40. *The Crotonic Acid Series. Part II. Nitrogen Derivatives of α-Phenylcrotonic Acid.*

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The study of the nitrogen derivatives of crotonic acids commenced by Newbery (J., 1925, **127**, 295) and continued by the author (J., 1926, 2979) has been extended to the carbamides and the amide of α-phenylcrotonic (β-methylatropic) acid. Attention is called to the exceedingly reactive nature of the bromine atom in derivatives of α-bromo-α-phenylbutyric acid and to the extreme ease of hydrolysis of the unsaturated carbamides and of the unsaturated amide. In this respect these nitrogen derivatives of α-phenylcrotonic acid resemble the corresponding derivatives of crotonic acid and contrast with those of α-ethylcrotonic acid. In connection with this work, *α-bromophenylbutyrylcarbamide* and NN'-*bis*-(*α-phenylbutyryl*)*carbamide* were prepared.

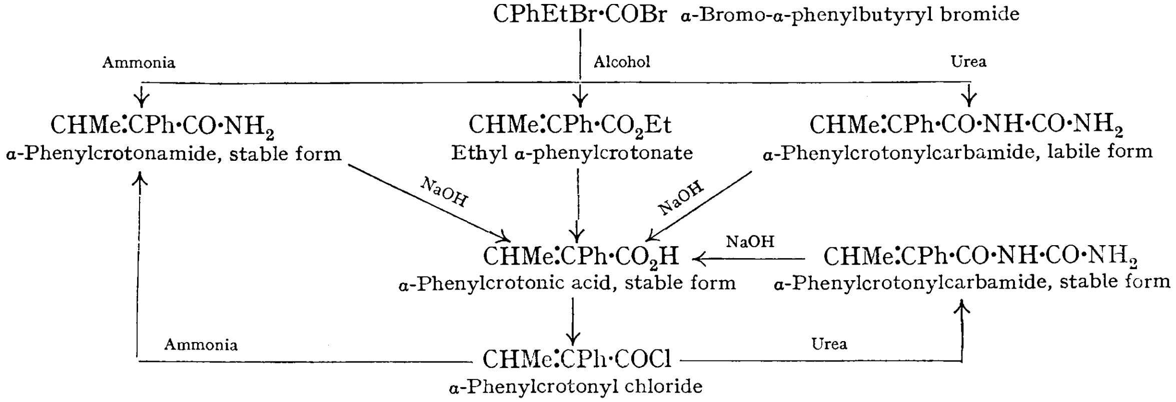
It has been shown by Newbery (J., 1925, **127**, 295) that the action of caustic alkali on α-bromo-α-ethylbutyrylcarbamide (carbromal B.P.) gives mainly labile α-ethylcrotonylcarbamide, the bromine atom being removed as hydrogen bromide with some ease. The unsaturated carbamide and its stable isomeride are both hydrolysed with caustic alkali to give the corresponding forms of α-ethylcrotonamide, both of which were found to be surprisingly stable towards further treatment with sodium hydroxide. This author also showed that the stable form of the amide was more readily hydrolysed by treatment with caustic alkali than was the labile form.

In Part I (Phillips, J., 1926, 2979) the investigation was extended to the study of the amides and carbamides of crotonic acid itself. It was shown that, as in the case of the higher homologues, the action of caustic alkali on α-bromobutyrylcarbamide gave labile crotonylcarbamide, and the isomeric unsaturated carbamide was formed from crotonyl chloride and urea. Further action even of limited amounts of sodium hydroxide solution on both these carbamides gave, not amide, but the corresponding form of crotonic acid. In consequence only the stable form of crotonamide was obtained. This was formed by the action of ammonia on crotonyl chloride, and was found to be hydrolysed by caustic alkali with extreme ease, the absence of amide in the action of alkali on the two forms of the carbamide thus being explained.

It has now been shown that similar principles apply to the nitrogen derivatives of α-phenylcrotonic acid. α-Bromo-α-phenylbutyrylcarbamide could not, however, be obtained from *α-bromo-α-phenylbutyryl bromide* and urea on account of the extreme ease with which the bromine atom is removed. This ease of removal of bromine as hydrogen bromide is very marked in this series of compounds; for example, the action of alcohol on the bromo-bromide gives mainly α-phenylcrotonic ester, and ammonia even under mild conditions gives α-phenylcrotonamide. The action of urea was shown to give one form of *α-phenylcrotonylcarbamide*. The other (lower-melting) form of the carbamide, designated the stable form by analogy with the corresponding form of α-ethylcrotonylcarbamide obtained by Newbery (*loc. cit.*), was obtained from *α-phenylcrotonyl chloride* and urea. Both forms of the carbamide are reduced to give α-phenylbutyrylcarbamide. On attempting to obtain the two forms of the amide by treatment of the isomeric carbamides with sodium hydroxide, it was found that both gave, under very mild conditions, excellent yields of the same, evidently the stable, form of α-phenylcrotonic acid identical with that prepared by Oglioloro (*Gazzetta*, 1885, **15**, 514) from paraldehyde, sodium phenylacetate and sodium acetate. α-Phenylcrotonamide, presumably the stable form, prepared from the acid chloride and ammonia gave an almost quantitative yield of α-phenylcrotonic acid on relatively mild treatment with caustic alkali.

The above series of derivatives of α-phenylcrotonic acid evidently resemble the simple crotonic acid series in their lability towards caustic alkali and stand in marked contrast to the α-ethylcrotonic acid derivatives described by Newbery (*loc. cit.*). This unexpected result can only be related to the positive nature of the phenyl radical. The ease with which the bromine atom is eliminated in the α-bromo-α-phenylbutyric acid series as compared with the relative stability in both the α-bromobutyryl and the α-bromo-α-ethylbutyryl series may be a further example of this.

The reactions described above are illustrated below:



Since the object of this work was the synthesis of α-bromo-α-phenylbutyrylcarbamide for comparison with α-bromo-α-ethylbutyrylcarbamide as an hypnotic agent, the bromination of α-phenylbutyrylcarbamide was attempted, but the bromine atom entered the benzene nucleus. This was shown by hydrolysis of the *α-bromophenylbutyrylcarbamide* formed, an α-bromophenylbutyric acid being obtained. The orientation of the bromine atom within the benzene nucleus has not been determined, but the compound is probably an *o*- or *p*-bromophenyl derivative. α-Phenylbutyrylcarbamide was obtained from *α-phenylbutyryl chloride* and urea at low temperatures; at higher temperatures NN′-*bis*-(*α-phenylbutyryl*)-*carbamide* is formed.

Tests on mice indicated that α-bromophenylbutyrylcarbamide has about one half the hypnotic activity of and is considerably more toxic than α-bromo-α-ethylbutyrylcarbamide.

EXPERIMENTAL.

α-Bromo-α-phenylbutyryl Bromide.—Dry bromine (144 g.) was added at 50° to α-phenylbutyryl chloride (Rising and Schwartz, *J. Amer. Chem. Soc.*, 1932, **54**, 2024) (157 g.), and the mixture refluxed until the bromine had been absorbed (2¼ hours). After aspiration to remove dissolved hydrogen chloride, the residue was fractionated under reduced pressure. The *bromide* (195 g., 74% of the theoretical amount) was a colourless oil, b. p. 150—154°/22 mm. (Found : Br, 51·9. $C_{10}H_{10}OBr_2$ requires Br, 52·3%).

Action of Alcohol on α-Bromo-α-phenylbutyryl Bromide.—The acid bromide (50 g.) was added slowly at 60° to absolute alcohol (150 c.c.), the temperature being controlled by the rate of addition. After refluxing for 30 minutes and removal of the excess of alcohol, the residue was fractionated at 10 mm.; all boiled between 127° and 129°. The material contained 2·0% of bromine and, although careful refractionation indicated that the brominated ester was concentrated in the higher-boiling fractions, it was not found possible to obtain an ester completely free from bromine. The lowest fraction, b. p. 123—124°/10 mm., containing 0·5% of bromine, was hydrolysed by treatment of 3·8 g. with a solution of potassium hydroxide (2·5 g.) in 95% alcohol (50 c.c.) at the b. p. for 2 hours. Removal of alcohol and acidification gave 3·1 g. (96% of the theoretical amount) of crude α-phenylcrotonic acid, m. p. 130° (136° after crystallisation from 50% alcohol). Ethyl α-phenylcrotonate is described by Dimroth and Feuchter (*Ber.*, 1903, **36**, 2253) as an oil, b. p. 128—131°/15 mm.

Action of Ammonia on α-Bromo-α-phenylbutyryl Bromide.—The acid bromide (3·1 g.) was added slowly with stirring to aqueous ammonia (15 c.c.; *d* 0·880) at 40°. The oil was collected after 1 hour and crystallised from 50% alcohol (yield, 1·2 g. or 75% of the theoretical). The substance melted at 104° and was identical with α-phenylcrotonamide prepared from α-phenylcrotonyl chloride as described below (Found : N, 8·6. Calc. : N, 8·7%). The aqueous mother-liquor from the reaction mixture contained 2 equivs. of bromide ion. This unsaturated amide is probably identical with the amide, m. p. 98—99°, described by Pfeiffer, Engelhardt, and Alfuss (*Annalen*, 1928, **467**, 158).

Action of Urea on α-Bromo-α-phenylbutyryl Bromide.—A mixture of the acid bromide (7·5 g.) and urea (3·0 g.) was heated at 55° for 3 hours. On addition of water an oil was formed which solidified on chilling. This (3·8 g.) was crystallised from alcohol until the m. p. was constant (167°); the material then contained 2·3% of bromine, which could not be diminished by further crystallisation. Analysis indicated that this was substantially α-phenylcrotonylcarbamide (Found : N, 13·5%).

Hydrolysis of Impure α-Phenylcrotonylcarbamide. Isolation of the Pure High-melting Carbamide.—The impure carbamide, m. p. 167°, containing 2·3% of bromine (5 g.) was heated for 12 hours at 50° with a 1% solution of sodium hydroxide (100 c.c.). After cooling, the crystalline solid (A) was removed, and the filtrate acidified with hydrochloric acid. The precipitated solid (B) was collected. The solid A (1·0 g., m. p. 191°) crystallised from alcohol, in which it was sparingly soluble, in colourless needles, m. p. 197°. Analysis showed it to be *α-phenylcrotonylcarbamide* (Found : C, 64·6; H, 6·05; N, 13·6. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). The solid B (2·5 g., m. p. 126°) was α-phenylcrotonic acid, m. p. 136° after crystallisation from 50% alcohol (Found : equiv., 161. Calc. : equiv., 162).

α-Phenylcrotonamide.—α-Phenylcrotonic acid was converted into the *acid chloride* (b. p. 131°/10 mm.) by treatment with thionyl chloride; yield, 95% (Found : Cl, 20·5. $C_{10}H_9OCl$ requires Cl, 19·6%). Addition of the acid chloride (9 g.) to 15% aqueous ammonia (50 c.c.) gave α-phenylcrotonamide, m. p. 103° after crystallisation from alcohol (Found : N, 8·8. Calc. : N, 8·7%); yield, 88%.

Hydrolysis of α-Phenylcrotonamide.—The amide (2·0 g.) was refluxed for 1 hour with N-sodium hydroxide (100 c.c.). Acidification and ether extraction gave 1·9 g. (95% of the calculated amount) of α-phenylcrotonic acid, m. p. 135° (Found : equiv., 161).

Low-melting (Stable) α-Phenylcrotonylcarbamide.—α-Phenylcrotonyl chloride (9 g.) and urea (7 g.) were mixed and kept at 30° for 24 hours. Water was added at 60° in order to break up the viscous mass. The colourless prisms formed (7·1 g.; 70%) had m. p. 185°, not raised by crystallisation from alcohol (Found : C, 64·7; H, 6·15; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). Like its isomeride, this *form* decolorises bromine water on gentle warming. A mixture of the two isomerides shows a considerable depression of m. p.

Hydrolysis of the Two α-Phenylcrotonylcarbamides.—(i) *High-melting (labile) form.* The carbamide (5 g.), m. p. 197°, was refluxed with a 1% solution of sodium hydroxide (100 c.c.) for various periods. After cooling, the unchanged carbamide was collected, and the filtrate treated with hydrochloric acid. The precipitate was in all cases practically pure α-phenylcrotonic acid, m. p. 130°. After 1, 12, and 24 hours the hydrolysis % was 13, 72, and 90 respectively.

(ii) *Low-melting (stable) form.* The carbamide (2 g.), m. p. 185°, was refluxed for 30 minutes with 10% sodium hydroxide solution (20 c.c.); after cooling, acidification, and extraction with ether, 1·45 g. (90% of the calculated amount) of α-phenylcrotonic acid, m. p. 136°, were obtained.

α-Phenylbutyrylcarbamide.—(i) Reduction of either form of α-phenylcrotonylcarbamide with 4% sodium amalgam as described by Newbery (*loc. cit.*) for the reduction of the two α-ethylcrotonylcarbamides gave 85% of the calculated amount of α-phenylbutyrylcarbamide, m. p. 147° after crystallisation from alcohol (Found : N, 13·6, 13·55 in the two cases. Calc. : N, 13·6%). (ii) α-Phenylbutyryl chloride (25 g.) was mixed with urea (25 g.) and heated at 30° for 48 hours. Water was added, and the crystals collected and recrystallised from alcohol. The m. p. 147° was undepressed by the product from (i). Yield, 17 g., 60% (compare D.R.-P. 249,241).

NN'-Bis-(α-phenylbutyryl)carbamide.—α--Phenylbutyryl chloride (18 g.) and urea (12 g.) were mixed and heated at 90° for 24 hours. After addition of water and cooling, the *carbamide* (12 g.) was obtained; it crystallised from alcohol in colourless plates. m. p. 172° (Found: N, 8·0. $C_{21}H_{24}O_3N_2$ requires N, 8·0%).

Hydrolysis of NN'-Bis-(α-phenylbutyryl)carbamide.—The carbamide (15 g.) was heated with N-sodium hydroxide (50 c.c.) and alcohol (50 c.c.) for 2 hours at 90°. After removal of alcohol, addition of water precipitated α-phenylbutyramide (1 g.), m. p. 85° after crystallisation from alcohol. Acidification of the filtrate gave α-phenylbutyric acid (10 g.), m. p. 38°, identified by its equivalent (Found: 162. Calc.: 164) and by comparison with a genuine specimen.

Bromination of α-Phenylbutyrylcarbamide.—Bromine (27 g.) was added to the carbamide (17 g.) suspended in water (130 c.c.) at 20°. The mixture was refluxed and agitated until the bromine had been absorbed. The oil formed solidified on cooling; after being washed with water, dried, and crystallised from 95% alcohol, *α-(bromophenyl)butyrylcarbamide* was obtained in colourless plates (10 g.), m. p. 178—179° (Found: N, 10·0; Br, 27·9. $C_{11}H_{13}O_2N_2Br$ requires N, 9·8; Br, 28·1%).

Hydrolysis of α-(Bromophenyl)butyrylcarbamide.—The bromo-carbamide (2·5 g.) was refluxed with a solution of potassium hydroxide (2·5 g.) in 90% alcohol (25 c.c.) for 3 hours. Removal of alcohol and addition of dilute hydrochloric acid gave an oil, which was extracted in ether, dried (anhydrous sodium sulphate), and recovered (1·8 g.). It solidified on chilling and had m. p. 40—43° after crystallisation from 50% alcohol. Analysis showed it to be an *α-(bromophenyl)butyric acid* (Found: Br, 32·4; equiv., 237. $C_{10}H_{11}O_2Br$ requires Br, 32·9%; equiv., 243).

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