pump-thaw cycles using argon as the inert atmosphere and then heated at 70 °C. After 20% reaction as determined by GC, the volatiles were removed under vacuum to afford 5 g of a jellylike material which was extracted with diethyl ether until a white powder remained. The powder was purified by redissolving in THF followed by precipitation with hexane. The weight of polymer recovered was 1.0 g and the molecular weight was 10000 Daltons (HPLC gel permeation chromatography; polystyrene standards): IR (KBr) 1780, 1720 cm^{-1}; ^{13}C NMR see Table II. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.32; H, 5.39.

Acknowledgment. We thank T. M. Bargar for assisting in the development of the synthesis of 1-vinyl 4-methyl itaconate and J. I. Shulman for helpful discussions.

Registry No. **2b**, 102634-12-8; **2b** (homopolymer), 102634-13-9; **3a**, 85753-88-4; **3a** (homopolymer), 85947-43-9; **3b**, 102651-51-4; **6**, 7338-27-4; **8**, 102651-52-5; **9**, 13668-05-8; **10a**, 102651-53-6; **10b**, 102651-54-7; **11a**, 102651-55-8; **11b**, 102651-56-9; vinyl acetate, 108-05-4; itaconic anhydride, 2170-03-8; trichloroethanol, 115-20-8; 1-methyl 4-trichloroethyl itaconate, 102651-57-0; itaconic acid, 97-65-4; ethyl acetosuccinate, 1115-30-6; methyl iodide, 74-88-4.

The Oxidative Decarboxylation of *N*-Aroylglycines to *N*-(Acetoxymethyl)benzamides and *N*-Formylbenzamides with Lead(IV) Acetate[1]

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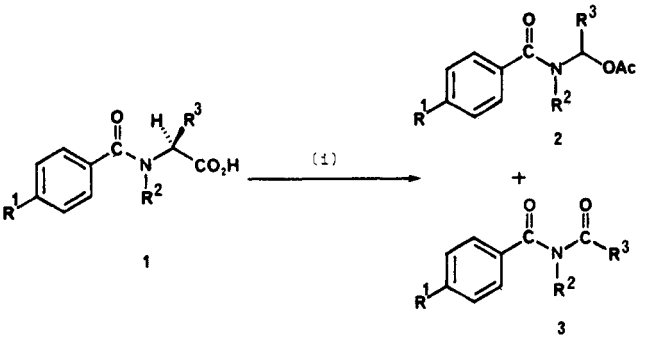
Treatment of *N*-aroylglycines that do not bear a strong electron-withdrawing substituent with lead(IV) acetate in acetic acid/acetic anhydride mixtures at 60–100 °C rapidly gives the corresponding *N*-(acetoxymethyl)benzamides and *N*-formylbenzamides in moderate yields after chromatography. These compounds are of interest in the study of the metabolism of xenobiotic *N*-methylbenzamides. *N*-(4-Nitrobenzoyl)glycine gives only *N*-(acetoxymethyl)-4-nitrobenzamide. 4-Chloro-*N*-methylbenzamide, *N*-aroylproline, and esters of *N*-aroylglycines are unaffected. Deuterium incorporation and other studies are consistent with a mechanism involving initial ligand exchange at lead followed by N-acetoxylation. Decarboxylation and elimination then ensue; final readdition of acetic acid to *N*-aroylimines leads to the observed products.

Many *N*-methyl-containing drugs and other compounds are metabolized to the corresponding *N*-hydroxymethyl analogue by preparations of murine liver.[2] The antitumor agent hexamethylmelamine,[3] the herbicide Monuron [*N*-(4-chlorophenyl)-*N'*,*N'*-dimethylurea],[4] and the common industrial solvent *N*,*N*-dimethylformamide[1] have been shown to be C-hydroxylated metabolically in vitro or in whole animals. The generated *N*-hydroxymethyl moieties are then either excreted as such or undergo further enzymic metabolism or intracellular chemical reaction. The relatively labile *N*-hydroxymethylamines may hydrolyze to give formaldehyde, a mutagen; while *N*-hydroxymethylbenzamide is sufficiently stable to be a substrate for further oxidation by cytosolic enzymes to *N*-formylbenzamide.[5] Hepatic metabolites containing the carbinolamine group may also act as electrophiles, either through the intermediacy of a small equilibrium concentration of the corresponding iminium ion or imine (recently reviewed[6]) or through biological derivatization of the alcohol (e.g., acetylation) which enhances its leaving group ability. We therefore sought a general preparation of *N*-(acetoxymethyl)benzamides and *N*-formylbenzamides as reference compounds for metabolic work and for study of their chemical reactivity in order to predict their biochemical reactions with cellular nucleophiles. Although *N*-(acetoxymethyl)benzamide (**2a**) has been prepared by acetylation of *N*-(hydroxymethyl)benzamide[7] and benzamide can be N-formylated with difficulty,[5] the present method furnishes both desired products from one reaction on one substrate. The oxidative decarboxylation of *N*-benzoylglycine (**1a**) by treatment with lead(IV) acetate to *N*-(acetoxymethyl)benzamide has been briefly reported by Süs and Rosenberger,[8] although the product was not well characterized. this paper now describes the results of our investigation into this reaction as regards synthetic utility, scope, limitations, and mechanistic pathway.

Scheme I. The Oxidative Decarboxylation of *N*-Aryl Amino Acids[a]



[a] (i) $Pb(OAc)_4/AcOH/Ac_2O$.

(1) Part 8 of the series "The Formation and Metabolism of *N*-Hydroxymethyl Compounds". For Part 7, see: Kestell, P.; Gill, M. H.; Threadgill, M. D.; Gescher, A.; Howarth, O. W.; Curzon, E. H. *Life Sci.* **1986**, *38*, 719.
(2) Gescher, A.; Hickman, J. A.; Stevens, M. F. G. *Biochem. Pharmacol.* **1979**, *28*, 3235.
(3) Borm, P.; Mingels, M.-J.; Hulshoff, A.; Franzhuizen-Sierevogel, A.; Noordhoek, J. *Life Sci.* **1983**, *33*, 2113.
(4) Ross, D.; Farmer, P. B.; Gescher, A.; Hickman, J. A.; Threadgill, M. D. *Biochem. Pharmacol.* **1982**, *31*, 3621.
(5) Ross, D.; Farmer, P. B.; Gescher, A.; Hickman, J. A.; Threadgill, M. D. *Biochem. Pharmacol.* **1983**, *32*, 1773.
(6) Overton, M.; Hickman, J. A.; Threadgill, M. D.; Vaughan, K.; Gescher, A. *Biochem. Pharmacol.* **1985**, *34*, 2055.
(7) Gate, E. N.; Hooper, D. L.; Stevens, M. F. G.; Threadgill, M. D.; Vaughan, K. *Magn. Reson. Chem.* **1985**, *23*, 78.
(8) Süs, O.; Rosenberger, S. *Justus Liebigs Ann. Chem.* **1949**, *564*, 137.

0022-3263/86/1951-3196$01.50/0

Table I

1	R^1	R^2	R^3	yield of 2, %	yield of 3, %
1a	H	H	H	10	22
1b	Cl	H	H	39[a]	28[a]
1c	Me	H	H	2.5[a]	11[a]
1d	NO_2	H	H	72[a]	0
1e	OMe	H	H	21[a]	12[a]
1f	Cl	Me	H	0	0
1g	Cl	H	Me	0	21[a]
1h	Cl	$CH_2CH_2CH_2$		0	0

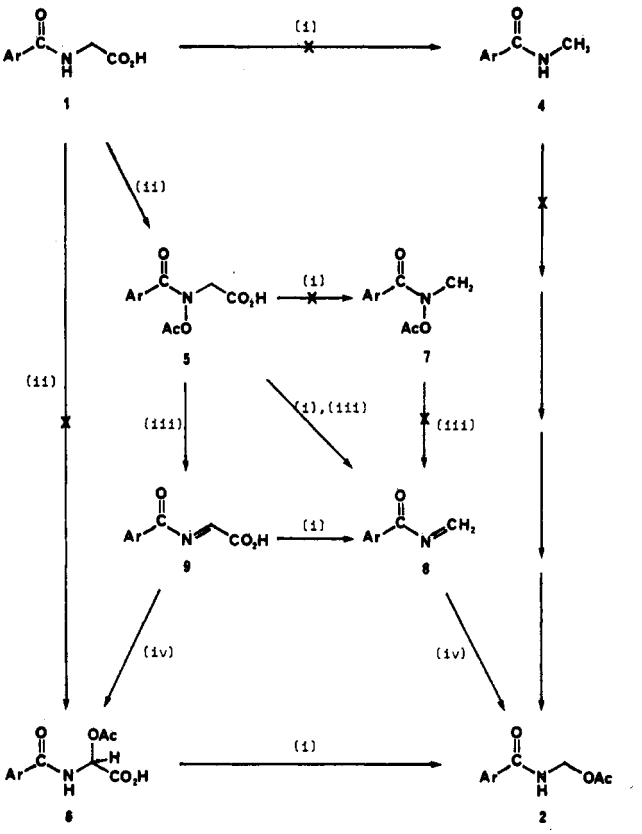
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table and for **2d**.

Aryl-substituted *N*-benzoylglycines **1a–c** and *N*-4-chlorobenzoyl amino acids **1f–h** were prepared by conventional Schotten–Baumann techniques[9] by addition of the aroyl chloride to the amino acid in aqueous sodium hydroxide solution at ambient temperature with vigorous stirring, acidification and collection of the *N*-aryl amino acid by filtration followed by recrystallization, usually from aqueous ethanol. *N*-(4-Chlorobenzoyl)sarcosine (**1b**) proved difficult to recrystallize but was purified after conversion to its diisopropylamine salt. The free acid was released by precipitation with hydrochloric acid from aqueous solution before oxidation was attempted.

N-(4-Chlorobenzoyl)glycine (**1b**) was the substrate used in preliminar experiments designed to optimize the reaction conditions so as to give acceptable yields of both products **2b** and **3b** in the same preparative run (Scheme I). The best yields were obtained by carrying out the reaction at 60 °C with reaction times between 30 min and 2 h in a solvent mixture comprising ca. 10% acetic anhydride and 90% acetic acid and by use of between 1 and 2 equiv of lead(IV) acetate. Higher temperatures, such as the 100 °C employed by Süs[8] or boiling under reflux, speeded the already conveniently rapid reaction but also facilitated side reactions; significantly lower yields of both products were isolated. The reaction did not proceed at a measurable rate at ambient temperature. As shown in Table I, substitution at various positions in the substrate hippuric acids has a profound effect on the outcome of the reaction. Substitution in the para position of the benzoyl moiety with groups that are not strongly electron-withdrawing as in **1a–c,e** gave moderate to good yields of both oxidized products **2a–c,e** and **3a–c,e**. However, when a strong electron-withdrawing group is present on the aromatic ring, as in the nitro group of substrate **1d**, only the acetoxymethyl compound **2d** could be isolated. Interestingly, the maximum yield (72%) of **2d** was obtained using 2 equiv of lead(IV) acetate. Hence, it can be seen that the product distribution is markedly affected by the electronic nature of the para substituent; further oxidation taking place when a methoxy group (Hammett substituent constant $\sigma = -0.27$)[10] is present on the aromatic ring but not with the nitro derivative ($\sigma = +0.78$).[10]

Substitution at nitrogen, in the case of substrate **1f**, leads to a reaction mixture in which neither *N*-(acetoxymethyl)-4-chloro-*N*-methylbenzamide (**2f**) nor 4-chloro-*N*-formyl-*N*-methylbenzamide (**3f**) could be identified. TLC analysis showed that **1f** was very largely unaffected by the oxidant. The presence of a methyl group at the α-carbon of the glycine moiety (in substrate **1g**), on the other hand, did not prevent oxidative decarboxylation. In this case, the sole isolated material was the doubly oxidized product *N*-acetyl-4-chlorobenzamide (**3g**) in modest yield.

Scheme II. Possible Mechanistic Pathways for the Oxidative Decarboxylation of Hippuric Acids 1 to *N*-(Acetoxymethyl)benzamides 2[a-c]



[a] Paths with ⊬ have been shown by experiment not to take place. [b] (i)–CO_2; (ii) $Pb(OAc)_4$; (iii) –AcOH; (iv) +AcOH. [c] Ar = 4-$R^1C_6H_4$ (R^1 as in Table I).

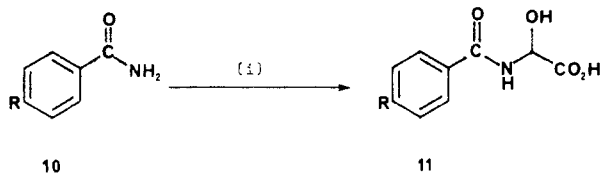
It may be that the 1-acetoxy ethyl compound **2g** was formed during the reaction but was unstable. No oxidized products were obtained from **1h** which has substitution at both nitrogen and aliphatic carbon by annulation.

An attempt to extend the scope of the synthetic reaction by selection of a different lead(IV) carboxylate was unsuccessful. Neither of the expected oxidative decarboxylation products [4-chloro-*N*-(trifluoroacetoxymethyl)-benzamide and **3b**] were obtained from treatment of substrate **1b** with a solution of lead(IV) oxide in a mixture of trifluoroacetic acid and trifluoroacetic anhydride. The former ester may be hydrolyzed during the mildly basic aqueous workup, but the corresponding alcohol, 4-chloro-*N*-hydroxymethylbenzamide, was also not obtained as a product of the reaction.

Mechanistic Studies. As shown in Scheme II, the first intermediates on the path from starting hippuric acid **1** to the first isolated oxidation product **2** may arise either from initial decarboxylation (in the case of the *N*-methylbenzamide **4**) or from acetoxylation (to give **5** or **6**). However, the intermediacy of **4** can be discounted on the following grounds. First, no trace of the corresponding *N*-methylbenzamide **4** is evident on TLC examination (compared with authentic materials[5,11]) of any of the reaction mixtures involving lead(IV) acetate oxidative of hippuric acids **1**. Second, although there are several reports[12] of oxidation of *N*-alkyl compounds α to nitrogen

(9) Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longmans: London, 1978.
(10) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.
(11) Auerbach, J.; Zamore, McF.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725.
(12) Galliani, G.; Rindone, B.; Scolastico, C. *Tetrahedron Lett.* **1975**, 1285.

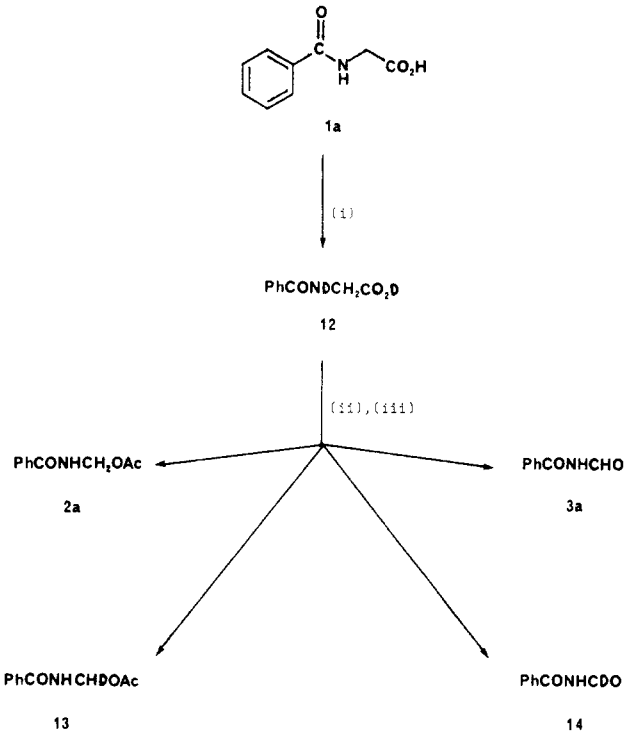
Scheme III. Condensation of 4-Chlorobenzamide with Glyoxylic Acid[a]



10 11

[a] (i) $OHCCO_2H$/1,4-dioxane.

Scheme IV. Deuterium Incorporation Experiments[a]



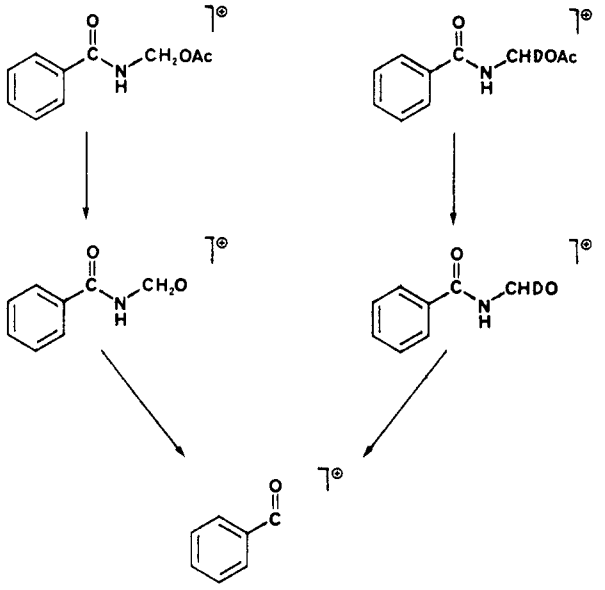
1a 12 2a 3a 13 14

[a] (i) D_2O; (ii) $Pb(OAc)_4/CH_3CO_2D/Ac_2O$; (iii) $H_2O/NaHCO_3$.

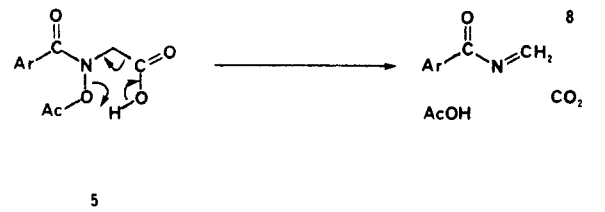
by acetates of metals in high oxidation states, no consumption of 4-chloro-*N*-methylbenzamide (**4b**) was observed under the general conditions employed. Hence oxidation precedes rather than succeeds decarboxylation.

Several experiments were conducted to investigate whether oxidation occurs at carbon, converting **1** directly to the 2-acetoxyhippuric acid **6**, or at nitrogen, giving the *N*-acetoxyhippuric acid **5**. In the first, *N*-(4-chlorobenzoyl)-2-hydroxyglycine **11** was prepared in excellent yield by treatment of 4-chlorobenzamide **10** with glyoxylic acid hydrate (Scheme III). All attempts to acetylate **11** to give the proposed intermediate 2-acetoxy-*N*-(4-chlorobenzoyl)glycine (**6b**) by using acetic anhydride or acetyl chloride in the presence of inorganic or organic base were unsuccessful, intractable mixtures being obtained. With **6b** thus not available as an isolated characterizable material for further investigation, a more indirect approach was sought. Esterification of **11** to give **6b** might well take place in the warm acetic acid/acetic anhydride medium of the principal oxidative decarboxylation experiments. Treatment of **11** with such Ac_2O/AcOH mixtures in the presence or absence of lead(II) acetate (added to mimic the main reaction conditions more closely) gave the acetoxymethyl compound **2b**. Replacement of the nonoxidizing lead(II) acetate by lead(IV) acetate led to markedly decreased yields of **2b**. Hence, it is highly likely, but not completely rigorously proven, that at least some of the yield of **2** in the oxidation of **1** with lead(IV) acetate

Scheme V. Partial Mass Fragmentation of 2a



Scheme VI. Proposed Simultaneous Elimination/Decarboxylation

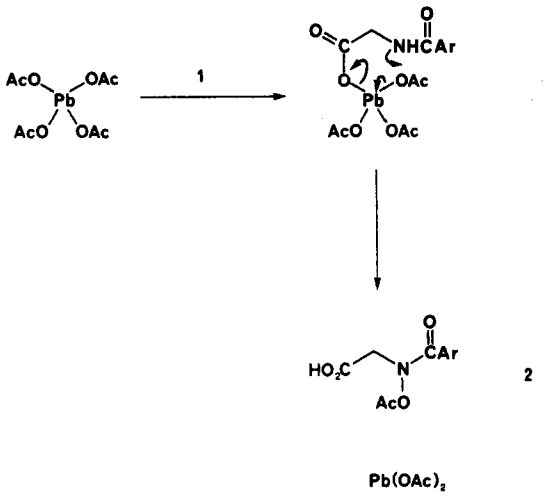


5

arises through the intermediacy of **6**.

The most useful evidence for contributions (or otherwise) of pathways to the overall reaction sequence comes from the deuterium incorporation experiments shown in Scheme IV. For ease of interpretation of the mass spectroscopic analysis of products, the unsubstituted benzoyl series (**1a**, etc.) was employed for these experiments. The carboxylic acid and amine NH protons of hippuric acid (**1a**) were exchanged for deuterium to an extent greater than 95% (judged by ^1H NMR in $CDCl_3$) by repeated recrystallization from deuterium oxide. The oxidative decarboxylation was then carried out under the standard conditions using lead(IV) acetate (free from acetic acid), monodeuterioacetic acid (CH_3CO_2D; 98 atom %), and acetic anhydride [$(CH_3CO)_2O$], followed by normal aqueous workup. Of the *N*-(acetoxymethyl)benzamide formed, 60–80% (varying between experiments) was found by mass spectrometry not to contain deuterium (m/z 193, 150), i.e., to be $PhCONHCH_2OAc$. A corresponding 20–40% of the material contained one deuterium atom ($PhCONHCHDOAc$). Examination of the mass spectral fragmentation pattern confirmed the location of the deuteron in the methylene group (Scheme V). As expected, no ions corresponding to the dideuterio compound, $PhCONHCD_2OAc$, were observed, and control experiments showed that deuterium is neither gained nor lost by exchange of hydrogens of product **2a** with solvent. These data are consistent only with the initial formation of the *N*-acetoxyhippuric acid **5**, followed by a mixed mechanism. The major proportion of **5** then undergoes a simultaneous elimination/decarboxylation, giving **8** (Scheme VI). With the minor part, elimination of acetic acid gives the imine carboxylic acid **9**, which could then either add acetic acid (giving **6**) or decarboxylate (giving **8**). Evidence for the involvement of **6** is presented below in that it appears to

Scheme VII. A Possible Mechanism of N-Acetoxylation of Hippuric Acids by Lead(IV) Acetate



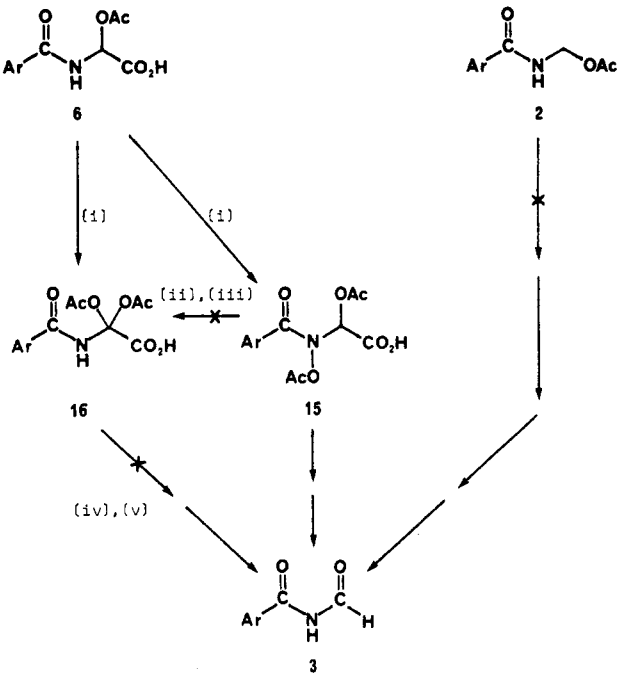
be the intermediate which is further oxidized, giving **3** as the final product.

A related reaction has been reported[13] in triazene chemistry in that 3-hydroxy-3-methyl-1-phenyltriazene has been converted to 3-(acetoxymethyl)-3-acetyl-1-phenyltriazene by treatment with acetic anhydride via elimination/addition. However, no *N*-(acetoxymethyl)-4-chlorobenzamide (**2b**) was formed when 4-chloro-*N*-hydroxy-*N*-methylbenzamide was heated with mixtures of acetic acid and acetic anhydride in the presence or absence of lead(II) acetate, thus ruling out **7** as an intermediate. This observation is consistent with our previous report that this *N*-methylhydroxamic acid does not eliminate water to generate an iminium ion on treatment with trifluoroacetic acid.[14] As shown in Table I, *N*-(4-chlorobenzoyl)glycine (**1b**) is readily converted to acetoxymethyl compound **2b**, whereas all attempts to carry out the same conversion on the *N*-blocked analogue, *N*-(4-chlorobenzoyl)-*N*-methylglycine (**1f**), to give **2f** failed. Thus, direct C-acetoxylation of **1** to **6** does not occur. Additionally, none of the expected further oxidation product, **3f**, could be isolated from this reaction. Hence, it would appear that the NH is important for the reaction to take place; a deduction that supports the formation of the *C*-acetoxy compound **6** via an elimination/addition rearrangement from the *N*-acetoxy species **5**.

It would appear that the carboxylic acid moiety is essential for the reaction to take place since no oxidation of methyl [(4-chlorobenzoyl)amino]acetate could be detected under the usual reaction conditions. A rationalization could be that the initial step of the N-acetoxylation is carboxylate "ligand" exchange at lead (Scheme VII). This would be followed by an essentially intramolecular oxidation at nitrogen.

The reaction pathways leading to the further oxidation products **3** are much more complex, involving steps of oxidation, elimination, addition, and, perhaps, decarboxylation, culminating in hydrolysis on workup. The first question (Scheme VIII) is whether the isolable product of the first oxidation, **2**, is itself acetoxylated or whether one of the other intermediates in Scheme II is the substrate for lead(IV) acetate, leading ultimately to the *N*-formylbenzamide **3**. A pure sample of **2b** was subjected to

Scheme VIII. Possible Pathways to *N*-Formylbenzamides[a,b]



[a] Paths with ⊣ have been shown by experiment not to take place. [b] (i) $Pb(OAc)_4$; (ii) −AcOH; (iii) +AcOH; (iv) $-CO_2$; (v) hydrolytic workup.

treatment with lead(IV) acetate under the standard conditions. No conversion to **3b** was observed, and the sole effect of higher temperatures and/or longer reaction times led to decomposition of the starting *N*-(acetoxymethyl)-4-chlorobenzamide to unidentifiable products. This result shows that compounds **2** are indeed subject to oxidation by lead(IV) acetate but that this oxidation is degradative. Thus **2** does not lie on the pathway from **1** to **3**. This finding is further supported by the total lack of deuterium incorporation into product **3a** when the overall reaction is carried out in $Pb(OAc)_4/CH_3CO_2D/Ac_2O$ mixture.

The involvement of **6** in the formation of **3** is also indicated by the successful experimental conversion of the glyoxylic acid adduct **11** to **3b** under the standard experimental conditions. One may therefore speculate that the *C*-acetoxy compound **6** is the intermediate actually oxidized. As in the first stage oxidation of **1** above, acetoxylation either at carbon or at nitrogen is conceivable. However, the *C*,*C*-diacetoxy compound **16** (Scheme VII) is not an intermediate since decarboxylation of **16** in the deuterate medium would lead, after subsequent hydrolysis, to PhCONHCDO rather than the sole oberved moiety PhCONHCHO (**3a**). Clearly, intermediates of type **16** are impossible in the observed conversion of **1g** to **3g**. The excellent yield (72%) of **2d** under the standard conditions together with the complete absence of the *N*-formyl compound **3d** in the *p*-nitro series also lends weight to the proposal that **6** is directly N-acetoxylated to give **15**. The nitro group would have the effect of markedly reducing the electron density at the amide nitrogen atom, thus disfavoring oxidation by an electrophilic oxidant. It is tempting to speculate that a simultaneous elimination and oxidation step is involved, which is similar to that shown in Scheme VI for the other series of products.

In conclusion, it can be seen that a useful simultaneous synthetic route to the *N*-(acetoxymethyl)benzamides **2** and *N*-formylbenzamides **3** has been developed. These compounds are likely to be of biological and toxicological interest as weak electrophiles. The characterization of their

(13) Foster, K.; Hess, F.; Grozinger, K. *Justus Liebigs Ann. Chem.* **1973**, 811.
(14) Addison, S. J.; Cunningham, B. D. M.; Gate, E. N.; Shah, P. Z.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 75.

chemical and biochemical electrophilic reactivity is in progress and will be presented in a future paper.[15] The mechanism of the oxidative decarboxylation of hippuric acids has been shown to involve two simultaneous routes to the first isolated oxidation products **2**, but only one intermediate is further oxidized leading to compounds **3**.

Experimental Section

General. IR spectra were determined as Nujol mulls. NMR spectra were obtained at 60 MHz with a Varian EM 360A spectrometer using tetramethylsilane as internal standard. Mass spectrometric studies were carried out with a VG Micromass 12 instrument in electron-impact mode at 70 eV. Melting points are uncorrected.

***N*-(4-Chlorobenzoyl)-*N*-methylglycine Diisopropylamine Salt (1f).** A mixture of 4-chlorobenzoyl chloride (8.75 g; 50 mmol), *N*-methylglycine (4.45; 50 mmol), KOH (5.6 g, 100 mmol), and water (100 mL) was stirred at ambient temperature for 3 h before being acidified by addition of 10 M hydrochloric acid. The resulting suspension was extracted with CH_2Cl_2. This extract was dried (Na_2SO_4) and filtered and the solvent evaporated under reduced pressure to give the acylsarcosine **1f** as a slightly gummy solid, mp 119–121 °C (lit.[16] mp 133–134 °C). The melting point could not be raised by recrystallization from aqueous ethanol. The solid, in ethanol (100 mL), was treated with diisopropylamine (20 mL), and the volatile materials were again evaporated. Recrystallization of the residue from propan-2-ol gave the diisopropylamine salt of *N*-(4-chlorobenzoyl)-*N*-methylglycine (10.9 g; 66%) as white needles: mp 129–130 °C; IR 2700, 2450, 1630, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (12 H, d, J = 7 Hz, $(CH_3)_2CH$), 3.10 (3 H, s, NCH_3), 3.27 (2 H, septet, J = 7 Hz, $(CH_3)_2CH$), 3.75 (2 H, s, NCH_2), 7.2–7.6 (6 H, m, Ar H, N^+H_2). Anal. Calcd for $C_{16}H_{25}ClN_2O_3$: C, 58.45; H, 7.65; N, 8.5. Found: C, 58.15; H, 7.65; N, 8.35.

***N*-(4-Chlorobenzoyl)-L-alanine (1g).** 4-Chlorobenzoyl chloride (5.25 g, 30 mmol) was added to L-alanine (2.67 g; 30 mmol) and KOH (3.9 g, 70 mmol) in water (50 mL). After being stirred vigorously for 13 h, the mixture was acidified by addition of 10 M hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl and dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford, after recrystallization from aqueous propan-2-ol, the *N*-acylalanine **1g** (5.05 g, 74%) as white needles: mp 161–163 °C; IR 3290, 2750, 1710, 1640, 1600, 1550 cm^{-1}; NMR (2:1 $CDCl_3/(CD_3)_2SO$) δ 1.45 (3 H, d, J = 7 Hz, $CHCH_3$), 4.52 (1 H, quintet, J = 7 Hz, alanine H), 5.4 (1 H, br, CO_2H), 7.43 (2 H, d, J = 8 Hz) and 7.92 (2 H, d, J = 8 Hz) [Ar H], 8.45 (1 H, d, J = 7 Hz, NH). Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.75; H, 4.45; N, 6.15. Found: C, 52.5; H, 4.35; N, 6.05.

***N*-(Acetoxymethyl)-4-chlorobenzamide (2b) and 4-Chloro-*N*-formylbenzamide (3b).** *N*-(4-Chlorobenzoyl)glycine (**1b**) (6.27 g, 30 mmol) and $Pb(OAc)_4$ (13.29 g, 30 mmol) were stirred at 60 °C for 10 min in acetic acid (80 mL) and acetic anhydride (8 mL) before evaporation of the solvents under reduced pressure. The residue, in CH_2Cl_2, was washed twice with water, twice with saturated aqueous $NaHCO_3$, and once with saturated aqueous NaCl before being dried (Na_2SO_4) and filtered. Evaporation of the solvent under reduced pressure gave a viscous yellow oil, which, on chromatography [silica gel; 1:4 ethyl acetate–redistilled light petroleum (bp 60–80 °C)], furnished, as the faster running fraction, 4-chloro-*N*-formylbenzamide (**3b**) (1.53 g, 28%) as a pale yellow solid: mp 95–96 °C; IR 3280, 1730, 1685 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (3 H, s, Ac), 5.40 (2 H, d, J = 7 Hz, NCH_2O), 7.40 (2 H, d, J = 9 Hz) and 7.85 (2 H, d, J = 9 Hz) [Ar H], 8.25 (1 H, br t, J = 7 Hz, NH); mass spectrum m/z 185/183 (M^+). The slower fraction, after evaporation of the eluant under reduced pressure, comprised *N*-(acetoxymethyl)-4-chlorobenzamide (**2b**) (2.69 g, 39%) as an off-white powder: mp 163–165 °C; IR 3320, 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.55 (2 H, d, J = 8 Hz) and 8.10 (2 H, d, J = 8 Hz) [Ar H], 9.50 (1 H, d, J = 10 Hz, CHO), 10.7 (1 H, br, NH); mass spectrum, m/z 229/227 (M^+).

***N*-(Acetoxymethyl)benzamide (2a) and *N*-Formylbenzamide (3a).** *N*-Benzoylglycine (**1a**) (4.5 g, 25 mmol) was treated with $Pb(OAc)_4$ (20.5 g, 50 mmol), and the products were isolated as for the preparation of **2b** and **3b** above. *N*-Formylbenzamide (**3a**) (80 mg, 22%) was obtained as a pale yellow solid: mp 109–110 °C (lit.[17] mp 112–113 °C); IR 3280, 1730, 1685 cm^{-1}; NMR ($CDCl_3$) δ 7.5–8.3 (5 H, m, Ar H), 9.45 (1 H, d, J = 10 Hz, CHO), 10.5 (1 H, br, NH); mass spectrum, m/z 193 (M^+), 150, 122, 121, 105 (100). *N*-(Acetoxymethyl)benzamide (**2a**) (480 mg, 10%) was isolated as a colorless viscous oil identical with a sample previously prepared by us by another route.[7]

***N*-(Acetoxymethyl)-4-methylbenzamide (2c) and *N*-Formyl-4-methylbenzamide (3c).** *N*-(4-Methylbenzoyl)glycine (**1c**) (9.65 g, 50 mmol) was treated with $Pb(OAc)_4$ (41.0 g, 92.5 mmol), and the products were isolated as for the reaction of **1b** above. *N*-Formyl-4-methylbenzamide (**3c**) (920 mg; 11%) was obtained as a white solid: mp 104 °C; IR 3320, 1745, 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (3 H, s, $ArCH_3$), 7.25 (2 H, d, J = 8 Hz) and 7.90 (2 H, d, J = 8 Hz) [ArH], 9.35 (1 H, d, J = 9 Hz, CHO), 10.45 (1 H, ca. d, J = 9 Hz, NH); mass spectrum, m/z 163 (M^+), 135, 119 (100), 91. *N*-(acetoxymethyl)-4-methylbenzamide (**2c**) (260 mg, 2.5%) was obtained as a white solid: mp 49 °C; IR 3320, 1760, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (3 H, s, $COCH_3$), 2.35 (3 H, s, $ArCH_3$), 5.40 (2 H, d, J = 7 Hz, NCH_2O), 7.15 (2 H, d, J = 8 Hz) and 7.75 (2 H, d, J = 8 Hz) [Ar H], 8.30 (1 H, t, J = 7 Hz, NH); mass spectrum, m/z 207 (M^+), 164, 148, 119 (100).

***N*-(Acetoxymethyl)-4-nitrobenzamide (2d).** *N*-(4-Nitrobenzoyl)glycine (**1d**) (5.60 g, 25 mmol) was treated with $Pb(OAc)_4$ (22.15 g, 50 mmol) as for the preparation of **2b** above except that chromatography was replaced by recrystallization from ethyl acetate/light petroleum (bp 60–80 °C). The acetoxymethylbenzamide **2d** (4.28 g, 72%) was obtained as a very pale greenish yellow solid: mp 94 °C (lit.[18] mp 120 °C); IR 3370, 1760, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (3 H, s, $COCH_3$), 5.45 (2 H, d, J = 7 Hz, NCH_2O), 7.90 (1 H, ca. t, J = 7 Hz, NH), 8.05 (2 H, d, J = 8 Hz) and 8.35 (2 H, d, J = 8 Hz) [Ar H].

***N*-(Acetoxymethyl)-4-methoxybenzamide (2e) and *N*-Formyl-4-methoxybenzamide (3e).** *N*-(4-Methoxybenzoyl)-glycine (**1e**) (2.99 g, 10 mmol) was treated with $Pb(OAc)_4$ (8.86g; 29 mmol) as for the preparation of **2b** and **3b** above. *N*-Formyl-4-methoxybenzamide (**3e**) (215 mg, 12%) was obtained as a white solid: mp 42–46 °C dec; NMR ($CDCl_3$) δ 3.60 (3 H, s, OCH_3), 6.95 (2 H, d, J = 8 Hz) and 7.85 (2 H, d, J = 8 Hz) [Ar H], 9.30 (1 H, d, J = 9 Hz, CHO), 10.0 (1 H, br, NH); mass spectrum, m/z 179 (M^+). *N*-(Acetoxymethyl)-4-methoxybenzamide (**2e**) (470 mg, 21%) was a white waxy solid of indefinite low mp: NMR ($CDCl_3$) δ 2.00 (3 H, s, $COCH_3$), 3.55 (3 H, s, OCH_3), 5.35 (2 H, d, J = 7 Hz, NCH_2O), 7.00 (2 H, d, J = 8 Hz) and 7.75 (2 H, d, J = 8 Hz) [Ar H], 8.60 (1 H, br, NH); mass spectrum, m/z 223 (M^+).

***N*-Acetyl-4-chlorobenzamide (3g).** *N*-(4-Chlorobenzoyl)-L-alanine (**1g**) (910 mg, 4 mmol) was treated with $Pb(OAc)_4$ (2.22 g, 5 mmol) as for the preparation of **2b** and **3b** above. *N*-Acetyl-4-chlorobenzamide (**3g**) (166 mg, 21%) was obtained as a colorless oil: IR 3370, 1700, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.60 (3 H, s, $COCH_3$), 7.50 (2 H, d, J = 8 Hz) and 7.80 (2 H, d, J = 8 Hz) [Ar H], 9.6 (1 H, br, NH); mass spectrum m/z 199/197 (M^+).

***N*-(4-Chlorobenzoyl)-2-hydroxyglycine (11).** 4-Chlorobenzamide (3.3 g; 20 mmol) was stirred with glyoxylic acid hydrate (1.84 g; 20 mmol) in 1,4-dioxane (50 mL) at 60 °C for 1 h. Evaporation of the solvent under reduced pressure afforded the adduct **11** (4.1 g; 89%) as white crystals: mp 150 °C dec; IR 3300, 2750, 1720, 1665 cm^{-1}; NMR (1:1 $CDCl_3/(CD_3)_2SO$) δ 5.75 (1 H, d, J = 8 Hz, NCHO), 7.50 (2 H, d, J = 8 Hz) and 7.90 (2 H, d, J = 8 Hz) [Ar H], 8.0 (1 H, br, CO_2H), 8.20 (1 H, brs, $CHOH$), 8.95 (1H, d, J = 8 Hz, NH).

Reaction of *N*-(4-Chlorobenzoyl)-2-hydroxyglycine (1f) with Acetic Acid and Acetic Anhydride. A solution of **11** (500 mg, 2.2 mmol) in acetic acid (4.0 mL) and acetic anhydride (2.0 mL) was stirred at 60 °C for 4 h in the presence of $Pb(OAc)_2$ (800 mg, 2 mmol). Evaporation of the solvents under reduced pressure gave a pale yellow gum, which, on column chromatography [silica

(15) Overton, M.; Threadgill, M. D.; Chipman, J. K.; Gescher, A.; Hickman, J. A. *Biochem. Pharmacol.*, in press.
(16) Boyd, G. V.; Wright, P. H. *J. Chem. Soc., Perkin. Trans. 1* **1972**, 909.
(17) Thompson, Q. E. *J. Am. Chem. Soc.* **1951**, *73*, 5914.
(18) Zawadowska, I.; Zawadowski, T. *Acta Pol. Pharm.* **1969**, *26*, 409.

gel; 1:4 ethyl acetate–redistilled light petroleum (bp 60–80 °C)], afforded *N*-(acetoxymethyl)-4-chlorobenzamide (**2b**) (80 mg; 12%) with physical properties identical with those of the sample described above.

Reaction of *N*-(4-Chlorobenzoyl)-2-hydroxyglycine (11) with Lead(IV) Acetate. Glyoxylic acid adduct **11** (500 mg, 2.2 mmol) was treated with $Pb(OAc)_4$ (1.8 g, 4.06 mmol) according to the general method for the preparation of **2b** and **3b** above to furnish 4-chloro-*N*-formylbenzamide (**3b**) (110 g, 27%) with physical properties identical with those of the sample described above.

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Mechanistic Studies by Deuterium Labeling and Related Kinetic Investigations of the [1,5]-Sigmatropic Hydrogen Shift of Vitamin D Type Vinylallenes[1]

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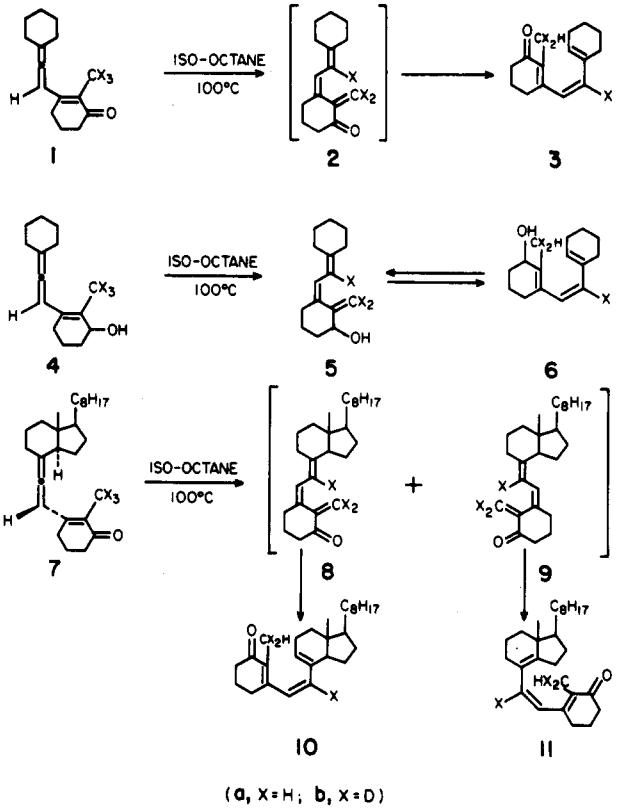
Kinetic investigations of the thermal [1,5]-sigmatropic hydrogen shift of deuterated and nondeuterated vinylallenes **1**, **4**, and **7** afforded primary kinetic deuterium isotope effects in the range 6.3–7.6 at 98.4 °C. This information together with Arrhenius data for the vinylallenone **1a** suggests a mechanistic similarity between the allenic and nonallenic variants of the [1,5]-shift process. Vinylallenes **24a** and **24b** were also studied in comparison with **1a** and **4a** in order to assess the effect of allylic substituents on reactivity. Finally, the rearrangement of **12b** and **13b** was examined in terms of the stereochemical course of the [1,5]-shift reaction.

In earlier investigations from this laboratory,[2] heating vinylallene **1a** in refluxing isooctane (ca, 100 °C) afforded the trienone **3a**[3] in quantitative yield. It was assumed that **1a** isomerized initially to **2a** via a rate-limiting [1,5]-sigmatropic shift followed by a spontaneous [1,7]-sigmatropic shift to afford the thermodynamically more stable, linearly conjugated system **3a** (Chart I). In the case of the corresponding alcohol **4a**,[3] a similar result was obtained except that the analogous alcohols **5a** and **6a** were obtained as a ~1:4 equilibrium mixture. The vinylallenone **7a**,[4] more closely related to vitamin D itself, behaves in a manner similar to **1a**[4b] except that due to the unsymmetrical moiety residing at the allene terminus, a pair of geometrically isomeric products **10a** and **11a** are obtained. The intramolecular nature of the [1,5]-sigmatropic rearrangement assures the geometry about the central double bond of the product be cis. However, the geometry at the Δ^7 double bond (exocyclic to the C ring of the steroid) is dependent upon two competing [1,5]-sigmatropic shifts. In one pathway, the desired (7*E*)-trienone **8a** is obtained. In the alternate pathway, the (7*Z*)-trienone **9a** is obtained.

Heating the diastereomeric vitamin D type vinylallenols **12a** or **13a**[4b] gave a result similar to that of **7a** except that the primary thermolysis products (**14a** and **16a** or **15a** and **17a**, respectively; Chart II) are rearranged to or in equilibrium with secondary and tertiary thermolysis products. Interestingly, although **8a** and **9a** are produced in equal amounts from **7a**, **12a** produces an excess of **16a** over **14a** (ca. 4:1); its epimer **13a** results in just the opposite ratio, an excess of **15a** over **17a** (ca. 4:1). This *E*/*Z* ratio (**14** or **15** to **16** or **17**) is general and results from a π-facial

Chart I



(1) This is paper 29 in the series "Studies on Vitamin D (Calciferol) and Its Analogues". For paper 28, see: Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268–270.
(2) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81–88.
(3) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4011–4015.
(4) (a) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907–4908. (b) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *Ibid.* **1980**, *102*, 6259–6267. See also: (c) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015–4020. (d) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099–6105. (e) Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1984**, *49*, 2152–2158.

0022-3263/86/1951-3201$01.50/0