The temperature is kept at 40° by cooling. During the reaction tetramethylammonium bromide precipitates and is recovered practically *in toto* by filtration. The precipitated salt is washed with ether and the etheric solution is added to the filtrate from which the 2,3-dibromopropanol is obtained by fractionation *in vacuo*. The yield is 85%.

When dibromopropanol is prepared according to Kohler[3] or according to Read and Hurst,[4] low temperatures and diluents such as carbon disulfide or alcohol and water must be employed and the yield is substantially lower.

Mixtures of tetramethylammonium bromide-bromine are not suitable for brominations which are sluggish. In the case of benzene the reaction is slow and stops as soon as the composition $(CH_3)_4NBr_3$ is reached.

When the liquid mixtures mentioned are heated above 70° hydrobromic acid is gradually formed, apparently by bromine substitution of the hydrogen in the methyl groups.

Finally it should be mentioned that these liquids do not cause any injuries when in contact with the skin even for several minutes.

(3) Kohler, *Am. Chem. J.*, **42**, 381 (1909).

(4) Read and Hurst, *J. Chem. Soc.*, **121**, 995 (1922).

DEPARTMENT OF PHYSICAL CHEMISTRY
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Preparation of Some N-Substituted Amino Acid Analogs

BY EMERY M. GAL[1]

Friedman and Gutman,[2] while studying phenylalanine derivatives, reported excellent yields of the N-methylphenylalanine through cold condensation of phenyl-α-bromopropionic acid with methylamine and subsequent slow crystallization over a period of three weeks. This method with modifications proved to be very satisfactory, and led to yields of 60–80% as calculated from the alpha halo-acid. Crystallization set in within three days.

These compounds are very poorly soluble in either cold or hot water. At *p*H 7.4 their solubility is 1.25–1.50 g./100 ml., with the exception of α-amino-*n*-butyric acid and the norvaline derivative, which are soluble to the extent of 4–6 g./100 ml. Their solubility in organic solvents is varying. The phenyl derivatives are soluble to the extent of 2.5 g./100 ml. of absolute alcohol, whereas the propyl and isopropyl derivatives only to the extent of 0.7–1 g./100 ml. in hot absolute alcohol, and are almost insoluble in ether, benzene and propylene glycol.

Table I presents the compounds prepared by the author with the aid of this method. All compounds are DL-amino acid derivatives. One example will demonstrate the mode and ease of preparation.

Experimental

N-Propyl-phenylalanine.—22.9 g. (0.1 mole) of phenyl-α-bromopropionic acid, prepared according to the method of Fischer,[3] distilled at 120° (2 mm.) with slight decomposition and obtained in 70% yield, was cooled to 0°. To this compound 15 g. (0.127 mole) of propylamine (Eastman Kodak Co.) in 40 ml. of ice cold water was added dropwise and carefully shaken after each addition of the amine. (Too fast addition of the amine results in heating up of the mixture and in decrease of yield.) After the amine was added, the mixture was shaken for thirty minutes and left to stand overnight. Next morning, either crystals or a slight turbidity appeared. The mixture was then refluxed for ten minutes and left to crystallize. After a day or two, densely grown crystals of N-propylphenylalanine separated out. The crystals were collected on a Büchner funnel, washed several times with ice cold water to remove the amine hydrobromide salt, and finally washed with 30 ml. of ice cold 95% alcohol in three portions. The crude product was recrystallized from hot absolute alcohol to yield analytically pure samples of white crystals; yield 10 g. (73.9%).

A small sample of the crude product was recrystallized from twenty times its weight of hot water and dried in a desiccator over phosphorus pentoxide. The analytical results obtained with this sample were closely identical with those from alcohol recrystallization.

TABLE I

Product	Formula	M. p., °C.	Point of sublimation, °C.	Composition, % Calculated Carbon	Calculated Hydrogen	Calculated Nitrogen	Found Carbon	Found Hydrogen	Found Nitrogen
N-Ethylvaline	$C_7H_{15}NO_2$	...	250	57.92	10.31	9.65	57.60	10.00	9.48
N-Propylvaline	$C_8H_{17}NO_2$	...	250	60.32	10.64	8.80	59.97	10.60	9.24
N-Isopropylvaline	$C_8H_{17}NO_2$	...	250	60.32	10.64	8.80	59.71	10.25	9.16
N-Phenylvaline	$C_{11}H_{15}NO_2$	125[a]	...	68.47	7.77	7.25	68.13	7.64	7.25
N-Ethylleucine	$C_8H_{17}NO_2$	...	250	60.32	10.64	8.80	59.58	10.58	8.80
N-Propylleucine	$C_9H_{19}NO_2$	...	230	62.75	10.99	8.09	62.45	10.84	8.12
N-Isopropylleucine	$C_9H_{19}NO_2$	...	260	62.75	10.99	8.09	62.88	10.10	8.19
N-Phenylleucine	$C_{12}H_{17}NO_2$	158[b]	...	69.59	8.21	6.76	69.41	8.46	6.24
N-Ethylphenylalanine	$C_{11}H_{15}NO_2$	...	270	68.47	7.77	7.25	68.15	7.63	7.60
N-Propylphenylalanine	$C_{12}H_{17}NO_2$	...	290	69.54	8.21	6.76	69.49	8.44	6.79
N-Isopropylphenylalanine	$C_{12}H_{17}NO_2$	...	280	69.54	8.21	6.76	68.24	8.35	5.86
N-Phenylphenylalanine	$C_{15}H_{15}NO_2$	165	...	75.52	6.28	5.85	74.79	6.48	6.08
N-Ethylnorvaline	$C_7H_{15}NO_2$	...	265	57.92	10.31	9.65	57.84	10.43	9.60
N-Phenylnorvaline	$C_{11}H_{15}NO_2$	115–120	...	68.47	7.77	7.25	67.69	7.32	7.80
N-Ethyl-α-amino-*n*-butyric acid	$C_6H_{13}NO_2$	282 d.	...	54.90	9.92	10.62	54.73	9.70	10.03

[a] Bischoff (*Ber.*, **30**, 898, 2470 (1897)) reports 135°. [b] Miller and Ploechl (*Ber.*, **25**, 2040 (1892)) report 168–170°.

(1) U. S. Public Health Special Fellow. This work was supported by a grant from the Cancer Research Grants Branch, U. S. Public Health Service, to D. M. Greenberg.

(2) Friedman and Gutman *Biochem. Z.*, **27**, 493 (1910).

(3) Fischer, *Ber.*, **37**, 3062 (1904).

The pure crystals sublime without sign of decomposition at 280°. *Anal.* Calcd.: N, 6.76. Found: N, 6.79.

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Diphenylacetonitrile

BY DAVID GINSBURG[1] AND MANUEL M. BAIZER

The preparation of diphenylacetonitrile, a starting material in the synthesis of Methadone (Amidone) and related analgetics, has recently been the subject of several publications.[2]

Schultz, Robb and Sprague,[2e] and Robb and Schultz[2f] report an adaptation of Hoch's synthesis,[3] in which benzyl cyanide is brominated and the resultant α-bromo-α-phenylacetonitrile is condensed with benzene in the presence of anhydrous aluminum chloride; they obtain yields of 50–60%.

The modification of Hoch's procedure which we have employed minimizes the possibility of exposure to the intermediate α-bromo-α-phenylacetonitrile, which is a potent lachrymator, and provides yields of 80% of pure diphenylacetonitrile.

Experimental

In a five-liter, three-necked flask equipped with a dropping funnel whose stem extends below the surface of the liquid, a mercury-sealed stirrer and a reflux condenser protected by a calcium chloride tube is placed 441 g. (3.76 moles, 290 ml.) of benzyl cyanide.[4] Stirring is started and the cyanide is heated to 105–110° by means of an oil-bath. Now 608 g. (3.80 moles, 195 ml.) of bromine is added in the course of sixty to ninety minutes. Throughout this period the temperature is maintained within the range indicated above. The hydrogen bromide evolved may be absorbed in a water-trap. After addition is complete, two liters of dry benzene is added and the mixture is heated under reflux for about one hour, until virtually all the hydrogen bromide has escaped. The dropping funnel is now instantly replaced by a solid rubber stopper.[5]

The reaction mixture is cooled to 20°. Stirring is continued and 507 g. (3.81 moles) of powdered anhydrous aluminum chloride is added in portions in the course of about one hour with the usual precautions.[6] The temperature in this period is maintained at 20–25°. When the addition of catalyst is complete, the temperature of the mixture is slowly raised. In about fifteen minutes, when the temperature has reached 35–40°, vigorous evolution of hydrogen bromide commences. Upon abatement of the reaction, the mixture is heated under reflux for sixty to ninety minutes and then cooled to room temperature. It is poured slowly and with stirring into a mixture of 1800 g. of ice and 760 ml. of 1:1 hydrochloric acid.

The layers are separated. The aqueous portion is extracted twice with 800-ml. portions of benzene. The combined benzene extracts are washed successively with one liter of water, one liter of 5% sodium carbonate and one liter of water. The washings are discarded; the benzene solution is dried over 250 g. of anhydrous sodium sulfate.

The benzene is distilled at atmospheric pressure and the residue is distilled under reduced pressure using a steam-heated condenser; b. p. 160–170° (5 mm.). The crude product is recrystallized from methanol (0.5 cc./g.); yield (in two crops) 585 g. (80% based on benzyl cyanide); m. p. 73–74°.

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(1) Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

(2) (a) Reid and Hunter, THIS JOURNAL, **70**, 3515 (1948); (b) Homeyer, U. S. Pat. 2,443,246; *C. A.*, **42**, 7338a (1948); (c) U. S. Pat. 2,447,419; (d) Freeman, *et al.*, THIS JOURNAL, **69**, 858 (1947); (e) Schultz, Robb and Sprague, *ibid.*, **69**, 2458 (1947); (f) Robb and Schultz, *Org. Syn.*, **28**, 55 (1948).

(3) Hoch, *Compt. rend.*, **197**, 770 (1933).

(4) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 107.

(5) The equipment may be originally assembled so that one of the side-necks of the flask carries a two-necked adapter. Then no detachment need be made, and all possibility of exposure to α-brom-α-phenylacetonitrile can be eliminated.

(6) It is convenient to weigh the aluminum chloride into an Erlenmeyer flask and to attach the latter by a rubber sleeve to the available neck of the flask.

Reinvestigation of the Reaction of Ethylmagnesium Bromide with Pyridine

BY NYDIA GOETZ-LUTHY

Recently it has been reported[1] that 2-ethylpyridine prepared by unequivocal methods yielded a picrate which melted at 108.5–110° rather than 187–189° as reported by Bergstrom.[2] The work of Gregg and Craig was repeated and confirmed. Thus when 2-vinylpyridine (Reilly product) was reduced by hydrogenation over old Raney nickel at room temperature, there was obtained an excellent yield of a clear, colorless liquid boiling 148–150°[3] at atmospheric pressure. The picrate of 2-ethylpyridine so obtained melted at 108–109° in agreement with the results reported by Gregg and Craig.

In an effort to throw light on the discrepancy and to find out more about the nature of the reaction of pyridine with ethylmagnesium bromide at elevated temperatures, the following experiments were undertaken. An attempt was made to repeat the earlier work[4] but after three runs it became apparent that ethylmagnesium bromide and pyridine in ether solution react at 150–160° to give a mixture of products in which 2-ethylpyridine, if formed, is present in so small a quantity as to escape ready identification by the usual laboratory methods. The chief products isolated were unreacted pyridine and high boiling materials, presumably dipyridyls.

No substance boiling at 148–150° forming a picrate having a m. p. 187–189°[2,4] was obtained from the various fractions collected upon distillation of the product. Picrates were obtained which melted 165–166° and which did not lower the melting point of the picrate of a known sample of pyridine. The picrate of a higher boiling material (74–75° at about 33 mm.) which melted at 199–203° (uncor.) corresponded more

(1) Earl C. Gregg, Jr., and David Craig, THIS JOURNAL, **70**, 3138 (1948).

(2) F. W. Bergstrom and S. H. McAllister, *ibid.*, **52**, 2848 (1930).

(3) I. M. Heilbron, "Dictionary of Organic Compounds," gives the boiling point of 2-ethylpyridine at 148–150°.

(4) S. H. McAllister, Master's Thesis, Stanford University, Stanford, Calif., 1930.