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REACTION OF LEAD TETRA-ACETATE WITH PRIMARY AMIDES. FORMATION OF ALKYL CARBAMATES.

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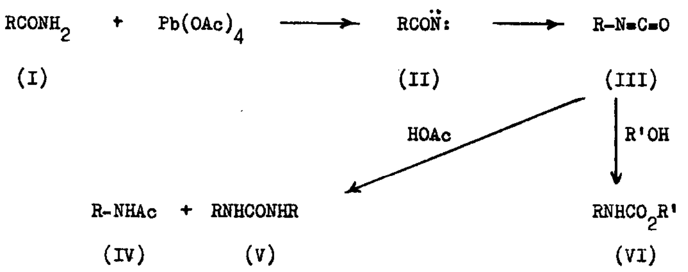
In a previous communication[1] we described the formation of N-acetylamines and N,N'-dialkylureas by interaction of primary amides and lead tetra-acetate in benzene or preferably in acetic acid. Evidence was presented in support of the hypothesis that the reaction proceeds initially to the appropriate isocyanate (III) from which the final products, (IV) and (V), were formed by reaction with acetic acid. It was also suggested that the rearrangement (I ⟶ III) involves the intermediacy of an acylnitrene (II). Independently, the reaction of lead tetra-acetate with primary amides and t-butanol in the presence of triethylamine was studied by Baumgarten and Staklis[2] who showed that t-butyl carbamates (VI, R'=t-Bu) are produced under these conditions. These authors confirmed the initial formation of the isocyanate and they further suggested that the reaction proceeds via a nitrene intermediate.



We also have studied the reaction of lead tetra-acetate with primary amides in the presence of alcohols. The discordance of some of our results with observations of Baumgarten and Staklis[2] prompts us to report them herein. Specifically, we find the reaction to be of much wider application than was previously recognised. Thus it was stated[2] that the reaction fails with compounds containing active methylene groups (phenylacetamide), or olefinic double bonds (cinnamamide) and can not be carried out in methanol or ethanol solvent. However, in our hands the reaction has proceeded smoothly in all these cases.

The results of our experiments are summarised in the accompanying table. The successful formation of alkyl carbamates when the reaction was conducted in alcoholic solvents was observed in experiments 1 to 9. In ethanol and methanol at the reflux temperature the reaction usually proceeds rapidly, and its completion, marked by the disappearance of the yellow colour first formed upon mixing of the reactants occurs in most instances in less than 1 hour. In a typical experiment (1) cyclohexanecarboxamide (1.0 g) and lead tetra-acetate (3.8 g) in methanol (50 ml) were stirred under nitrogen at 55-60°. After 1 hour the mixture was diluted with aqueous sodium carbonate and extracted with ether. Evaporation of the extract afforded methyl N-cyclohexylcarbamate

Table 1

Products from Interaction of Lead Tetra-acetate, Primary Amides and Alcohols

Expt.	Amide (I)	Alcohol[a]	Reaction Time	Yields (%)	
				Carbamate (VI)	Urea (V)
1	R= cyclohexyl	MeOH	30 min	96	nil
2	"	EtOH	60 "	88	"
3	"	t-BuOH	60 "	33	27
4	"	t-BuOH[b]	60 "	49	14
5	24-nor-5β-cholanyl	MeOH[c,d]	3 hr	58	nil[e]
6	" "	MeOH	4 hr	86	"
7	phenyl	"	20 min	62	"
8	p-nitrophenyl	"	30 "	69	"
9	benzyl	"	5 "	67	"
10	phenyl	cholesterol[b,c]	60 "	35	"
11	dec-9-enyl	EtOH[c]	2 hr	51	"
12	3β-acetoxyandrost-5-en-17β-yl	MeOH	10 min	57	"

[a] Unless otherwise stated the alcohol was also used as solvent.

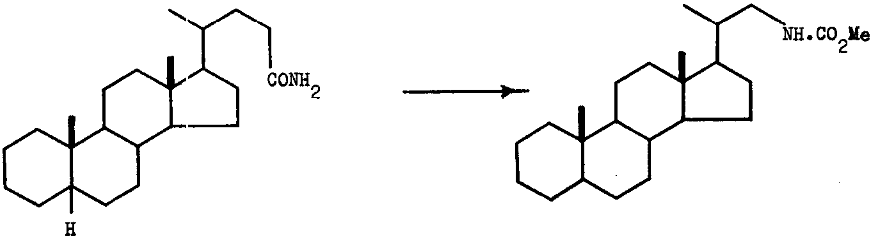
[b] Reaction conducted in the presence of pyridine.

[c] Benzene solvent.

[d] Methanol present as solvent of crystallization.

[e] Products included N-acetyl-24-nor-5β-cholanylamine (29%).

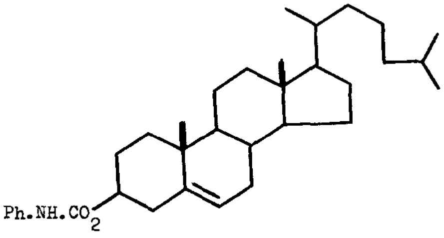
Of special interest, in that it illustrates well the ease of the reaction, is the formation of methyl N-(24-nor-5β-cholanyl)carbamate (VIII) by treatment of cholanamide (VII) with lead tetra-acetate (expt. 5). Although the only methanol available was that present as solvent of crystallization the product consisted mainly of the urethane (VIII), together with a smaller amount of N-acetyl-24-nor-5β-cholanylamine. The latter acetyl compound was the sole product when scrupulously dried amide was treated with lead tetra-acetate in benzene.[2] Conversely, when methanol was employed as solvent for the reaction only the urethane (VIII) was isolated (expt. 6).



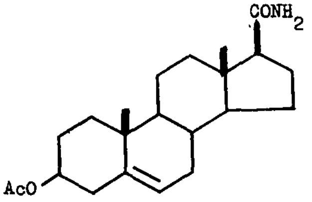
(VII) (VIII)

In accord with previous observations[2] we found that neat t-butanol is not a satisfactory solvent for the preparation of urethanes. Thus, cyclohexanecarboxamide when treated with lead tetra-acetate in t-butanol (expt. 3) afforded comparable amounts of t-butyl N-cyclohexylcarbamate (VI; R=cyclohexyl, R'=t-Bu) and N,N'-dicyclohexylurea. However when the reaction was repeated in the presence of pyridine (expt. 4) the yield of urea was greatly decreased, and that of the urethane proportionately increased.

The successful preparation of cholesteryl N-phenyl carbamate (IX) by interaction of lead tetra-acetate, benzamide, and cholesterol in benzene-pyridine is particularly significant in that it illustrates the applicability of the reaction to the formation of urethanes containing complex alkyl groups. Other examples of the reaction when applied to olefinic starting materials are the preparation of carbamates from 10-undecenamide (expt. 11) and from 3β-acetoxyandrost-5-ene-17β-carboxamide (X) (expt. 12).



(IX)



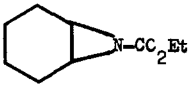
(X)

The reaction also has been successfully applied to a substituted aromatic amide (p-nitrobenzamide) and to an amide containing a reactive methylene group (phenylacetamide).

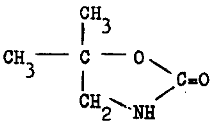
With a view to obtain evidence concerning the intermediacy of acylnitrenes in the reaction we have attempted to apply it to alkyl carbamates (XI) containing an unsubstituted $-NH_2$ group. Nitrenes potentially capable of formation from this type of precursor undergo rearrangement only with difficulty[4] and thus may be readily detected by their intermolecular reaction with suitable acceptors, e.g. olefins.[5]

$ROCONH_2$

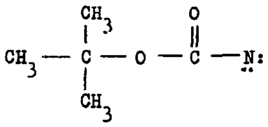
(XI)



(XII)



(XIII)



$CH_3-C(CH_3)_2-O-C(=O)-\ddot{N}:$

(XIV)

However, treatment of ethyl carbamate (XI, R=Et) with lead tetra-acetate in cyclohexene afforded solely 3-cylohexenyl acetate, and the aziridine (XII) known to be formed by addition of carbethoxynitrene to cyclohexene[5] could not be detected. When ethanol was employed as solvent acetaldehyde was formed in high yield and the carbamate was recovered unchanged. It was noted that the oxidation of ethanol by lead tetra-acetate proceeded very much faster in the presence of ethyl carbamate, than in its absence. Methanol was similarly rapidly oxidized by lead tetra-acetate in the presence of ethyl carbamate or t-butyl carbamate (XI, R=t-Bu). The latter compound (XI, R=t-Bu) was recovered unchanged after refluxion with lead tetra-acetate in benzene for one week. There was no evidence for the formation of the cyclic compound (XIII) which is obtained in good yield by an intramolecular insertion process from the appropriate nitrene (XIV) when generated photochemically.[6] The mechanistic implications of these observations will be discussed in detail elsewhere. In summary our conclusions are that the reaction of carbamates with lead tetra-acetate does not lead to nitrenes, and that probably the conversion (I → III) of carboxamides into isocyanates also does not proceed via nitrenes but involves a concerted oxidative rearrangement of a tetravalent lead - amide complex.

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