[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

Raney Nickel Catalyzed N-Alkylation of Aniline and Benzidine with Alcohols

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A reaction is described in which a primary arylamine is refluxed with an excess of a primary aliphatic alcohol in the presence of Raney nickel to yield an N-alkylarylamine.

N-Alkylation of amines with alcohols catalyzed by Raney nickel has been observed during the reduction of hydrazobenzene and azoxybenzene,[1] the hydrolysis of phenyl thioacetopiperidide,[2] and the desulfurization of benzidine sulfone.[3] N-kylbenzidines in good yields without the formation of significant amounts of tertiary amines.

The alkylation is accomplished by refluxing a mixture of amine, Raney nickel, and an excess of an alcohol which serves as both reactant and solvent. The nickel is removed by filtration and the product is obtained from the filtrate by distillation or crystallization. The optimum conditions were determined for 25 ml. (0.275 mole) of aniline and 100 ml. of propanol, as indicated in Table I. It appears that with larger amounts of Raney nickel catalyst, shorter periods of reflux time are required to give the maximum yield of alkylated amine. Secondary amines synthesized from other alcohols are listed in Table II. The yields of N-alkylanilines prepared from the straight chain primary alcohols other than methanol were 72–83%, while those from branched chain primary alcohols were 41–49%. Aniline did not react with methyl, isopropyl or *sec*-butyl alcohols under these conditions. N,N′-Dialkylbenzidines were obtained in 63 and 52% yields from ethyl and butyl alcohols, respectively. Methanol did not react to give N,N′-dimethylbenzidine.

TABLE I

EFFECT OF AMOUNT OF NICKEL CATALYST AND TIME OF REFLUX ON THE N-PROPYLATION OF 0.275 MOLE OF ANILINE

Raney nickel, g.	Reflux time, hr.	Yield of N-propylaniline, %
5	17	39
5	29	80
5	48	74
10	18	73
15	16	82[a]
15[b]	16	28
25	6	78
25	18	73

[a] An 88% yield was obtained by six-hour extraction of the filtered and washed nickel with an ethanol–propanol mixture in a Soxhlet apparatus. [b] The nickel catalyst used was that recovered and extracted as in (*a*). In addition to N-propylaniline, 43% of the aniline was recovered unchanged.

TABLE II

SECONDARY AMINES FROM ANILINE AND BENZIDINE

Product	Yield, %	M.p. or b.p. (mm), °C.	n^tD	*t*, °C.	Derivative	M.p., °C.	Reptd. m.p. °C.
Anilines							
N-Ethyl-	83	91–92 (24)	1.5519	22	Phenylthiourea	87–89	89[4]
N-Propyl-	82	98.5–100 (11)	1.5406	22	Phenylthiourea	101–102	104[4]
N-Butyl-	82	124–126 (25)	1.5298	25	*p*-Bromobenzenesulfonamide	84–86	87[5]
N-Isobutyl-	41[a]	90–95 (7)	1.5318	20	*p*-Toluenesulfonamide	124–126	122–123[6]
N-Pentyl-	82	135 (18)	1.5287	20	*p*-Toluenesulfonamide	72–73	74[7]
N-Isopentyl-	49	119–121 (10)	1.5249	21	*m*-Nitrobenzenesulfonamide	104–105	104–105[8]
N-Hexyl-	72	152.5 (22)	1.5173	20	*p*-Toluenesulfonamide	66–68	67–68[7]
N-Benzyl-	80	165–167 (6) 34–36	....		Benzenesulfonamide	118–119	119[4]
Benzidines							
N,N′-Diethyl-	63	115–116	....		.....	.....	115[3]
N,N′-Dibutyl-	52	68–69	....		.....	.....	72[9]

[a] The product contained some primary amine which was not eliminated after two distillations. The yield given is that obtained after the second distillation.

Ethylaniline, N-ethylpiperidine and N,N′-diethylbenzidine, respectively, were obtained when these reactions were carried out in refluxing ethanol in the presence of Raney nickel. The work of Shah and co-workers[3] now has been extended to provide a facile synthesis of N-alkylanilines and N,N′-dial-

The mechanism of the over-all reaction is believed to be dehydrogenation of the alcohol to form an aldehyde, which then reacts with the amine to

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(1) R. Mozingo, C. Spencer and K. Folkers, THIS JOURNAL, **66**, 1859 (1944).

(2) E. C. Kornfeld, *J. Org. Chem.*, **16**, 131 (1951).

(3) K. H. Shah, B. D. Tilak and K. Venkataraman, *Proc. Indian Acad Sci.*, **28A**, 145 (1948).

(4) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Third Ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(5) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 211.

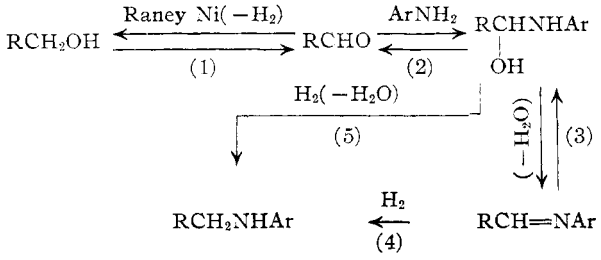
(6) W. J. Hickinbottom, *J. Chem. Soc.*, 994 (1930).

(7) W. J. Hickinbottom, *ibid.*, 1119 (1937).

(8) W. J. Hickinbottom, *ibid.*, 2399 (1932).

(9) J. A. Goodson, L. J. Goodwin, J. H. Gorvin, M. D. Goss, K. S. Kirby, J. A. Lock, R. A. Neal, T. M. Sharp and W. Solomon, *Brit. J. Pharmacol.*, **3**, 67 (1948).

form either an N-alkylideneamine (Schiff base) or an α-hydroxyamine. Under the conditions of this synthesis, *e.g.*, a large nickel surface saturated with hydrogen and a polar solvent, both the Schiff base and/or the α-hydroxyamine may be hydrogenated to the corresponding secondary amine:



Steps 2 through 5 correspond to the accepted mechanism for the formation of secondary amines by reductive alkylation procedures[10]; however, these are usually carried out under pressure and at higher temperatures.

Evidence for the existence of the dehydrogenation step 1 was obtained when ethanol was refluxed over Raney nickel and the aldehyde vapors were passed directly into a solution of 2,4-dinitrophenylhydrazine. The characteristic 2,4-dinitrophenylhydrazone of acetaldehyde began to precipitate within ten minutes after refluxing had started. A similar experiment performed with aniline present in the reaction mixture resulted in the formation of the 2,4-dinitrophenylhydrazone of acetaldehyde only after 30 hours of refluxing. Under the conditions of the experiment this was approximately the amount of time required to obtain the maximum yield of N-ethylaniline, and, therefore, was roughly equal to the time necessary for the aniline to be consumed by reaction with the aldehyde. This is an indication that the aldehyde formed is a reactant and not simply a by-product. The presence of aldehyde in the benzyl and isopentyl alcohol reaction mixtures after refluxing was demonstrated by means of fuchsin–aldehyde and 2,4-dinitrophenylhydrazine tests.

The existence of the Schiff base as a possible intermediate was shown when aniline was replaced with N-benzylideneaniline and benzyl alcohol was used as the reactant and solvent. N-Benzylaniline was obtained in 81% yield. In a similar experiment with ethanol as the reactant–solvent a 51% yield of N-benzylaniline and a 32% yield of N-ethylaniline was obtained. The exchange of the benzylidene and ethylidene groups is an indication of the reversibility of steps 2 and 3.

The non-reactivity of methanol may be explained by the fact that no formaldehyde, or formaldehyde derivative, was isolated when methanol was refluxed over Raney nickel. With ethyl and isopropyl alcohols and Raney nickel, however, dehydrogenation did occur and acetaldehyde and acetone, respectively, were isolated. The failure of the acetone to react further might be attributed to the lesser degree of reactivity of the ketone as compared to the aldehyde.

The yield of secondary amine varied both with the time of refluxing and with the amount of Raney nickel present as indicated in Table I.

When U.O.P. nickel catalyst[11] was substituted for the Raney nickel, no reaction took place. Apparently the dehydrogenation of the alcohol is dependent upon the activation of the catalyst, since acetaldehyde was not formed when ethanol was refluxed over the U.O.P. catalyst.

Experimental[12]

Materials.—Aniline was distilled and stored under nitrogen. Benzidine was prepared by neutralization of an aqueous solution of benzidine dihydrochloride with alkali followed by crystallization of the free base from aqueous ethanol. N-Benzylideneaniline was prepared by a known procedure.[13] The alcohols were of reagent grade and were stored over Drierite. Raney nickel was prepared by the method of Mozingo[14] and stored under absolute ethanol.

General Procedure.—A mixture of 25 ml. (0.275 mole) of aniline, 15 g. of Raney nickel (which had been washed three times with 20-ml. portions of propanol to remove most of the ethanol) and 100 ml. of propanol was stirred and refluxed 16 hours, cooled, filtered through fluted Whatman No. 40 filter paper, and the nickel residue was washed several times with 95% ethanol. The filtrate and washings were combined, the alcohols removed by distillation at atmospheric pressure, and the residue distilled through a 25-cm. Vigreux column under reduced pressure. The yield of N-propylaniline was 30.3 g. (82%), b.p. 98.5–100° (11 mm.), $n^{22}D$ 1.5406.

N-Alkylanilines obtained from other alcohols are given in Table II. Since the yields given are those obtained after a single distillation, it is entirely possible that the products, especially those of lower molecular weight, were contaminated to some extent with primary amine. Unchanged aniline was recovered only from the reactions involving isobutyl and isopentyl alcohols. The N-isobutylaniline gave a positive test for primary amine by the nickel chloride–5-nitrosalicylaldehyde test[4] after two distillations; however, this test was negative in the case of N-isopentylaniline after a single distillation.

Substitution of 15 g. of ground U.O.P. nickel catalyst for the Raney nickel in a standard synthesis using ethanol yielded only unchanged aniline after 72 hours of refluxing.

In another synthesis of N-propylaniline the reaction mixture after refluxing was filtered through the thimble in a Soxhlet apparatus; the transfer was facilitated by means of 95% ethanol. After extraction of the residue for six hours with the mixed filtrates, distillation of the extract afforded an 88% yield of N-propylaniline.

N,N'-Diethylbenzidine.—The general procedure for the synthesis of N-alkylanilines was followed using 22.5 g. (0.122 mole) of benzidine. After the nickel had been washed with 95% ethanol, the filtrate and washings were combined, evaporated on a hot-plate to a volume of about 100 ml. and the product allowed to crystallize slowly. The yield of crude product was 22.7 g. (77%), m.p. 112–15°, which on recrystallization from 95% ethanol gave 18.2 g. (63% yield) of N,N'-diethylbenzidine, m.p. 115–116°.

N,N'-Dibutylbenzidine.—The procedure for the synthesis of N,N'-diethylbenzidine was followed using 15 g. (0.0815 mole) of benzidine. There was obtained 14.8 g. of crude product, m.p. 62–64°, which on recrystallization from 95% ethanol yielded 12.5 g. (52%) of N,N'-dibutylbenzidine, m.p. 68–69°.

Dehydrogenation of Alcohols.—A mixture of 5 g. of Raney nickel and 100 ml. of absolute ethanol was stirred, refluxed and the aldehyde vapors were passed through a solution of 2,4-dinitrophenylhydrazine.[4] The 2,4-dinitrophenylhydrazone of acetaldehyde, which began to form within ten minutes after refluxing had started, was recrystallized twice from 95% ethanol, giving an orange solid which melted at 166–168° (lit. value[4] 168°). When 25 ml. (0.275 mole) of

(10) W. S. Emerson, in "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 175.

(11) Universal Oil Products Company, 310 S. Michigan Avenue, Chicago 4, Ill.

(12) All boiling points and melting points are uncorrected.

(13) L. A. Bigelow and H. Eatough, "Organic Syntheses," Coll. Vol. 1, second ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 80.

(14) R. Mozingo, *Org. Syntheses*, **21**, 15 (1947).

aniline was present in a similar experiment the 2,4-dinitrophenylhydrazone of acetaldehyde began to form only after 30 hours of refluxing. No acetaldehyde was produced when U.O.P. nickel catalyst was substituted for the Raney nickel.

Distillation of 100 ml. of isopropyl alcohol from 5 g. of Raney nickel through a 50-cm. Vigreux column at a take-off rate of about 0.1 ml. per minute gave a distillate from which the 2,4-dinitrophenylhydrazone of acetone was prepared; m.p. 124–125° after recrystallization from 95% ethanol (lit. value[4] 126°).

N-Benzylaniline from N-Benzylideneaniline.—The procedure of the standard synthesis was followed using 25 g. (0.138 mole) of N-benzylideneaniline and 100 ml. of benzyl alcohol, giving 20.5 g. (81% yield) of N-benzylaniline, b.p. 164–167° (7 mm.), m.p. 34–36° (lit. value[4] 37°).

In a similar experiment using 25 g. (0.138 mole) of N-benzylideneaniline and 100 ml. of ethanol, there was obtained 5.30 g. (32% yield) of N-ethylaniline, b.p. 85–89° (12 mm.), $n^{22}D$ 1.5519, and 12.80 g. (51% yield) of N-benzylaniline.

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Some Compounds Related to Chloromycetin[1]

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Several types of compounds related to Chloromycetin were synthesized. These included 1-(2,5-dimethoxy-4-nitrophenyl)-, 1-(4-thiazolyl)-, 1-*p*-cyclohexylphenyl- and 1-*p*-isopropylphenyl-2-dichloroacetamido-1,3-propanediols. The preparation of α-acetamido- and α-dichloroacetamido-α-hydroxy and α-alkyloxy-*p*-nitroacetophenones is described together with a group of DL-*threo*-1-*p*-nitrophenyl-2-α-aminoacylamido-1,3-propanediols.

Several considerations have prompted the preparation of compounds related to Chloromycetin. During a systematic study of the effect of structural variations in the Chloromycetin molecule on activity against microörganisms sensitive to the antibiotic, compounds also were screened against several groups of less sensitive pathogenic organisms. In the process, Hillegas found that β-hydroxy-α-dichloroacetamido-*p*-nitropropiopheneone, a compound described by Long and Troutman,[2] was somewhat more active than Chloromycetin in inhibiting the growth of certain fungi. Other derivatives of the antibiotic have been prepared with specific product formulations in mind. Still other types of compounds were synthesized for use in studies to elucidate the mechanism of action of the antibiotic and its fate in experimental animals. A number of Chloromycetin related compounds falling into these several categories are described below.

Recently Phillips[3] reported that N-(2,5-dimethoxy-4-nitrophenethyl)-dichloroacetamide had activity against the Rift Valley Fever virus and prepared a number of similar compounds which did not include 1-(2,5-dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol. Aside from the possibility that the latter compound might have activity against the smaller virus group, it was of interest to synthesize this derivative of Chloromycetin for studies to determine the effect of the methoxyl groups in the 2- and 5-positions of the phenyl ring on the ability of the substance to inhibit the growth of bacteria sensitive to the antibiotic. The method of Long and Troutman[4] for the synthesis of Chloromycetin and Chloromycetin-related compounds provided a straightforward route to the desired product. Dimethoxyquinacetophenone[5] which served as starting material was obtained by the methylation of quinacetophenone.[6] The latter compound was brominated and the substituted phenacyl bromide product converted to the hexamethylenetetramine complex. The amino ketone hydrochloride obtained from this intermediate by acid hydrolysis was dichloroacetylated without purification, as described in a preceding paper.[7] Introduction of the hydroxymethyl group by condensation with formaldehyde followed by the Meerwein–Verley–Ponndorf reduction of the carbonyl group gave the desired 1-(2,5-dimethoxyphenyl)-2-dichloroacetamido-1,3-propanediol intermediate. The latter product was acetylated and the nitro group was then introduced by treatment with a mixture of concentrated nitric and glacial acetic acids. The protective acetyl groups were removed selectively using the Kunz hydrolysis,[8] and the desired 1-(2,5-dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol product was isolated. The assignment of the nitro group to the "4"-position was indicated by theoretical considerations and by direct comparison of the ultraviolet absorption spectrum[9] with the absorption spectra of 4-nitro-2,5-dimethoxyphenyl alkanes. The absorption maxima for the compound related to Chloromycetin were found at λ 218, 240, 273 and 372, in water solution.

The preparation of 1-(5-nitro-2-thienyl)-2-dichloroacetimido-1,3-propanediol was first described in the scientific literature by Carrara, *et al.*[10] The 1-(4-pyridyl)-2-dichloroacetamido-1,3-propanediol was reported by Van Der Meer, *et al.*,[11] and Gentry[12] and Clark[13] in H. S. Mosher's laboratory have

(1) Parke, Davis and Company trademark for chloramphenicol.

(2) L. M. Long and H. D. Troutman, THIS JOURNAL, **73**, 481 (1951).

(3) A. P. Phillips, *ibid.*, **74**, 6125 (1952); **75**, 621 (1953).

(4) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469 (1949).

(5) G. C. Amin and N. M. Shah, *Org. Syntheses*, **28**, 42 (1948).

(6) G. C. Amin and N. M. Shah, *Org. Syntheses*, **31**, 91 (1951).

(7) M. C. Rebstock, C. D. Stratton and L. M. Bambas, THIS JOURNAL, **77**, 24 (1955).

(8) A. Kunz and C. S. Hudson, *ibid.*, **48**, 1982 (1926).

(9) We are indebted to Dr. J. M. Vandenbelt and Miss Carola Henrich and co-workers for the ultraviolet absorption studies described in this paper.

(10) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **81**, 142 (1951).

(11) S. Van Der Meer, H. Kofman and H. Veldstra, *Rec. trav. chim.*, **72**, 236 (1953).

(12) R. E. Gentry, Jr., Ph.D. Thesis, Stanford University, Dec. 1953.

(13) D. E. Clark, Doctoral Dissertations No. 20, 38 (1952–1953).