

A 2 g. sample of the mono-acid-amide III readily dissolved in cold dilute potassium hydroxide solution. On refluxing this solution for 3 hr., ammonia was evolved, and there was obtained, on acidification of the cooled solution, 1.6 g. (80%) of diacid II, m.p. 216–217°. This melting point was not depressed on admixture with diacid II prepared from the conjugate addition of phenylacetic acid and ethyl cinnamate as described above. A mixed melting point with the mono-acid-amide III was depressed to 185–190°.

Conjugate addition of ethyl phenylacetate with ethyl cinnamate. To a stirred solution of 0.1 mole of sodium amide in 300 ml. of liquid ammonia was added 16.4 g. (0.1 mole) of ethyl phenylacetate in an equal volume of ether, and the resulting solution stirred for 15 min. A solution of 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of ether was added, and the ammonia was replaced by ether. The resulting ether suspension was refluxed on the steam bath for 30 min., cooled, and decomposed with ice water. The ethereal layer (with which was combined three ether extracts of the aqueous layer) was dried over Drierite, and the solvent removed. The residue was distilled *in vacuo* to give 6.5 g. of recovered ethyl cinnamate, leaving a residue that solidified after standing at room temperature for one day. This solid was recrystallized from ethanol to give 22 g. (65%) of white diester IV, m.p. 76–77° (lit. m.p. 75–75.5°).⁷ The higher melting isomer of diester IV is reported to melt at 92–93°.¹⁷

A 6 g. sample of diester IV was refluxed 6 hr. with an

aqueous solution of potassium hydroxide containing approximately an equimolar amount of this base. After cooling and removing a small amount of gummy residue, the alkaline solution was acidified with iced hydrochloric acid. The resulting white precipitate was recrystallized from a mixture of ether and petroleum ether (b.p. 30–60°) to give 2.5 g. (50%) of diacid II, m.p. 193–196°. This melting point was not depressed on admixture with a sample of diacid II.

Cyclization of diacid II. A solution of 5 g. of diacid II in 150 g. of liquid hydrogen fluoride contained in a polyethylene bottle was allowed to stand in a hood at room temperature overnight, during which time the hydrogen fluoride had evaporated. The resulting gummy residue was dissolved in ether, and the yellow solution was poured into dilute potassium hydroxide. The two layers were separated. The orange-red aqueous alkaline layer was cooled in an ice bath and acidified with iced hydrochloric acid to precipitate 4.5 g. of a white semi-solid which was presumably hydrindone V. This product resisted crystallization from the usual organic solvents, but it readily gave a yellow-orange 2,4-dinitrophenylhydrazone in 48% over-all yield. After two recrystallizations from ethanol, this derivative melted at 262–263° (softened at 258°) in agreement with the melting point reported for it when hydrindone V was prepared by the cyclization of the anhydride of II by means of aluminum chloride.⁸

Anal. Calcd. for C₂₃H₁₈O₆N₄: C, 61.88; H, 4.06; N, 12.55. Found: C, 61.66; H, 4.17; N, 12.75.

DURHAM, N. C.

(17) W. Borsche, *Ber.*, **42**, 4497 (1909).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Stability of Mixed Carboxylic-Carbonic Anhydrides

D. STANLEY TARBELL AND NORMAN A. LEISTER¹

Received February 3, 1958

Preparation of a considerable number of mixed carboxylic-carbonic anhydrides shows that they are more stable than previously supposed. Some are stable crystalline solids, and many of the liquid ones can be distilled without decomposition. They have been characterized by analysis, except in the case of some liquids which could not be distilled, and by the preparation of solid derivatives.

The mixed carboxylic-carbonic anhydrides, RCOOCOOR, have been widely used for the preparation of amide and particularly of peptide linkages.^{2,3} It has also been found that they can be used for numerous acylation reactions on carbon, such as acylation of malonic and acetoacetic ester,⁴ the formation of ketones from organocadmium compounds,⁴ and preparation of diazoketones from

diazomethane.^{4,5} In the recent work in which the mixed anhydrides were utilized,^{2–5} generally no attempts were made to isolate them, and the impression is given that they are unstable compounds.^{2,3} In early work,⁶ several mixed anhydrides were prepared from the acid and ethyl chlorocarbonate; they were described as unstable oils and were not characterized suitably. More recently, the mixed anhydride has been isolated from benzylpenicillin in the form of a rather unstable gum.⁷ Small yields of the mixed anhydrides III and IV have been obtained by oxidation of α -keto esters I and II by

(1) Monsanto Fellow, 1956–57.

(2) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951)

(3) *E.g.*, J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952); J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953); **76**, 2474 (1954); V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953); **76**, 3107 (1954); B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

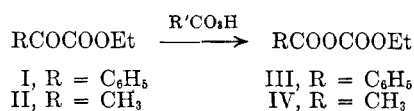
(4) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

(5) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **18**, 161 (1953).

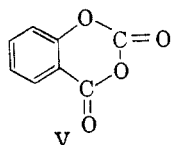
(6) Knoll and Co., German Patent **117,267** [*Chem. Zentr.*, **72**, 347 (1901); *Friedländer*, **VI**, 146].

(7) R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jensen, M. E. Trevelt, and G. B. Webb, *J. Chem. Soc.*, 3733 (1953); D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3636 (1953).

peracids; the products were purified by fractional distillation, and showed satisfactory analyses.⁸

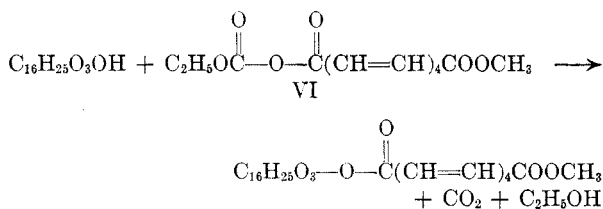


Cyclic anhydrides, of the Type V, derived from salicylic or glycolic acid, have been prepared, and show reasonable stability.⁹ Nevertheless, as far as we have been able to discover, there was no



crystalline mixed anhydride of the type III-IV known, and only the examples mentioned above appear to have been obtained pure.

We were therefore surprised to isolate¹⁰ a stable crystalline compound, whose analysis, infrared spectrum, and conversion to the amide showed that it had the structure VI. This compound was obtained from an attempt to regenerate fumagillin methyl ester by an esterification using the mixed anhydride VI and the alcohol moiety of fumagillin.¹¹ The mixed anhydride VI was pre-



pared in the usual way from methyl hydrogen decatetraenedioate¹² and was used *in situ*; the mixed anhydride was isolated from the reaction mixture.

This result suggested that mixed anhydrides derived from high-melting carboxylic acids might be stable compounds. Furthermore, the availability of stable pure mixed anhydrides would permit the investigation of a number of problems of both

(8) P. Karrer and F. Haab, *Helv. Chim. Acta*, **32**, 950 (1949).

(9) L. A. Dupont, French Patent 771,653 [*Chem. Abstr.*, **29**, 816 (1935)]; A. E. Chichibabin, *Compt. rend.*, **213**, 355 (1941); W. H. Davies, *J. Chem. Soc.*, 1357 (1951). A cyclic anhydride similar to V has been obtained by D. Burn and W. Rigby, *J. Chem. Soc.*, 2967 (1957) by degradation of marrubiin.

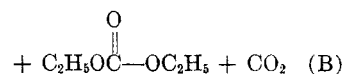
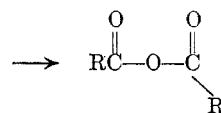
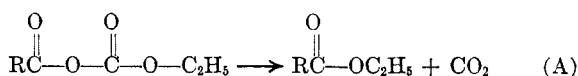
(10) We are indebted to Dr. John A. Price for this experiment.

(11) For studies on the structure of fumagillin, see J. R. Schenck, M. P. Hargie, and A. Isarasena, *J. Am. Chem. Soc.*, **77**, 5606 (1955); D. S. Tarbell, P. Hoffman, H. R. Al-Kazimi, G. A. Page, J. M. Ross, H. R. Vogt and B. Wargotz, *J. Am. Chem. Soc.*, **77**, 5610 (1955); J. M. Ross, D. S. Tarbell, W. E. Lovett and A. D. Cross, *J. Am. Chem. Soc.*, **78**, 4675 (1956).

(12) C. J. Brown and J. K. Landquist, *Chem. and Ind. (London)*, 973 (1953).

synthetic and mechanistic character, which would increase our knowledge of the chemistry of this class. We have therefore undertaken a survey of the preparation of representative mixed anhydrides, the results of which are shown in Table I.

The assignment of the mixed carbonic-carboxylic anhydride structures to these materials is based on the elementary analysis, the typical anhydride double peaks (separated by about 60 cm.⁻¹) in the carbonyl region of the infrared, and, in a number of cases, the preparation of solid derivatives. The mixed anhydrides can decompose by the following paths¹³



The occurrence of either of these modes of reaction in our samples would be apparent from the elementary analysis, since both paths A and B involve elimination of carbon dioxide; furthermore, A yields the ester RCOOC₂H₅, and B gives the dialkyl carbonate C₂H₅O—COOC₂H₅. These types have normal ester carbonyl absorption in the infrared, and their absence in the mixed anhydride samples is clear from the infrared spectra of these samples.

The method of preparation of the mixed anhydrides involved washing with aqueous bicarbonate solution, and it is apparent that this treatment does not decompose the anhydrides. The mixed anhydrides can therefore be made at room temperature and without particular regard to the exclusion of water. This was demonstrated by the preparation of the propionic anhydride, in refluxing ether and with undried undistilled reagents. The product prepared under these conditions gave the same yield of propionanilide as the product prepared at 0° under anhydrous conditions.

It is possible, of course, that mixed anhydrides derived from acylaminoacids, which are the ones most carefully investigated heretofore,^{2,3} are more unstable than the unaminated types described here.

EXPERIMENTAL¹⁴

Preparation and isolation of carboxylic-carbonic anhydrides. A dry ethereal solution of equimolar quantities of the

(13) J. Herzog, *Ber.*, **42**, 2557 (1909); A. Einhorn, *Ber.*, **42**, p. 2772; T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(14) Melting points are uncorrected. Microanalyses are by Miss Annette Smith and Microtech Laboratories. Yields are based on starting materials taken and do not take into account any recovered starting material.

TABLE I
MIXED CARBOXYLIC-CARBONIC ANHYDRIDES

R	M.P. or B.P., °C.	Formula	Carbon, %		Hydrogen, %		Infrared Bands, Cm. ⁻¹	Stability ^a	Derivative, RCONHR ¹ R ¹
			Calcd.	Found	Calcd.	Found			
CH ₃ OOC(CH=CH) ₄ CH ₃ OOC(CH=CH) ₂ CH ₃ (CH=CH) ₂	120-123	C ₁₄ H ₁₆ O ₆	59.99	59.72	5.75	5.79	1792, 1727, 1701	++ +	H ^b
	66-67.5	C ₁₀ H ₁₂ O ₆	52.63	53.08	5.30	5.37	1808, 1732, 1712	++ +	C ₆ H ₆ , m.p. 154-156° ^c
	148 (20 mm.) <i>n</i> _D ²⁰ 1.4930	C ₈ H ₁₀ O ₄	58.69	59.34	6.57	6.93	1792, 1727	++ +	
C ₆ H ₅ CH=CH C ₃ H ₇ OOCCH=CH (<i>trans</i>) CH ₃ OOCCH=CH (<i>cis</i>) CH ₃ CH=CH (<i>trans</i>)	<i>n</i> _D ²⁸ 1.5529 ^d	C ₁₂ H ₁₄ O ₄	65.44	66.32	5.49	5.56	1797, 1730	+	C ₆ H ₅ , m.p. 152-154° ^e
	<i>n</i> _D ²⁸ 1.4465	C ₉ H ₁₀ O ₆	50.00	51.75 ^f	5.60	5.69	1810, 1755, 1722	++	C ₆ H ₅ , m.p. 107.5-109° ^g
	<i>n</i> _D ²⁶ 1.4481	C ₈ H ₁₀ O ₆	47.53	48.31 ^f	4.99	4.93	1812, 1733	++	^h C ₆ H ₅ , m.p. 112.5-114.5° ⁱ
	55-56 (0.5 mm.) <i>n</i> _D ²⁶ 1.4392	C ₇ H ₁₀ O ₄	53.16	53.49	6.37	6.40	1798, 1730	++	
C ₈ H ₄ NO ₂ (<i>p</i>) 1-Naphthyl C ₈ H ₇ COOCCH ₂ (<i>p</i>) C ₈ H ₇ COOCCH ₂ (<i>o</i>) (CH ₃) ₂ CHCH ₂	56-57 <i>j</i>	C ₁₀ H ₉ NO ₆	50.21	50.30	3.79	3.94	1802, 1735	++ +	^k
	48-50	C ₁₄ H ₁₂ O ₄	68.84	68.86 ^f	4.95	5.14	1795, 1735	++ +	
	<i>n</i> _D ²⁵ 1.4915	C ₁₂ H ₁₂ O ₆	57.14	57.10	4.80	5.10	1798, 1732, 1716	++ +	
	44-54 (0.5 mm.)	C ₁₅ H ₁₈ O ₆	61.21	61.13	6.17	6.39	1815, 1754, 1721	++ +	C ₆ H ₅ , m.p. 105-107° ^l
	<i>n</i> _D ²⁶ 1.4053-1.4079	C ₈ H ₁₄ O ₄	55.16	55.20	8.10	8.15	1810, 1755	++ +	C ₆ H ₅ , m.p. 104-106° ^m
CH ₃ CH ₂ CH ₃	65-78 (20 mm.) <i>n</i> _D ²⁷ 1.3965-1.3980	C ₈ H ₁₀ O ₄	49.31	50.37	6.90	7.13	1815, 1750	++ +	C ₆ H ₅ , m.p. 102-104°
	64-67 (20 mm.) <i>n</i> _D ²⁶ 1.3911	C ₈ H ₈ O ₄	45.45	45.51	6.10	6.25	1827, 1755	++ +	C ₆ H ₅ , m.p. 112-114° ⁿ

^a ++, noticeable decomposition in a few days; + + +, stable, all referring to room temperature. ^b See Experimental. ^c Reported by O. Doebner and A. Wolff, *Ber.*, **34**, 2222 (1901), as 153°. ^d Sample decomposed on attempted distillation; after standing several days, cinnamic anhydride, m.p. 131-134°, was deposited. Analysis was on undistilled material. ^e Reported by W. Autentrieth, *Ber.*, **34**, 186 (1901) as 150°. ^f Undistilled sample; distillation caused decomposition. ^g Calcd. for C₁₂H₁₄NO₃; C, 65.74; H, 5.98. Found: C, 65.76; H, 6.00. ^h Attempted preparation of the anilide gave a mixture. ⁱ Reported by W. Autentrieth and P. Spiess, *Ber.*, **34**, 189 (1901) as 115°. ^j Attempted distillation gave ethyl carbonate and 1-naphthoic anhydride. ^k Treatment with aniline gave a mixture of 1-naphthoic anilide, m.p. 161-163° and ethyl *N*-phenylcarbamate, m.p. 48.5-50°. ^l Calcd. for C₁₅H₁₈NO₃; C, 72.70; H, 6.44. Found: C, 72.59; H, 6.47. ^m Reported by A. Crossley and W. Perkin, *J. Chem. Soc.*, **73**, 16 (1898) as 109-111°. ⁿ P. Karrer and F. Haab, *Helv. Chem. Acta*, **32**, 957 (1949), give the b.p. as 44-52° (9 mm.).

pure acid and freshly distilled triethylamine was cooled to 0° in an ice bath. With stirring, an equivalent amount of ethyl chlorocarbonate was slowly added so that the temperature remained near 0°. The mixture was stirred an additional 1.5 hr. during which time it slowly warmed to room temperature. The amine salt was filtered (nearly quantitative yield in every case) and washed with ether. The combined filtrate was washed with sodium bicarbonate solution and water, and after drying over magnesium sulfate was evaporated under vacuum at room temperature. The crystalline mixed anhydrides were recrystallized for analysis from ether-petroleum ether or benzene-petroleum ether.

Methyl hydrogen decatetraene-dioate was prepared¹² by the action of methanolic sodium hydroxide on fumagillin and melted at 209–210°; the reported¹² value is 217–218°.

Methyl hydrogen decatetraene-dioic acid chloride and amide.

A mixture of 0.50 g. of methyl hydrogen decatetraenedioate, 0.6 g. of phosphorus pentachloride, and 10 cc. of petroleum ether was refluxed for 1.75 hr. The solvent and phosphorus oxychloride were removed under reduced pressure, yielding 0.28 g. of product, m.p. 151–154° with decomposition.

Anal. Calcd. for C₁₁H₁₁ClO₃: C, 58.28; H, 4.90. Found: C, 58.32; H, 5.05.

Treatment of a chloroform solution of the ester acid chloride above with ammonia gas gave a white precipitate of the corresponding *amide*, m.p. 209–210° after recrystallization from aqueous methanol. This product gave no depression on mixed melting point with the amide prepared by action of ammonia gas on the mixed anhydride VI.

Anal. Calcd. for C₁₁H₁₃NO₃: C, 63.75; H, 6.32. Found: C, 63.33; H, 6.50.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Action of Secondary Amines on Mixed Carboxylic-Carbonic Anhydrides; the Factors Favoring Urethan Formation Instead of Amide Formation¹

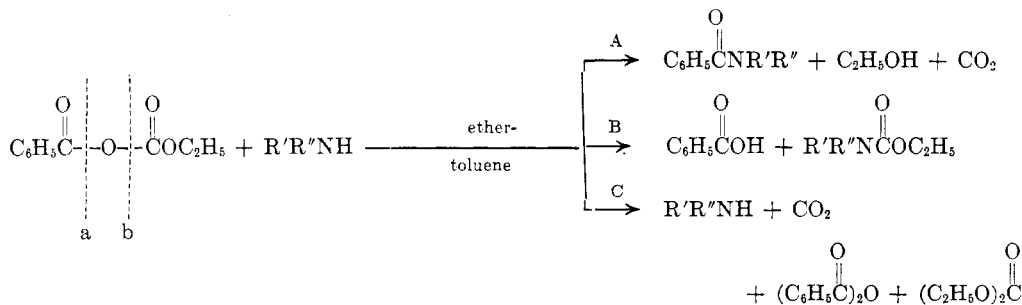
NORMAN A. LEISTER² AND D. STANLEY TARBELL

Received February 3, 1958

The action of a series of ten secondary amines on benzoic-carbonic anhydride leads in each case to urethan formation in addition to amide formation, with urethan predominating in most cases. Increasing the steric hindrance around the amino nitrogen increases the ratio of urethan to amide. A series of mixed anhydrides in which the carboxylic acid component was varied was treated with *N*-methylaniline. Pivalic acid and aromatic acids gave more urethan than amide; other acids, without alkyl or aryl substitution on the α -carbon, gave more amide than urethan. The results are discussed in the light of other work on reactions of unsymmetrical anhydrides.

It has been shown that mixed carboxylic-carbonic anhydrides are very useful for acylation of primary amines to form amides,¹ and for formation of phthalimides from phthalamic acids,³ as well as for various acylations on carbon.^{1,4} We were therefore surprised to find that an attempt to prepare the bisamide from *N*-methylaniline and a phthalic acid derivative gave a very unsatisfactory result. A study of the action of *N*-methylaniline on benzoic-carbonic anhydride showed that the main product was *N*-methyl-*N*-phenylcarbamate, instead of the

expected *N*-methylanilide. The action of a series of representative secondary amines on this mixed anhydride was therefore studied, as well as the action of *N*-methylaniline on a series of mixed anhydrides in which the carboxylic acid component was varied. The results show that secondary amines usually react with mixed carbonic anhydrides to form a mixture of urethan and amide; the former may predominate, depending on the compounds involved. These results may be useful in considering the mixed carbonic anhydrides for synthetic operations.



(1) Previous papers in this field: (a) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957); (b) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958). Reference 1b contains adequate references to the earlier literature.

(2) Monsanto Fellow, 1956–1957.

(3) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(4) J. A. Price and D. S. Tarbell, *Org. Syntheses*, **37**, 20 (1957).