

Reduction of α -Dimethylaminobenzyl Butyl Ether. (A) With *t*-Butylmagnesium Chloride.—In apparatus identical to that described in the general procedure were placed 10 g. (0.41 g.-atom) of magnesium turnings and 100 ml. of anhydrous ether. Several milliliters of *t*-butyl chloride (total 27.7 g., 0.3 mole) were added and the reaction initiated with a few drops of methyl iodide. The halide, in 100 ml. of dry ether, was added slowly, according to the observations of Whitmore²¹ for maximum yields with this material, and stirred an additional 3 hours.

To the stirred *t*-butylmagnesium chloride solution was added 20.7 g. (0.1 mole) of α -dimethylaminobenzyl butyl ether in an equal volume of dry ether. The reaction mixture was stirred 2 hours at room temperature, refluxed 4 hours, cooled, and poured onto an ammonium chloride-ice mixture. The amine was taken up in ether, the ether dried, removed, and the residue distilled. There was obtained 10.7 g. (80%) of benzyldimethylamine boiling at 76–78° at 20 mm., n_D^{20} 1.4986 (reported n_D^{20} 1.5000²²). The picrate

(21) (a) F. C. Whitmore and D. E. Badertscher, *THIS JOURNAL*, **55**, 1559 (1933); (b) F. C. Whitmore and A. L. Houk, *ibid.*, **54**, 3716 (1932).

(22) A. D. F. Toy, *ibid.*, **73**, 4670 (1951).

of this product, recrystallized from ethanol, melted at 96–97°; reported m.p. 94°.²³

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.35; H, 4.57; N, 15.42.

(B) With Hydrogen.—The amino ether (20.7 g., 0.1 mole), was dissolved in 300 ml. of commercial absolute ethanol contained in a 500-ml. erlenmeyer flask. Several milligrams of Adams catalyst was added and the flask attached to an atmospheric, buret-type hydrogenator; agitation was provided by a magnetic stirrer. Over an 8-hour period, at room temperature, the hydrogen uptake was greater than 0.096 mole.

The catalyst was removed by filtration and the solvent distilled at atmospheric pressure. The remaining material was fractionated *in vacuo* to give 6 g. of impure butanol-1 and 10.2 g. (75%) of benzyldimethylamine, b.p. 79–83° at 28 mm., essentially at 82–83°, n_D^{20} 1.5003. The picrate, after three recrystallizations from methanol, melted at 95–95.5°; reported m.p. 94°.²³

(23) T. S. Stevens, J. M. Cowan and J. Mackinnon, *J. Chem. Soc.*, 2568 (1931).

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[CONTRIBUTION FROM THE ROHM AND HAAS Co.]

Reactive Nitrile Groups. I. The Reaction of α,ω -Dinitriles with Aqueous Amines¹

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Acetonitrile, *n*-butyronitrile and benzonitrile failed to react at 100° with aqueous solutions of such amines as methylamine, benzylamine, morpholine and piperidine. However, under the same conditions, malonitrile, succinonitrile and glutaronitrile were converted to the corresponding N,N' -disubstituted amides by reaction with aqueous methylamine, *n*-butylamine, *n*-octylamine, benzylamine and morpholine. Phthalonitrile reacted similarly. Adiponitrile did not react. Exceptions to the general reaction were the reactions of succinonitrile with aniline, which failed, and with piperidine and 1,1,3,3-tetramethylbutylamine, respectively, which gave the corresponding amine salts of succinamic acid.

The reaction of a nitrile with an amine to yield the N -substituted amidine, or with aqueous amine to yield the N -substituted amide customarily does not proceed at any obvious rate. A reaction with aqueous ammonia has been observed in a few special cases.^{2,3} It is demonstrated here, for example, that butyronitrile can be recovered almost quantitatively after a long refluxing period with aqueous morpholine, and even with so strong a base as aqueous piperidine. Aqueous methylamine does not convert acetonitrile to the amide, nor does aqueous benzylamine convert benzonitrile to the amide, at 100° and at reflux, respectively. For the lack of any direct route, therefore, the conventional methods used have entailed the conversion of the nitrile to an intermediate, such as the imino-ester hydrochloride.⁴ Recently, N -arylamidines were prepared by the severe conditions of the use of sodium amide⁵ or similar strong base catalyst.

It has been observed in concurrent work by Elvidge and Linstead⁶ that succinonitrile shows remarkable reactivity toward ammonia. Thus, Elvidge and Linstead were able to prepare 2,5-diphenyliminopyrrolidine by reaction of succinonitrile

with ammonia to yield succinimidine, followed by reaction with aniline. Further reaction with water gave succinamylide. Both succinonitrile and phthalonitrile have been observed to react rapidly with aniline hydrochloride.^{6,7} Couch and Krewson² obtained succinamide by reaction of succinonitrile with aqueous ammonia at high temperatures.

In our own work, we had early arrived at the same observations of the unique reactivity of succinonitrile from the reaction of that dinitrile with aqueous solutions of primary aliphatic amines. It seemed most likely that the reactions of succinonitrile involved cyclization to some form of succinimide intermediate. Since it was also possible that the reactivity of dinitriles could result simply from inductive effects transmitted through the chain, our studies have taken the course of a general investigation of the reaction of α,ω -dinitriles with a variety of amines in water solution.

The reaction of two moles of most primary amines with one mole of dinitrile in the presence of two to six moles of water yielded N,N' -disubstituted amides in the cases of malononitrile, succinonitrile and glutaronitrile. Phthalonitrile also gave a diamide under similar conditions. Adiponitrile was found to be unreactive. In most cases, temperatures of 100° or reflux (usually about 100°) were necessary for a reasonable reaction rate. It may be deduced from yield data and the necessary conditions of reaction, that the reactivity of succino-

(1) Given at the 126th meeting of the American Chemical Society, New York, N. Y., September 14, 1954.

(2) J. F. Couch and C. F. Krewson, *Offic. Gas. U. S. Patent Office*, **644**, 307 (1951); *C. A.*, **46**, 10195 (1952).

(3) J. F. Couch and C. F. Krewson, *THIS JOURNAL*, **65**, 2256 (1943).

(4) A. Pinner, *Ber.*, **16**, 1654 (1883).

(5) F. Cooper and M. Partridge, *J. Chem. Soc.*, 255 (1953).

(6) J. Elvidge and R. Linstead, *ibid.*, 442 (1954).

(7) R. Blochmann, *Ber.*, **20**, 1856 (1887).

TABLE I
 N,N'-DISUBSTITUTED AMIDES FROM DINITRILES, RNHCO(CH₂)₂CONHR

R	<i>x</i>	Mole ratio nitrile:amine:H ₂ O			Time, hr.	Temp., °C.	Yield, %	M.p., °C., uncor.	Empirical formula	Nitrogen, % Calcd.	Found
CH ₃	1	1.0	4.0	7.0	6	100 ^a	31	136 ^b	C ₅ H ₁₀ N ₂ O ₂	21.5	21.4
C ₆ H ₅ CH ₂	1	1.0	4.0	12.0	48	95–100 ^c	40	140	C ₁₇ H ₁₈ N ₂ O ₂	9.9	10.0
CH ₃	2	1.0	2.4	6.8	8	100 ^a	86	167–171 ^d	C ₆ H ₁₂ N ₂ O ₂	19.4	19.0
<i>n</i> -C ₄ H ₉	2	1.0	2.3	2.0	48	80–100 ^c	22	183–185 ^e	C ₁₂ H ₂₄ N ₂ O ₂	12.3	12.2
<i>n</i> -C ₈ H ₁₇	2	1.0	2.0	2.2	52	104–120 ^c	59	162–164	C ₂₀ H ₄₀ N ₂ O ₂	8.2	8.2
C ₆ H ₅ CH ₂	2	1.0	4.0	12.0	24	95–100 ^c	50	210–211	C ₁₈ H ₂₀ N ₂ O ₂	9.4	9.3
CH ₃	3	1.0	2.5	2.5	23	100 ^a	6	119–121	C ₇ H ₁₄ N ₂ O ₂	17.7	17.5
<i>n</i> -C ₄ H ₉	3	1.0	2.3	2.0	240	80–100 ^c	14.5	151–152	C ₁₃ H ₂₆ N ₂ O ₂	11.6	11.6
<i>n</i> -C ₈ H ₁₇	3	1.0	2.0	2.2	144	105 ^c	17	144–145	C ₂₁ H ₄₂ N ₂ O ₂	7.9	7.7
C ₆ H ₅ CH ₂	3	1.0	4.0	12.0	48	100–105 ^c	17	165–166	C ₁₉ H ₂₂ N ₂ O ₂ ^f	9.0	9.0
C ₆ H ₅ CH ₂	4	1.0	4.0	12.0	48	100–105 ^c	0	^g	C ₂₀ H ₄₄ N ₂ O ₂		
C ₆ H ₅ CH ₂	Ph ^h	1.0	4.0	12.0	48	100–110 ^c	30	172–173	C ₂₂ H ₂₀ N ₂ O ₂ ⁱ	8.1	8.2

^a Reactions run in an autoclave. ^b A. Franchimont, *Rec. trav. chim.*, **4**, 199 (1885), reported m.p. 136°. ^c Reactions run under reflux at atmospheric pressure. ^d H. Backer, *J. Chem. Soc.*, 101, 596 (1912), reported m.p. 175°. Mixed m.p. with an authentic sample prepared from diethyl succinate (m.p. 170–173°) did not depress. ^e Mixed m.p. with an authentic sample prepared from diethyl succinate (m.p. 186–188°) did not depress. ^f % C, calcd. 73.6, found 73.6; % H calcd. 7.1, found 7.2. ^g 96% of benzylamine, b.p. 184–187°, and 94% of adiponitrile, b.p. 101–104°, recovered by distillation. ^h Phthalonitrile. ⁱ % C, calcd. 76.8, found 76.9; % N calcd. 5.8; found 5.8.

nitrile is much higher than that of glutaronitrile or phthalonitrile. Data on comparable primary amines are given in Table I.

The reaction with malononitrile is complicated by the base-catalyzed decomposition of that nitrile (presumably through self-condensation). Otherwise the results of these reactions showing decreasing reactivity with distance between the nitrile groups may be explained by a polarizing effect transmitted through the chain, as well as by a reaction path involving some form of imide intermediate. The observed differences in reactivity between succinonitrile, glutaronitrile, adiponitrile and phthalonitrile may be predicted from molecular models, on the basis of ease of formation of the cyclic intermediates.

The aminolytic reactions of succinonitrile are also influenced by the base strength and structure of the amine. Thus the reaction of aniline and water with succinonitrile failed. This can only be ascribed to the very weak base strength of the aromatic base. It will be noted that in the work of Elvidge and Linstead,⁶ ammonia was used in an intermediate step, or the reaction was carried out with aniline hydrochloride.

In the reaction of succinonitrile with a highly branched primary amine, 1,1,3,3-tetramethylbutylamine, of base strength comparable with that of methylamine, attack by the hindered amine does not seem to take place. Instead there is sufficient hydroxyl ion present for some hydrolysis to occur, and the product isolated, in only 20% yield, was 1,1,3,3-tetramethylbutylammonium succinamate. Hydrolytic reaction also occurred with piperidine, an unhindered secondary amine, to give a 58% yield of piperidinium succinamate. It is probable that this is owing to the exceptionally high base strength of piperidine, since morpholine, a secondary amine of much lower base strength, gave the dimorpholide, although in low yield (29%). These hydrolytic reactions probably occur through a succinimide intermediate. A further discussion of these anomalous reactions will be undertaken in a subsequent paper of this series.

Acknowledgment.—To Mr. C. W. Nash and Mr. Thomas Callan, with their staffs, for analytical data reported.

Experimental

All melting points are uncorrected. The amines and dinitriles used were of good commercial grades and were purified by distillation when necessary.

Aqueous Aminolysis of α,ω -Dinitriles. A. General Procedure for Atmospheric Pressure Reactions.—The dinitrile, amine and water were mixed in the molar ratio listed in Table I for each reaction. The mixture, which was a homogeneous solution, was refluxed for the given number of hours (see Table I). Rapid evolution of ammonia commenced soon after heating was begun. At the end of the reflux period, the evolution of ammonia was very slow. The reaction was then stripped of excess water and amine under aspirator vacuum, and at a pot temperature of up to 120°. The residue was recrystallized from isopropyl alcohol. Yields and melting points are listed in Table I.

B. General Procedure for Pressure Reactions.—Reactions of methylamine were carried out in a one-liter autoclave designed for pressure up to 500 p.s.i.g. Maximum pressures developed in these reactions were of the order of 40–60 p.s.i.g. The mixture of dinitrile, methylamine and water were charged to the autoclave, and the mixture heated at 100° for the given amount of time. The product was worked up as before.

Aqueous Aminolyses of Succinonitrile with Amines Not Listed in Table I.—These reactions were all carried out in a molar ratio of nitrile:amine:water of 1:4:12, according to the general procedure for atmospheric reactions described above. The reflux temperatures were between 95 and 105°, and the reflux times were 48 hours in each case.

(a) **With Morpholine.**—The stripped reaction mixture crystallized in part, upon the addition of isopropyl alcohol. Succinomorpholide, m.p. 177–178°, was isolated by filtration in 29% yield. *Anal.* Calcd. for C₁₂H₂₀N₂O₄: C, 56.2; H, 7.9; N, 10.9. Found: C, 56.2; H, 7.9; N, 10.9. The mother liquor was stripped to an oil which failed to crystallize further after a long period in the cold. The residue was insoluble in water and did not release an odor of amine when made basic, indicating it not to be an amine salt.

(b) **With Piperidine.**—The stripped reaction mixture crystallized upon the addition of isopropyl alcohol. The sole product obtained on filtration was identified as piperidinium succinamate, m.p. 169–170° with decomposition, obtained in 58% yield. *Anal.* Calcd. for C₉H₁₈N₂O₂: C, 53.5; H, 8.9; N, 13.8. Found: C, 53.5; H, 9.0; N, 13.7. By titration with perchloric acid in glacial acetic acid, there was obtained an equivalent weight of 208, theory 202.5. This product was acidified with concentrated aqueous hydrochloric acid. The solution was partially

evaporated. The first material to come out of solution was filtered, and recrystallized from acetone, m.p. 156–157°. Mixed melting point of this with an authentic sample of succinamic acid, prepared from succinic anhydride and ammonia, showed no depression. It was also identified by heating to 200°. Water was given off, and the resulting solid melted at 126–127°, corresponding to the melting point of succinimide. Further evaporation of the acidified solution yield a white solid, m.p. 244–245°; mixed m.p. with an authentic sample of piperidine hydrochloride showed no depression. The original mother liquor was stripped to a residue which did not crystallize. The residue was soluble in water and released piperidine when made basic, indicating it to be a salt.

(c) **With 1,1,3,3-Tetramethylbutylamine.**—The stripped reaction mixture crystallized in isopropyl alcohol. 1,1,3,3-Tetramethylbutylammonium succinamate was isolated by filtration in 20% yield, m.p. 176–178°. *Anal.* Calcd. for $C_{12}H_{26}O_3N_2$: N, 11.4. Found: N, 11.2. By titration with perchloric acid in glacial acetic acid, there was obtained an equivalent weight of 250, theory 246. Acidification of the product with hydrochloric acid yielded a solid, m.p. 257–259°, mixed m.p. with a sample of 1,1,3,3-tetramethylbutylammonium chloride gave no depression. Mixed m.p. of the reaction product with the salt prepared by the reaction of *t*-octylamine with succinamic acid, m.p. 180–181°, showed no depression below 176°. The residue failed to crystallize further. It was found to be water soluble and to contain more salt as seen by the release of the free amine when treated with cold alkali.

(d) **With Aniline.**—After the refluxing period, the reaction mixture was distilled to yield 99% of the starting aniline, b.p. 183°, and 94% of the starting nitrile, b.p. 142° (22 mm.).

Attempted Aqueous Reactions of Mononitriles with Amines. (a) **Methylamine and Acetonitrile.**—A solution of the nitrile, amine and water in the molar ratio of 1:2:5.6 was heated in an autoclave at 100° for eight hours. On distillation of the reaction mixture, no material boiling as high as *N*-methylacetamide was obtained.

(b) **Piperidine and *n*-Butyronitrile.**—A solution of 69 g. (1.0 mole) of butyronitrile, 170 g. (2.0 moles) of piperidine and 108 g. (6.0 moles) of water was refluxed for 48 hours. No ammonia was detected. On distillation at atmospheric pressure, the entire reaction mixture distilled up to 100°, leaving essentially no residue. The distillate was acidified with concentrated hydrochloric acid. The nitrile layer which separated was distilled, yielding 63.5 g. (92%) of starting *n*-butyronitrile, b.p. 118°.

(c) **Morpholine and *n*-Butyronitrile.**—The nitrile, amine and water ratio (1:2:6) and the reaction conditions were the same as that described in (b) above. A 93% recovery of *n*-butyronitrile was obtained on two distillations.

(d) **Benzylamine and Benzonitrile.**—The reaction conditions were the same as those described in (b) above. The reaction mixture was acidified with concentrated hydrochloric acid and the starting benzylamine was recovered in 98% yield as benzylammonium chloride, m.p. 248°; mixed m.p. with an authentic sample did not depress.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Axial Effect in the Rearrangement with Nitrous Acid of *cis*- and *trans*-2-Amino-1-phenylcyclohexanol¹

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cis-2-Amino-1-phenylcyclohexanol and *cis*-2-amino-1-*p*-methoxyphenylcyclohexanol have been shown to rearrange with 99 and 98.8% alkyl migration (*i.e.*, ring contraction) and only about 1 or 1.2%, respectively, of aryl migration. These migration ratios contrast sharply with results obtained previously by other workers with acyclic compounds. The difference is interpreted as due to steric strain in the transition state for aryl migration when the aryl group is in an axial position in a cyclohexane ring. *cis*-2-Chloro-1-phenylcyclohexanol reacts with silver oxide in hexane to give, principally, ring contraction, but also extensive amounts of 2-phenylcyclohexanone which may or may not be formed by phenyl migration. *trans*-2-Amino-1-phenylcyclohexanol yields with nitrous acid a mixture of glycols, glycol esters and ketones. Since under the reaction conditions 1-phenylcyclohexene oxide gives a similar mixture, it is inferred that the oxide or its conjugate acid is a probable intermediate in the principal reaction path.

Both *cis*- and *trans*-2-chloro-1-phenylcyclohexanol³ (*cis*- and *trans*-I) have been reported to yield only 2-phenylcyclohexanone (with phenyl migration) when caused to rearrange by treatment with ethylmagnesium bromide.⁴ In other reactions related as this one appears to be, to the pinacol rearrangement such a preference of aryl migration over migration of an alkyl group is well known.⁵ It appeared surprising, however, on stereochemical grounds to be discussed below, that a phenyl group should migrate readily when attached to a cyclohexane ring.

For this reason it was decided to examine the

(1) From the Ph.D. Dissertation submitted to Columbia University by Seymour Schmukler. Presented at the 124th Meeting of the American Chemical Society, Chicago, Ill., 1953, Abstracts, p. 18-O.

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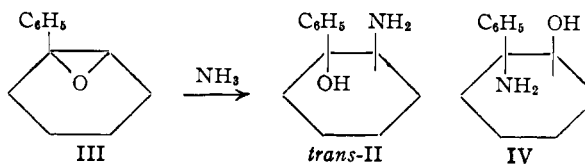
(3) Throughout this paper the designations "*cis*" and "*trans*" will be used to refer to the relative positions of the hydroxyl and chlorine or hydroxyl and amine groups.

(4) M. Tiffeneau, B. Tchoubar and S. LeTellier, *Compt. rend.*, **217**, 588 (1943).

(5) C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 477.

rearrangement with nitrous acid of the *cis*- and *trans*-amino alcohols (*cis*- and *trans*-II) and to re-examine the rearrangement of the *cis*-chlorohydrin (*cis*-I) under other conditions.

Syntheses and Establishment of Configuration of Compounds to be Studied.—Levy and Sfiras⁶ had prepared an amino alcohol (m.p. 105°, hydrochloride m.p. 140°) by the reaction of 1-phenylcyclohexene oxide (III) with ammonia. No evidence for the structure or configuration was advanced, however. Repetition of their work gave an amino alcohol (m.p. 111–112°, hydrochloride, m.p. 216–217°) which was shown to be *trans*-2-amino-1-phenylcyclohexanol (*trans*-II) rather than the alternative 2-amino-2-phenylcyclohexanol (IV).



(6) J. Levy and J. Sfiras, *Bull. soc. chim.*, **49**, 1830 (1931).