CCCXCIX.—*The Crotonic Acid Series. Part I. Nitrogen Derivatives of Crotonic Acid.*

By MONTAGUE ALEXANDRA PHILLIPS.

THE great difference in the rates of hydrolysis by aqueous sodium hydroxide of the isomeric α-ethylcrotonamides has been demonstrated by Newbery (J., 1925, **127**, 295). This author also showed the relationships existing between the carbamides and amides of the α-ethylcrotonic acids, and there is little doubt that the carbamide, m. p. 198°, and the amide, m. p. 104°, are labile forms, and the carbamide, m. p. 158°, and amide, m. p. 118°, the corresponding stable forms.

It was thought worth while to extend this investigation to the simplest member of the series which can display *cis–trans* isomerism, and the present paper deals with some nitrogen derivatives of crotonic acid.

Crotonic acid is known in a stable (m. p. 72°, b. p. 189°) and a labile (m. p. 15°, b. p. 169°) form. Two amides have been described. One of these, the labile form, m. p. 102°, is obtained from the other, the stable isomeride, m. p. 158°, by the action of ultra-violet radiation (Stoermer and Roberts, *Ber.*, 1922, **55**, 1030). By no simple chemical means, however, has the author been able to obtain any form of the amide other than that melting at 158°. This amide, on hydrolysis by caustic alkali, is quantitatively converted into the stable crotonic acid, m. p. 72°.

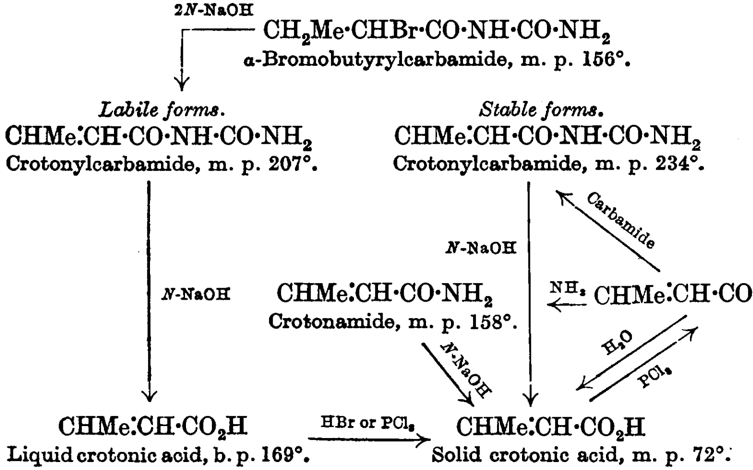
Two *carbamides* have now been prepared. One, m. p. 207°, was obtained from α-bromobutyrylcarbamide by the action of aqueous sodium hydroxide (1 mol.), and on hydrolysis even with one molecular proportion of sodium hydroxide gave a mixture of *cis*- and *trans*-crotonic acids which did not solidify at 0°. This mixture was readily and quantitatively converted into the *trans*-acid, m. p. 72°, by the action of phosphorus trichloride followed by water at the ordinary temperature, or by a trace of hydrobromic acid. The carbamide of m. p. 207° is therefore the labile or *cis*-form.

The isomeric *carbamide*, m. p. 234°, was obtained by the action of carbamide on crotonyl chloride (made by the action of phosphorus trichloride on the *cis*-acid, the *trans*-acid, or a mixture of the two). It gave a quantitative yield of crotonic acid, m. p. 72°, on treatment with one molecular proportion of sodium hydroxide and is therefore the stable or *trans*-form.

Both carbamides gave *n*-butyric acid on reduction with sodium and alcohol; and from both, on hydrolysis, carbamide was produced, but no trace of amide. The lower-melting carbamide decomposed on treatment with hydrobromic acid and therefore could not thus be converted into the isomeride.

The stability of the crotonamide, m. p. 158°, is evidently of a very different order from that of the α-ethylcrotonamides described by Newbery (*loc. cit.*), as might have been expected owing to the removal of the protecting ethyl group in the α-position. A direct comparison of the rates of hydrolysis confirmed this view, for on heating crotonamide, m. p. 158°, with *N*-caustic alkali at 80° for 30 minutes a quantitative yield of crotonic acid, m. p. 72°, was obtained. Similar treatment of the α-ethylcrotonamides left the materials largely unchanged.

A scheme is given showing the relationships between the preceding compounds.



EXPERIMENTAL.

α-Bromobutyrylcarbamide.—α-Bromobutyryl bromide (b. p. 100—110°/100 mm.) was prepared in 80% yield from commercial butyric acid by the Hell–Volhard–Zelinski method (*Ber.*, 1887, **20**, 2026).

A mixture of 14 g. of dry carbamide with 21·7 g. of α-bromobutyryl bromide was kept at 60° for 15—20 minutes, 100 c.c. of water were then added and the mixture was heated on the water-bath to decompose the sticky mass. After being washed with water and recrystallised from alcohol, the *carbamide* had m. p. 156° (Found : N, 13·5; Br, 38·4. $C_5H_9O_2N_2Br$ requires N, 13·4; Br, 38·2%).

trans-Crotonic acid was prepared in 40—50% yield from malonic acid and acetaldehyde by the method of Schiebler and Magasanik (*Ber.*, 1915, **48**, 1810). An alternative method, giving a 70—80% yield of the mixed isomerides, was treatment of α-bromobutyryl bromide with alcoholic potassium hydroxide (1 mol.) followed by acidification and ether-extraction.

Crotonyl chloride, b. p. 124—127°, was prepared in 70% yield by treating 43 g. of the *trans*-acid (or the *cis–trans*-mixture) with 25 g. of phosphorus trichloride, decanting the upper layer after 3—4 hours, and distilling it.

Crotonamide (4 g.) was obtained by dropping 10 g. of crotonyl chloride slowly into 15 c.c. of cooled ammonia (*d* 0·880). After being washed and crystallised from benzene, it melted at 158° (Found : N, 16·3. Calc. : N, 16·5%).

Crotonylcarbamide, m. p. 234°.—A mixture of 16 g. of crotonyl chloride and 20 g. of dry carbamide was kept at 70° for 30 minutes, 100 c.c. of water were then added, and the mixture was heated on the water-bath until the sticky mass had decomposed (15—20 minutes). After cooling, the crystalline mass was filtered off, washed, and recrystallised from alcohol. The yield varied from 40—60% of the theoretical (Found : C, 46·5; H, 6·4; N, 22·1, 22·0. $C_5H_8O_2N_2$ requires C, 46·8; H, 6·25; N, 21·9%).

Crotonylcarbamide, m. p. 234°, is not appreciably soluble in water or alcohol, and does not decolorise bromine water in the cold, behaving in this respect like the α-ethylcrotonylcarbamides (Newbery, *loc. cit.*).

Crotonylcarbamide, m. p. 207°.—α-Bromobutyrylcarbamide (55 g.) was heated on the steam-bath with a solution of 11 g. of sodium hydroxide in 135 c.c. of water. Ammonia was evolved at once, and after 15 minutes the solution became acid to litmus. The heating was continued for 10 minutes, the solution then made alkaline with 2*N*-sodium hydroxide, excess of sodium chloride added, and the crystalline precipitate filtered off (*a*). The filtrate was exhaustively extracted with (*b*) chloroform and (*c*) ether. The aqueous residue was made acid to Congo-red, and exhaustively extracted with ether (*d*).

After recrystallisation from alcohol, the solid (*a*) weighed 10 g., had m. p. 207°, and was the isomeric *crotonylcarbamide* (Found: C, 46·6; H, 6·2; N, 21·9, 22·0%). On evaporation the chloroform extract (*b*) left 2·5 g. of unchanged bromo-carbamide, and the ethereal extract (*c*) left no residue. The acid ethereal extract (*d*), on drying and removal of solvent, left 8·0 g. of viscous oil, b. p. 140—190°/28 mm., which was not unsaturated and was probably impure *s*-di-α-hydroxybutyrylcarbamide; it was not further examined. On the assumption that 7 g. of the disubstituted carbamide were formed, the total amount of hydrolytic products obtained accounts for almost all the α-bromo-carbamide taken.

Crotonylcarbamide, m. p. 207°, is not very soluble in water, cold alcohol, ether, or chloroform. It resembles its isomeride in not decolorising bromine water in the cold.

The action of 2 mols. of caustic alkali on α-bromobutyrylcarbamide produced an almost quantitative yield of an unsaturated acid mixture which, on treatment with phosphorus trichloride followed by water, was quantitatively converted into solid crotonic acid, m. p. 72°.

Hydrolysis of Crotonamide, m. p. 158°.—A mixture of 8·5 g. of crotonamide with 100 c.c. of *N*-sodium hydroxide was heated on the steam-bath for 30 minutes. On cooling and extracting the product with benzene, no unchanged amide was obtained. The aqueous residue, when acidified (Congo-red), gave an immediate precipitate (8·3 g., isolated by means of ether) of crotonic acid, m. p. 70° (theo. yield of acid, 8·6 g.).

Hydrolysis of Crotonylcarbamide, m. p. 234°.—When the carbamide (12·8 g.) was heated on the steam-bath with 100 c.c. of *N*-sodium hydroxide, ammonia was evolved at once. At the end of 45 minutes the still alkaline solution was saturated with sodium chloride and extracted (*a*) with chloroform (*b*) with hot benzene. The aqueous residue, when acidified with hydrochloric acid, gave immediately a precipitate of solid crotonic acid, which was extracted with ether (*c*). On drying and removal of solvents (*a*) and (*b*) gave no residue; (*c*), on drying and evaporation, left solid crotonic acid, m. p. 70—71° (7·4 g., representing 90% of the carbamide taken). The aqueous residue, on neutralisation, evaporation under reduced pressure, filtration from sodium chloride, and addition of concentrated nitric acid, gave characteristic crystals of urea nitrate.

Hydrolysis of Crotonylcarbamide, m. p. 207°.—The carbamide (12·8 g.), treated exactly as its isomeride, gave the following result:

From (*a*) and (*b*) no residue was obtained; (*c*) gave 7·0 g. of a mixture of crotonic acids which did not solidify when kept at 0° for 1 week. On treating this mixture with phosphorus trichloride followed by water at 25—30°, 6·5 g. of solid crotonic acid, m. p. 70°, were obtained. The aqueous residue contained urea.

Attempts to obtain Labile Crotonamide.—(i) *Action of caustic alkali on α-bromobutyramide in the cold.* 4·8 G. of α-bromobutyramide of m. p. 111° were kept for 2 hours in 20 c.c. of *N*-potassium hydroxide. Ammonia was evolved after 10 minutes. The solid, after crystallisation from alcohol, melted at 111° and was unchanged α-bromobutyramide. The filtrate contained traces of halide and cyanide.

(ii) *Action of caustic alkali on α-bromobutyramide at* 100°. A similar mixture was gently boiled, and the gases evolved were passed through 50% sulphuric acid into a solution of semicarbazide in acetic acid. Crystals of propaldehydesemicarbazone (m. p. 150°) soon began to separate from this solution (Found: N, 36·6. Calc.: N, 36·5%) (compare Mossler, *Monatsh.*, 1908, **29**, 69).

(iii) *Action of water on α-bromobutyramide.* After 11 g. of α-bromobutyramide had been boiled for 1½ hours with 35 c.c. of water, 10 g. of unchanged bromo-amide were recovered. The halide in solution corresponded with 1 g. of hydrolysed bromo-amide, but no unsaturated amide could be obtained.

(iv) *Action of sodium ethoxide on α-bromobutyramide.* α-Bromobutyramide (17 g.) was added to sodium ethoxide (2·3 g. of sodium in 50 c.c. of alcohol) and the mixture was refluxed for 1 hour. On removal of alcohol, addition of water, extraction with chloroform, and removal of this solvent after drying, a gum was left which did not crystallise after being kept at 0° for some weeks. The aqueous residue was acidified; ether extracted nothing from it.

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