TABLE I

ACYL DERIVATIVES OF AZO- AND AZOXYPHENOLS

Acryl Derivative	Solvent of Crystln.[a]	Color	M.P., °C.	Formula	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2,2′-Diacetoxyazobenzene	A	Orange	154–155	$C_{16}H_{14}N_2O_4$	64.42	64.23	4.69	4.58	9.39	9.45
3,3′-Diacetoxyazoxybenzene	B	Reddish brown	102–103	$C_{16}H_{14}N_2O_5$	61.14	61.16	4.45	4.58	8.92	8.82
4,4′-Diacetoxyazobenzene[b]	C	Golden yellow	198–199	$C_{16}H_{14}N_2O_4$						
2,2′-Dibenzoyloxyazobenzene	A	Orange	172–173	$C_{26}H_{18}N_2O_4$	73.93	73.88	4.26	4.20	6.63	6.67
3,3′-Dibenzoyloxyazoxybenzene	B	Yellowish brown	174–175	$C_{26}H_{18}N_2O_5$	71.23	71.10	4.11	4.06	6.39	6.47
4,4′-Dibenzoyloxyazobenzene[b]	A	Reddish yellow	210–211 249–251	$C_{26}H_{18}N_2O_4$						

[a] A, benzene; B, alcohol; C, glacial acetic acid. [b] Willstatter and Benz, *Ber.*, **40**, 1582 (1907).

TABLE II

ACYL DERIVATIVES OF THE THREE SYMMETRICAL HYDRAZOPHENOLS

Acyl Hydrazophenol	Solvent of Crystln.[a]	M.P., °C.	Formula	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Diacetyl-*o*-hydrazophenol[b]	A	146–147	$C_{16}H_{16}N_2O_4$	64.00	64.09	5.33	5.11	9.33	9.36
Diacetyl-*m*-hydrazophenol	A	136	$C_{16}H_{16}N_2O_4$	64.00	64.05	5.33	5.27	9.33	9.38
Diacetyl-*p*-hydrazophenol-[c]	B	138–140	$C_{16}H_{16}N_2O_4$	64.00	63.81	5.33	5.17	9.33	9.29
Dibenzoyl-*o*-hydrazophenol	C	169–170[d]	$C_{26}H_{20}N_2O_4$	73.58	73.52	4.71	4.64	6.60	6.50
Dibenzoyl-*m*-hydrazophenol	A	146–147	$C_{26}H_{20}N_2O_4$	73.58	73.72	4.71	4.75	6.60	6.69
Dibenzoyl-*p*-hydrazophenol	C	188–190	$C_{26}H_{20}N_2O_4$	73.58	74.11	4.71	4.65	6.60	6.56

[a] A, aq. alc.; B, benzene–pet. ether (80–100°); C, alcohol. [b] Purified by refluxing its alcoholic solution with charcoal in an atmosphere of nitrogen. [c] Hydrolysis with 5% sodium hydroxide did not yield the free hydrazophenol, but instead afforded the oxidation product viz. *p*-azophenol. [d] Ref. 1, m.p. 186°.

Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines. V. The Mechanism of Formation of Cyclohexanes. Utility of the Reducing Medium in Effecting Stereospecific Reductions

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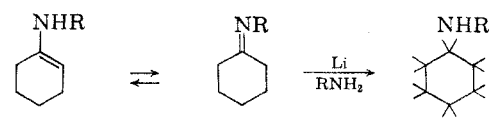
It was reported in a previous paper[1] in this series that reduction of aromatic nitro compounds with the lithium-amine reagent stops rather cleanly at the aromatic amine. On the other hand, aromatic amines (primary, secondary, or tertiary) are reduced by excess lithium in ethylamine to cyclohexane derivatives principally. This unusual behavior was shown to be due to the generation of alkyl amide ions during the reduction of the nitro group. These maintain the aromatic amino group as the anilide ion which resists further reduction. However, when one starts with an aromatic amine, the ring is reduced rapidly at first, since little or no amide ion is present, and hence reasonably good yields of reduction product can be realized in many instances.

In extending this work, we have found that all three isomeric toluidines are reduced to methylcyclohexylamines with excess lithium. In every case the most stable cyclohexane isomer was the predominant product (all substituent groups equatorial). Hence it appears that the lithium-amine reducing system should prove a valuable tool in the stereospecific synthesis of certain cyclohexanes.[2]

It was suggested previously[1] that complete saturation of the aromatic ring of certain 1° and 2° amines occurs because of the facile reduction of imine intermediates, arising from the isomerization of 1-aminocyclohexene isomers (enamines). Fur-



(1) R. A. Benkeser, R. F. Lambert, P. W. Ryan, and D. G. Stoffey, *J. Am. Chem. Soc.*, **81**, 228 (1959).

(2) We have observed also that certain of the xylidines undergo what appear to be similar stereospecific reductions. Details of these, and other stereospecific reductions will be published later.

thermore, any 3- or 4-olefin isomers formed in such reductions would undergo ready reduction as well.

This hypothesis has now been substantiated by a detailed study of the reduction of *N*-methylaniline and *N,N*-dimethylaniline. In the latter case, through the use of four equivalents of lithium as the reducing agent, a 40% yield of cyclohexanone was obtained following hydrolysis. Previous work[1] showed that cyclohexanone arises in this case only from hydrolytic cleavage of the enamine, 1-dimethylaminocyclohexene. Thus, a minimum yield of 38% of this olefin in the reduction mixture is indicated. Analysis of the basic fraction of the hydrolysate by gas chromatography indicated an olefin distribution of about 33% 3-dimethylaminocyclohexene and 62% 4-dimethylaminocyclohexene. When the reduction was repeated using an excess of lithium, a 35% yield of cyclohexanone was again obtained following hydrolysis. Analysis of the basic fraction of the hydrolysate indicated that virtually all of the 3- and 4-olefin isomers had been removed by reduction, with cyclohexyldimethylamine remaining as the principal product. When *N*-methylaniline was reduced with excess lithium only a trace of cyclohexanone could be detected in the hydrolysate of the reduction product. Thus it is clear that the enamine arising from *N*-methylaniline is reduced readily in this system, while the enamine from *N,N*-dimethylaniline is not. Reduction *via* an imine intermediate in the former case is clearly indicated.

These findings immediately raised the issue of whether the saturated products reported in earlier work[3] also were arising from a 1,2-reduction of 3- and 4-olefin isomers hitherto unreported. Accordingly a systematic study of the reduction of toluene, ethylbenzene, cumene, and *t*-butylbenzene was undertaken using both four equivalents of metal as well as an excess. The products were analyzed by gas chromatography (a technique not avilable when the initial work[3] on this reduction was done) and are listed in Table I.

TABLE I

REDUCTION OF AROMATIC HYDROCARBONS WITH LITHIUM IN METHYLAMINE[a,b]

	1-Alkylcyclohexene	3 + 4-Alkylcyclohexene	Alkylcyclohexane	B.P. Range
Toluene	59 (58)%	37 (23)%	4 (18)%	100–110°
Ethylbenzene	62 (60)	38 (30)	0 (10)	130–136
Isopropylbenzene	46 (46)	54 (44)	0 (10)	150–156
t-Butylbenzene	43 (40)	57 (52)	0 (9)	169–172

[a] The olefin mixtures were analyzed by gas chromatography utilizing a 14-ft. column packed with either dibutylphthalate, di-*n*-octylphthalate or β,β′-oxydipropionitrile on firebrick. [b] The first percentage listed in each case was obtained using four equivalents of lithium. The percentage in parentheses resulted from six equivalents of lithium.

(3) R. A. Benkeser *et al.*, *J. Am. Chem. Soc.*, **77**, 3230 (1955) and **77**, 6042 (1955).

It becomes immediately apparent from Table I that appreciable quantities of 3- and 4-alkylcyclohexenes do form under the conditions employed.[4] It is also apparent that the cyclohexanes which are formed in the presence of excess lithium arise principally from a reduction of the 3- and 4-olefins rather than from reduction of the 1-isomer. As further confirmation of this point several alkylcyclohexenes were reduced under comparable conditions with two equivalents of lithium in methylamine (Table II). It is obvious that the rate of reduction of the 1-alkyl isomers is very slow relative to that of the 3- and 4-isomers. This is understandable in terms of an electronic influence, wherein the inductive effect of the alkyl group slows down the uptake of electrons by the double bond.[5]

TABLE II

REDUCTION OF 1-ALKYLCYCLOHEXENES WITH LITHIUM IN METHYLAMINE[a,b]

Compound	Reaction Time, Hr.	Alkylcyclohexane, %
1-Methylcyclohexene	3	4
4-Methylcyclohexene	3	59
1-Isopropylcyclohexene	3	1
4-Isopropylcyclohexene	3	21
	5	39

[a] Analysis was by gas chromatography. See (a) of Table II. [b] Two equivalents of lithium were employed in every case.

Another interesting piece of information which can be gleaned from Table I is that the percentage of 1-alkylcyclohexene gradually drops as the +I effect (and also steric bulk) of the substituent alkyl group increases. The significance of this observation is presently under investigation.

EXPERIMENTAL

Reduction of the toluidines with lithium in ethylamine. To a mixture of 10 g. (1.4 g. atoms) of lithium in 300 ml. of ethylamine was added 21 g. (0.2 mole) of the toluidine. The mixture was stirred for 6 hr. The remaining lithium was then removed and the mixture hydrolyzed by the slow addition of 200 ml. of water. The ethylamine was evaporated with a steam cone and the product was dissolved in ether, dried, and distilled through a Todd column.

o-Toluidine. A 20% conversion (4.5 g.) into *trans*-2-methylcyclohexylamine was obtained (b.p. 151–153°, n_D^{20}

(4) It is possible that the percentages of 1-isomer reported in our earlier work (ref. 3) were high in some cases since the 1-isomer may have been contaminated with the 3- and 4-olefins. The conditions employed in these early reductions, however (excess lithium, prolonged reaction time), would tend to diminish the amounts of 3- and 4-olefins relative to the 1-isomer. There are indications that other techniques (to be reported later) can be employed as well to diminish the quantity of 3- and 4-isomer. We are at present reevaluating by gas chromatography some of the percentage yields we reported in our earlier work (ref. 3).

(5) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

1.4547), and 10.5 g. (50%) of starting material was recovered. The product formed a benzamide derivative melting at 148–149.5° when crude, and at 150–150.5° after recrystallization from 95% ethanol (reported[6] m.p. for the benzamide, 151°). Its phenylthiourea derivative melted at 150–151° (reported[7] m.p. for phenylthiourea 145°).

Anal. Calcd. for $C_{14}H_{20}N_2S$ (phenylthiourea): C, 67.73; H, 8.13. Found: C, 67.76; H, 8.42.

m-Toluidine. A 41% conversion (9 g.) into *cis*-3-methylcyclohexylamine was obtained (b.p. 149–150°, n_D^{20} 1.4512) and 7 g. (33%) of starting material was recovered. The product formed a benzamide derivative melting at 126–127° (reported[8] m.p. 124.5-125.8°) and a phenylthiourea melting at 139–140° (reported[7,9] m.p. 105–106°).

Anal. Calcd. for $C_{14}H_{20}N_2S$ (phenylthiourea derivative): C, 67.73; H, 8.13; N, 11.20. Found: C, 67.80; H, 8.40; N, 11.23.

p-Toluidine.[1] A 49% conversion (11 g.) into *trans*-4-methylcyclohexylamine was obtained (n_D^{20} 1.4509),[1] and 3 g. (14%) of starting material was recovered.

Alkylbenzenes (Table I). The alkylbenzene reductions were carried out in the usual fashion with 500–600 ml. of methylamine, 0.34 mole of aromatic and either 4 or 6 equivalents of lithium. In the cases where 4 equivalents of metal were used, the reaction was allowed to proceed for approximately 3 hr. With six equivalents the reaction time was about 6 hr.

Alkylcyclohexenes (Table II). The alkylcyclohexenes were reduced in approximately 300 ml. of methylamine using 0.2 mole of olefin and two equivalents of lithium.

N,N-Dimethylaniline. (*a*) (*4-Equivalents of lithium*). The reduction of 41.2 g. (0.34 mole) of *N,N*-dimethylaniline by 10.2 g. (1.45 g. atoms) of lithium in 500 ml. of methylamine was carried out in the usual manner. After 2 hr. the solution was colorless, and the solvent was then allowed to evaporate. Five hundred ml. of water was added and then 10% hydrochloric acid until the aqueous layer was acidic. This aqueous layer was then extracted thoroughly with ether and the ether solution dried over anhydrous sodium sulfate (extract No. 1). The acidic solution remaining was made basic with solid sodium hydroxide, and the basic solution was then extracted with ether. This extract (extract No. 2) was also dried over anhydrous sodium sulfate. Subsequent distillation of extract No. 1 through a Todd column, gave 13.2 g. (40%) of cyclohexanone (b.p. 154–155°; n_D^{21} 1.4490). Distillation of extract No. 2 gave 13.7 g. of material boiling at 162–164° (n_D^{22} 1.4673). An infrared spectrum of this cut showed an olefin band at 6 microns. Subsequent analysis of this material by gas chromatography (carbowax "1500" on firebrick packing) showed it to contain approximately 5% *N,N*-dimethylcyclohexylamine, 33% 3-dimethylaminocyclohexene and 62% 4-dimethylaminocyclohexene.

(*b*) *Excess lithium.* The reduction was repeated with 41.2 g. of *N,N*-dimethylaniline (0.34 mole) and 16.8 g. (2.4 g. atoms) of lithium in 500 ml. of methylamine. The reaction time was 7 hr., after which the product was worked up as described above. Distillation of extract No. 1 gave 11.7 g. (35%) of cyclohexanone (b.p. 154–155°, n_D^{21} 1.4492). Distillation of extract No. 2 gave 11.5 g. (27%) of cyclohexyldimethylamine (b.p. 159–161°, n_D^{22} 1.4540). A gas phase chromatogram showed the latter to be only slightly contaminated with 3- and 4-dimethylaminocyclohexenes.

N-Methylaniline (*excess lithium*). The product from the reduction of 36.4 g. (0.34 mole) of *N*-methylaniline with 16.8 g. (2.4 g. atom) of lithium in 500 ml. of methylamine for 7 hr. was worked up as described above. Distillation of extract No. 1 gave 1 g. of residue whose infrared spectrum showed no carbonyl band. Distillation of extract No. 2 gave 6.1 g. (16%) of *N*-methylcyclohexylamine (b.p. 148–150°, n_D^{24} 1.4562) and 22.7 g. (62%) of recovered *N*-methylaniline (b.p. 195–196°, n_D^{24} 1.5685). A gas phase chromatogram and an infrared spectrum of the *N*-methylcyclohexylamine showed it to be slightly contaminated with cyclohexanone.

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(6) D. S. Noyce and F. W. Bachelor, *J. Am. Chem. Soc.*, **74**, 4577 (1952).

(7) A. Skita, *Ber.*, **56**, 1014 (1923).

(8) D. S. Noyce and R. J. Nagle, *J. Am. Chem. Soc.*, **75**, 127 (1953).

(9) It should be noted that Skita's assignment of configuration for *cis*- and *trans*-3-methylcycylohexylamine was reversed. See ref. 8.

Substituted 12-Aminobenz[*a*]acridines

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The activity of a number of substituted 7-aminobenz[*c*]acridines against *E. histolytica in vitro* and in intestinal amaebiasis in rats has been reported by Elslager and co-workers[1,2] and by Short and co-workers.[3] The present communication deals with the preparation of a number of substituted 12-aminobenz[*a*]acridines for trials against *E. histolytica*.

The acridine derivatives were obtained by the interaction of 0.005 mole of 12-chlorobenz[*a*]-acridine, prepared from *N*-(2-naphthyl)anthranilic acid according to Bachman and Picha,[4] with a slight excess of the appropriate amine in phenol at 120 for a period of 2 hr. in the presence of powdered sodium carbonate to neutralize the liberated hydrochloric acid. The reaction mixture was poured into an excess of an aqueous solution of potassium hydroxide and the sticky precipitate, on solidification, was filtered off and dried after washing with water. The dry solid was dissolved in ether and the ether extract was treated with hydrogen chloride gas to precipitate the hydrochloride, or with a solution of salicylic acid in ether to precipitate and salicylate. The salt was purified by crystal-

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(2) E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 451, (1958).

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(4) G. B. Bachman & G. M. Picha, *J. Am. Chem. Soc.*, **68**, 1599 (1946).