The Amination of Carboxylic Acid Derivatives by Tetrakis(dimethylamino)titanium

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A number of common derivatives of carboxylic acids were converted by tetrakis(dimethylamino)titanium to tris(dimethylamino)methane, $HC[N(CH_3)_2]_3$, or vinylidinebisdimethylamines, $R_2C{=}C[N(CH_3)_2]_2$, depending on the structure of the starting compound. The series of products obtained, five of which are new, serve to demonstrate the generality of the reaction.

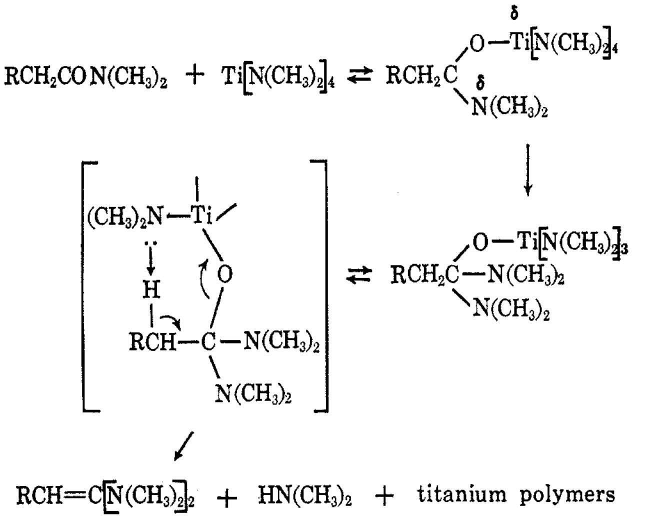
We would like to report a new synthetic route to *gem*-triamines and vinylidinebisdialkylamines (ketene N,N-acetals).[1] The analogous triaminoethane, 1,1,1-tripiperidinoethane, was reported as early as 1887[2] and the same compound again in 1940.[3] However, both assignments were shown to be incorrect[4] and the first authentic *gem*-triamino compound, N,N′,N′′-triphenyl-N,N′,N′′-trimethyltriaminomethane, was reported by Clemens, Shropshire, and Emmons[5] in 1962. The first examples of vinylidinebisdialkylamines appear to be those reported by Ott, Dittus, and Weissenberger[6] in 1943 and by McElvain and Tate[7] in 1945. Since then several other elegant synthetic routes have been reported,[8] but in general the methods for preparing triaminomethanes and vinylidinebisdialkylamines are either multistep, poor to moderate in yield, or not adaptable to use with the more volatile amines. We believe the method described in the present paper is relatively direct and versatile and affords moderate to good yields.

Results and Discussion

Recently we observed a vigorous, exothermic reaction on mixing esters of carboxylic acids and tetrakis(dimethylamino)titanium. A more detailed examination of the reaction revealed the products to be *gem*-triamines or vinylidinebisdialkylamines depending on the structure of the starting ester. The titanium was precipitated as the dioxide. Furthermore, we learned the reaction could be carried out with most of the common acid derivatives (free acid, ester, amide, anhydride) giving essentially the same results. The N,N-dialkylamide was found to be the starting material of choice and, indeed, all the reactions using other acid derivatives were shown to proceed to product *via* the amide. Significant quantities of amide were identified by proton nmr in all of our experiments. Reactions using the dialkylamide as starting material not only afford higher yields but require less of the titanium compound.

The experimental results are summarized in Table I. The compounds **2** and **3** have been reported previously in the literature[8] the others, to our knowledge, are reported here for the first time.

SCHEME I



A probable mechanism for the reaction is shown in Scheme I.

When no β protons are available for elimination then another dialkylamino group can be transferred from the titanium to the carbon in a four center exchange or an ionization step to yield *gem*-triamine.

A number of other carboxylic acid systems were examined but they gave different results than those reported in Table I. N,N-Dimethylacrylamide led only to polymers; N,N,N′,N′-tetramethylmalonamide gave chelates; N,N-dimethylbenzamide and tetramethyloxamide gave complex results which are as yet unclear. We expect to report on these more complex systems in the near future as well as the kinetics and mechanism of the over-all reaction.

Experimental Section

Proton nmr spectra were obtained from a Varian Model A-60 spectrometer. The tetrakis(dimethylamino)titanium was prepared by the method of Bradley and Thomas.[9] The ethyl ether solvent was purified by distillation from $LiAlH_4$. The amides were either the best commercial grades available or prepared by standard methods.

Synthesis of Tris(dimethylamino)methane.—A solution of 3.36 g (0.015 mole) tetrakis(dimethylamino)titanium in 40 ml of dry ether was prepared. To this solution was added dropwise with stirring 2.2 g (0.030 mole) of dimethylformamide. More ether may be added to loosen the precipitate. The reaction mixture was allowed to stand overnight. The mixture was then filtered and the solvent removed from the filtrate at reduced pressure. The residual oil was distilled yielding 3.6 g (83% yield) of tris(dimethylamino)methane, bp 70° (50 mm).

Synthesis of Vinylidinebisdimethylamine.—A solution of 7 g (0.031 mole) of tetrakis(dimethylamino)titanium in 40 ml of ethyl

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[2] A. Kekule, *Ber.*, **20**, 3247 (1887).

[3] H. M. Barnes, D. Kundiger, and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1281 (1940).

[4] H. Bohme and F. Soldan, *Ber.*, **94**, 3109 (1961).

[5] D. H. Clemens, E. Y. Shropshire, and W. D. Emmons, *J. Org. Chem.*, **27**, 3664 (1962).

[6] E. Ott, G. Dittus, and H. Weisenberger, *Ber.*, **76**, 84 (1943).

[7] S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **67**, 202 (1945).

[8] H. Bredereck, F. Effenberg, and H. P. Beyerlin, *Ber.*, **97**, 3081 (1964).

[9] D. C. Bradley and T. M. Thomas, *J. Chem. Soc.*, 3857 (1960).

TABLE I

	Product	C, %		H, %		N, %		$n^{25}D$	Mol wt		Nmr,[a] τ	Bp, °C (mm)	Yield, %
		Calcd	Found	Calcd	Found	Calcd	Found		Calcd	Found			
1	$HC[N(CH_3)_2]_3$	57.9	57.9	13.2	13.3	28.9	29.3	1.4348	145	144[b]	(s) 6.98, (s) 7.69 (1:18)	70 (50)	83
2	$CH_2{=}C[N(CH_3)_2]_2$	63.1	62.7	12.4	12.1	24.5	24.3	1.4500	114	114	(s) 6.60, (s) 7.53 (1:6)	115 (744)	87
3	$CH_3CH{=}C[N(CH_3)_2]_2$	65.5	65.2	12.7	12.8	21.8	21.5	1.4552	128	128	(q) 7.46, (s) 7.36, (s) 7.65, (d) 8.29 (1:6:6:3)	74 (80)	73
4	$(CH_3)_2C{=}C[N(CH_3)_2]_2$	67.5	67.3	12.8	12.9	19.7	19.5	1.4579	142	142	(s) 7.46, (s) 8.32 (2:1)	60 (30)	70
5	$C_6H_5CH{=}C[N(CH_3)_3]_2$	75.8	75.6	9.5	9.2	14.7	14.1	1.5905	190	190	(m) 3.05, (s) 5.52[c] (s) 7.34, (s) 7.40 (5:1:6:6)	80 (1)	88
6	$Cl_2C{=}C[N(CH_3)_2]_2$[d]	39.3	39.4	6.6	7.0			1.5903	183	183	(s) 7.59	54 (3)	68
7	$\{-CH{=}C[N(CH_3)_2]_2\}_2$	63.7	63.4	11.6	11.3	24.8	24.6	1.5408	226	226	(s) 5.25, (s) 7.25 (s) 7.56 (1:6:6)	74 (1)	53

[a] Benzene solvent, TMS internal standard. [b] By cryoscopy (all others by mass spectroscopy). [c] Carbon tetrachloride solvent, TMS internal standard. [d] Calcd for Cl: 38.8. Found: 39.1.

ether was prepared. To this solution was added dropwise with stirring 4.7 g (0.054 mole) of dimethylacetamide. The reaction mixture was allowed to stand overnight, then filtered, and the solvent removed. The residual oil was fractionally distilled yielding 4.8 g (78%) of vinylidinebisdimethylamine, bp 115° (749 mm).

Synthesis of Propenylidenebisdimethylamine.—A solution of 4.04 g (0.04 mole) of N,N-dimethylpropionamide (Eastman) in 20 ml of dry ether was prepared. To it was added dropwise with stirring a solution of 4.52 g (0.021 mole) of tetrakis(dimethylamino)titanium in 5 ml of dry ether. The reaction mixture was allowed to stand for 3 days, then filtered, and the solvent removed. The resulting oil was fractionally distilled yielding 3.74 g (73% yield) of propenylidenebisdimethylamine, bp 74° (80 mm).

Preparation of 2-Methylpropenylidinebisdimethylamine.—To 3.3 g (0.015 mole) of tetrakis(dimethylamino)titanium in a 25-ml round-bottom flask was added 3.25 g (0.028 mole) of N,N-dimethylisobutyramide. The reaction flask was placed in an oil bath kept at 90°. The flask was vented to the atmosphere through a tube of Drierite. After 16 hr in the bath the reaction mixture was a dark solid mass. It was cooled; ethyl ether was added; it was shaken vigorously and filtered. The ether was removed and the residual oil distilled yielding 2.8 g (70%) of 2-methylpropenylidinebisdimethylamine, bp 60° (30 mm).

Preparation of 2-Phenylvinylidinebisdimethylamine.—A solution of 4.89 g (0.030 mole) of N,N-dimethylphenylacetamide in 15 ml of dry ether was prepared. To this solution was added a solution of 3.36 g (0.015 mole) of tetrakis(dimethylamino)titanium in 5 ml of ether; 10 ml of ether was added to break up the precipitate which formed. The reaction mixture was allowed to stand overnight. The mixture was filtered and the solvent removed from the filtrate. The residual oil was distilled yielding 5.02 g (88% yield) of 2-phenylvinylidinebisdimethylamine, bp 80° (0.9 mm).

Synthesis of 2,2-Dichlorovinylidinebisdimethylamine.—A solution of 3.12 g (0.02 mole) of N,N-dimethyl-2,2-dichloroacetamide in 20 ml of dry ether was prepared. A solution of 2.30 g (0.0103 mole) of tetrakis(dimethylamino)titanium in 10 ml of dry ether was added dropwise with stirring. The reaction mixture was allowed to stand overnight, then filtered, and the solvent removed. The resulting oil was fractionally distilled yielding 2.49 g (68% yield) of 2,2-dichlorovinylidenebisdimethylamine, bp 55° (3 mm).

Synthesis of 1,1,4,4-Tetrakis(dimethylamino)butadiene.—A solution of tetrakis(dimethylamino)titanium (7 g, 0.031 mole) in 40 ml of ethyl ether was prepared. To this solution was added dropwise with stirring a solution of 2 g (0.02 mole) of succinic anhydride in a minimum of warm dioxane. The reaction mixture was allowed to stand for 60 hr at room temperature; the precipitate was then filtered off and the filtrate removed by distillation. The residual oil was fractionally distilled to yield 2.6 g (58%) of 1,1,4,4-tetrakis(dimethylamino)butadiene, bp 74° (1 mm).

A Novel Synthesis of N-Carboxydehydro-α-amino Acid Anhydrides and Their Reactions

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New pseudoxazolones, 2-isopropylidene-4-isobutyl-3-oxazolin-5-one and 2-isopropylidene-4-isopropyl-3-oxazolin-5-one, were easily copolymerized with oxygen to give polyperoxides. By thermal decomposition of each polyperoxide, 4-isobutylidene-2,5-oxazolidinedione (dehydroleucine NCA) and 4-isopropylidene-2,5-oxazolidinedione (dehydrovaline NCA) were obtained in 28 and 16% yields, respectively. From these results, the structure of the polyperoxides was discussed. Dehydroleucine NCA and dehydrovaline NCA gave the corresponding α-keto acids by hydrolysis and anilides by reaction with aniline. In contrast to the saturated NCA, dehydroleucine NCA and dehydrovaline NCA did not give polypeptides by reaction with triethylamine. Hydrogenation of dehydroleucine NCA afforded polyleucine.

As examples of unsaturated N-carboxy-α-amino acid anhydrides (NCA), allylglycine NCA[1] (4-allyl-2,5-oxazolidinedione) and propargylglycine NCA[2] (4-propargyl-2,5-oxazolidinedione) have been reported by Schlögl. Dehydroalanine NCA[3] (4-methylene-2,5-oxazolidinedione), in which the double bond was directly attached to the five-membered ring, has been synthesized by Sakakibara from benzyl carbamate and pyruvic acid. We have found that polyperoxides[4] (IIa and IIb) are obtained by copolymerization of 2-

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[1] K. Schlögl and H. Fabitschowitz, *Monatsch. Chem.*, **85**, 1060 (1954).

[2] K. Schlögl and H. Pelousek, *ibid.*, **91**, 227 (1960).

[3] S. Sakakibara, *Bull. Chem. Soc. Japan*, **32**, 13 (1957).

[4] F. Toda, *Bull. Tokyo Inst. Technol.*, **No 57**, 93 (1964); this will be reported separately in detail.