrazide gave only 4% of methyl benzoate * (the ester was stable in the reaction conditions and the work-up procedure) and might be expected to give more significant yields of aromatic ketone when generated in benzene or, especially, in anisole. (The cation ArSO$_2$$^+$ has likewise been shown not to be involved when arenesulphonylhydrazines are oxidised by bromine to arenesulphonyl bromides.[16]) The second possibility can be discounted for essentially the same reason so far as the formation of the (mixed) anhydride is concerned, since methanol is a more powerful nucleophile than acetic acid,[17] and reaction in methanol should lead to a predominance of the methyl ester. We infer that the intramolecular pathway is the preferred route to the mixed anhydride (cf. the reaction of ketone arylhydrazones with lead tetra-acetate [12]). However, it is possible that, when the oxidant is added to a solution of the acylhydrazine so that the latter is in excess for most of the reaction, nucleophilic attack by the hydrazine (Scheme) can compete effectively with the intramolecular reaction, giving the *NN'*-diacylhydrazine (and thence, by further reaction, the triacylhydrazine); were this product formed by the obvious alternative pathway, *i.e.*, displacement by the hydrazine on the anhydride, we should have expected to isolate also a small proportion at least of *N*-acetyl-*N'*-benzoylhydrazine.

Since an acyldi-imide should be less strongly nucleophilic than an acylhydrazine (just as imino-nitrogen is less strongly basic than amino-nitrogen), it is possible that, with a weaker oxidising agent than lead tetra-acetate, an acylhydrazine would be converted into the corresponding aldehyde through the acyldi-imide; this may underlie the formation of aldehydes from acylhydrazines with potassium ferricyanide [6,7] or sodium metaperiodate,[7] especially since basic conditions have been

---

* The predominance of methyl 4-nitrobenzoate from reaction of 4-nitrobenzhydrazide in methanol is not exceptional, since the corresponding anhydride should be more reactive towards methanol than benzoic anhydride, and the reaction was conducted at 60°.

[15] J. B. Aylward, W. A. F. Gladstone, and R. O. C. Norman, to be published.

[16] A. C. Poshkus, J. E. Herweh, and F. A. Magnotta, *J. Org. Chem.*, 1963, **28**, 2766.

[17] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959, p. 301.

employed in these reactions. We therefore studied the oxidation of benzhydrazide by mercuric acetate. As expected, reaction was slower than with lead tetra-acetate, and the mixture was warmed to increase the reaction rate. However, benzaldehyde was not formed; when the hydrazine was added slowly to a solution of mercuric acetate in water at 50°, only benzoic acid (86%) was obtained, and when a mixture of the reagents was warmed only *NN'*-dibenzoylhydrazine (78%) was isolated.

EXPERIMENTAL

Materials.—Benzhydrazide and its 4-methyl derivative were obtained commercially, and these and 4-chloro-, 4-methoxy-, and 4-nitro-benzhydrazide, which were prepared by standard procedures, had the properties previously recorded.[18] The 4-nitro-compound was dried under a vacuum at 100° to eliminate solvent of crystallisation, and the other aroylhydrazines were dried in a vacuum-desiccator overnight. The 4-substituted benzoic acids were available commercially. *NN'*-Dibenzoylhydrazine was prepared following Curtius,[2] and tribenzoylhydrazine was prepared following Stolle and Weindel.[19]

Lead tetra-acetate (B.D.H. reagent grade) was recrystallised from acetic acid and stored in a vacuum-desiccator over sodium hydroxide pellets. Mercuric acetate (Hopkin and Williams general-purpose reagent) was used without further purification. Benzene (analytical reagent) was dried over sodium, methylene dichloride was distilled from phosphorus pentoxide, and methanol was distilled from calcium oxide.

Where products were formed in small yield they were not isolated, but identified by comparison of their retention times on each of two gas chromatography columns with those of authentic materials. The columns contained silicone fluid (MS 550) (10% w/w) on Celite (80—100 mesh) and Carbowax 20M (10% w/w) on Embacel.

Oxidations.—(*i*) Benzhydrazide (1·75 g.) was added during 30 min., with stirring, to a solution of lead tetra-acetate (14·2 g.) in benzene (40 ml.). Effervescence began at once and ceased within *ca.* 2 min. of the final addition. The mixture was poured into water, and the ether extract was washed with water and dried ($MgSO_4$). A small portion was set aside for gas chromatography, and the remainder was distilled to leave a residue which was identified, after recrystallisation from water, as benzoic acid (m.p., mixed m.p., and infrared spectrum).

4-Chloro-, 4-methyl-, 4-methoxy-, and 4-nitro-benzhydrazide were oxidised in a similar manner. With the first three compounds, rapid effervescence occurred on addition of the hydrazine, but with the 4-nitro-compound it was barely perceptible and oxidation was conducted at 60° for 2 hr.

Benzhydrazide was also oxidised in this way except that methylene dichloride, methanol, or anisole (40 ml.) was used as solvent in place of benzene. 4-Nitrobenzhydrazide was oxidised similarly in methanol, but at 60° for 2 hr.; after work-up as above, both 4-nitrobenzoic acid and the corresponding methyl ester [identical (m.p., mixed m.p., and infrared spectrum) with an authentic sample] were isolated by fractional recrystallisation from ethanol.

When the product from the oxidation of benzhydrazide in benzene was submitted to gas chromatography before work-up, both acetic anhydride and benzoic anhydride (*ca.* 20% of each) were detected.

(*ii*) Lead tetra-acetate (14·2 g.) was added during 30 min., with stirring, to benzhydrazide (3·5 g.) in acetic acid (40 ml.). When effervescence had ceased, the mixture was poured into water, the ether extract was dried ($MgSO_4$), and ether and acetic acid were distilled off under reduced pressure. Fractional recrystallisation of the residue from aqueous ethanol gave benzoic acid (0·94 g.), *NN'*-dibenzoylhydrazine (0·4 g.), and tribenzoylhydrazine (0·18 g.), each identical with an authentic sample (m.p., mixed m.p., and infrared spectrum). In another experiment, benzene (40 ml.) was used in place of acetic acid.

(*iii*) Lead tetra-acetate (6·6 g.) in methylene dichloride (300 ml.) was added during 6 hr., with vigorous stirring, to a solution of benzhydrazide (2 g.) in methylene dichloride (500 ml.). The resulting mixture was extracted with water and then concentrated to *ca.* 25 ml. The precipitated *NN'*-dibenzoylhydrazine (0·72 g.) was removed by filtration, a small portion of the filtrate was analysed by gas chromatography for benzaldehyde, and the remainder was evaporated to dryness. Recrystallisation of the residue from chloroform yielded a further quantity of *NN'*-dibenzoylhydrazine (0·17 g.), and evaporation of the mother-liquors followed by recrystallisation from ethanol gave 2,5-diphenyl-1,3,4-oxadiazole (0·06 g.), identical (m.p., mixed m.p., and infrared spectrum) with an authentic sample.[15] The experiment was repeated with the inclusion of triethylamine (40 ml.) in the benzhydrazide solution.

(*iv*) Benzhydrazide (1 g.) was added to a solution of mercuric acetate (2·4 g.) in water (30 ml.). Effervescence was just detectable. When the solution was warmed to 50° more vigorous effervescence occurred. When it had ceased, the ether extract was dried ($MgSO_4$) and evaporated, to leave *NN'*-dibenzoylhydrazine, m.p. 240° (from ethanol) (78%).

(*v*) Benzhydrazide (1 g.) was added during 1 hr. to a solution of mercuric acetate (4·8 g.) in water (30 ml.) at 50°. Effervescence ceased almost immediately after the final addition, and the solution was extracted repeatedly with ether. The extract was dried ($MgSO_4$) and evaporated, to leave benzoic acid, m.p. 122° (from water) (86%).

We thank the S.R.C. for their support of this work.

[8/647 *Received, May 9th*, 1968]

[18] I. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' 4th edn., Eyre and Spottiswoode, London, 1965.

[19] R. Stolle and A. Weindel, *J. prakt. Chem.*, 1913, **69**, 156.