reaction product consisted of 3.5 g. of 2-bromo-1-hexene and 41 g. of 1,2-dibromohexane.

One-half mole of hydrogen bromide was passed for nine hours into a solution of 32.6 g. of peroxide-free 2-bromo-1-hexene in 39 g. of benzene; 0.2 g. each of hydroquinone and ferrous bromide were used to inhibit peroxide formation. The temperature of the reaction was 23°. The reaction product contained 10 g. of unreacted 2-bromo-1-hexene, 24 g. of 2,2-dibromohexane and 4 g. of 1,2-dibromohexane.

Identification of Products.—The properties of 2-bromo-1-hexene, b. p. 132.5–133.5° (740 mm.), $n^{19}\mathrm{D}$ 1.4555, d_{20} 1.1960, agree closely with those reported by Bourguel:[10] b. p. 134° (760 mm.), $n^{19}\mathrm{D}$ 1.455, d_{19} 1.203.

The 1-bromo-1-hexene had the properties: b. p. 139–141° (751 mm.), $n^{20}\mathrm{D}$ 1.4596, d_{21} 1.1998. Bachman[11] reported for this compound: b. p. 138–140° (747 mm.), $n^{20}\mathrm{D}$ 1.4584, $d^{20}{}_{20}$ 1.1910. The slight discrepancy in these physical constants may be caused by a difference in the ratio of *cis-trans* isomers obtained in the two cases. The 1-bromo-1-hexene was analyzed for bromine by the method of Chablay, as modified by Vaughn and Nieuwland:[12] calcd. for $C_6H_{11}Br$, 49.0; found, Br, 49.1.

The properties of the 1,2-dibromohexane, b. p. 89–90° (18 mm.), $n^{20}\mathrm{D}$ 1.5023, d_{21} 1.5767, agree well with those reported by Schmitt and Boord:[13] b. p. 89–90° (18 mm.), $n^{20}\mathrm{D}$ 1.5024, d_{20} 1.5774.

The 2,2-dibromohexane has not been reported previously. The following physical constants were obtained: b. p. 83.5–84.0° (24 mm.), $n^{22}\mathrm{D}$ 1.4930, calcd. $\mathrm{MR_D}$ 45.45, found $\mathrm{MR_D}$ 45.57, d_{22} 1.5463. *Anal.*:[12] calcd. for $C_6H_{12}Br_2$: Br, 65.5; found: Br, 65.4. The identity of the 2,2-dibromohexane was established by hydrolyzing it to 2-hexanone. This was accomplished by refluxing with silver sulfate in 10% sulfuric acid. The 2-hexanone boiled at 126.1° (747 mm.), reported b. p. 126.0–126.5° (760 mm.),[14] and the semicarbazone melted at 118°, reported m. p. 118°.[15]

Summary

1. The addition of hydrogen bromide to butylacetylene in the presence of peroxides derived from butylacetylene yielded 1-bromo-1-hexene and 1,2-dibromohexane.

2. In the absence of peroxides hydrogen bromide yielded mainly 2-bromo-1-hexene and 2,2-dibromohexane.

3. The addition of hydrogen bromide was much more rapid in the presence of peroxides than in their absence.

4. The addition of hydrogen bromide to 1-bromo-1-hexene in the presence of peroxides formed only 1,2-dibromohexane, while in the absence of peroxides scarcely any reaction occurred under the conditions used. No 1,1-dibromohexane was formed in either case.

5. In the presence of peroxides 2-bromo-1-hexene yielded with hydrogen bromide only 1,2-dibromohexane; under peroxide-free conditions the chief product was 2,2-dibromohexane, the other product being 1,2-dibromohexane.

NOTRE DAME, INDIANA RECEIVED MARCH 28, 1936

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[10] Bourguel, *Compt. rend.*, **177**, 688 (1923).

[11] Bachman, THIS JOURNAL, **55**, 4282 (1933).

[12] Vaughn and Nieuwland, *Ind. Eng. Chem.*, *Anal. Ed.*, **3**, 274 (1931).

[13] Schmitt and Boord, THIS JOURNAL, **54**, 760 (1932).

[14] Clarke, *ibid.*, **34**, 681 (1912).

[15] Michael, *ibid.*, **41**, 416 (1919).

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

Extensions of the Leuckart Synthesis of Amines

BY A. W. INGERSOLL, J. H. BROWN, C. K. KIM, W. D. BEAUCHAMP AND GARLAND JENNINGS

The conversion of certain ketones (and aldehydes) to the corresponding amines by heating with excess ammonium formate was described by Leuckart[1] as early as 1885. The mechanism of the reaction has been discussed by Wallach,[2c] but is not definitely known. The equation

$$R{-}CO{-}R' + 2HCO_2NH_4 \longrightarrow R{-}CH(NHCHO)R' + 2H_2O + NH_3 + CO_2$$

appears to summarize the primary reaction, although formamide is doubtless an intermediate and may be used instead of ammonium formate. The amine is formed by subsequent hydrolysis of the formyl derivative.

Although Leuckart's method has been applied by Wallach[2] to a number of alicyclic and terpenoid ketones, and appears to be rather general, it has found little use by others. Possibly the obvious advantages of economy and simplicity have appeared to be outweighed by the unsatisfactory procedures that have so far been suggested. Leuckart himself, and also Wallach, ordinarily heated the reagents in a sealed tube at 210–240°. In some instances, however, Wallach[2b,2c] and others[3] have shown that the primary reaction

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[1] Leuckart, *et al.*, *Ber.*, **18**, 2341 (1885); **19**, 2128 (1886); **20**, 104 (1887); **22**, 1409, 1851 (1889).

[2] Wallach, *et al.*, (a) *ibid.*, **24**, 3992 (1891); *Ann.*, **269**, 347 (1892); **276**, 306 (1893); (b) *ibid.*, **300**, 283 (1898); (c) *ibid.*, **343**, 54 (1905).

[3] (a) Freylon, *Ann. Chim.*, [8] **15**, 141 (1908); (b) Read and Robertson, *J. Chem. Soc.*, 2217 (1926); (c) Read and Johnston, *ibid.*, 231 (1934).

occurs, though rather slowly, upon refluxing the reagents at atmospheric pressure. In a recent example Read and Johnston[3c] have reported only a 20–25% conversion of carvomenthone to carvomenthylamines after forty-eight hours of refluxing at 130°. Thus neither the sealed tube process nor the refluxing process is attractive and the method is also known to yield the corresponding secondary and tertiary amines as by-products.

Since other work in this Laboratory required large quantities of a variety of asymmetric amines, which are conveniently derived from ketones, it was sought to improve Leuckart's method with a view to adapt it to large scale laboratory use and, if possible, to extend its scope. As the result of several years of experience a simple procedure has been worked out which, when applied to some twenty ketones of various types, has given the corresponding primary amines in yields usually ranging from 60 to 85% of the theoretical and in amounts as large as several hundred grams per run. It has been found that the proportion of secondary and tertiary amine produced is so small as to cause no difficulties. In most cases a uniform procedure can be followed, with slight modifications for special cases. A number of amines have been prepared by this method for which no other method of synthesis appears feasible.

In preliminary experiments with the refluxing procedure it soon appeared that formamide rather than ammonium formate must be made the effective reagent. Thus when the process was tried with acetophenone and initially solid ammonium formate, as suggested by Freylon,[3a] it was found that the mixture boiled freely at 150–160° but remained in two layers; no appreciable reaction occurred in ten hours. On the other hand, when water was allowed to distil during the process or when formamide was used initially, the mixture soon became homogeneous and the reaction occurred in a few hours at 150 to 190°. The improved procedure involves, therefore, essentially a slow distillation, with occasional return of any ketone that may distil; both processes may be combined by the use of an automatic separator. The general procedure is described in the Experimental part.

Scope of the Method.—The improved method has been studied thus far principally in instances in which the main concern was the suitability of the amine for other work. In its usual form the method appears best adapted to the conversion of stable, water-insoluble ketones boiling at about 120° or higher. These include the higher aliphatic ketones, acetophenone and its numerous analogs, and certain terpenoid ketones. For such ketones the yields are consistently good and the method is definitely superior in economy and convenience to the familiar methods involving the formation and reduction of ketoximes.

Of even greater interest is the fact that the method can be used successfully in instances in which the reduction of an oxime is inadmissible. Thus it was found that when *p*-chloroacetophenoneoxime was reduced in the usual way with sodium and alcohol or with sodium amalgam and acetic acid, about half of the resulting mixture of amines was α-phenylethylamine, formed by the removal of nuclear halogen. On the other hand, the improved Leuckart method gave a high yield of pure α-*p*-chlorophenylethylamine. In the same way *p*-bromoacetophenone and even *m*-nitroacetophenone were readily converted to the corresponding amines.

When applied to benzalacetone or to carvone the method yielded chiefly a neutral resin and only small amounts of the corresponding amines. From present experience the method is believed to be unsuitable for application to α,β-unsaturated ketones, but otherwise appears widely applicable.

Most of the amines that were prepared have not been described previously. For these the principal constants, derivatives and analyses are given in the accompanying table. It is hoped to describe the new amines more fully in later papers. There are also included in the table yield data on these amines and on a few other representative amines. In most cases the stated yields are the average of two or more runs and make no allowance for recovered ketone.

Experimental

General Procedure.—A satisfactory ammonium formate–formamide reagent, sufficient for one mole of ketone, is made most economically as follows. In a 1-liter round-bottomed flask is placed 215 g. (4 mole-equivalents of ammonia) of commercial ammonium carbonate–carbamate. The flask is fitted with a cork bearing a thermometer that extends nearly to the bottom, a small separatory funnel, and a wide bent tube attached for distillation to a short, wide condenser. There is then added cautiously 215–230 g. (4.1 moles) of commercial 85–90% formic acid. When the reaction moderates the mixture is heated cautiously and then slowly distilled until the temperature is about 165°. The same amount of reagent can

TABLE I

Ketones	Amines	Yield, %	B. p., °C.[j]	Sp. gr.	$n^{25}\text{D}$	Benzoyl deriv., °C.[j]	Hydrochloride		
							M. p., °C.[j]	Analysis, %Cl ion Calcd.	Found
Acetophenone	*dl*-α-Phenylethyl-[c]	72	184–185	...	...	...	...	...	...
p-Methylacetophenone	*dl*-α-*p*-Tolylethyl-[d]	72	204–205	...	...	...	...	...	...
m-Methylacetophenone[a]	*dl*-α-*m*-Tolylethyl-[f]	70	204–205	0.9344^{20}_{20}	1.4924	113–114	164–165	20.60	20.79
p-Chloroacetophenone	*dl*-α-*p*-Chlorophenylethyl-[f]	82	105/10 mm.	1.1178^{20}_{20}	1.5420	144–145	192–193	18.46	18.47
p-Bromoacetophenone	*dl*-α-*p*-Bromophenylethyl-[f]	79	116/10 mm.	1.3910^{20}_{20}	1.5641	150–151	213–214	14.99	15.02
p-Methoxyacetophenone	*dl*-α-*p*-Methoxyphenylethyl-[f]	68	126/20 mm.	1.0174^{25}_{4}	1.5280	117–118	160–161	18.90	18.79
p-Phenylacetophenone	*dl*-α-*p*-Xenylethyl-[e]	77	[i]	...	...	178–179	220–221		
p-Phenoxyacetophenone[b]	*dl*-α-*p*-Phenoxyphenylethyl-[f]	69	[i]	...	...	113–114	180–181	14.21	14.09
β-Acetonaphthone	*dl*-Methyl-β-naphthylcarbin-[f]	84	[i]	...	...	151–152	198–199	17.09	17.19
m-Nitroacetophenone	*dl*-α-*m*-Nitrophenylethyl-[f]	56	[i]	...	...	156–157	223–224	18.81	18.76
dl-Fenchone	*dl*-Fenchyl-[f]	85	190–191	0.8971^{20}_{20}	1.4711	131–133	>250	18.70	18.72
d-Camphor	*d*-Bornyl- + neobornyl-[g]	62	...	...	...	...	...	...	...
Pinacolone	*dl*-Methyl-*t*-butylcarbin-[h]	52	102–103	...	...	98–99	>250	...	...

[a] Prepared from *m*-tolylmagnesium bromide and acetonitrile. The yield was poor. *Cf.* Jaspers, *Bull. soc. chim. belg.*, **34,** 182 (1925). [b] From diphenyl ether and acetic anhydride in 90–94% yields by the procedure of Noller and Adams, THIS JOURNAL, **46,** 1892 (1924). B. p. 182° (8 mm.), m. p. 50°; oxime m. p. 136°; semicarbazone m. p. 164°; 2,4-dinitrophenylhydrazone m. p. 213°, *cf.* Kipper, *Ber.*, **38,** 2491 (1905). [c] Kraft, *ibid.*, **23,** 2783 (1890). [d] Stenberg, *Z. physik. Chem.*, **70,** 534 (1910). [e] Ingersoll and White, THIS JOURNAL, **54,** 274 (1932). [f] Not previously described. [g] The mixture contains about 70% of neobornylamine. *Cf.* Forster, *J. Chem. Soc.*, **73,** 386 (1898). [h] Markownikoff, *Ber.*, **32,** 1448 (1889). [i] Distilled with partial decomposition at 10 mm. Purified by crystallization of the hydrochloride or *p*-toluene sulfonate. [j] Temperature taken with short range thermometer without further correction.

be obtained by distilling 250 g. of commercial solid ammonium formate instead of the reagents mentioned, but this offers no advantage.

To the reagent described above the ketone is added and the heating continued with a small flame. The reaction occurs fairly rapidly in the range 160–185° and may be accompanied by mild foaming. Water, ammonia, carbon dioxide and more or less ketone distil. The distillate is conveniently collected in a separatory funnel. The mixture gradually becomes homogeneous as the proportion of formamide increases. The distilled ketone, if any, is separated from time to time and returned to the reaction mixture. Alternatively, when rather volatile ketones are used, the reaction may be run in a flask fitted with a simple automatic separator so arranged as to return the (upper) ketone layer and discharge the aqueous layer.

When distillation of water practically ceases and the temperature reaches 175–185°, the temperature is maintained in this range for three to ten hours longer. In most cases three to four hours is sufficient; a longer time was found necessary only for "hindered" ketones such as camphor and fenchone. The end of the reaction is fairly clearly marked when the deposition of ammonium carbonate in the condenser nearly ceases. The rate of reaction increases somewhat with temperature, but above about 185° a faint odor of cyanide becomes apparent and the mixture tends to change from straw-color to dark brown The heating may be interrupted and resumed at any time.

When the reaction is complete the mixture is cooled and stirred thoroughly with twice its volume of water. The aqueous layer is separated and may be used for the recovery of formamide by distilling to 165°. Recovered formamide should be used only with the same ketone. The formyl derivative of the amine, mixed with unused ketone, may or may not solidify. It can be purified by vacuum distillation or crystallization, but this is not necessary. The crude, water-insoluble material is refluxed with about 100 cc. of concentrated hydrochloric acid for each mole of ketone used. Water may be added, if necessary, to keep the amine hydrochloride in solution. Hydrolysis is usually complete in thirty to fifty minutes, as shown by the solution of all but a small amount of inert material, consisting of unchanged ketone and condensation products. This is extracted with small portions of benzene and discarded or saved for recovery of the ketone. The latter may sometimes be recovered conveniently by steam distillation of the acid mixture. When the ketone is resinified by the action of hot acid, it may best be steam-distilled previously to hydrolysis. The corresponding formyl derivative of the amine is usually much less volatile, but may also distil with steam.

The amine is obtained from the aqueous acid solution by a method appropriate to its physical properties. When sufficiently volatile it is best purified by liberation with alkali and distillation with steam. The small amounts of secondary and tertiary amines present are thereby almost completely left behind. The distilled amine is extracted with benzene, dried, and redistilled as usual. When the amine is not very volatile it may often be obtained directly from the acid solution by fractional crystallization of the hydrochloride or may be purified in other ways.

Notes and Modifications.—The above procedure was not satisfactory with camphor because the sublimate rapidly clogged the apparatus. This difficulty was readily overcome by adding to the camphor about one-half its weight of nitrobenzene. The latter is unaffected by heating with formamide and serves to liquefy the camphor in both the reaction mixture and the distillate. The nitrobenzene and unchanged camphor are removed by steam distillation following the hydrolysis of the amine.

A similar procedure was fairly successful when applied to pinacolone. The nitrobenzene in this case appeared to diminish the distillation of the rather volatile ketone (b. p. 106°) and also served to extract it from the aqueous portion of the distillate. However, the general procedure described above is not regarded as suitable for the more volatile and water-soluble ketones. With such ketones it would appear better to start with substantially pure formamide and carry out the reaction entirely by refluxing. The small amount of water formed in the reaction causes no difficulty. In comparative experiments upon acetophenone and fenchone the yield was 4–6% better with pure formamide (4 moles) than with the usual reagent. With cheap ketones, however, the use of formamide is not justified, because of the extra cost.

In a series of experiments with acetophenone the percentage yields of amine were 53, 62, 72 and 72, respectively, when the molar ratios of reagent to ketone were 3.0, 3.5, 4.0 and 5.0. In experiments with 2:1 and 4:1 ratios of pure formamide the yields were 23 and 78%, respectively.

Runs were made with from 0.1 mole to 4.0 moles of ketone without important variations in yield. There is no apparent reason why the scale may not be as large as desired.

Summary

1. The Leuckart synthesis of amines from ketones has been improved and adapted to large scale use. A general procedure is described.

2. Eight new amines have been prepared and described.

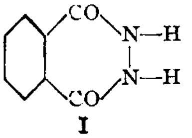
NASHVILLE, TENNESSEE RECEIVED JUNE 29, 1936

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

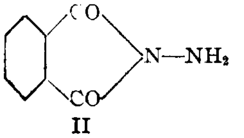
The Methyl and Phenyl Derivatives of the Nitrophthalhydrazides

BY C. N. ZELLNER AND GREGG DOUGHERTY

The brilliant chemiluminescence of some of the phthalhydrazide derivatives has created an interest in the chemistry and structure of these compounds. Of the three structures which have been proposed for phthalhydrazide



I



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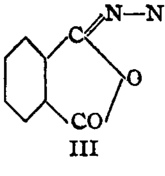

III

I and II have received the most serious consideration. The work of Radulescu and Georgescu,[1] Moyer,[2] and Rowe and Peters[3] on the various methylated and acetylated phthalhydrazides has indicated that structure I or a tautomeric modification of it is preferable to structure II. These workers confined their efforts to phthalhydrazide which was not substituted in the benzene ring.

It is obvious that, if the hydrazide structure I is correct, the presence of a substituent in the aromatic nucleus would make possible the existence of various isomeric non-nuclear alkyl or aryl derivatives not capable of existence on the basis of the aminophthalimide formula II. Also the study of a nuclear substituted hydrazide should give some indication of the normal tautomeric condition of the molecule. In order to test these points the present work with the nitrophthalhydrazides was undertaken.

The reaction of 3-nitrophthalic anhydride with methylhydrazine acetate gave two isomeric monoethyl derivatives which were produced in almost equal proportions, one melting at 305°, and the other at 273°. Both were readily acetylated, the two monomethyl monoacetyl derivatives melting at 211 and 144°, respectively. (All melting points have been corrected.) The existence of two *n*-methyl compounds is easily accounted for on the basis of the hydrazide structure

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[1] Radulescu and Georgescu, *Bull. soc. chim.*, **37**, 881 (1925).

[2] Moyer, private communication.

[3] Rowe and Peters, *J. Chem. Soc.*, 1331 (1933).