[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF PURDUE UNIVERSITY]

Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines. IV. The Effect of Nitro and Amino Groups on the Course of the Reduction

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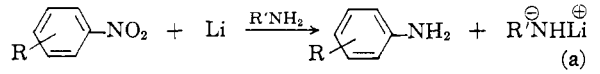
Reduction of aromatic nitro compounds in the lithium–amine system results largely in the formation of aromatic amines. This is ascribed to the rapid reduction of the nitro group and the concomitant generation of alkyl amide ions which convert –NH– groupings to anilide ions. The latter are resistant to reduction because of their negative charge. Aromatic prim., sec. and tert. amines are in themselves reduced by the lithium–amine system with the formation of relatively large amounts of aminocyclohexanes. In the case of prim. and sec. amines these saturated compounds probably arise, at least in part, from the reduction of imine intermediates. It is shown that the cyclohexanes resulting from the reduction of tert. amines can arise from a 1,2-reduction of the 3- or 4-aminocyclohexene isomers. An application of these principles permits one to reduce only one of two phenyl groups in a compound like 2-phenyl-N-phenylethylamine. A 46% yield of 2-(1-cyclohexenyl)-N-phenylethylamine is obtained in this instance.

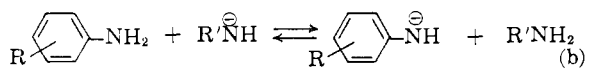
It was demonstrated in previous papers from this Laboratory[1–4] that lithium dissolved in certain low molecular weight amines is very effective in reducing aromatic rings selectively to monoölefins. Aromatic compounds containing reducible functional groups often undergo side chain as well as ring reduction in this system.[5]

Aromatic Nitro Compounds.—It has been found that aromatic nitro compounds are reduced predominantly to aromatic amines by lithium in methylamine. Thus *p*-nitrotoluene was reduced to *p*-toluidine in a 65% yield with methylamine as solvent. In ethylamine, a mixture of *p*-toluidine and *trans*-4-methylcyclohexylamine was obtained. The latter compound was identified by comparing it with an authentic sample prepared by reducing the oxime of 4-methylcyclohexanone with sodium in alcohol. Similarly in the reduction of nitrobenzene, and *o*- and *m*-nitrotoluene aromatic amines are the dominating products.[6] Cyclohexyl amino compounds were also detected in these cases, with somewhat larger quantities being formed in reductions carried out in ethyl rather than methylamine.

It is at first sight surprising that the reduction of an aromatic nitro compound should essentially stop at the aromatic amine, since the lithium–amine reagent has shown a great propensity for reducing aromatic systems. Since it is obvious that the nitro function is undergoing more rapid reduction than the aromatic ring, any explanation for the failure of ring reductions in these cases must necessarily involve the aromatic amine rather than the nitro compound.



(a)



(b)

It will be noted that as the nitro group is being reduced, the concentration of alkyl amide ions in the system is constantly increasing. As a result an equilibrium will be established between the aromatic amine and the anilide ions. Equilibrium (b) would be expected to lie well to the right since alkyl amide ions are much stronger bases than anilide ions.[7] The latter, because of their negative charge, are not prone to take on electrons, particularly at low temperatures. It is this formation of anilide ions which is undoubtedly responsible for the reduction of aromatic nitro compounds stopping at the aromatic amine stage.

If the aforegoing reasoning is correct, it would be predicted that aromatic amines themselves might well undergo reduction in the lithium–amine system. At least in the early stages of such reductions there would be no alkyl amide ions present to react with the aromatic amine. In keeping with this prediction it was found that *p*-toluidine is reduced in six hours by lithium in ethylamine to *trans*-methylcyclohexylamine in 50% yield. Under comparable conditions only 11% of this product resulted when methylamine was employed as the solvent. We are inclined to believe that this variation in yield is due to a temperature effect (b.p. methylamine, −7°; ethylamine, +17°) and not to any subtle difference between the two solvents. When the reduction of *p*-toluidine was carried out in ethylamine at about 0° (immersed in an ice-bath) the yield of *trans*-methylcyclohexylamine was reduced to 17%, closely approximating the yield obtained in methylamine. However, a high boiling liquid also was isolated in this case which has not yet been identified. Consequently, sufficient data are not yet available to state unequivocally that the difference in yield noted in the two solvents is due solely to a temperature effect.

Aromatic Amines.—It was noted in the previous section that *p*-toluidine is reduced to *trans*-methylcyclohexylamine in the lithium–amine system. In a similar fashion, reduction of N-methylaniline in methylamine resulted in a 27% yield of N-methylcyclohexylamine (38% starting material recovered). This is in contrast to usual reductions in this system wherein monoölefins are the predominant products.[3] A likely explanation for these results seemed to be that monoölefin was formed (a 1-

(1) R. A. Benkeser, R. E. Robinson and H. Landesman, THIS JOURNAL, **74**, 5699 (1952).

(2) R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *ibid.*, **76**, 631 (1954).

(3) R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *ibid.*, **77**, 3230 (1955).

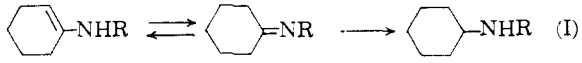
(4) R. A. Benkeser, G. Schroll and D. M. Sauve, *ibid.*, **77**, 3378 (1955).

(5) R. A. Benkeser, C. Arnold, Jr., R. F. Lambert and O. H. Thomas, *ibid.*, **77**, 6042 (1955).

(6) Unpublished studies by Mr. Sidney Kilsheimer.

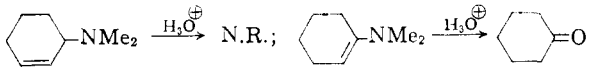
(7) The ionization constants of anilines are of the order of 10^{-10}, while those of the lower alkyl amines are approximately 10^{-4}.

aminocyclohexene isomer) but isomerized to the imine which then was reduced.[8] To test this

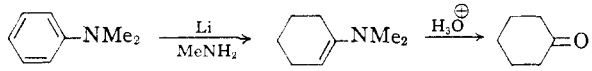


(I)

postulate, dimethylaniline was reduced in methylamine. Obviously, in this case, the formation of an intermediate imine was precluded. After hydrolysis with acid, a 44% yield of N,N-dimethylcyclohexylamine was obtained, along with 21% of cyclohexanone. When an authentic sample of 3-dimethylaminocyclohexene (prepared from 1,2-dibromocyclohexane and dimethylamine) was refluxed with an aqueous acid solution (conditions identical to those afforded the reduction product), no cyclohexanone was formed. On the other hand, when authentic 1-dimethylaminocyclohexene was subjected to this acid treatment, copious quantities of cyclohexanone were produced.

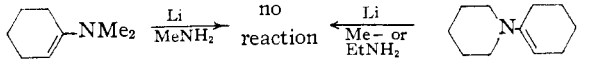


These results clearly indicated that the cyclohexanone produced in the hydrolysis of the reduction mixture was arising from hydrolytic cleavage of the 1-isomer.

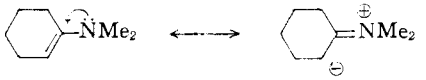


The fact that cyclohexanone or 4-methylcyclohexanone was not isolated in the reduction of methylaniline or *p*-toluidine would indicate that 1-olefins are not present in the reduction products at the time of hydrolysis. This lends support to the idea of an imine intermediate which undergoes reduction forming the cyclohexyl compound (equation I).

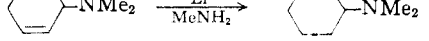
It is obvious that the large amounts of dimethylcyclohexylamine (44%) resulting from the reduction of dimethylaniline (a tert. amine) could not have arisen *via* the imine route, and hence another explanation was sought. When an attempt was made to reduce an authentic sample of 1-dimethylaminocyclohexene with lithium in methylamine, no reaction occurred. Only cyclohexanone was isolated after hydrolysis. The same results were obtained when 1-piperidinocyclohexene was treated with lithium in *either* methyl- or ethylamine



These results are not surprising. The double bond of such enamines is particularly electron-rich since it can participate in resonance with the nitrogen atom. It is because of resonance of this type that such enamines are particularly susceptible to reduction by formic acid.[9]

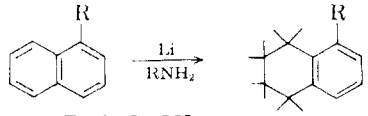


In contrast to the difficulties encountered in the reduction of 1-dimethylaminocyclohexene, the 3-isomer was found to undergo reduction by lithium in methylamine with comparative ease.



Very likely the 4-isomer would undergo reduction under the same conditions (this point is presently under investigation). It becomes apparent, therefore, that if for some reason the 3- or 4-isomers are formed to any extent in the reduction of dimethylaniline, both could undergo further reduction and thus account for the relatively large amounts of dimethylcyclohexylamine that are produced. A further treatment of this subject will appear in a subsequent paper.

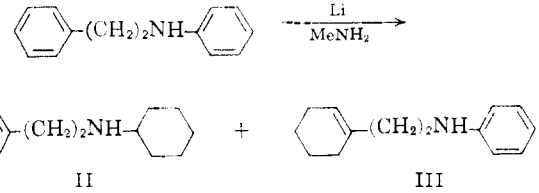
Reduction of 1-amino and 1-hydroxynaphthalene by the lithium–amine system resulted in excellent yields of the 5,6,7,8-tetrahydro compound. Very



R = NH_2; OH

likely, the negative charges produced by reaction of the amino and hydroxy groups with alkyl amide generated in the system, prevented reduction of the substituted ring. Thus it was noted that far more extensive reduction of 1-methoxy- and 1-dimethylaminonaphthalene occurred. In the former case $\Delta^{1,9}$-octalin (29%) was produced in addition to 5,6,7,8-tetrahydronaphthol (10%). In the latter both $\Delta^{1,9}$-octalin and *trans*-1-decalone were produced.

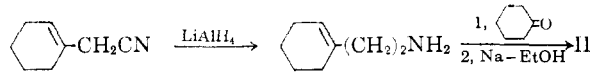
Discussion.—It is clear from the above examples that the development of a negative charge on a group attached to a benzene ring greatly inhibits the reduction of that ring by the lithium–amine system. It should therefore be possible to carry out essentially a *selective* reduction of one of two benzene rings in a molecule, provided one of these contains an active hydrogen substituent like an amine or phenol. Such a selective reduction was achieved in the case of 2-phenyl-N-phenylethylamine.



II III

The principal product, 2-(1-cyclohexenyl)-N-phenylethylamine (III), contains an unreduced phenyl group attached to the nitrogen. This electron-rich ring (enhanced by the negative charge on the nitrogen) is much slower to reduce than the other. It will be noted, however, that reduction of this ring leads to complete saturation (II) for reasons discussed in the previous section.

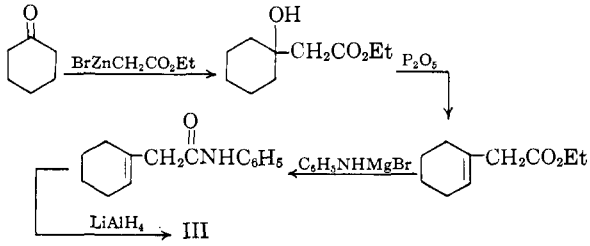
An authentic sample of II was prepared by the sequence of reactions



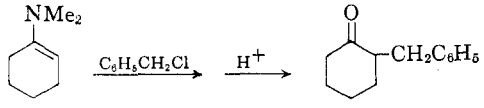
(8) See A. J. Birch, *Nature*, **160**, 754 (1947), where a similar explanation was invoked in the sodium–ammonia system.

(9) See N. J. Leonard and R. R. Sauers, THIS JOURNAL, **79**, 6210 (1957), and previous papers in this series.

An authentic sample of III was prepared as



An interesting adjunct to this work was the observation that 1-dimethylaminocyclohexene undergoes alkylation with benzyl chloride in a manner similar to the alkylation of pyrrolidine enamines.[10]



Although the yield of 2-benzylcyclohexanone was poor, the reaction was not investigated extensively. It is quite possible that variation in conditions might improve the yield.

Experimental

General Procedure for Lithium–Amine Reductions.—The material to be reduced (or its solution in a small amount of anhydrous ethyl ether) was added to a suspension of lithium in ethyl- or methylamine as rapidly as the vigor of the reaction would permit. Occasionally more lithium was added during the course of the reaction to maintain a blue color in the solution. At the end of the reaction (2 to 10 hours) solid ammonium chloride was added carefully until the mixture became colorless. This was followed by the slow addition of 150 ml. of water. The amine was distilled off, and the aqueous layer was cooled and extracted with ether. After drying and removal of the ether, the products were isolated by distillation.

Reduction of 2-Phenyl-N-phenylethylamine with Lithium in Methylamine.—Following the general reduction procedure, 20 g. (0.1 mole) of 2-phenyl-N-phenylethylamine[11] was reduced in 250 ml. of methylamine using 5 g. (0.71 g. atom) of lithium. The reaction time was two hours. Two fractions were obtained by distilling the product through a Todd column. The first fraction (2.0 g., b.p. 123° (2 mm.), $n^{20}D$ 1.5027) was shown to be 2-(1-cyclohexenyl)-N-cyclohexylethylamine by virtue of its phenylthiourea derivative melting at 106–108°. The latter did not depress the melting point of an authentic sample. The yield of this product was 9.5%.

The second fraction (9.5 g., b.p. 140–142° (2 mm.), $n^{20}D$ 1.5595) was identified as predominantly 2-(1-cyclohexenyl)-N-phenylethylamine (46%) by its infrared spectrum which was identical with that of an authentic sample. It also formed a benzamide (m.p. 44–46°) which did not depress the melting point of an authentic specimen (m.p. 45–47°).

A phenylthiourea derivative of this second fraction melted at 90–92° after repeated recrystallizations from 95% ethanol. However when this derivative was melted and then allowed to resolidify its melting point rose to 103–105°. An infrared spectrum of this derivative (m.p. 90–92°) in carbon tetrachloride solution was identical with that of an authentic sample (m.p. 107–108°). When this authentic sample was recrystallized from petroleum ether it melted at 88–90°. The latter modification did not depress the melting point of the derivative from the reduction product.

The second fraction gave a hydrochloride which had a wide melting range even after repeated recrystallizations, thus indicating the presence of small amounts of other amines.

Preparation of 2-(1-Cyclohexenyl)-ethylamine.—This material was prepared by the reduction of 1-cyclohexenylacetonitrile[12] with lithium aluminum hydride.[13] The experimental procedure for reduction of nitriles to amines given by Amundsen and Nelson[14] was followed. The product (b.p. 79–80° (15 mm.), $n^{20}D$ 1.4875) was obtained in 60% yield.

Preparation of 2-(1-Cyclohexenyl)-N-cyclohexylethylamine.—A solution of 20.6 g. (0.21 mole) of cyclohexanone and 27 g. (0.22 mole) of 2-(1-cyclohexenyl)-ethylamine in 80 ml. of absolute ethanol was allowed to stand at room temperature for several days. The solution then was diluted with an additional 200 ml. of absolute ethanol and was heated to reflux. The external heating was stopped and 20 g. (0.87 g. atom) of sodium, cut in small strips, was added through the condenser at a rate that maintained refluxing of the alcohol. After the sodium had reacted completely, 200 ml. of water was added carefully, followed by concentrated hydrochloric acid until the solution was acid to congo red. The solution then was evaporated until the amine hydrochloride began to precipitate. After the solution was cooled the hydrochloride (36 g., 71%) was obtained by filtration. The free 2-(1-cyclohexenyl)-N-cyclohexylethylamine was obtained by stirring the hydrochloride with 40% sodium hydroxide. The organic layer which resulted was dissolved in ether, dried with Drierite and distilled (b.p. 129–131° (3 mm.), $n^{20}D$ 1.4971). The phenylthiourea of the product melted at 108.5–109.5°.

Anal. Calcd. for $C_{21}H_{30}N_2S$: C, 73.63; H, 8.83; N, 8.18. Found: C, 73.52; H, 8.68; N, 8.21.

Preparation of Authentic 2-(1-Cyclohexenyl)-N-phenylethylamine.—Twenty-nine grams (0.13 mole) of 1-cyclohexenylacetanilide[15] was added slowly as a slurry in 250 ml. of anhydrous ether to 7.7 g. of lithium aluminum hydride in 300 ml. of anhydrous ether. The mixture (protected from moisture with a drying tube) was stirred at room temperature for two hours and then heated at reflux for one hour more. The flask now was cooled in an ice-bath and hydrolysis was accomplished by the careful addition of 8 ml. of water, 6 ml. of 20% sodium hydroxide solution and 28 ml. of water in that order. The ether layer was decanted and the solvent evaporated. The remaining product was distilled to give 17 g. (66% yield) of the desired product, b.p. 164–165° (5 mm.), $n^{20}D$ 1.5630. Two grams of unreduced anilide was recovered.

The product formed a benzamide melting at 45–47° after two recrystallizations from low boiling petroleum ether.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.59; H, 7.59. Found: C, 82.62; H, 7.47.

A hydrochloride melted at 93–94° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{20}NCl$: C, 70.72; H, 8.48. Found: C, 71.00; H, 8.80.

A phenylthiourea derivative was obtained by heating a small amount of the amine with phenyl isothiocyanate. The resulting material was dissolved in petroleum ether and allowed to crystallize. The solid obtained melted at 88–90°. After recrystallization from ethanol the melting point was raised to 107–108°. The modification melting at 88–90° did not depress the melting point of the phenylthiourea of fraction "two" of the 2-phenyl-N-phenylethylamine reduction product.

Anal. Calcd. for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.32. Found: C, 74.53; H, 7.26.

Reduction of *p*-Nitrotoluene.—Thirteen and seven-tenths grams (0.1 mole) of *p*-nitrotoluene was reduced using 7 g. (1 g. atom) of lithium in 250 ml. of methylamine. The reaction time was 6 hours. Seven grams (65% yield) of *p*-toluidine was the only product isolated. The product melted at 43–44° and gave an acetyl derivative melting at 148–151° which did not depress the melting point of au-

(10) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954); G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).

(11) R. Wegler and G. Pieper, *Ber.*, **83**, 1 (1950).

(12) *Org. Syntheses*, **31**, 25 (1951).

(13) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).

(14) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

(15) Prepared by the sequence: ethyl 1-hydroxycyclohexylacetate ("Organic Reactions," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 17) → ethyl 1-cyclohexenylacetate (G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932) → 1-cyclohexenylacetanilide (C. F. Koelsch and D. Tenenbaum, THIS JOURNAL, **55**, 3049 (1933)).

thentic acetyl-*p*-toluidine (reported[16] for *p*-toluidine, m.p. 45°; for acetyl-*p*-toluidine, m.p. 153°).

This reduction was repeated using ethylamine as the solvent rather than methylamine. By distillation of the product through a Todd column 2.0 g. (18% yield) of *trans*-4-methylcyclohexylamine (b.p. 149–150°, $n^{20}D$ 1.4521) was obtained. This product formed an acetamide melting at 141–142° which did not depress the melting point of an authentic derivative. Two grams (19% yield) of *p*-toluidine also was obtained. In this ethylamine reduction a large amount of tar was produced.

Reduction of *p*-Toluidine.—Twenty-one grams (0.2 mole) of *p*-toluidine was reduced in 300 ml. of ethylamine using 10 g. (1.4 g. atoms) of lithium. The reaction time was 6 hours. Eleven grams (49% conversion) of *trans*-4-methylcyclohexylamine ($n^{20}D$ 1.4509) was obtained. A phenylthiourea derivative melted at 160–162°, an acetamide at 141–142°, and a benzamide at 176–178°. These derivatives did not depress the melting points of authentic samples. Three grams (14%) of starting material was recovered.

The reduction of *p*-toluidine in ethylamine was repeated using 10.7 g. (0.1 mole) of *p*-toluidine and 4 g. (0.57 g. atom) of lithium. The reaction mixture was kept in an ice-salt-bath (−5 to 0°) during the reaction. The reaction time was 6 hours. From this reaction 1.9 g. (17% yield) of *trans*-4-methylcyclohexylamine was obtained.

Using methylamine as a solvent and a 6-hour reaction time 10.7 g. (0.1 mole) of *p*-toluidine was reduced with 4 g. (0.57 g. atom) of lithium. From this reduction 1.3 g. (11% conversion) of *trans* 4-methylcyclohexylamine was obtained. Five and five-tenths grams (51%) of starting material was recovered.

Preparation of Authentic *trans*-4-Methylcyclohexylamine.—The oxime of 4-methylcyclohexanone[17] was reduced by sodium and alcohol to the desired *trans*-4-methylcyclohexylamine by the procedure of Nightingale *et al.*[18] The product gave a phenylthiourea melting at 159–160°, a benzamide melting at 178–179°, and an acetamide melting at 140–141° (reported:[19] phenylthiourea, m.p. 159°; benzamide, m.p. 180°; acetamide, m.p. 70°).

Anal. Calcd. for $C_9H_{17}NO$ (acetamide): C, 69.64; H, 11.04; N, 9.02. Found: C, 69.94; H, 11.00; N, 8.96.

Reduction of N,N-Dimethylaniline.—Twenty-four grams (0.2 mole) of N,N-dimethylaniline was reduced using 8.4 g. (1.2 g. atoms) of lithium in 250 ml. of methylamine. The reduction time was 6 hours. The product was refluxed for 2 hours in 10% hydrochloric acid solution. After cooling, the acid-insoluble material was extracted into ether and dried. Removal of the ether gave 4.2 g. (21% yield) of cyclohexanone. The cyclohexanone gave a 2,4-dinitrophenylhydrazone melting at 159–161°, which did not depress the melting point of an authentic derivative. The acid-soluble material was then isolated by making the aqueous layer basic with sodium hydroxide. The organic layer was dissolved in ether which was then dried and distilled. Eleven and four-tenths grams (44% yield) of N,N-dimethylcyclohexylamine (b.p. 153–155°, $n^{20}D$ 1.4549) was obtained. This material gave a picrate melting at 176–178° which did not depress the melting point of an authentic sample. The slightly elevated index of refraction of this material indicates probable contamination by a monoölefin.

Preparation of N,N-Dimethylcyclohexylamine.—In a 500-ml., three-necked flask immersed in an ice-bath were placed 19.8 g. (0.2 mole) of cyclohexylamine and 52.1 g. (1 mole) of 88% formic acid; 45 ml. of 40% formalin was added to the resulting solution and the mixture was refluxed for 8 hours. The water was distilled; the residue was treated with 100 ml. of 12 *N* sodium hydroxide and the layers were separated. The aqueous portion was extracted twice with benzene. The benzene extracts were combined with the original organic layer and dried with sodium sulfate. The benzene was removed and the residue distilled to give 12.9 g. (52% yield) of N,N-dimethylcyclohexylamine, b.p. 158–159°, $n^{20}D$ 1.4528. This amine gave a picrate melting at 177–178° (reported[20] m.p. 177–178°).

Reduction of N-Methylaniline.—The same procedure which was used for the reduction of N,N-dimethylaniline was followed in this case. The product obtained was refluxed with dilute hydrochloric acid, but no cyclohexanone could be isolated. However, after the acid treatment, a definite ketone odor could be detected indicating that at least a small amount of cyclohexanone had been formed. The acid-soluble fraction was isolated and distilled to give 5.8 g. (27% yield) of N-methylcyclohexylamine boiling at 42–43° (11 mm.), $n^{20}D$ 1.4588, picrate m.p. 168–169°, benzamide m.p. 83–85° (reported[21] for N-methylcyclohexylamine: picrate m.p. 170°, benzamide 85–86°). There was a recovery of 8.1 g. (38%) of N-methylaniline.

Reduction of 1-Aminonaphthalene.—Fourteen and three-tenths grams (0.1 mole) of 1-aminonaphthalene was added to 7 g. (1 g. atom) of lithium in 250 ml. of ethylamine and the solution was stirred for 9 hours. The only product isolated was 10.5 g. (75%) of 5,6,7,8-tetrahydro-1-naphthylamine,[10] boiling at 138° (8 mm.), $n^{20}D$ 1.5902, benzamide m.p. 160–161° and acetamide m.p. 155–157°. These derivatives did not depress the melting points of authentic samples. The reported melting point for the acetamide[22] is 156–157°, and for the benzamide[23] 154°.

Anal. Calcd. for $C_{17}H_{17}NO$ (benzamide): C, 81.24; H, 6.82; N, 5.57. Found: C, 80.82; H, 6.65; N, 5.63.

Reduction of 1-Naphthol.—The reduction was carried out in methylamine using 14.6 g. (0.1 mole) of 1-naphthol, 7 g. (1 g. atom) of lithium and a reaction time of six hours. As the only product 13.2 g. (88%) of 5,6,7,8-tetrahydro-1-naphthol was obtained melting at 64–66° (benzoate m.p. 44–45°). For 5,6,7,8-tetrahydro-1-naphthol the reported melting point is 68.5–69° and for its benzoate 46°.[24]

Reduction of 1-Methoxynaphthalene.—Sixteen grams of this compound was reduced in methylamine for 7 hours using 7 g. (1 g. atom) of lithium. The product was extracted with 10% sodium hydroxide solution. Acidification of this basic extract gave 1.5 g. (10%) of 5,6,7,8-tetrahydro-1-naphthol, m.p. 67–69°. The base-insoluble fraction was dried and distilled to give 4 g. of material, b.p. 180–182°, $n^{20}D$ 1.4948, plus 3 g. of tarry residue. The distillate gave a white nitrosyl chloride melting at 125–126°. This was shown to be the nitrosyl chloride of $\Delta^{1,9}$-octalin since it could be converted to $\Delta^{9,10}$-1-ketoöctahydronaphthalene 2,4-dinitrophenylhydrazone (m.p. 266–267°) by heating with 2,4-dinitrophenylhydrazine.[3] The infrared spectrum of the distillate was consistent with the conclusion that this material was mainly $\Delta^{1,9}$-octalin.

Reduction of N,N-Dimethyl-1-aminonaphthalene.—The reduction of 14 g. (0.08 mole) of this material was carried out in methylamine using 7 g. (1 g. atom) of lithium. The reaction time was 6 hours. Distillation of the product gave 4.2 g. of material shown to be largely $\Delta^{1,9}$-octalin by the procedure described above. Also 1.7 g. of material boiling at 120–121° (12 mm.) ($n^{20}D$ 1.5005) was obtained. When a small portion of this higher boiling fraction in 3 ml. of ethanol was added to a solution of 1 g. of 2,4-dinitrophenylhydrazine in 10 ml. of 50% sulfuric acid, a 2,4-dinitrophenylhydrazone formed. This derivative melted at 224–226° after recrystallization from a mixture of ethanol and ethyl acetate. This 2,4-dinitrophenylhydrazone showed no depression in melting point when mixed with the 2,4-dinitrophenylhydrazone[25a] of authentic *trans*-1-decalone.[25b]

1-Piperidinocyclohexene.—The method of preparation was patterned after that employed to make the corresponding pyrrolidine derivative.[26] From 1 mole of cyclohexanone, 70 g. (42%) of product was obtained boiling at 120–122° (17 mm.). The compound is reported[27] to boil at 116–118° (16 mm.).

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Hydrolytic Cleavage of 1-Dimethylaminocyclohexene.[27]—When 5 drops of dimethylaminocyclohexene (b.p. 175.5°) was added to 5 ml. of 10% hydrochloric acid in a test-tube and the solution warmed, cyclohexanone was formed. Addition of a solution of 2,4-dinitrophenylhydrazine in sulfuric acid caused the immediate precipitation of the 2,4-dinitrophenylhydrazone derivative which melted at 160°. The reported[16] m.p. of this derivative is 161°.

Alkylation of 1-Dimethylaminocyclohexene with Benzyl Chloride.—A mixture of 12.6 g. (0.1 mole) of the enamine and 12.6 g. (0.1 mole) of benzyl chloride in 25 ml. of methanol was refluxed overnight. It was hydrolyzed with 10% hydrochloric acid and then made basic. Extraction with ether and evaporation of the solvent gave a small amount of liquid residue. This was crudely distilled by the use of a small distillation flask (b.p. 125° (1.5 mm.)). The distillate gave a semicarbazone derivative which melted at 165°. The reported melting point for the semicarbazone of 2-benzylcyclohexanone[28] is 166–167°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.45; H, 7.52; N, 17.22.

Attempted Reduction of 1-Dimethylaminocyclohexene.—A reduction (3 hr. duration) of 25.2 g. (0.2 mole) of the enamine was attempted using 2.8 g. (0.4 g. atom) of lithium in methylamine. After acid hydrolysis of the product, distillation yielded 12.4 g. (63%) of cyclohexanone boiling at 154–156° ($n^{20}D$ 1.4510). There was no evidence of any dimethylaminocyclohexane.

Attempted Reduction of 1-Piperidinocyclohexene.—The attempted reduction (3 hr. duration) of 33 g. (0.2 mole) of the enamine with 2.8 g. (0.4 g. atom) of lithium in methylamine gave, upon hydrolysis, and subsequent distillation 3.2 g. of cyclohexanone (b.p. 46–47° (14 mm.), $n^{20}D$ 1.4520; 2,4-dinitrophenylhydrazone m.p. 160°) and 16.4 g. (50%) of starting material (b.p. 120–122° (17 mm.)).

Similar results were noted when the reduction was carried out in ethylamine.

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3-Dimethylaminocyclohexene.[29]—This compound was prepared using 90 g. (2 moles) of dimethylamine and 81 g. (0.33 mole) of 1,2-dibromocyclohexane in 310 g. of benzene. Distillation gave 28 g. (83%) of product boiling at 161–163° ($n^{20}D$ 1.4685). The reported boiling point is 161–163° (725 mm.).[30] A styphnate derivative melted at 167–169° (reported m.p. 163–164°).[30]

Reduction of 3-Dimethylaminocyclohexene.—Twelve and one-half grams (0.1 mole) of this olefin in methylamine was reduced for 3 hr. with 1.4 g. (0.2 g. atom) of lithium. Subsequent hydrolysis and distillation gave 4.3 g. of product boiling at 161.5–162.5° ($n^{20}D$ 1.4565). This corresponds to a mixture of starting material and completely saturated amine. A picrate could be isolated from this fraction, which after two recrystallizations melted at 176–178° and did not depress the melting point of the same derivative prepared from authentic N,N-dimethylcyclohexylamine. Likewise an infrared spectra showed that a considerable portion of the original olefin had been reduced.

Attempted Acid Hydrolysis of 3-Dimethylaminocyclohexene.—Twelve and five-tenths grams (0.1 mole) of 3-dimethylaminocyclohexene was dissolved in 50 ml. of 10% hydrochloric acid and the solution was refluxed for 30 minutes. After cooling, the solution was extracted thoroughly with ether. Evaporation of the ether extract left no residue, showing that no cyclohexanone or other acid-insoluble material had formed. The aqueous acid portion then was made basic with sodium hydroxide solution and 11.5 g. of the 3-dimethylaminocyclohexene was recovered.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE, AND THE KETTERING–MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XIII. The Thiourethan Neighboring Group. I. A New Synthesis of Amino Sugars

BY B. R. BAKER, KATHLEEN HEWSON,[2] LEON GOODMAN AND ALLEN BENITEZ

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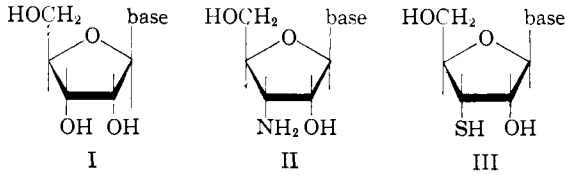
Reaction of the sodio derivative of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII) with phenyl isothiocyanate afforded a 53% yield of the amorphous 2-phenylthiourethan XIII and a 21% yield of the crystalline 3-phenylthiourethan XV, the structures of which were proved unequivocally. Mesylation of the 3-phenylthiourethan XV followed by ring closure with methanolic sodium methoxide, then alkaline hydrolysis, afforded methyl 2-anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (XIV). The potential use of this new amino sugar synthesis, whereby a 1,2-*trans*-glycol system of a sugar can be converted to a 1,2-*cis*-amino alcohol system, is discussed.

The substitution of the amino or mercapto group for the hydroxyl groups of natural purines such as hypoxanthine and guanine has led to compounds that inhibit nucleotide metabolism as exemplified by 2,6-diaminopurine, 6-mercaptopurine and thioguanine.[3] It would therefore be logical to assume that substitution of an amino or mercapto group for one of the hydroxyl groups of the sugar moiety of a natural riboside (I) could also lead to active inhibitors. An example of the substitution of amino for one hydroxyl of the ribose moiety is 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine (II), the "aminonucleoside" de-



I II III

rived from the antibiotic puromycin. This aminonucleoside II, active against the adenocarcinoma of the C3H mouse,[4] Leukemia L-1210[5] and Adenocar-

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper of this series *cf.* L. Goodman, L. O. Ross and B. R. Baker, *J. Org. Chem.*, in press.

(2) Southern Research Institute, Birmingham 5, Ala.

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(5) Unpublished data by Dr. J. H. Burchenal, Sloan-Kettering Institute.