[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

α,β-DIAMINOBUTYRIC ACIDS, AMIDES, AND ESTERS[1]

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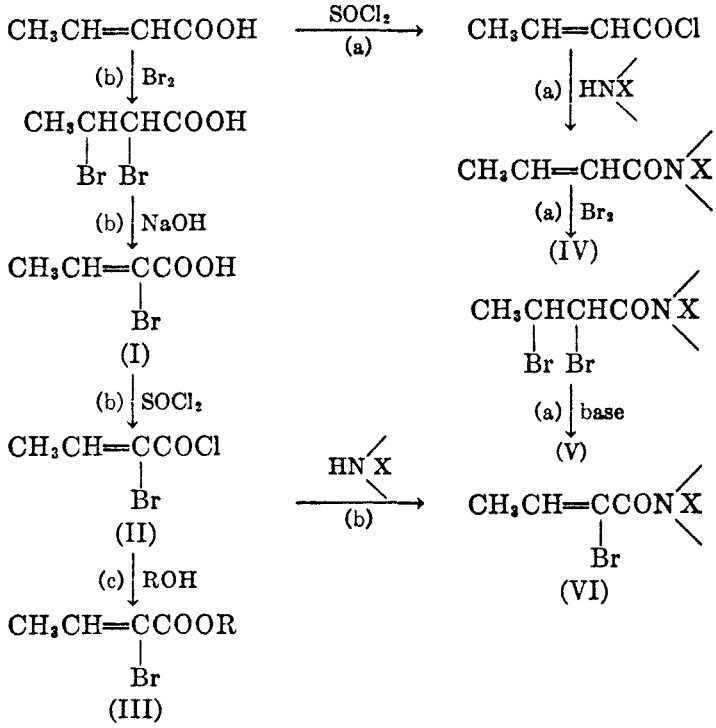
Previous to the present investigations no studies of the reactions of amines with α-halo-α,β-unsaturated amides or acids had been reported. In a series of two papers Roberts (1) showed that α-haloethylcinnamates and crotonates both react with piperidine or dimethylamine to give the corresponding α,β-diamino esters. Later Moureu (2) showed that α,β-dibromoethylbutyrate reacted with piperidine *via* the α-bromoethylcrotonate to form the α,β-dipiperidinoethylbutyrate.

It was the main purpose of the present studies to compare the reactions of amines with the α-bromo-α,β-unsaturated acids, amides, and esters, with the similar investigations which have been made of the α-bromo-α,β-unsaturated ketones (3). It was realized that these new types of amino acids, amides and esters might prove of interest for pharmacological screening.

There were two obvious routes, (a) or (b) to the synthesis of the required α-bromocrotonamides, starting with crotonic acid.



[1] Abstracted from the Ph.D. thesis of Floy Pelletier (1950); Smith, Kline, and French Laboratories Research Fellow, 1947–1950.

The feasibility of route (a) was established by carrying out the indicated reactions for the preparation of compounds (IV), (V), and (VI) where —N<X was the morpholino group. In contrast to the related cinnamamide dibromides studied in an earlier investigation (4), these α,β-dibromobutyramides (V) readily lost hydrogen bromide to produce (VI) in a manner analogous to the behavior of the α,β-dibromo ketones which give the α-bromo-α,β-unsaturated ketones. The cinnamamide dibromides show a considerable tendency to lose bromine to reform the cinnamamides.

Although it was found that the over-all yields of the α-bromocrotonamides (VI) by either method (a) or (b) were of the same order, method (b) had the

TABLE I

PHYSICAL AND ANALYTICAL DATA OF α-BROMOCROTONAMIDES

α-BROMOCROTON-	B.P., °C.	YIELD, %	FORMULA	ANALYSES					
				CARBON		HYDROGEN		NITROGEN	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
piperidide[a]	105–107 (1 mm.)	81	$C_9H_{14}BrNO$	46.55	46.34	6.04	5.83	6.04	6.08
morpholide	110–112[b] (1 mm.)	70	$C_8H_{12}BrNO_2$	41.04	41.32	5.13	5.12	5.98	5.82
β′-naphthalamide	[c]	96	$C_{14}H_{12}BrNO$	57.80	57.57	4.14	4.09	4.83	4.88
p-ethoxyanilide	[d]	87	$C_{12}H_{14}BrNO_2$	50.71	50.70	4.97	5.01	4.93	5.20
N-diethylamide[e]	111 (1.2 mm.)	76	$C_8H_{14}BrNO$	43.64	43.84	6.41	6.32	6.36	6.15
N-dimethylamide[f]	120 (18 mm.)	85	$C_6H_{10}BrNO$	37.61	37.41	5.25	5.08	7.29	6.99

[a] n_D^{20} 1.5311. [b] M.p., 60–62°. [c] M.p., 78–79°. [d] M.p., 100–105°. [e] n_D^{20} 1.4990. [f] n_D^{20} 1.5138.

obvious advantage of involving the syntheses of the required α-bromocrotonic acid (I) and the versatile new reagent, α-bromocrotonyl chloride (II) needed for the other studies. This latter reagent could obviously be used to prepare the required α-bromocrotonic acid esters (III) as well as the amides (VI). Route (b) was therefore chosen for the preparation of the α-bromocrotonamides listed in Table I. The various α-bromocrotonates (III) which were prepared from α-bromocrotonyl chloride (II) by reaction (c) are to be found in Table II.

The only α,β-diaminobutyric acid to be found in the literature was the parent compound itself which had been prepared first by Neuberg (5) from α,β-dibromobutyric acid and ammonium carbonate. Using dimethylamine and piperidine, respectively, along with α-bromocrotonic acid (I) and heating the mixtures to

60° for several hours, the α,β-diaminobutyric acids were obtained in good yields. The dipiperidino acid was fractionally recrystallized to give the two possible racemates. We also obtained the higher-melting racemate, m.p. 212°, in considerably lower yields by either acidic or alkaline hydrolysis of the known ethyl-α,β-dipiperidinobutyrate (1, 2).

Several attempts to convert the high-melting racemate of α,β-dipiperidinobutyric acid into the corresponding α,β-dipiperidinobutyryl chloride were un-

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR α-BROMOCROTONATES

R IN α-BROMOCROTONATE ESTERS	B.P., °C. MM.	YIELD, %	FORMULA	ANALYSES			
				C		H	
				Calc'd	Found	Calc'd	Found
Benzyl	141 (20)	51	$C_{11}H_{11}BrO_2$	51.79	52.15	4.35	4.53
Benzohydryl	[a]	71	$C_{17}H_{15}BrO_2$	61.64	61.37	4.56	4.51
γ'-Di-N-butylamino-propyl	142 (0.3)	72	$C_{15}H_{28}BrNO_2$	—	—	—	—
β'-Diethylaminoethyl	125 (2.5)	85	$C_{10}H_{18}BrNO_2$	—	—	—	—

[a] M.p., 48–49°.

TABLE III

PHYSICAL AND ANALYTICAL DATA FOR α,β-DIAMINOBUTYRATES

DIAMINOBUTYRATES	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
				C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
α,β-Dipiperidinobutyrate									
Benzyl	100–101	86	$C_{21}H_{32}N_2O_2$	73.21	73.48	9.36	9.43	8.15	8.30
Benzohydryl	115–117	80	$C_{27}H_{36}N_2O_2$	77.10	76.86	8.62	8.35	6.66	6.91
α,β-*Bis*-dimethylamino-butyrate	79–80								
γ'-Dibutylaminopropyl	[b]	80	$C_{19}H_{41}N_3O_2$	66.42	66.36	12.03	11.86	12.23	12.09
β'-Diethylaminoethyl	[c]	75	$C_{14}H_{31}N_3O_2$	61.49	61.49	11.43	11.14	—	—

[a] Isomers separated by fractional crystallization from alcohol-water solvent. [b] B.p., 137°/0.04 mm.; n_D^{20} 1.4531. [c] B.p., 120°/0.6 mm.; n_D^{20} 1.4551.

successful. Using thionyl chloride and such solvents as pyridine or chloroform or ether, and either the diamino acid or its dihydrochloride, only tars resulted. These results are similar to those experienced by Emil Fischer (6) who tried unsuccessfully to prepare an acid chloride of a diamino acid.

Using dimethylamine and piperidine, the various α,β-diaminocrotonates listed in Table III were readily prepared from the corresponding α-bromocrotonates (III). The reactions proceeded rapidly in benzene or ether solution at room temperature.

The α-bromocrotonamides (VI) were found to react quite slowly even with piperidine in benzene solution at reflux temperature. Moreover the yields of the α,β-dipiperidinobutyramides were very low (8–10%). Using a polar solvent such as absolute alcohol the reactions were more rapid and the yields of the α,β-diaminobutyramides were increased. See Table IV. The basic strength and the steric requirements of the secondary amines used in these reactions had to be considered. The best amines studied in the order of their effectiveness were piperidine, dimethylamine, and morpholine. This is also the order of their basic strengths. The steric requirements of these three bases are similar. Diethylamine, which is of the same order of basic strength as piperidine, reacted with α-bromo-N-(*p*-phenetyl)crotonamide to give apparently only the α-amino-α,β-unsatu-

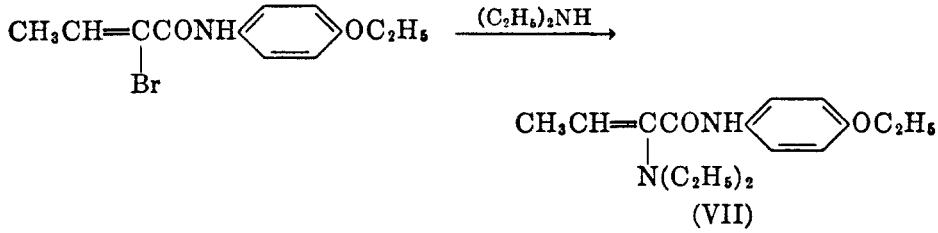
TABLE IV

PHYSICAL AND ANALYTICAL DATA FOR α,β-DIAMINOBUTYRAMIDES

DIAMINOAMIDES	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
				C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
Butyrpiperidide									
α,β-Dipiperidino	95–96.5	48	$C_{19}H_{35}N_3O$	71.02	71.05	10.90	10.78	13.08	12.93
α,β-Dimorpholino	126–127	25.5	$C_{17}H_{31}N_3O_3$	62.80	62.86	9.53	9.61	12.92	13.17
α,β-*Bis*-dimethylamino[a]	63–65	28	$C_{13}H_{27}N_3O$	64.68	64.98	11.28	11.12	17.45	17.64
α,β-Dipiperidinobutyrmorpholide	115–116	50	$C_{18}H_{33}N_3O_2$	66.83	66.74	10.28	10.35	12.99	13.24
p-ethoxyanilide	178–179	30	$C_{22}H_{35}N_3O_2$	70.73	70.56	9.44	9.20	11.25	11.25
	139–141	59	$C_{22}H_{35}N_3O_2$	70.73	70.50	9.44	9.67	11.25	11.20

[a] In using dimethylamine the reaction was carried out in a pressure bomb or sealed tube to allow the reaction mixture to be heated to 60°.

rated amide (VII). The structure of this compound was not studied. The steric requirements of the diethylamino group in such reactions are greater than those



(VII)

of the above mentioned secondary amines. Similar results were previously obtained when diethylamine was used in the reaction with an α-bromo-α,β-unsaturated ketone (7).

Several attempts were made to obtain the suspected intermediate α-bromo-β-aminobutyramides by adding one mole of the amine to the α-bromo-α,β-

unsaturated amide. Apparently the speed of this initial reaction was considerably slower than the subsequent reactions which led to the formation of the α,β-diaminobutyramides, the only products isolated from such experiments. Also the high solubility of these intermediates in the usual organic solvents probably helped to prevent their isolation.

It seems probable that all of these α-bromo-α,β-unsaturated carbonyl compounds react with amines according to the mechanisms previously outlined for the ketone series (3, 8).

EXPERIMENTAL[2]

Crotonmorpholide. One equivalent of crotonyl chloride was dissolved in benzene and cooled. A cold benzene solution containing two equivalents of morpholine was slowly added. The morpholine hydrochloride was removed by filtration and the product recovered by vacuum-distillation, b.p. 147° (18 mm.), m.p. 54–55°, recrystallized from low-boiling petroleum ether; yield 80%.

Anal. Calc'd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03.

Found: C, 62.24; H, 8.15; N, 9.22.

α,β-Dibromobutyrmorpholide. When bromine was added to crotonmorpholide in carbon tetrachloride solution, a 90% yield of a colorless solid resulted which was recrystallized from 50% ethyl alcohol, m.p. 122–123°.

Anal. Calc'd for $C_8H_{13}Br_2NO_2$: N, 4.44; Br, 50.74.

Found: N, 4.31; Br, 50.91.

When a sample of this dibromide was heated at reflux temperature for six hours with four equivalents of morpholine in absolute alcohol a 90% yield of the *α-bromocrotonmorpholide* resulted; b.p. 110–114° (1 mm.), m.p. 60–61°. This product was identical with that listed in Table I which was prepared from α-bromocrotonyl chloride.

α-Bromocrotonic acid. The *cis-trans* mixed acid was prepared by a modification of the method reported by James (9). Two equivalents of potassium hydroxide were dissolved in water and cooled to about 5°. A one-molar equivalent of solid α,β-dibromobutyric acid was slowly added with stirring. The reaction mixture was heated on the steam-bath for 15 minutes, then cooled and acidified with hydrochloric acid. The white crystalline product which separated on cooling was purified by recrystallization from petroleum ether (b.p. 60–70°). yield 90%, m.p. 87–94°.

α-Bromocrotonyl chloride. A one-molar equivalent of α-bromocrotonic acid was mixed with 1½ equivalents of pure thionyl chloride and heated under reflux for two hours. The product was obtained by vacuum-distillation, b.p. 108–109° (112 mm.), yield 82%, n_D^{29} 1.5201.

Anal. Calc'd for C_4H_4BrClO: C, 26.23; H, 2.19.

Found: C, 26.22; H, 2.03.

α-Bromocrotonamides. A cold benzene solution containing two molar-equivalents of the amine was slowly added to a cold dry benzene solution of one molar-equivalent of α-bromocrotonyl chloride. The reaction mixture was allowed to warm to room temperature and to remain at that temperature for one or two hours. The side product, an amine hydrochloride, was removed by filtration. The benzene was evaporated and the residue extracted with dry ether. The ether was evaporated and the crude products purified by vacuum-distillation or recrystallization from alcohol-water mixtures. The products prepared in this way are described in Table I.

α-Bromocrotonates. A dry benzene solution containing one molar-equivalent each of the corresponding alcohol and of pyridine was treated slowly with an equivalent of α-bromocrotonyl chloride in dry benzene at 0–5°. The reaction mixture was allowed to warm to

[2] Microanalyses for carbon, hydrogen, and nitrogen are by the Cark Microanalyticall Laboratory, Urbana, Illinois.

room temperature and stand at this temperature for a few hours. The pyridine hydrochloride was removed by filtration. The benzene was evaporated and the product extracted from the residue with dry ether. In the case of the reaction with benzyl alcohol the product was obtained by vacuum-distillation. The benzohydryl ester was purified by recrystallization from absolute alcohol. In preparing the α-bromocrotonates of the amino alcohols the pyridine was omitted from the reaction mixtures and an extra equivalent of the amino alcohol used instead. These products formed oily hydrochlorides and polymerized on attempted distillation. They were used in the crude form to prepare the α,β-diaminocrotonates. See Table II for a description of the α-bromocrotonates.

α,β-Dipiperidino- and α,β-Bis-(dimethylamino)-butyric acids. Method A. One equivalent of α-bromocrotonic acid was mixed with four molar-equivalents of piperidine and dimethylamine, respectively, and the reaction mixtures heated at 60° for 6–8 hours. The dimethylamine reaction mixture was heated in a sealed tube. The reaction mixtures were diluted with a combination of ether-ethanol (9:1). These mixtures were cooled and the by-product amine hydrobromides removed by filtration. The solvent was removed by distillation and the residues recrystallized from ether-alcohol (9:1) solution.

The α,β-dipiperidinobutyric acid was resolved into two racemic mixtures by fractional recrystallization.

Anal. Calc'd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.21; N, 11.01.

Found: C, 66.39; H, 10.18; N, 11.03; m.p. 124–126°, 20% yield.

Found: C, 66.29; H, 9.95; N, 11.29; m.p. 210–212°, 40% yield.

The α,β-bis-(dimethylamino)butyric acid resulted in 85% yield, m.p. 160–161°.

Anal. Calc'd for $C_8H_{18}N_2O_2$: C, 55.14; H, 10.41; N, 16.08.

Found: C, 55.19; H, 10.44; N, 15.97.

Method B. The high-melting isomer of α,β-dipiperidinobutyric acid was also obtained by hydrolysis of the known ethyl α,β-dipiperidinobutyrate (1, 2).

(a) One equivalent of ethyl-α,β-dipiperidinobutyrate and ten molar-equivalents of sodium hydroxide were dissolved in 80% ethyl alcohol and heated under reflux for three hours. The reaction mixture was then neutralized with a calculated amount of conc'd hydrochloric acid and the solvent removed by vacuum-distillation. The residue was extracted with an ether-alcohol (8:2) solution. The ether-alcohol solution was evaporated and the product recrystallized from petroleum ether (b.p. 60–70°), m.p. 211–212°, yield, 23%.

(b) An acid hydrolysis using 2% hydrochloric acid gave a 20% yield of the high-melting isomer. A maple syrup-like odor was observed in each of these hydrolysis reaction mixtures.

α,β-Diaminobutyrates. A cold benzene or ether solution containing three molar-equivalents of the amine was slowly added to one equivalent of the α-bromocrotonate dissolved in cold benzene or ether. The reaction mixture was allowed to warm up to room temperature and to stand at this temperature for 5–8 hours. The amine hydrobromide was removed by filtration and the solvent removed by distillation. The diaminobutyrates were purified by recrystallization from alcohol-water solutions or by distillation under reduced pressure. See Table III for the list of products prepared by this method.

α,β-Diaminobutyramides. Three molar-equivalents of the amine were refluxed for 8–12 hours with one equivalent of the α-bromocrotonamide in absolute alcohol. The solvent was removed by distillation and the product extracted from the residue with dry ether. The ether solution was saturated with dry hydrogen chloride to precipitate a hydrochloride of the diaminobutyramide. In general the α-bromocrotonamides did not form hydrochlorides under these conditions. The hydrochloride of the product was dissolved in water and the solution made strongly alkaline with sodium hydroxide. The resulting amides were purified by recrystallization from ethyl alcohol and water mixtures. The diaminobutyramides prepared in this way are described in Table IV.

α-Diethylamino-N-(p-phenetyl)crotonamide. An alcohol solution containing 5.0 g. (0.0194 mole) of α-bromo-N-(*p*-phenetyl)crotonamide (α-bromocroton-*p*-ethoxyanilide) and 4.5 g. (0.058 mole) of diethylamine was refluxed for 50 hours. The alcohol was removed by distillation and the residue extracted with dry ether. The dry ether solution was saturated

with dry hydrogen chloride and the oily precipitate recrystallized from alcohol and ether mixtures. This hydrochloride product was dissolved in water and the solution made alkaline with sodium hydroxide. The free amine separated as a colorless solid which was recrystallized from an 80% alcohol solution to give colorless plates, 1.0 g., (20% yield), m.p. 128–130°.

Anal. Calc'd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14.

Found: C, 69.83; H, 8.95; N, 10.30.

SUMMARY

1. A new and versatile reagent, α-bromocrotonyl chloride, has been prepared which may be used to synthesize α,β-diaminobutyramides and esters *via* the corresponding α-bromocrotonamides and esters.

2. Two α,β-diaminobutyric acids have been prepared.

3. The mechanisms of the reactions of these α-bromo-α,β-unsaturated carbonyl compounds with amines seem to be similar to those of the reactions of the previously studied α-bromo-α,β-unsaturated ketones (3, 8). The reactivity of the α-bromo-α,β-unsaturated carbonyl system in the amides is less than that in the ketones, esters or acids.

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