The Chemistry of β-Bromopropionyl Isocyanate. I. Synthesis of 1-Aryldihydrouracils[1]

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The ready availability of β-bromopropionyl isocyanate[2,3] (I) has made a study of its chemistry desirable, since its structure indicated that it might have considerable utility in the synthesis of heterocyclic compounds. This is the first of a group of studies designed to explore the chemistry of I.

The reaction of I with several aromatic primary amines led to *N*-β-bromopropionyl-*N'*-aryl ureas (II) in good yield. The II proved to be somewhat more difficult to dehydrohalogenate than had been anticipated. Treatment with triethylamine or 2,6-lutidine in refluxing chloroform or refluxing with excess triethylamine gave only starting material. Treatment with triethylamine (or silver oxide) in refluxing dimethylformamide led to the desired *N*-acrylyl-*N'*-aryl ureas (III) in good yield. The III are the key intermediates in the dihydrouracil synthesis of Gabel and Binkley,[4] and the present work thus offers a route to 1-aryldihydrouracils using their cyclization reaction. The present route to III is a considerable improvement in both time and convenience over the original methods involving the synthesis of acryly isocyanate from the chloride and silver cyanate. *N*-Bromosuccinimide is a stable compound which is easily rearranged to the desired bromoisocyanate as needed, and the II can be formed in the same flask in which the rearrangement was effected.

The II could be converted to 1-aryldihydrouracils by refluxing with silver carbonate in propionic acid for 48 hr. The yields were lower, however, and the products were more difficult to purify than those prepared by the Gabel-Binkley cyclization. Treatment of *N*-β-bromopropionyl-*N'*-*p*-ethoxyphenyl urea with silver oxide, silver sulfate, or silver nitrate in DMF or propionic acid gave only a blue material from which no products have been isolated.

In an attempt to prepare an authentic sample of *N*-acrylyl-*N'*-phenyl urea, acrylyl chloride was allowed to react with phenyl urea in tetrahydrofuran. 1-Phenyldihydrouracil was isolated directly from the reaction mixture. The reaction was not studied further because of the emphasis of this series, but it might indicate another profitable entry into the dihydoruracils.

The III and 1-aryldihydrouracils were identified by comparison of melting points and infrared spectra with samples prepared according to Gabel and Binkley.[4]

EXPERIMENTAL[5]

Melting points were measured on a Fischer-Johns block and were not corrected.

β-Bromopropionyl isocyanate (I). A mixture of 10.0 g. of *N*-bromosuccinimide (0.0562 mole), 5 ml. allyl chloride, and 100 ml. dry chloroform was heated to reflux and approximately 0.2 g. benzoyl peroxide was added. The refluxing was continued about 2 hr. until no test was obtained with starch-iodide solution.

N-β-Bromopropionyl-N'-aryl ureas (II). The clear solution of the above isocyanate was allowed to cool protected with a drying tube, and a solution of 0.0562 mole of the appropriate amine in chloroform or ether was added slowly with swirling. After the vigorous reaction subsided, the flask was allowed to cool and then placed in an ice bath. The suspension was filtered, and the precipitate was washed with chloroform or acetone. The material was then crystallized from methanol, 95% ethanol, or chloroform. The following compounds were prepared: *N*-β-bromopropionyl-*N'*-phenyl urea (70%), colorless needles, m.p. 183–184°, analysis previously reported[3]; *N*-β-bromopropionyl-*N'*-α-naphthyl urea (75%), colorless hairlike crystals, m.p. 215–217° (*Anal.* Calcd. for $C_{14}H_{13}N_2O_2Br$: C, 47.2; H, 4.38; N, 9.43. Found, C, 47.4; H, 4.2; N, 9.0); *N*-β-bromopropionyl-*N'*-*p*-ethoxyphenyl urea (60%), short colorless needles very soluble in mentioned solvents, m.p. 169–170° (*Anal.* Calcd. for $C_{12}N_{15}N_2O_3$: C, 45.7; H, 4.8; N, 8.9. Found, C, 46.0; H, 5.1; N, 9.0); *N*-β-bromopropionyl-*N'*-*p*-chlorophenyl urea (70%), colorless needles, m.p. 210–211° (*Anal.* Calcd. for $C_{10}H_{10}N_2O_2BrCl$: C, 39.4; H, 3.3; N, 9.2. Found: C, 39.9, H, 3.6; N, 9.6.)

N-Acrylyl-N'-aryl ureas (III). A solution of 1.0 g. of the β-bromopropionyl aryl urea was refluxed with 3–5 ml. of triethyl amine in 20 ml. of dimethylformamide for 30 min. The mixture was poured into water, and the white precipitate was filtered and recrystallized from 95% ethanol, chloroform, or dioxane. Thus prepared were *N*-acrylyl-*N'*-phenyl urea (80%), m.p. and mixed m.p. 146–148°; *N*-acrylyl-*N'*-*p*-ethoxyphenyl urea (50%—very soluble in mentioned solvents), m.p. and mixed m.p. 122–124°; *N*-acrylyl-*N'*-*p*-chlorophenyl urea (80%), m.p. and mixed m.p. 202–204°; and *N*-acrylyl-*N'*-α-naphthyl urea (75%), m.p. and mixed m.p. 174–175°.

Alternatively, 1.0 gram of the bromo compound was refluxed with 0.5 g. silver oxide in 25 ml. of DMF for 30 min. The mixture was filtered while hot and poured into water; the pink material was filtered and recrystallized as above. Usually a second crystallization was needed to obtain the correct m.p. Yields in the order above were 50%, 30%, 70%, and 60%. The low yields are presumed to be due to crystallization losses.

1-Aryldihydrouracils. A mixture of 1.0 gram of the β-bromopropionylaryl urea, 0.4 g. of silver carbonate, and 30 ml. propionic acid was refluxed for 48 hr. The mixture was filtered, and the brown solution was evaporated under reduced pressure. The residue was recrystallized from dioxane or chloroform. The following dihydrouracils were prepared: 1-phenyl, m.p. 185–187° (25%); 1-*p*-chloro, m.p. 223–225° (20%); 1-*p*-ethoxyphenyl, m.p. 200–203° (18%); 1-α-naphthyl, m.p. 250–254° (25%).

1-Phenyldihydrouracil. A solution of 10.0 g. of phenylurea (0.11 mole) and 15 g. acrylyl chloride (8.11 mole) in 100 ml.

(1) This work was supported in part by a grant from the Research Corporation.

(2) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957).

(3) H. W. Johnson, Jr. and D. E. Bublitz, *J. Am. Chem. Soc.*, **79**, 753 (1957); **80**, 3150 (1958).

(4) N. W. Gabel and S. B. Binkley, *J. Org. Chem.*, **23**, 643 (1958).

(5) Analyses by C. F. Geiger, 312 Yale St., Ontario, Calif.

dry tetrahydrofuran was allowed to reflux 4 hr. Upon evaporation of the solvent and crystallization of the residue from ethanol there was obtained 9.4 g. (45%) 1-phenyldihydrouracil, m.p. and mixed m.p. 184–186°.

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Synthesis of Mixed α- and γ-Glutamylhomocysteinylglycines[1]

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The participation of glutathione in cell growth and division and in various enzyme catalyzed reactions suggests that an investigation of glutathione homologs and analogs for inhibitory properties might be of interest and potential therapeutic value. A number of such compounds have been investigated by Kermack and Matheson[4] and were found to be inhibitors of the glyoxalase reaction. In these compounds alteration of glutathione was limited to *S*-alkylation and replacement of the cysteinyl residue with glycyl, alanyl, and cysteyl residues. Since the thiol group of glutathione is functionally important, it appeared to be of interest to synthesize a thiol-containing homolog and in this paper the synthesis of γ-glutamylhomocysteinylglycine accompanied by the α-tripeptide is reported.

The synthesis[5] was effected by condensation of *N*-*p*-tosyl-γ-L-glutamyl azide with *S*-benzyl-DL-homocysteinylglycine ethyl ester followed by saponification and then simultaneous debenzylation and detosylation with sodium in liquid ammonia. The required *N*-*p*-tosyl-γ-L-glutamyl azide was prepared from *N*-*p*-tosyl-γ-L-glutamyl hydrazide,[6] the latter being prepared from L-glutamic acid by a known sequence of reactions[7] and *S*-benzylhomocysteinylglycine ethyl ester was prepared by decarbobenzoxylation of *N*-carbobenzoxymethionylglycine ethyl ester with ethanolic hydrogen chloride[8] or with acetic acid–hydrogen bromide.[5]

In view of the fact that the synthetic route gave rise to a mixture[9] of α- and γ-tripeptides, rearrangement of a γ-glutamyl derivative to an α-glutamyl derivative must have occurred during the course of the synthesis. As a rule, rearrangements[10–12] of γ-glutamyl and β-aspartyl peptides to the corresponding α-peptides occur under conditions which permit nucleophilic attack by the peptide nitrogen atom on the carbonyl carbon atom of the α-carboxyl function, the α-carboxyl being suitably substituted, and expulsion of the substituent group. Usually these requirements are met by an alkaline reaction medium and an esterified α-carboxyl group. In the present case, the α-carboxyl group is not substituted and it is difficult to visualize rearrangement occurring *via* peptide nitrogen attack with expulsion of an oxide or hydroxide ion. Since the *N*-*p*-tosyl-γ-L-glutamyl hydrazide is free[6,13] of α-hydrazide, rearrangement to an α-derivative must have occurred during azide formation or subsequent reaction of azide with the amine moiety.[14] A similar rearrangement has been definitely shown to occur[15] when *N*-carbobenzyloxy-γ-L-glutamyl hydrazide is used *via* the azide, for γ-peptide synthesis.

The tripeptide mixture has no inhibitory effect on the growth of Sarcoma 180 in the mouse.[16] The γ-peptide[4] is an inhibitor of the glyoxalase reaction.[4]

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(2) Abstracted in part from the doctoral thesis, June 1957, of Frank Draus.

(3) Present address, School of Dentistry, University of Pittsburgh.

(4) W. O. Kermack and N. A. Matheson, Proc. Biochem. Soc., *Biochem. J.*, **57**, XXII (1954).

(5) During the course of this work a synthesis of γ-glutamylhomocysteinylglycine *via* condensation of the γ-azide of *N*-carbobenzoxyglutamic acid with *S*-benzyl-homocysteinylglycine ethyl ester was reported by E. C. Herrick and C. W. Todd, U.S. Patents **2,723,972** and **2,723,973**; *Chem. Abstr.*, **50**, 4214, 4215 (1956). Paper chromatography of the product yielded only one spot. Other evidence for the absence of α-peptide in the product is not presented.

(6) J. Rudinger, *Coll. Czechoslov. Chem. Communs.*, **19**, 365 (1954).

(7) C. R. Harrington and R. C. Morridge, *J. Chem. Soc.*, 706 (1940).

(8) O. Gawron and F. Draus, *J. Org. Chem.*, **23**, 1040 (1958).

(9) As shown by α-carboxyl CO_2 determination. Chromatography on paper yielded only one spot.

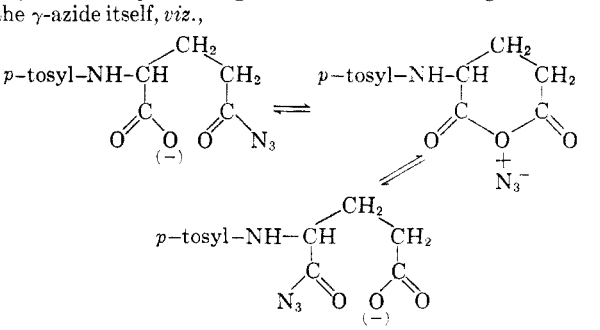
(10) E. Sondheimer and R. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954).

(11) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).

(12) D. W. Clayton, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc.*, 371 (1956).

(13) A potentiometric titration gave a theoretical titration curve for a compound with one carboxyl group of pK 3.65 and no indication of a carboxyl group with a higher pK value. The pK_a value of 3.65 is typical for the α-carboxyl group of *N*-acyl-γ-substituted glutamic acid derivatives (Ref. 10).

(14) A likely rearrangement involves rearrangement of the γ-azide itself, *viz.*,



This is an elaboration of the suggestion of Sachs and Brand (Ref. 15). The anhydride, of course, would yield a mixture of α- and γ-peptides.

(15) H. Sachs and E. Brand, *J. Am. Chem. Soc.*, **76**, 1815 (1954).

(16) Courtesy of Drs. C. C. Stock and R. Barclay, Sloan-Kettering Institute for Cancer Research.