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N-Alkylation of Aromatic Amines by Means of Alcohol. IV.[1] Syntheses of N-Alkylanilines and Related Compounds

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Because of the general availability of alcohols, methods for the alkylation of aromatic amines by means of alcohols have been widely studied. Benzyl alcohol has been found to react with aniline to give N-benzylaniline in the presence of activated nickel catalyst and potassium benzylate[3] or more conveniently, in the presence of potassium hydroxide only.[4,5]

The ease with which 2- and 4-pyridinemethanol also work in this type of alkylation has been demonstrated by one of the authors[6,7] and in the present investigation our attention has been focused to the N-alkylation of aniline by means of a seires of aliphatic alcohols.

In contrast to monobenzylation of aniline by benzyl alcohol, monoalkylation of aniline by aliphatic alcohol has been scarecly studied. Besides an earlier paper of N-alkylation of aniline by dry sodium alkoxides by Nef,[8] Pratt and Frazza reported[3] the alkylation of aniline with *n*-hexyl and *n*-decyl alcohol, employing similar conditions to those in their benzylation,[3] *e.g.* in the presence of metallic potassium benzylate and U.P.O. nickel catalyst. More recently Rice and Kohn[9] successfully alkylated aniline and benzidine with aliphatic alco-

Table I. N-Alkylation of Aniline[a,b]

$$C_6H_5NH_2 + R\text{-}OH \xrightarrow{Na} C_6H_5NH\text{-}R + H_2O$$

R	Aniline[c] (mole)	Alcohol[d] (mole)	Temp. (°C)	Time[e] (hr)	Product bp (°C/mm)	Product n_D^{25}	Product Yield (%)
n-Propyl	0.4	0.44	280—290	5	118/30	1.5399	20
n-Butyl	0.2	0.22	300	4	130—131/26	1.5319	34.4
n-Amyl	0.3	0.33	280	4	105/2	1.5254	37.8
Isoamyl	0.4	0.4	260—270	5	139/26	1.5241	41.6
n-Hexyl	0.2	0.4	290	5	160/27	1.5195	62.1
n-Heptyl	0.2	0.2	280	4	115—116/2	1.5159	46.3
n-Octyl	0.4	0.44	280	5	150—151/5	1.5121	64.5
2-Ethylhexyl	0.2	0.22	280—290	4	118—119/2	1.5194	34.9
n-Nonyl	0.3	0.33	280—300	6	147—149/2.5	1.5099	72

a) Autoclave with electro-magnetic stirring device was employed.
b) Boiling points of the product listed in this Table were identidal to the literature values. See ref. 9).
c) Freshly distilled aniline.
d) Commercial products as received were employed without purification.
e) This designates the time from the point when the reaction temperature specified is reached to the interrruption of heating.

1) Part III: S. Miyano, N. Abe, and A. Abe, *Chem. Pharm. Bull.* (Tokyo), **18**, 511 (1970).
2) Location: *Nanakuma, Fukuoka.*
3) E.F. Pratt and E.J. Frazza, *J. Am. Chem. Soc.*, **76**, 6174 (1954); U.O.P. nickel catalyst (purchased from Universal Oil Products Co.) and metal potassium were employed as catalyst.
4) I. Hirao and M. Hayashi, *Yakugaku Zasshi*, **74**, 853 (1954).
5) Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 3207 (1956).
6) S. Miyano, *Chem. Pharm. Bull.* (Tokyo), **13**, 1135 (1965).
7) S. Miyano, A. Uno, and N. Abe, *Chem. Pharm. Bull.* (Tokyo), **15**, 515 (1967).
8) J.U. Nef, *Ann.*, **318**, 137 (1901).
9) R.G. Rice and E.J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

hols in the presence of Raney nickel. Although the latter method, a Raney nickel catalyzed alkylation, appears to be of wide application, it suffers from the fact that larger amount of Raney nickel is required.

Our present method consists in heating a mixture of aniline, excess of aliphatic alcohol and metallic sodium alkoxide in an autoclave for several hours, the reaction condition being similar to that of Guerbet condensation,[10,11] a condensation of aliphatic alcohol at high temperature under the influence of sodium alkoxide (Table I). All of the N-alkylanilines obtained except 2-ethylhexylaniline are known compounds and were identified by deriving them to their *p*-toluenesulfonamides, 3,5-dinitrobenzamides or hydrochlorides (Table II).

TABLE II. Derivatives of N-Monoalkylanilines

Compound	mp[a] (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N
p-Tosyl-*n*-propylaniline	55	$C_{16}H_{19}O_2NS$	66.42/66.67	6.62/6.53	4.84/4.63
n-Butylaniline hydrochloride	114—115[b]	$C_{10}H_{16}NCl$	64.69/64.99	8.63/8.91	7.55/7.58
p-Tosyl-*n*-amylaniline	73—74[c]	$C_{18}H_{23}O_2NS$	68.12/67.84	7.31/7.12	4.41/4.71
p-Tosylisoamylaniline	77—78	$C_{18}H_{23}O_2NS$	68.12/68.24	7.31/7.55	4.41/4.43
p-Tosyl-*n*-hexylaniline	66—67	$C_{19}H_{25}O_2NS$	68.86/68.60	7.60/7.41	4.23/4.10
p-Tosyl-*n*-heptylaniline	75—76	$C_{20}H_{27}O_2NS$	69.54/70.04	7.88/7.97	4.06/4.22
3,5-Dinitrobenzoyl-*n*-octylaniline	50	$C_{21}H_{25}O_5N_3$	63.14/63.52	6.31/6.20	10.52/10.42
2-Ethylhexylaniline[d]		$C_{14}H_{23}N$	81.89/81.81	11.29/10.97	6.82/7.21
3,5-Dinitrobenzoyl-*n*-nonylaniline	87—88	$C_{22}H_{27}O_5N_3$	63.90/64.06	6.58/6.47	10.16/10.18

a) These melting points are in good accord with the literature values.
b) R. Foster and D. Ll. Hammick, *J. Chem. Soc.*, **1954**, 2685.
c) W.J. Hickinbottom, *J. Chem. Soc.*, **1937**, 1119.
d) New compound,identified as free base. bp 118—119°/2 mm.

As a modification of the benzylation of aniline for which mechanism is well established,[3,5-7] the reaction is considered to proceed according to the following scheme (Chart 1).

$$\text{R-CH}_2\text{OH} \xrightarrow{-\text{H}_2} \text{R-CHO}$$

$$\text{R-CHO} + \text{C}_6\text{H}_5\text{NH}_2 \longrightarrow \text{R-CH=N-C}_6\text{H}_5 + \text{H}_2\text{O}$$

$$\text{R-CH=N-C}_6\text{H}_5 + \text{R-CH}_2\text{OH} \longrightarrow \text{R-CH}_2\text{NH-C}_6\text{H}_5 + \text{R-CHO}$$

Chart 1

The choice of sodium alkoxide as a condensing agent is based on the following considerations: Presence of a small amount of aldehyde is essential to initiate the reaction as shown in the mechanism (Chart 1). To this effect sodium alkoxide is considered to be efficient, since, from the evidence obtained[12] for the mechanism of Guerbet condensation (Chart 2), it is apparent that aliphatic alcohol, in the presence of sodium alkoxide, is first dehydrogenated to the corresponding aldehyde which then initiate the whole reaction.

$$2\text{C}_3\text{H}_7\text{-CH}_2\text{OH} \xrightarrow{-2\text{H}_2} 2\text{C}_3\text{H}_7\text{-CHO} \longrightarrow \text{C}_3\text{H}_7\text{-CH=C(C}_2\text{H}_5\text{)-CHO} \xrightarrow{+2\text{H}_2} \text{C}_4\text{H}_9\text{-CH(C}_2\text{H}_5\text{)-CH}_2\text{OH}$$

Chart 2

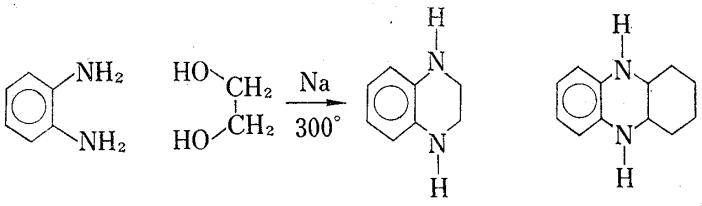
10) C. Weizmann, E. Bergmann, and L. Haskelberg, *Chem. Ind.* (London), **1937**, 587.
11) C. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Org. Chem.*, **15**, 54 (1950).
12) W. Hückel and H. Naab, *Ber.*, **64**, 2137 (1931).

It was observed that in the N-butylation of aniline the yields are roughly proportional to the reaction temperature; whereas starting materials were recovered at 200° for 4 hours' heating, the yields increased to 18.4% at 270°, and almost doubled at 300°. The yields of N-alkylanilines are also dependent on the molar ratio of reactants and the effects of varying the amount of *n*-hexyl alcohol was shown in Table III; the best yield was obtained with twice the equimolar amount of *n*-hexyl alcohol. However, respectable yields were sometimes observed with the use of a little excess of alcohol (Table I) and no attempt has been made to determine the optimum ratio of the reactants in individual experiments.

Table III. Effect of Varying the Amount of *n*-Hexyl Alcohol[a,b]

Alcohol used		Mole ratio of alcohol/aniline	Product yield, %
g	mole		
20.4	0.2	1	47.7
25.4	0.25	1.25	48.6
30.6	0.3	1.67	55.5
40.8	0.4	2	62.1

a) 18.6 g. (0.2 mole) of aniline was used.
b) The reactions were conducted at 290° for 5 hr.



I II

Chart 3

Extension of this alkylation involves preparation of 1,2,3,4-tetrahydroquinoxaline (I)[13] which consists of heating a mixture of *o*-phenylenediamine and ethylene glycol in the presence of sodium (Chart 3). Yield was 34%. The reaction was conducted at 300° for 5 hours and no use of autoclave was required. While 1,2,3,4-tetrahydroquinoxaline has been prepared by catalytic reduction of quinoxaline,[14–16] condensation of N,N-dibenzenesulfonyl-*o*-phenylenediamine with ethylene dibromide followed by hydrolysis,[17] and condensation of catechol with ethylenediamine,[18] the procedure just described is characterized by the use of *o*-phenylenediamine as a starting material for obtaining simple tetrahydroquinoxaline.

The method was successfully applicable to the preparation of 1,2,3,4,4a,5,10,10a-octahydrophenazine (II)[19] which was likewise obtained by alkylation of *o*-phenylenediamine with 1,2-cyclohexanediols.

Experimental

Preparation of N-Monoalkylanilines——All experiments were carried out in an autoclave. The following procedure for the N-hexylation of aniline is illustrative: To a suspension[20] of 6.9 g (0.3 mole) of sodium

13) Reviews were given in R.C. Elderfield, "Heterocyclic Compounds," Vol. 6, John Wiley & Sons, Inc., New York, N.Y., 1957, p. 487 and J.G.E. Simpson, "Condensed Pyridazine and Pyrazine Rings," in A. Weissberger (ed.), "Chemistry of Heterocyclic Compounds," Interscience Publishers Inc., New York, N.Y., 1957, p. 325.
14) K. Maurer and B. Boettger, *Ber.*, **71**, 1383 (1938).
15) J.C. Cavagnol and F.Y. Wiselogle, *J. Am. Chem. Soc.*, **69**, 795 (1947).
16) Ger. Pat., 49511 [*Chem. Abstr.*, **24**, 3251 (1930)].
17) O. Hinsberg and A. Stupler, *Ann.*, **287**, 225 (1895).
18) V. Merz and C. Ris, *Ber.*, **20**, 1190 (1887).
19) G.A. Swan and D.G. Felton "Phenazines" in A. Weissberger (ed.) "The Chemistry of Heterocyclic Compounds," Interscience Publishers Inc., New York, N.Y., 1957, p. 55.
20) At this ratio of sodium/hexyl alcohol only a part of sodium came into solution.

in 46 g (0.44 mole) of *n*-hexyl alcohol was added 37.2 g (0.4 mole) of aniline. The autoclave was closed and heated to 290—300° under the constant stirring for 5 hr. The pressure raised to about 50 kg/cm². The resulting mixture was diluted with water and extracted with two portions of ether. The combined ethereal extracts were washed with saturated sodium chloride solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent, followed by fractionaol distillation gave 44 g (62.1%) of *n*-hexylaniline, bp 160° (27 mmHg).[9] IR ν_{max} cm^{-1}: 3378 (>NH).

p-Tosylalkylanilines and 3,5-Dinitrobenzoylalkylanilines——The procedure for the preparation of these derivatives are essentially the same with the conventional method. To a solution of 0.01 mole of N-alkylaniline in pyridine was added dropwise 0.011 mole of *p*-tosyl chloride or 3,5-dinitrobenzoyl chloride under stirring at room temperature[21] and the mixture was stirred for 2 hr. Water was then added and the resulting mixture was extracted with ether. The ethereal layer was washed with 10% HCl, dried over anhydrous Na_2SO_4, and the ether removed. The residual crystals were purified by recrystallization from appropriate solvent.

1,2,3,4-Tetrahydroquinoxaline[13]——To a suspension of 9.2 g (0.4 mole) of sodium in 24.8 g (0.4 mole) of ethylene glycol was added 21.6 g (0.2 mole) of *o*-phenylenediamine. The resulting mixture was heated at 300° for 5 hr under constant stirring. Addition of water to the dark-brown mixture gave crude 1,2,3,4-tetrahydroquinoxaline as an insoluble brown precipitate which was collected and air-dried. The product was purified by fractional distillation followed by recrystallization of the readily solidified fraction, bp 150—170° (15 mmHg), from ether. 9.1 g (34% based on *o*-phenylenediamine) of 1,2,3,4-tetrahydroquinoxaline was obtained as colorless leaflets, mp 96—97°.[22] *Anal.* Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.51; H, 7.70; N, 21.04. N,N'-Diacetyl derivative was obtained as colorless clusters (from EtOH), mp 143.[23]

***cis*- and *trans*-1,2,3,4,4a,5,10,10a-Octahydrophenazine**[19]——To 8.55 g (0.075 mole) of molten 1,2-cyclohexanediol which was heated at 110° was added 1.15 g (0.05 mole) of powdered sodium. 5.4 g (0.05 mole) of *o*-phenylenediamine was added to the resulting suspension and the mixture was heated at 300° for 4 hr under constant stirring. The lump was powdered, triturated with water and extracted with ether. Concentration of ethereal extracts afforded *cis*-octahydrophenazine[24] which is less soluble in ether and ether-soluble *trans*-isomer[25] as colorless flakes, mp 143—144° (from ether) and colorless plates, mp 152—153° (from EtOH), respectively. *Anal.* Calcd. for $C_{12}H_{16}N_2$ (*cis*-isomer): C, 76.55; H, 8.57; N, 14.88. Found: C, 76.49; H, 8.88; N, 15.09. *Anal.* Calcd. for $C_{12}H_{16}N_2$ (*trans*-isomer): C, 76.55; H, 8.57; N, 14.88. Found: C, 76.58; H, 8.53; N, 14.75. However, the isomers could be separated and purified more readily *via* their hydrochlorides, the solubility of *trans*-isomer hydrochloride being less. *cis*-Isomer hydrochloride: colorless powder (from EtOH–acetone), mp 245—250°. *trans*-Isomer hydrochloride: colorless hexagonal plates (from MeOH), mp 315—318°.

The ratio of the two isomers of 1,2,3,4,4a,5,10,10a-octahydrophenazine thus obtained was varied upon the 1,2-cyclohexanediols employed:

	cis-Isomer	*trans*-Isomer
From *cis*-1, 2-cyclohexanediol	2.7g	0.3g
From *trans*-1,2-cyclohexanediol	1.1g	—
From a mixture of *cis*-and *trans*-1,2-cyclohexanediol	1.9g	0.2g

21) Cooling is necessary when the reaction is the exothermic.
22) Lit. mp 97.5°, C.Y. Almond and F.G. Mann, *J. Chem. Soc.*, **1951**, 1906.
23) Lit. mp 147—147.5°, J.S. Morley, *J. Chem. Soc.*, **1952**, 4002.
24) Lit. mp 145°, M.J. Haddadin and C.H. Issidorides, *Tetrahedron Letters*, **36**, 3253 (1956).
25) Lit. mp 152—153°, see reference 19.