

Ethyl anisate and benzal chloride were obtained from 4-methoxyphenyl α,α -dichlorobenzyl ketone; ethyl anisate and *o*-chlorobenzal chloride from 4-methoxyphenyl α,α -2-trichlorobenzyl ketone and ethyl veratrate, and *o*-chlorobenzal chloride from 3,4-dimethoxyphenyl α,α -2-trichlorobenzyl ketone. The reaction mixture from phenyl α,α -dichlorobenzyl ketone proved to be inseparable by fractional distillation; it was therefore heated for four hours at 150° with hydrochloric acid (1:2) and the product separated into benzaldehyde and benzoic acid.

Summary

1. The phenyl α,α -dichlorobenzyl ketones from three representative mixed benzoinis have been prepared and examined. They have been reduced catalytically to the phenyl α -chlorobenzyl ketones, and these in turn to the desoxy compounds. The conversion of the phenyl α -chlorobenzyl ketones to the parent benzoinis was also carried out.

2. It has been found that phosphorus pentachloride in the cold behaves chiefly as an oxidizing agent toward benzoinis, good yields of the benzils being obtained.

3. The phenyl α,α -dichlorobenzyl ketones, when treated with alcoholic sodium ethylate in the cold, rapidly break up into a mixture of the corresponding benzoic ester and the benzal chloride. Small amounts of the diethylacetal are also formed.

4. Parallel experiments on benzoin were carried out as a check.

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THE SYNTHESIS OF BETA-ETHOXYAMINES¹

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The method of preparation of β -ethoxyamines described in this paper was evolved with the idea that it might be possible to synthesize numerous substituted derivatives, in the manner that Boord² and his co-workers have used in the preparation of isomeric olefins. It was further felt that these ethoxyamines might be more easily resolved than the corresponding alcohols and the active ethers might then be split to yield various optically active β -hydroxyamines which should be of interest from a pharmaceutical point of view. A second point of interest concerning these ethoxyamines was their possible use as basic resolving agents. In this respect they form a continuation of a study by Brode and Littman³ on the synthesis and resolution of a quite different type of asymmetric amine. The method of

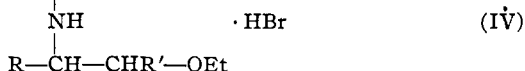
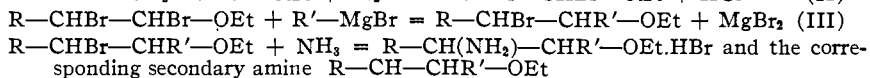
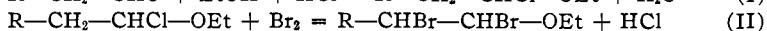
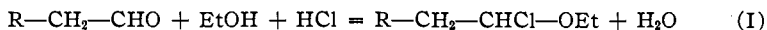
¹ Presented at the Mid-West regional meeting of the American Chemical Society, St. Louis, Mo., April 5, 1932.

² Boord and co-workers, *THIS JOURNAL*, **52**, 651, 3396 (1930); **53**, 1505 (1931); **54**, 751 (1932).

³ Brode and Littman, *ibid.*, **52**, 1655, 5056 (1930); **53**, 1531 (1931).

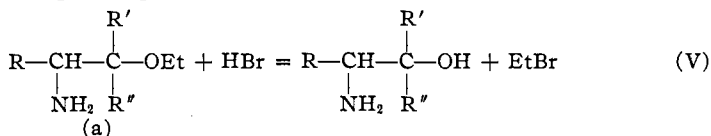
synthesis of the amines described in this paper is a combination of methods of Bookman,⁴ Houben and Führer⁵ and de Montmollin,⁶ with certain improvements and modifications as applied to β -bromoethyl ethyl ethers as prepared by the methods of Boord.²

The method of preparation of these amines can best be indicated by equations as follows



In (IV) amines such as RNH_2 or R_2NH may be used to yield mixed secondary or tertiary amines. Although reactions have been carried out indicating the practicality of the use of various aldehydes in (I), the work described in this paper was confined to the derivatives obtained from acetaldehyde, since this aldehyde yields an amine in equation (IV) of the type $\text{NH}_2-\text{CH}_2-\text{CHR}'-\text{OEt}$ which contains only one asymmetric carbon, and hence should be more easily resolved.

By the use of a method^{7,8} for the conversion of α -alkyl or aryl substituted β -bromo ethers of the type obtained in equation (III) into unsaturated ethers by the removal of hydrogen bromide, and by subsequent bromination, one obtains an α -alkyl or aryl-substituted α, β -dibromoethyl ether. Treatment of this ether with the same or a different Grignard reagent as in equation (III) yields an amine ether (a) which can be split to yield the corresponding alcohol.



Two methods were tried in the conversion of the β -bromo ethers into the corresponding amines. The first was to dissolve the bromo ether in methyl alcohol saturated with ammonia, and continue the introduction of ammonia gas into this solution over a period of several weeks. This method, while yielding the desired amines, was not satisfactory from the standpoint of convenience or yields obtained. The second and more satisfactory method was to dissolve the bromo ether in a solution of methyl

⁴ Bookman, *Ber.*, **28**, 3111 (1895).

⁵ Houben and Führer, *ibid.*, **40**, 4993 (1907).

⁶ De Montmollin and co-workers, *Helv. Chim. Acta*, **12**, 610, 873 (1929).

⁷ Lauer and Spielman, *THIS JOURNAL*, **53**, 1533 (1931).

⁸ Schmitt and Boord, *ibid.*, **54**, 751 (1932).

alcohol which had been saturated at 0° with ammonia. This solution, usually about 1500 cc. in volume, was then placed in a steel bomb with a capacity of about 2 liters. The bomb was sealed by a threaded steel plug and immersed in a water-bath which was kept at a temperature slightly below 100°. As will be noticed in Table I, an appreciable quantity of the secondary amine was formed in both methods, but better yields were in general obtained from the bomb method, a larger portion of which was the primary amine. In the case of the phenyl derivative no secondary amine was obtained, although a tarry residue indicated that some might have been formed. In no case were tertiary amines isolated, although they may have been formed and were part of the residues obtained in the isolation and distillation of the amines.

Both the primary and secondary amines are markedly stable, and while their boiling points are in general recorded at reduced pressures, many of them were subsequently distilled at atmospheric pressure without any noticeable decomposition or coloring. These amines are apparently unaffected by oxidation and can be kept for a long time without deterioration.

Experimental

Preparation of the 1-Bromo-2-ethoxy-2-(aryl or alkyl)-ethanes $\text{CH}_2\text{Br-CHR-OEt}$.—Previously described methods were used in the preparation of these compounds.² The average yield obtained in the preparation of the α -chloroethyl ethyl ether (equation I) was 89.1%. For the dibromo ether (equation II) an average yield of 92.6% was obtained and for the α -alkyl or aryl substituted β -bromo ethers an average yield of 72%.⁹

Preparation of the β -Ethoxyamines, $(\text{NH}_2\text{-CH}_2\text{-CHR-OEt}$, and the Corresponding Secondary Amines (Equation IV).—Two methods were used in the preparation of these

TABLE I
PREPARATION OF β -ETHOXYAMINES ($\text{C}_2\text{H}_5\text{-O-CHR-CH}_2\text{-NH}_2$ AND
 $(\text{C}_2\text{H}_5\text{-O-CHR-CH}_2)_2\text{NH}$)

| R | Bromo ether, g. | Liters of methyl alcohol | Time of reaction in weeks | Yield of primary amine | | Yield of secondary amine | | Total yield of amine % |
|--|-----------------|--------------------------|---------------------------|------------------------|------|--------------------------|------|------------------------|
| | | | | g. | % | g. | % | |
| A. Room temperature | | | | | | | | |
| C_2H_5 - | 230 | 1.5 | 7 | 62.8 | 42.2 | 27.0 | 19.4 | 61.6 |
| C_2H_5 - | 420 | 3 | 5 | 81.5 | 30.0 | 40.5 | 16.1 | 46.1 |
| <i>n</i> - C_3H_7 - | 309.5 | 2 | 15 | 92 | 44.2 | 56.5 | 29.0 | 73.2 |
| <i>n</i> - C_4H_9 - | 387 | 2 | 15 | 93 | 34.6 | 45.5 | 18.0 | 52.6 |
| <i>sec.</i> - C_4H_9 - | 316.5 | 2 | 12 | 90 | 40.9 | 40 | 19.3 | 60.2 |
| C_6H_5 - | 250 | 1.5 | 21 | 58 | 32.1 | .. | .. | 32.1 |
| B. At 90-100° (Bomb method) | | | | | | | | |
| <i>n</i> - C_4H_9 - | 600 | 3 | 36 hrs. | 252 | 60.4 | 61.5 | 15.5 | 76.1 |
| <i>sec.</i> - C_4H_9 - | 701 | 3.5 | 36 hrs. | 289.5 | 59.4 | 96 | 20.9 | 80.3 |
| C_6H_5 - | 500 | 2 | 48 hrs. | 222 | 61.6 | .. | .. | 61.6 |

⁹ This value does not include the yields obtained from the secondary butyl Grignard reagent and the α,β -dibromoethyl ethyl ether which were between 30 and 35% on several runs. Poor yields on this same reaction have been noted previously by other observers² and are probably due to the secondary character of the Grignard reagent.

TABLE II
PHYSICAL CONSTANTS AND ANALYSES OF β -ETHOXYAMINES

| Compound | B. p., °C. (mm.) | d_4^{20} | n_D^{20} | Mol. ref. | | Analysis, % N | |
|---|---------------------|------------|------------|-----------|-------|-------------------------------------|---------------------------------|
| | | | | Calcd. | Obs. | Calcd. | Found |
| β -Ethoxy- β -phenylethylamine | 107-9(12) | 0.9867 | 1.5102 | 49.84 | 50.04 | Previously described ⁵ | |
| N- β -Ethoxybutylamine | 153.5(21) | .9636 | 1.5174 | 60.44 | 60.68 | 15.44 (Cl) | 15.30, 15.40 (Cl) |
| β -Ethoxybutylamine | 138.5-140.5 | .8449 | 1.4190 | 34.97 | 35.01 | 11.95 (N) | 11.88, 11.75 (N) ^{4,6} |
| β, β' -Diethoxydibutylamine | 132-135(31) | .8657 | 1.4260 | 64.50 | 64.29 | Previously described ^{4,6} | |
| β -Ethoxyamylamine | 56.0-56.5(15) | .8427 | 1.4220 | 39.59 | 39.55 | 10.68 | 10.57, 10.48 |
| β, β' -Diethoxydiamylamine | 133.5-134.5(14) | .8627 | 1.4318 | 73.74 | 73.71 | 5.71 | 5.62, 5.81 |
| β -Ethoxy- γ -methylamylamine | 64-65(13) | .8507 | 1.4290 | 44.21 | 43.99 | 9.65 | 9.38, 9.37 |
| β, β' -Diethoxy- γ, γ' -dimethyldiamylamine | 144-147(14) | .8705 | 1.4380 | 82.97 | 82.42 | 5.13 | 5.00, 4.95 |
| β -Ethoxyhexylamine | 68-69(13) | .8429 | 1.4271 | 44.21 | 44.22 | 9.65 | 9.41, 9.54 |
| β, β' -Diethoxydihexylamine | 151-154(12) | .8618 | 1.4368 | 82.97 | 83.05 | 5.13 | 5.00, 4.98 |

amines, one at room temperature and atmospheric pressure, and the other at 100° and under pressure.

In the first procedure, the β -bromo ether was dissolved in a large amount of commercial methyl alcohol. Although the proportions varied, as shown in Table I, approximately 500 cc. of methyl alcohol was used per 100 g. of the bromo ether. This solution was saturated with ammonia gas at a temperature lower than 15°, thus ensuring complete saturation at room temperature (approximately 25°). This alcoholic solution was allowed to stand for several weeks, during which time additional ammonia was passed into the mixture at intervals of about one week.

The second procedure used in the synthesis of these amines was similar to the first, except that the methyl alcohol- β -bromo ether solution was saturated with ammonia at about 0°, the solution then poured into a steel bomb, sealed with a threaded steel plug and heated at a temperature of 90–100° for the periods of time indicated in Table I.

The same procedure was employed for the separation of the amines from the solutions obtained by either of the above two methods. As much of the methyl alcohol as possible was distilled from the solution, until severe bumping started, due to the separation of the amine hydrobromide. Five hundred to 1000 cc. of water was added and the oily material which separated was removed. If necessary the solution was extracted with ether to complete the removal of the oil. This oil, usually small in amount, included any unreacted β -bromo ether and certain decomposition products. Extraction of this oily material with dilute hydrochloric acid indicated the absence of any amines in this material.

The water was then removed by allowing the solution to boil slowly under reduced pressure. The distillation was stopped upon precipitation of the amine hydrobromide from the aqueous solution. By this time all of the excess ammonia and methyl alcohol had been removed. The solution was made strongly alkaline with concentrated sodium hydroxide and the amine layer which formed was removed with a separatory funnel. The solution was extracted three times with ether, the ethereal extract added to the amine and the whole dried over solid sodium hydroxide. Distillation first removed the ether and then gave in general two fractions of markedly different boiling points (the primary and secondary amines). These fractions were redistilled to obtain the pure amines. The percentage yields of the redistilled material are given in Table I.

In Table II are given the physical constants determined for these amines. The *N*- β -ethoxy-*n*-butylaniline was prepared by refluxing a methyl alcohol solution of aniline and the β -bromo ether at atmospheric pressure.

Summary

A method has been described for the synthesis of β -ethoxyamines. The following amines were prepared by this method: β -ethoxy- β -phenylethylamine, *N*- β -ethoxy-*n*-butylaniline, β,β' -diethoxydi-*n*-butylamine, β -ethoxy-*n*-amylamine, β,β' -diethoxydi-*n*-amylamine, β -ethoxy- γ -methyl-*n*-amylamine, β,β' -diethoxy- γ,γ' -dimethyldi-*n*-amylamine, β -ethoxy-*n*-hexylamine, and β,β' -diethoxydi-*n*-hexylamine. Of these amines only the β -ethoxy- β -phenylethylamine, the β,β' -diethoxydi-*n*-butylamine and the β -ethoxy-*n*-butylamine have been previously described.^{5,6} Physical constants of the prepared amines have been observed and recorded.