[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Substituted β-Aminopropionic Esters

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In the course of recent investigations it became necessary to prepare various ethyl esters of substituted β-aminopropionic acids. Compounds of this type have been prepared by the reaction of amines with β-halopropionic esters[1] (Method I), by the addition of amines to acrylic esters[1c,2] (Method II), and by the reaction of amines with α,α′-dibromoadipic esters[1e,3] (Method III).

Although we have employed methods I and II above, the method primarily studied in this Laboratory concerns the preparation of substituted β-aminopropionitriles[4] followed by alcoholysis of these nitriles to the desired esters (Method IV).

$$CH_2{=}CHCN + HNR_2 \longrightarrow R_2NCH_2CH_2CN$$

$$R_2NCH_2CH_2CN + C_2H_5OH + H_2O + \xrightarrow{H_2SO_4} R_2NCH_2CH_2COOC_2H_5 + NH_3$$

The nitriles and the esters were isolated by distillation at reduced pressures. In the cases of the di-*n*-butyl-, di-*n*-amyl- and di-*n*-hexyl-aminopropionic esters, prolonged heating resulted in the dissociation of the product into the amine and a residue of polymerized acrylic ester.

In the case of the piperidino-, diethylamino- and di-*n*-butylamino-propionic esters, both methods II and IV were used. The attempted addition of 8-amino-6-methoxyquinoline to ethyl acrylate or acrylonitrile under a variety of conditions and catalysts was completely unsuccessful. In the reaction of 8-amino-6-methoxyquinoline with ethyl β-bromopropionate, the theoretical amount of hydrogen bromide was split out and recovered as the hydrobromide of 8-amino-6-methoxyquinoline, but the remainder of the 8-amino-6-methoxyquinoline was recovered unchanged as the free base.

Table I gives the compounds prepared, their properties, and a comparison of the yields by the different methods.

It has been suggested[5] that the reaction of ethyl β-bromopropionate with primary and secondary amines proceeds by way of ethyl acrylate as an intermediate. Such a mechanism would resemble that discovered by Bischoff[6] for the action of sodiomalonic ester with α-bromoisobutyric ester to give eventually α-methylglutaric acid instead of the expected α,α-dimethylsuccinic acid.

It was hoped that the reaction of *m*-chloroaniline with both ethyl acrylate and ethyl β-bromopropionate under nearly identical conditions would throw light upon this question. The yield of ethyl β-(*m*-chloroanilino)-propionate is considerably better when the β-bromo ester is used than when ethyl acrylate is employed (80% as compared to 29%). Although this indicates dissimilar mechanisms, more data are necessary before any definite conclusions can be drawn.

Experimental

Method I. Ethyl β-(*m*-Chloroanilino)-propionate.—Ethyl β-bromopropionate,[7] 90.5 g. (0.5 mole) was refluxed in 500 ml. of toluene with *m*-chloroaniline, 127.5 g. (1.0 mole) in the presence of 3 g. of sodium iodide for thirty-six hours. It is quite possible that the reaction was complete in a very small fraction of this time. The precipitated *m*-chloroaniline hydrobromide was filtered and washed with ether, 98 g. (95%), m. p. 217–218°, being obtained. The solvent was distilled from the filtrate and the residue distilled *in vacuo* to give a total of 90.5 g. (80%) of product boiling at 140–145° (2.5 mm.), $n^{20}D$ 1.5422, d^{20} 1.1709, M.R. calcd. 60.7; found 61.2; picrate m. p. 82.5–83.0°. *Anal.* Calcd. for $C_{11}H_{14}O_2NCl \cdot C_6H_3O_7N_3$; N, 12.27. Found: N, 12.52.

This same compound was prepared from ethyl acrylate as follows: A mixture of 52 g. of *m*-chloroaniline hydrobromide[8] (0.25 mole), 32 g. of *m*-chloroaniline (0.25 mole), 25 g. of ethyl acrylate (0.25 mole) and 250 ml. of toluene was refluxed for thirty-six hours, cooled, filtered and the precipitate washed with ether to recover 50.5 g. of the *m*-chloroaniline hydrobromide. The filtrate was distilled *in vacuo* as above to give 16.3 g. (29%) of product boiling at 150–153° (3 mm.), $n^{20}D$ 1.5449. A picrate prepared from this material gave no depression of the melting point when mixed with the picrate obtained from the product prepared from ethyl β-bromopropionate.

Method II. Ethyl β-Piperidino-α-methylpropionate.—A mixture of 102 g. (0.89 mole) of freshly distilled ethyl methacrylate and 90 g. (1.06 moles) of piperidine was heated on the steam-bath for forty-four hours. The reaction mixture was then distilled under reduced pressure and the portion boiling at 127–129° (30 mm.) was collected. The yield was 147 g. (83%) of ethyl β-piperidino-α-methylpropionate with the following constants: $n^{20}D$ 1.4495, d^{20} 0.9469; M.R. calcd. 56.6, found 56.4; equivalent weight calcd. 199.3, found 200.5; hydrochloride m. p. 136.0–136.5°; picrate m. p. 95.5–96.0°.

Method IV. Ethyl β-Piperidinopropionate.—A mixture of 122.4 g. (0.89 mole) of β-piperidinopropionitrile[4] (b. p. 129–130° at 30 mm., $n^{20}D$ 1.4699), 3.5 moles of 95% ethanol and 3 moles of concentrated sulfuric acid was heated for thirteen hours on the steam-bath, cooled, and neutralized with aqueous ammonia. The oil was separated and the aqueous solution extracted with ether. The combined oil and ether extracts were dried, distilled under reduced pressure and the fraction boiling at 124–130° (30 mm.) was collected; yield 117.4 g. (70.8%).

(1) (a) Wedekind, *Ber.*, **32**, 727 (1899); (b) v. Braun, *ibid.*, **42**, 2049 (1909); (c) Flürscheim, *J. prakt. Chem.*, [2] **68**, 348 (1903); (d) Drake and McElvain, THIS JOURNAL, **56**, 697 (1934); (e) Fuson and Bradley, *ibid.*, **51**, 599 (1929).

(2) Phillippi and Galter, *Monatsh*, **51**, 253 (1929); Morsch, *ibid.*, **63**, 220 (1934); Hromatka, *Ber.*, **75B**, 131 (1942).

(3) (a) v. Braun, Leistner and Munch, *ibid.*, **59B**, 1950 (1926); (b) v. Braun, Jostes and Wagner, *ibid.*, **61B**, 1423 (1928).

(4) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

(5) Private communication, Dr. H. E. Carter, University of Illinois.

(6) Bischoff, *Ber.*, **23**, 3395, 3400 (1890).

(7) Made by the addition of hydrogen bromide to ethyl acrylate in 88% yield: see "Organic Syntheses," **22**, 64 (1940).

(8) This *m*-chloroaniline hydrobromide was taken from the washed crystalline precipitate from the previous experiment and contained the sodium iodide used as a catalyst in the above experiment.

TABLE I

ETHYL ESTERS OF SUBSTITUTED β-AMINOPROPIONIC ACIDS $RCH_2CH_2COOC_2H_5$

β-Substituent R	Yield, %	Method used	Boiling range °C.	Mm.	Picrate m. p., °C.	Refractive index $n^{20}D$	Density d^{20}	Molecular refraction Calcd.	Found	Equivalent weights Calcd.	Found
Piperidino-[a]	74	IV	124–130	25	127.5–128.0	1.4555	0.9664	51.9	51.8	184.7	185.3
	88	II									
Morpholino-	56	IV	138–140	25	106–107	1.4570	1.0484	48.5	48.8	185.6	187.1
Diethylamino-[b]	74	IV	95–98	23	75–76	1.4270	0.9005	49.4	49.4	175.1	173.3
	87	I									
	83	II									
Di-*n*-propylamino-[c]	77	IV	125–126	28	63–64	1.4313	0.8884	58.7	58.6	198.5	201.3
Di-*n*-butylamino-	66	IV	136–137	16	oil	1.4356	0.8787	68.3	67.8	229.3	230.0
	60	II									
Di-*n*-amylamino-	40[e]	IV	136–138	5	oil	1.4397	0.8779	77.2	77.0	5.67[d]	5.73[d]
Di-*n*-hexylamino-	50[e]	IV	137–145	3	oil	1.4431	0.8607	87.8	86.3	4.95[d]	4.91[d]

[a] See Wedekind, *Ber.*, **32**, 727 (1899). [b] See reference 1c. [c] Reported in ref. 3a erroneously as ethyl α-di-*n*-propylamino propionate; see ref. 1e. [d] Per cent. nitrogen by Kjeldahl method. [e] The yields with the higher members were lower mainly because of the tendency for these compounds to decompose upon prolonged heating during distillation.

Summary

The preparation of various substituted β-aminopropionic esters by three different methods has been studied and six new β-aminopropionic esters described.

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4- and 4′-Aminobiphenyl-2-carboxylic Acids

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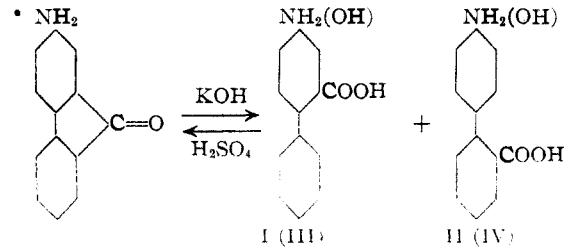
In continuation of work on the cleavage of fluorenones with potassium hydroxide in diphenyl ether,[1] the cleavage of 2-aminofluorenone was repeated and a successful isolation and separation was made of the two isomeric amino acids, 4- and 4′-aminobiphenyl-2-carboxylic acids, I and II, whose formation the earlier research had already proved.[2]



I (III) II (IV)

The further interest in these compounds resulted from a curious anomaly existing in the literature concerning their melting points and structures. Kühling[3] prepared the first isomer, m. p. 106–110°, which he believed to be 4′-aminobiphenyl-4-carboxylic acid but which later work[4] proved to be the corresponding 2-carboxylic acid. Diels[5] isolated another *p*-aminobiphenylcarboxylic acid, m. p. *ca.* 215°, from the alkaline cleavage of 2-aminofluorenone but did not indicate the relative positions of the carboxyl and amino groups. Beilstein,[6] however, assumed it to be the 4-acid, isomeric with Kühling's acid. More recently Finzi and Mangini[7] reported an acid, m. p. 215–216°, whose structure they definitely proved to be 4′-aminobiphenyl-2-carboxylic acid, II. Therefore, two compounds have been reported to have the same structure although their melting points differ by 100°.[8]

To solve this anomaly an exhaustive search of the literature was undertaken to check on the validity of the proofs of structure offered. No errors or inconsistencies could be found and several independent lines of evidence support the structures of certain of the intermediates. The more important references in the direct lines of proof are listed below.[9]

(1) Huntress and Seikel, THIS JOURNAL, **61**, 816, 1066, 1358 (1939).
(2) Huntress and Seikel, *ibid.*, **61**, 818, 821 (1939).
(3) Kühling, *Ber.*, **29**, 166–167 (1896).
(4) Kliegl and Huber, *ibid.*, **53**, 1640–1648 (1920).
(5) Diels, *ibid.*, **34**, 1760–1771 (1901).
(6) Beilstein, Vol. 14, p. 539.
(7) Finzi and Mangini, *Gazz. chim. ital.*, **62**, 1200–1201 (1932).
(8) The authors believe that Kühling's melting point is a typographical error as a melting point of 206–210° could be observed for the 4′-acid because it is difficult to purify and melts with decomposition. The figures, 106–110°, were printed only once.
(9) (A) For Finzi and Mangini's acid, m. p. 215–216°: Finzi and Mangini, *Gazz. chim. ital.*, **62**, 1193–1203 (1932); Finzi, *ibid.*, **61**, 33–42 (1931); for *p*-amino- and *p*-hydroxybiphenyl: Latschinoff and Engelhardt, *Ber.*, **6**, 194 (1873); Schultz, *Ann.*, **174**, 209–213 (1874); **207**, 348, 363 (1881); Hübner, *ibid.*, **209**, 340–349 (1881); Kaiser, *ibid.*, **257**, 101 (1890); for *o*-hydroxybiphenyl: Graebe and Aubin, *Ann.*, **247**, 257–288 (1888); Graebe and Schestakow, *ibid.*, **284**, 310–320 (1895); Schultz, *ibid.*, **207**, 352–353 (1881); Heusler, *ibid.*, **260**,