An Anomalous Alkylation of a Pyridine System[1]

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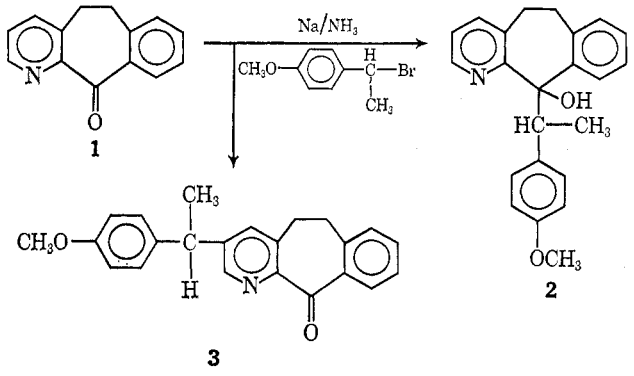
In the reductive alkylation[3] of the disodio derivative of 11*H*-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one[1b,4] (1) with 1-*p*-anisyl-1-bromoethane, two products were consistently obtained. The expected tertiary carbinol **2** was the major product (65–70% yield) and a smaller amount (10–15%) of a novel alkylation product **3** was isolated. The products were separated



1 2 3

by column chromatography on alumina using mixtures of benzene–chloroform whereby the tertiary carbinol was eluted first. The isolation of **3**, albeit in low yield and under the stringent steric requirements of the alkylating agent as discussed later, was unexpected in view of the known difficulty in alkylation of the β position of the pyridine ring.[5] Compound **3** shows strong carbonyl absorption in the ir at 6.0 μ, and its structure was assigned on the basis of the nmr spectrum as follows (10% soluion in $CDCl_3$, shifts reported in parts per million from internal TMS): δ 1.66 (3 H, α-$CHCH_3$, d, J = 7 Hz), 3.18 (4 H, ethylene bridge, s, 2 Hz wide), 3.79 (3 H, OCH_3, s), 4.18 (1 H, $CHCH_3$, q, J = 7 Hz), 6.7–7.6 (8 H, 7 phenyl plus the γ-pyridyl proton), 8.06 (1 H, the proton peri to CO, m), 8.62 (1 H, α-pyridyl proton, d, $J_{\alpha,\gamma}$ = 2 Hz). The appearance of the α-pyridyl signal as a weakly coupled doublet clearly indicates substitution at the β-pyridyl position. The α-pyridyl proton in the nmr spectrum of carbinol **2** appears at δ 8.42 as a quartet coupled to the β and γ protons, $J_{\alpha,\beta}$ = 4.5 Hz and $J_{\alpha,\gamma}$ = 2 Hz, respectively.

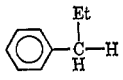
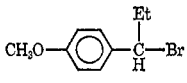
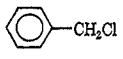
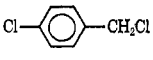
Sodium borohydride reduction of the carbonyl group of **3** gave the expected secondary carbinol.

Reductive alkylation of **1** using other secondary aromatic halides as, for example, 1-bromo-1-phenylpropane and 1-bromo-*p*-anisylpropane gave similar results (see Table I). However, when this reaction was carried out with primary aromatic halides, benzyl chloride, or *p*-chlorobenzyl chloride, or with a secondary aliphatic halide, *e.g.*, isopropyl bromide, only the tertiary carbinol of type **2** was obtained in excellent yields.

A similar alkylation of the nonbridged ketone, 2-benzoylpyridine, with 1-*p*-anisyl-1-bromopropane gave exclusively the tertiary carbinol **4**.

TABLE I

REDUCTIVE ALKYLATION OF 1[a]

Alkylating agent	Carbinol (type 2) % yield[b]	Carbinol (type 2) Registry no.	Carbinol (type 2) Mp, °C	Ketone (type 3) % yield	Ketone (type 3) Registry no.	Ketone (type 3) Mp, °C
	20	28795-67-7	101–102[c]	14	28795-72-4	94–95[c]
	24	28795-68-8	141–142[c]	17	28795-73-5	123–125[c]
	92	29795-69-9	84–85[d]			
	72	28795-70-2	109–110[d]			
$(CH_3)_2CHBr$	56	28795-71-3	94–96[d]			

[a] Satisfactory analytical data (±0.35% for C, H, and N) were reported for all compounds except the ketone, mp 123–125°, from 1-anisyl-1-bromopropane (calcd, C, 80.64; found, C, 81.12): Ed. [b] Yields do not represent the maximum obtainable. The recorded yields represent only one experiment and intermediate fractions from the chromatography containing both carbinol and ketone fractions were discarded. Ir and nmr spectra are in agreement with the structures as described in the text. [c] Recrystallized from isopropyl ether. [d] Recrystallized from hexane.

Experimental Section[6]

General Procedure.—To a well-stirred solution of 5.0 g (0.22 g-atom) of sodium metal in 300–400 ml of anhydrous liquid

(1) (a) Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and Related Compounds. IV. (b) For paper III, see F. J. Villani, P. J. Daniels, C. A. Ellis, T. A. Mann, and K. Wang, *J. Heterocycl. Chem.*, **8**, 73 (1971).

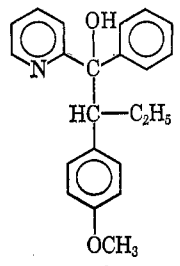
(2) (a) Department of Medicinal Chemistry; (b) Physical and Analytical Chemical Research Department.

(3) J. A. Gautier, M. Miocque, C. Fauran, and M. Duchon d'Engenières, *Bull. Chim. Soc.*, 3162 (1965).

(4) F. J. Villani, U. S. Patent 3,326,924 (1967).

(5) After this work was completed, two additional examples of β-alkylation of simple pyridine derivatives were described. See C. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970); R. Levine and W. M. Kadunce, *ibid.*, 921 (1970).

(6) Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer Infracord and nmr spectra on a Varian A-60A spectrometer. Microanalyses were carried out by the Physical and Analytical Chemical Research Department of the Schering Corp.



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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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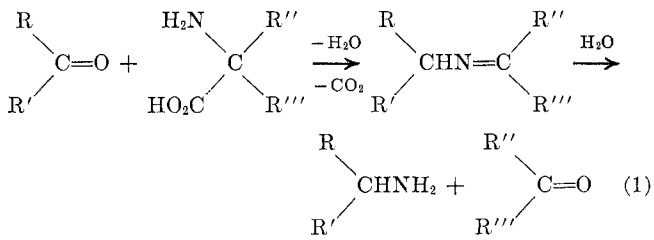
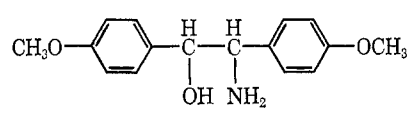
Because of their biological significance, the reactions of α-amino acids with carbonyl compounds have been widely studied.[1] It is unfortunate however, that only a few reports on this subject have dealt with these reactions from the synthetic chemist's point of view. A potentially useful but infrequently 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]



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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)].