

## SYNTHESIS OF THE LOWER ALIPHATIC AMIDES

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*Received September 21, 1953*

Methods for the synthesis of the aliphatic acid amides having from three to five or six carbon atoms are not satisfactory. The method of Aschan (1) gives low and impure yields in this range. The action of ammonia on acid chlorides has been reviewed by Sonntag (2). The method of Mitchell and Reid (3) gives good yields but the products are impure. The dehydration of ammonium salts requires autoclaving in many cases and the products are usually contaminated with ammonium salt or nitrile or both.

The treatment of acid chlorides with ammonia in non-aqueous media has not been systematically studied for the three to six carbon range. The method described in this paper involves the reaction of the acid chloride in anhydrous benzene with dry gaseous ammonia. The yields range from 65% to 95% for the amides prepared. The amides are easily purified with a high recovery from a mixture of benzene and petroleum ether. Anhydrous media prevent ammonium salt formation. The use of dry ether in place of the benzene gave lower yields and products with a lower melting point.

This method requires that ammonia be present in excess. To meet this requirement the acid chloride in benzene solution is dropped into hot benzene through which a stream of ammonia is passing. The reaction is carried out on a water-bath to prevent crystallization of the amide. If the ammonia is passed directly into a solution of the acid chloride, large quantities of the diamides are formed.

The amides are recrystallized from benzene-petroleum ether. The recovery of the amide usually lies between 90% and 96%. The products are odorless and have a constant melting point after two or three recrystallizations. The use of ether or alcohol for recrystallization gives lower melting points and the products have the odor of the parent acids.

Table I gives the yields and melting points of the amides prepared in this work. The literature melting points cited are based on a critical survey. The experimental part gives typical examples of syntheses on scales of 0.2 and 0.03 moles. The techniques are interchangeable.

EXPERIMENTAL<sup>1</sup>

The starting materials were purchased from the Distillation Products Division of the Eastman Kodak Corporation.

*Acid chlorides.* Propionyl chloride was purchased. The acid chlorides containing three to six carbon atoms were prepared from the corresponding acids by distillation with benzoyl chloride (11). One mole of the acid was mixed with 2.5 moles of benzoyl chloride and warmed until the evolution of hydrogen chloride was complete.<sup>2</sup> "Boileezers" were used to prevent bumping. The acid chloride was then distilled from the mixture through a 15

<sup>1</sup> Melting points were determined on a calibrated Fisher-Johns apparatus.

<sup>2</sup> In all of our preparations one mole of hydrogen chloride was evolved per mole of acid chloride formed. The hydrogen chloride was determined by titration with sodium hydroxide.

TABLE I  
 YIELDS AND PROPERTIES OF THE AMIDES

COMPOUND	YIELD, %	TIMES RECRYSTALLIZED	M.P., °C. (Obs.)	M.P., °C. (Lit.)	REF.
Propionamide.....	74	2	80.5-81.5	81.3	3
Butyramide.....	79	2	115.0-116.0	115	3
Isobutyramide.....	83	2	129.5-130.0	129-130	4
Valeramide.....	66	2	106.0-106.5	105.8	3
Isovaleramide.....	65	3	136.0-137.0	137	5
$\alpha$ -Methylbutyramide.....	78	2	112.0-112.5	111.7	6
$\alpha,\alpha$ -Dimethylpropionamide.....	71	2	156.0-157.0	155-156	7
Caproamide.....	93	2	101.0-101.5	101.5	3
Isocaproamide.....	91	2	120.5-121.0	121.0	8
$\alpha$ -Ethylbutyramide.....	91	2	114.0-114.5	112	9
Enanthamide.....	94	2	97.0-97.5	96.5	3
Caprylamide.....	95	2	106.5-107.5	106.0	3
$\alpha$ -Ethylcaproamide.....	93	2	103.5-104.0	101-102	10

mm.  $\times$  250 mm. Vigreux column. The acid chlorides containing seven or more carbon atoms were prepared by the usual phosphorus trichloride method. All acid chlorides were redistilled just before use.

*Butyramide.* A 500-ml. three-neck flask was fitted with a reflux condenser, a dropping-funnel with the tip drawn down to 0.5 mm. diameter, and a gas delivery tube of 8 mm. internal diameter. The top of the condenser was fitted with a calcium chloride guard tube. Benzene (250 ml.) dried by distillation was placed in the flask and a solution of butyryl chloride (21.3 g., 0.2 mole) in dry benzene (50 ml.) was placed in the dropping-funnel. The flask was heated by a boiling-water bath. Gaseous ammonia was passed through the benzene at the rate of 250 ml. per minute as measured by a Fisher and Porter "Flowrator". The acid chloride was added dropwise over one hour. Ammonia was passed through the mixture for one half hour longer. The reaction mixture was filtered through a medium porosity, preheated, glass Buchner funnel and the cake washed with two 25-ml. portions of hot benzene. The washings were combined with the filtrate. The benzene solution of the amide was reduced to 75 ml. by distillation and transferred to a beaker. Petroleum ether (b.p. 30-60°) was carefully added to the hot benzene solution until crystallization commenced. The mixture was reheated until clear then allowed to cool spontaneously. The butyramide was removed by filtration. The amide was recrystallized twice from benzene-petroleum ether in the same way. The product was dried in air. The yield of purified butyramide was 13.7 g. (78.7%) of odorless, shining, white leaflets, melting at 115-116° (reported m.p. 115°) (3).

*$\alpha$ -Ethylbutyramide.* A 125-ml. wide-mouth extraction flask was placed on a boiling-water bath and fitted with a rubber stopper through which passed a gas delivery tube of 8 mm. internal diameter, a cold finger condenser, and a dropping-funnel with an 0.5-mm. diameter tip. A groove was cut in the side of the stopper to permit the escape of excess ammonia. Dry benzene (50 ml.) was placed in the flask and a solution of  $\alpha$ -ethylbutyryl chloride (3.502 g., 0.026 mole) in dry benzene (25 ml.) was placed in the dropping-funnel. Ammonia was passed through the benzene at 150 ml. per minute. The acid chloride was added dropwise over one hour and ammonia was passed in for 20 minutes longer. The reaction mixture was worked up and the amide recrystallized by the same technique as was used for the butyramide. After two recrystallizations the yield of  $\alpha$ -ethylbutyramide was 2.72 g. (91%) of shining white, odorless needles, melting at 114.0-114.5°. (reported m.p. 112°) (9).

## SUMMARY

The preparation of thirteen aliphatic amides by the reaction of their acid chlorides with ammonia in dry benzene has been described. The necessary conditions for this reaction have been investigated. The effectiveness of various solvents for the purification of the amides has been studied.

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