evaporated to dryness and the residue was acetylated as above.

(b) **Use of Hydrochloric Acid.**—A solution of 50 g. of crude I in 100 ml. of acetic anhydride was treated with 14.9 ml. (1 equiv.) of concd. hydrochloric acid. The mixture was refluxed for two hours, cooled and treated with 12.5 g. of sodium acetate. After oxidation, the reaction mixture was processed as above and gave 5.2 g. of pregnadienolone acetate (IV), m.p. 165–170°; $[\alpha]_D^{25}$ −39.5°; *E*, 264 (233 mμ) (96.0% pure).

(c) **Use of Acetyl Chloride.**—A sample of 50 g. of crude I in 100 ml. of acetic anhydride was treated with 8.55 g. (1 equiv.) of acetyl chloride. The mixture was refluxed for four hours, treated with 12.5 g. of sodium acetate and worked up as usual after oxidation. The product weighed 4.4 g., m.p. 165–171°; $[\alpha]_D^{24}$ −38.9°; *E*, 259 (233 mμ) (94.3% pure).

(d) **Use of *p*-Toluenesulfonic Acid.**—Fifty grams of crude I in 100 ml. of acetic anhydride was treated with 2 g. of *p*-toluenesulfonic acid and refluxed for eight hours. Sodium acetate (1 g.) was added and the mixture was oxidized and worked up as usual. Only 0.9 g. of pregnadienolone acetate (IV) was obtained, m.p. 170–173°; $[\alpha]_D^{23}$ −40.2°; *E*, 275 (233 mμ) 100% pure). The mother liquor was treated with water and gave 21.5 g. of resin which contained 2.3 g. of pregnadienolone acetate as indicated by the ultraviolet absorption maximum, *E*, 30 (235 mμ).

(e) **Other Catalysts.**—Undesired reactions occurred so that the product could not be isolated using the following acid catalysts: $SnCl_4$, BF_3, $ZnCl_2$, $HClO_4$, oxalic acid and trichloroacetic acid. There was little reaction with traces of acids. For example, 20 g. of I in 100 ml. of acetic anhydride was unaffected after refluxing with 0.1 cc. H_2SO_4 for eight hours.

Thermal Cleavage of 5-Pregnen-3β,16β-diol-20-one-3-acetate-16-(δ-acetoxy-γ-methylvalerate) (III).—Fifty grams of I was treated according to the directions (a) for the preparation of IV. After the reduction of excess chromic acid with sodium bisulfite solution, the oxidation mixture containing III was concentrated *in vacuo* and extracted with ether. The ether solution was washed neutral and dried over anhydrous magnesium sulfate. A sample evaporated to dryness showed *E*, 91 (237 mμ) corresponding to 33% of 5,16-pregnadien-3β-ol-20-one acetate (IV) (already formed due to cleavage under the acid conditions in the reaction and processing) in the crude III.

The ether solution was concentrated and mixed with 65 ml. of xylene. The solution was distilled until the temperature reached 135° and the remainder was refluxed for one hour. A sample was evaporated to dryness and showed *E*, 136.6 (237 mμ). This corresponds to 49.6% of IV, an increase of 50% over the pretreated mixture of III and IV.

The solution was chilled overnight and the product collected. The yield was 9.0 g., m.p. 156.2–165.6°; *E*, 185 (235 mμ) corresponding to a content of 67.5% of IV. Two recrystallizations from acetic anhydride gave 4.1 g. of pregnadienolone acetate, m.p. 170.5–172.5°; *E*, 269 (233 mμ); $[\alpha]_D$ −39.1°.

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NOTES

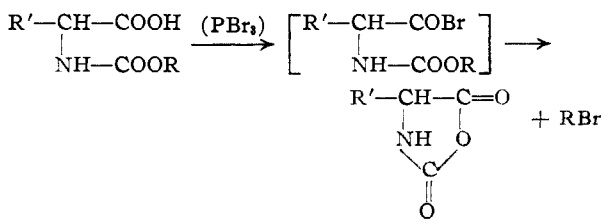
Synthesis of N-Carboxy-α-amino Acid Anhydrides from N-Carbalkoxy-α-amino Acids by the Use of Phosphorus Tribromide

BY DOV BEN-ISHAI AND EPHRAIM KATCHALSKI

RECEIVED FEBRUARY 6, 1952

The results of the investigation of the cyclization of N-carbalkoxy-β-haloalkylamines[1] and of the reaction between urethans and acetyl bromide and chloride,[2] suggested that N-carbalkoxy-α-amino acid bromides would cyclize more readily than the corresponding chlorides[3] to give N-carboxy-α-α-amino acid anhydrides.

It was, indeed, found that the N-carbalkoxy-α-amino acids given in Table I, when treated at room temperature with phosphorus tribromide, were converted with excellent yields, into the corresponding N-carboxy-α-amino acid anhydrides (oxazolidine-2,5-diones) (*cf.* Table II). The reaction is represented by the general equation



Under practically the same experimental conditions, N-carbethoxy- and N-carbobenzoxyanthranilic acid gave nearly quantitative yields of isatoic anhydride.

Experimental

N-Carbalkoxy-α-amino Acids.—The N-carbethoxy- and N-carbobenzoxyamino acids used were prepared by coupling ethyl chloroformate and carbobenzoxy chloride, respectively, with the corresponding α-amino acids in a manner similar to that prescribed for the synthesis of carbobenzoxyglycine.[4] The yields and analytical data are given in Table I.

N-Carboxy-α-amino Acid Anhydrides. General Procedure.—Phosphorus tribromide (0.02 mole) was added slowly to the N-carbalkoxy-α-amino acid (0.05 mole) dissolved or suspended in anhydrous ether (50 ml.). The reaction mixture was kept at room temperature for 12 hours. Dry petroleum ether (100 ml.) was added, and crystallization of anhydride promoted by keeping the reaction mixture for several hours at 4°. The anhydride, which separated out as a crystalline mass, was filtered, washed thoroughly with dry petroleum ether and recrystallized from a dry mixture of ethyl acetate and petroleum ether (Table II).

Isatoic Anhydride.—Phosphorus tribromide (0.035 mole) was added to 0.1 mole of N-carbethoxy or N-carbobenzoxyanthranilic acid (prepared by coupling anthranilic acid with the corresponding carbalkoxy chloride, in the usual way; *cf.* Table I) dissolved in anhydrous ether (100 ml.). After 24 hours at room temperature isatoic anhydride had separated as a microcrystalline product. It was filtered, washed with dry ether and recrystallized from alcohol; m.p. 240–243°,[5] yield about 90%.

Anal. Calcd. for $C_9H_5NO_3$: C, 58.9; H, 3.1; N, 8.6. Found: C, 58.5; H, 3.2; N, 8.3.

For further identification, the anhydride was converted

(1) E. Katchalski and D. Ben-Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

(2) D. Ben-Ishai and E. Katchalski, *ibid.*, **16**, 1025 (1951).

(3) H. Leuchs, *Ber.*, **39**, 857 (1906); H. Leuchs and W. Geiger, *ibid.*, **41**, 1721 (1908); F. Wessely, *E. physiol. Chem.*, **146**, 72 (1925).

(4) "Organic Syntheses," **23**, 14 (1943).

(5) E. Erdmann, *Ber.*, **32**, 2165 (1899), gives m.p. 240° (dec).

TABLE I

N-CARBALKOXY-α-AMINO ACIDS

Compound (Cbzo, carbobenzoxy; Cbetho, carbethoxy.)	Yield, %	M.p. (°C.) uncor.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
N-Cbetho-DL-phenylalanine	85	76	$C_{12}H_{15}NO_4$	60.8	60.6	6.3	6.4	5.9	6.2
N-Cbzo-DL-phenylalanine	80	102[a]	$C_{17}H_{17}NO_4$	68.2	68.5	5.7	5.8	4.7	4.8
N-Cbetho-DL-alanine	64	83[b]	$C_6H_{11}NO_4$	44.7	44.9	6.8	6.5	8.7	8.5
N-Cbzo-DL-alanine	76	114[c]	$C_{11}H_{13}NO_4$	59.2	59.0	5.8	5.9	6.3	6.5
N-Cbetho-DL-valine	86	56	$C_8H_{15}NO_4$	50.8	51.0	7.9	8.0	7.4	7.3
N-Cbzo-DL-valine	88	71	$C_{13}H_{17}NO_4$	62.2	62.4	6.8	6.6	5.6	5.8
N,N'-Dicbzo-L-lysine	82	150[d]	$C_{22}H_{26}N_2O_6$	63.8	63.6	6.3	6.6	6.8	7.1
N-Cbzo-sarcosine	87	53–54	$C_{11}H_{13}NO_4$	59.3	59.4	5.8	5.6	6.3	6.6
N-Cbetho-anthranilic acid	78	125 dec.	$C_{10}H_{11}NO_4$	57.4	57.4	5.3	5.4	6.7	6.8
N-Cbzo-anthranilic acid	55	141	$C_{15}H_{13}NO_4$	66.4	66.6	4.8	4.9	5.2	5.0

[a] M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932), give m.p. 103°. [b] E. Fischer and W. Axhausen, *Ann.*, **340**, 137 (1905), give m.p. 84° (cor.). [c] M. Bergmann and L. Zervas, ref. *a*, give m.p. 114–115° (cor.). [d] M. Bergmann, L. Zervas and W. F. Ross, *J. Biol. Chem.*, **111**, 245 (1935), give m.p. 150°. J. Bredt and H. Hof, *Ber.*, **33**, 26 (1900), give m.p. 126° (dec.).

TABLE II

N-CARBOXY-α-AMINO ACID ANHYDRIDES (OXAZOLIDINE-2,5-DIONES)

N-Carbalkoxy-α-amino acid	Oxazolidine-2,5-dione	Yield, %	M.p. (°C.) uncorrected	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
N-Cbetho-DL-phenylalanine	4-Benzyl	82	125–126 (dec.)[a]	$C_{10}H_9NO_3$	62.8	62.7	4.7	4.9	7.3	7.4
N-Cbzo-DL-phenylalanine	4-Benzyl	84	125–126 (dec.)[a]	$C_{10}H_9NO_3$	62.8	62.6	4.7	4.7	7.3	7.4
N-Cbetho-DL-alanine	4-Methyl	60	44–45[b]	$C_4H_5NO_3$	41.7	41.9	4.4	4.6	12.2	12.4
N-Cbzo-DL-alanine	4-Methyl	68	44–45[b]	$C_4H_5NO_3$	41.7	41.7	4.4	4.6	12.2	12.3
N-Cbetho-DL-valine	4-Isopropyl	85	77–79[c]	$C_6H_9NO_3$	50.4	50.1	6.3	6.4	9.8	10.0
N-Cbzo-DL-valine	4-Isopropyl	88	77–79[c]	$C_6H_9NO_3$	50.4	50.3	6.3	6.4	9.8	10.1
N,N'-Dicbzo-L-lysine	4-(δ,N-Cbzo-aminobutyl)	85	99 (dec.)[d]	$C_{15}H_{18}N_2O_5$	58.8	58.7	5.9	5.9	9.2	9.0
N-Cbzo-sarcosine	3-Methyl	90	99 (dec.)[e]	$C_4H_5NO_3$	41.7	41.9	4.4	4.1	12.2	12.1

[a] H. Leuchs and W. Geiger, *Ber.*, **41**, 1721 (1908), give m.p. 127–128° (dec.). [b] J. L. Bailey, *J. Chem. Soc.*, 3461 (1950), gives m.p. 45–46°. [c] W. E. Hanby, S. G. Waley and J. Watson, *ibid.*, 3009 (1950), give m.p. 78–79°. [d] M. Bergmann, L. Zervas and W. F. Ross, *J. Biol. Chem.*, **111**, 245 (1935), give m.p. 100° (dec.). [e] F. Sigmund and F. Wessely, *Z. physiol. Chem.*, **157**, 91 (1926), give m.p. 99–100° (dec.).

by aqueous ammonia into anthranilamide; from chloroform, m.p. 108–109°.[6]

Anal. Calcd. for $C_7H_8ON_2$: N, 20.6. Found: N, 20.8.

(6) Kolbe, *J. prakt. Chem.*, [2] **30**, 487 (1884).

THE WEIZMANN INSTITUTE OF SCIENCE
REHOVOTH, ISRAEL

Substituted Benzimidazoles[1]

BY CARL TABB BAHNER, HENRY A. RUTTER, JR., AND LYDIA MOORE RIVES

RECEIVED MARCH 15, 1952

It has been reported[2] that benzimidazole is an antagonist of adenine and it seemed worthwhile to investigate whether substituted benzimidazoles would inhibit the growth of cancers. In addition to a number of previously described compounds the following have been prepared.

5,7(or 4,6)-Dinitrobenzimidazole.—A solution of 1.0 g. of 1,2-diamino-4,6-dinitrobenzene[3] (0.005 mole) and 0.37 g. of formic acid (0.008 mole) in 5 ml. of 4 *N* HCl was refluxed 40 minutes, cooled and neutralized with ammonia. The precipitate was recrystallized once from water and twice from ethanol (with activated charcoal) to yield 0.50 g. of yellow crystals, m.p. 239–240° (dec.).

Anal.[4] Calcd. for $C_7H_4N_4O_4$: C, 40.39; H, 1.94. Found: C, 40.55; H, 1.79.

4(or 7)-Amino-6(or 5)-nitrobenzimidazole.—A solution of 3.36 g. of 5-nitro-1,2,3-triaminobenzene (0.02 mole) and 1.38 g. of formic acid (0.03 mole) in 20 ml. of 4 *N* HCl was refluxed 40 minutes and cooled to room temperature. The black, needle-shaped crystals (probably a hydrochloride salt of the benzimidazole) were filtered off, dissolved in boiling concentrated HCl, diluted with water, and neutralized with ammonia to produce a red precipitate which, after one recrystallization from water and two recrystallizations from alcohol (with activated charcoal), yielded 0.8 g. of yellow crystals, m.p. 240–241° (dec.). An additional 0.2 g. of product was obtained by neutralizing the original reaction mixture with ammonia and recrystallizing the precipitate.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.37. Found: C, 47.37; H, 3.35.

5(or 6)-Chloro-2-hydroxymethylbenzimidazole.—Prepared from *p*-chloro-*o*-phenylenediamine and glycolic acid and recrystallized from ethyl acetate this product melted at 206–208° (dec.). (Water and ethyl alcohol were unsatisfactory solvents for recrystallization.)

Anal. Calcd. for $C_8H_7ClN_2O$: C, 52.71; H, 3.86. Found: C, 52.78; H, 3.60.

5(or 6)-Nitro-2-hydroxymethylbenzimidazole.—Prepared from *p*-nitro-*o*-phenylenediamine and glycolic acid and recrystallized from ethyl acetate the yellow crystals melted at 194–195° (dec.).

Anal. Calcd. for $C_8H_7N_3O_3$: C, 49.74; H, 3.63. Found: C, 49.56; H, 3.60.

5(or 6)-Chlorobenzimidazole Hydrochloride.—A solution of 5(or 6)-chlorobenzimidazole[5] in concentrated HCl was

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(2) D. W. Wooley, *J. Biol. Chem.*, **152**, 225 (1944).

(3) *Cf.* R. Nietzke and H. Hagenbach, *Ber.*, **30**, 544 (1897).

(4) All carbon and hydrogen analyses by Galbraith Microanalytica Laboratories, Knoxville, Tennessee.

(5) O. Fischer, *Ber.*, **37**, 556 (1904).