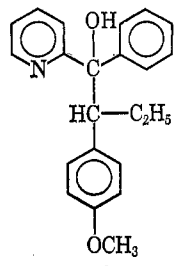

4

ammonia was added dropwise a solution of 21 g (0.1 mol) of ketone **1** in 150 ml of tetrahydrofuran (THF) (dried over calcium hydride) and the dark blue-purple mixture was stirred for 15 min. A solution of 1-*p*-anisyl-1-bromoethane (0.15 mol) prepared in toluene as previously described[7] was added dropwise and the mixture was stirred for 6 hr. Ammonium chloride (10 g) was added and, after the ammonia had evaporated, the THF was removed *in vacuo* on steam bath. To the residue, water and benzene was added and the mixture was separated and extracted with benzene. The combined benzene solutions were extracted with dilute (10%) hydrochloric acid and, after preliminary washing with ether, the acid solution was made basic with ammonium hydroxide and extracted with chloroform. The dark brown oily residue after removal of the chloroform was chromatographed on 650 g of alumina using benzene as the eluting agent; fractions of 650–700 ml were collected. Carbinol **2** [22.7 g (66%)] was obtained in the first three fractions. After an additional 2 l. of benzene was collected, the solvent was changed to 50% benzene–chloroform and an additional seven fractions were collected. Finally 100% chloroform was used to elute the last traces of ketone **3**.

Carbinol 2 was recrystallized from hexane, mp 103–105°, and showed a strong OH absorption at 3.1 μ.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.84; H, 6.93; N, 4:30.

Ketone 3 was recrystallized from hexane, mp 114–116°, ir 6.0 μ.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.56; H, 5.82; N, 4.03.

2-(*p*-Anisyl)-1-phenyl-1-(2-pyridyl)butanol (4).—Using the same procedure, this compound was obtained in 46% yield from 2-benzoylpyridine and 1-(*p*-anisyl)-1-bromopropane, mp 120–121° from hexane.

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.29; H, 6.95; N, 4.20. Found: C, 79.18; H, 6.94; N, 3.90.

Reduction of 3.—Ketone **3** (0.3 g) was dissolved in 15 ml of methanol and 0.2 g of sodium borohydride was added at 0–5°. After 2.5 hr the methanol was removed, water was added, and the product was extracted with chloroform. After removal of the solvent, the residue was recrystallized twice from petroleum ether (bp 30–90°), mp 118–122°.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.01; H, 6.90; N, 3.80.

Registry No.—**2**, 28795-63-3; **3**, 28795-64-4; **3** (reduced), 28795-65-5; **4**, 28795-66-6.

(7) F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970).

A Novel Synthesis of Benzylamines from Benzaldehydes

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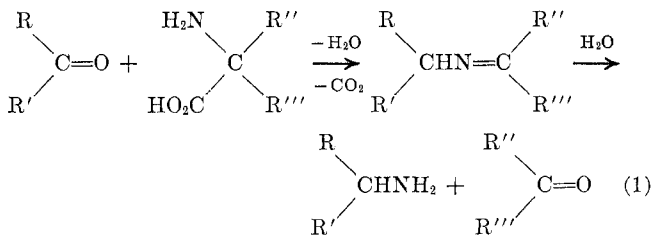
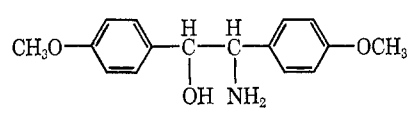
Because of their biological significance, the reactions of α-amino acids with carbonyl compounds have been widely studied.[1] It is unfortunate however, that only a few reports on this subject have dealt with these reactions from the synthetic chemist's point of view. A potentially useful but infrequently cited method for reductively aminating aldehydes and ketones is the reaction of carbonyl compounds with α-disubstituted amino acids under decarboxylation conditions followed by hydrolysis (eq 1).

The principal advantage of this method is that it accomplishes in essentially one step what is normally considered a two-step synthesis, *e.g.*, conversion of an aldehyde to an oxime, azine, phenylhydrazone, etc.,[2,3] followed by chemical reduction. Also, because the method does not require molecular hydrogen it should lend itself to selective reductive amination of an aldehyde function in the presence of otherwise reducible groups.



(1)

In 1964 Chatelus reported that the reaction of 2-amino-2-methylbutyric acid (isovaline) in fourfold molar excess of anisaldehyde gave *p*-methoxybenzylamine in quantitative yield.[4] In spite of the inherent simplicity in carrying out this reaction, we were not able to reproduce the yield claimed. Instead, we repeatedly isolated only 30–50% of *p*-methoxybenzylamine together with varying amounts of diastereomeric mixtures of alkamines **1**. This result was not too surprising since other workers had employed similar conditions (excess aldehyde) for the express purpose of synthesizing various alkamines.[5]



1

In this note we wish to describe an improved process for reductive amination of benzaldehydes in which a single mole of aldehyde is used per mole of amino acid. The method consists of slowly adding benzaldehyde or a substituted benzaldehyde to a refluxing slurry of commercially available *dl*-isovaline in dimethylformamide (DMF). Carbon dioxide is evolved rapidly during the addition and a nearly clear solution results shortly after all the aldehyde is added. DMF is removed by simple distillation or *via* a rotatory film evaporator, and the residue is boiled with 2 *N* HCl to hydrolyze the imine intermediate. In this way a benzylamine hydrochloride is formed in high

(1) A. F. Al-Sayyab and A. Lawson, *J. Chem. Soc. C*, 406 (1968); U. Gebert and B. v. Kerékjártó, *Justus Liebigs Ann. Chem.*, **718**, 249 (1968); G. D. Kalyankar and E. E. Snell, *Biochemistry*, **1**, 594 (1962); K. Dose, *Chem. Ber.*, **90**, 1251 (1957); D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem. Soc.*, **76**, 648 (1954).

(2) W. S. Emerson, *Org. React.*, **4**, 174 (1948).

(3) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).

(4) G. Chatelus, *Bull. Soc. Chim. Fr.*, 2523 (1964).

(5) D. Ll. Hammick, *et al.*, *J. Chem. Soc.*, 3825 (1953); E. Takagi, H. Ichikawa, and I. Ensaka, *J. Pharm. Soc. Jap.*, **71**, 652 (1951) [*Chem. Abstr.*, **46**, 8045 (1952)].

yield. The salt may be separated and purified at this stage or alternatively the crude reaction mixture can be treated with sodium carbonate and the free amine extracted with solvent. Results obtained with several benzaldehydes are shown in Table I. Our

TABLE I

AMINES FROM REDUCTIVE AMINATION OF BENZALDEHYDES

Aldehyde[a]	Amine product	% yield[b,c]	Bp, °C (mm)
Benzaldehyde	Benzylamine	59	182–184 (atm)[d]
p-Methoxybenzaldehyde	*p*-Methoxybenzylamine	64	121–123 (14)[e]
o-Chlorobenzaldehyde	*o*-Chlorobenzylamine	70	99.5–102 (11)[f]
p-Chlorobenzaldehyde	*p*-Chlorobenzylamine	77	106–108 (11–12)[g]

[a] Liquid aldehydes were freshly distilled before use; *p*-chlorobenzaldehyde was employed as a 50% solution in DMF. [b] Yields are based on weights of distilled amines. [c] Product infrared spectra were identical with spectra of known, commercially available amines. [d] Lit. bp 184° [J. L. E. Erickson, *Chem. Ber.*, **59**, 2665 (1926)]. [e] Lit. bp 122–124° (14 mm) [M. Tiffeneau, *Bull. Soc. Chim. Fr.*, **9**, 819 (1911)]. [f] Lit.[8] bp 103–104° (11 mm). [g] Lit. bp 106–107° (15 mm) [J. v. Braun, M. Kühn, and J. Weismantal, *Justus Liebigs Ann. Chem.*, **449**, 249 (1926)].

yields compared favorably with those obtained in other reductive aminations of aromatic aldehydes.[2]

When reactions were run without dropwise addition or when excess aldehyde was used as solvent, lower yields of benzylamines were obtained. The method was unsatisfactory for reductive amination of conjugated unsaturated aliphatic aldehydes.[6]

The reductive amination proceeded more slowly in diglyme. Thus, when 0.05-mol quantities of *p*-anisaldehyde and isovaline were refluxed in diglyme (30 ml), only 75% of the amino acid was consumed after 4 hr. Under these conditions the yield of *p*-methoxybenzylamine based on amino acid reacted was 62%. In this instance dropwise addition of aldehyde did not improve the yield of amine.

The reaction succeeded to a still lesser extent when isovaline was replaced with α-aminoisobutyric acid (α-methylalanine). When equimolar amounts of benzaldehyde and α-aminoisobutyric acid were refluxed in diglyme (40 ml) for 2.7 hr, 57% of the amino acid was consumed and the yield of benzylamine based on amino acid reacted was only 31%.

Experimental Section[7]

General Procedure for the Preparation of Benzylamines.—To a stirred, refluxing slurry of *dl*-2-amino-2-methylbutyric acid (5.81 g, 0.0493 mol) in 30 ml of reagent grade DMF was added dropwise 5.34 ml (0.0490 mol) of redistilled [bp 92° (13 mm)] *o*-chlorobenzaldehyde. The aldehyde was added over a period of 20 min. After the addition, the mixture was refluxed 1 hr, cooled to 25°, and filtered to remove 0.22 g of unchanged amino acid. The filtrate was concentrated to a viscous syrup under vacuum and the syrup was hydrolyzed by boiling it with 100 ml of 2 *N* aqueous HCl for 2 hr. The cooled acidic solution was extracted with benzene to remove traces of colored impurities and the aqueous phase was concentrated to yield crude *o*-chlorobenzylamine hydrochloride. The crystalline residue was treated with *ca.* 50 ml of 5% Na_2CO_3 solution and extracted with ether to remove the benzylamine. The ether solution was dried (Na_2SO_4) and concentrated on a rotatory film evaporator, and the residue was distilled to give 4.86 g of *o*-chlorobenzylamine, bp 99.5–102° (11 mm) [lit.[8] bp 103–104° (11 mm)]. The liquid film ir of the product was identical with the ir of commercially available *o*-chlorobenzylamine.

Registry No.—Benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *o*-chlorobenzaldehyde, 89-98-5 *p*-chlorobenzaldehyde, 104-88-1.

(6) In the case of citral, only 10–15% of citralamine was obtained; most of the aldehyde was converted to higher boiling products.

(7) All boiling points were not corrected. Reactions involving aldehydes were performed under an atmosphere of predried nitrogen. Substituted benzaldehydes, benzylamines, and *dl*-isovaline were purchased from Aldrich Chemical Co. Infrared spectra were obtained on liquid film samples on a Perkin-Elmer Model 137 instrument.

(8) H. Franzen, *Chem. Ber.*, **38**, 1415 (1905).

Preparation of 1,4-Bis(*p*-tolylsulfonyl)-hexahydro-6-hydroxy-1*H*-1,4-diazepine and 1,4-Bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine

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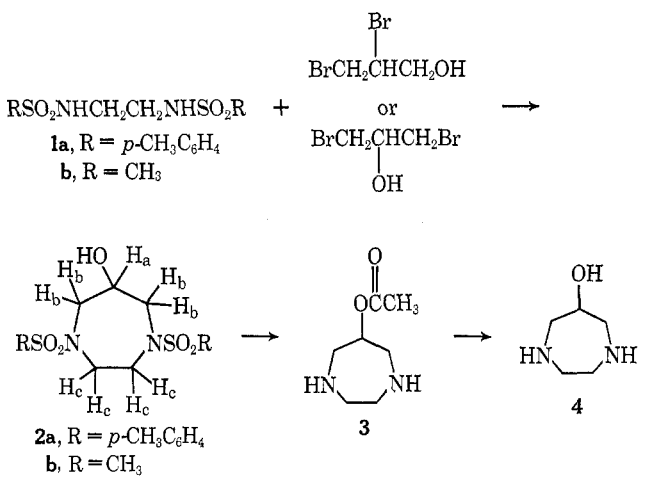
Synthesis of 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (**6a**) by reaction of the disodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) (**1a**) with 2,3-dibromo-1-propanol and conversion of the ditosylamide to 2-substituted piperazine derivatives has been reported several times.[1] We have found that the reaction of **1a** with 2,3-dibromo-1-propanol under these conditions gives only a small amount of the piperazine **6a**, the major product being the hexahydro-1*H*-1,4-diazepine **2a**.



Reaction of the disodium salt of **1a** with either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol in ethanol gave the same hexahydro-1*H*-1,4-diazepine **2a**, mp 175–177°, in 56–59% yield. Initially the hexahydrodiazepine structure was assigned to **2a** on the basis of its nmr spectrum in $CDCl_3$ which showed a one-proton multiplet at 4.0–4.4 ppm for the carbinol hydrogen, H_a. Addition of trichloroacetyl isocyanate to the solution shifted this one-proton multiplet down-

(1) (a) J. Gootjes, A. B. H. Funcke, H. M. Tersteege, and W. Th. Nauta, *Arzneim. Forsch.*, **16**, 1557 (1966); (b) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); (c) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Amer. Chem. Soc.*, **79**, 2221 (1957); (d) F. L. Bach, Jr., S. Kushner, and J. H. Williams, *ibid.*, **77**, 6049 (1955).