phthalimidoethyl-1,2,4-triazole[1] was added, dropwise, 1.9 ml. (0.03 mole) of methyl iodide. After standing at room temperature overnight the solvent was removed and the residue in 100 ml. of 6 *N* hydrochloric acid was heated under reflux for six hours. The phthalic acid which separated on cooling was removed, and the filtrate was taken to dryness by heating under reduced pressure. The residue was dissolved in 50 ml. of ethanol and treated with 2.4 g. (0.06 mole) of sodium hydroxide. After the solvent was evaporated the solid was extracted with 25 ml. of ethanol, and this solution was treated with 13.8 g. (0.06 mole) of picric acid dissolved in 100 ml. of ethanol. The picrate which formed on cooling was collected and extracted with 100 ml. of boiling water. The insoluble material remaining was dissolved in 300 ml. of boiling water and on cooling 2.2 g. of solid separated as prisms, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 35.00; H, 2.65; N, 24.01.

The compound was shown to be identical with 3β-aminoethyl-1-methyl-1,2,4-triazole dipicrate by mixed melting point determination and comparison of infrared absorption curves.

The 100-ml. hot-water extract of the crude picrate mixture was concentrated to 50 ml. and on cooling 5 g. of 5β-aminoethyl-1-methyl-1,2,4-triazole dipicrate separated as needles, m.p. 180–182°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 34.96; H, 2.73; N, 24.02.

The infrared absorption curve of this dipicrate was different from the above and also that of 3β-aminoethyl-4-methyl-1,2,4-triazole dipicrate.

5β-Aminoethyl-1-methyl-1,2,4-triazole dihydrochloride (IV) was obtained from the dipicrate in the usual manner. It was very hygroscopic.

Anal. Calcd. for $C_5H_{10}N_4 \cdot 2HCl$: C, 30.16; H, 6.08. Found: C, 29.91; H, 6.32.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

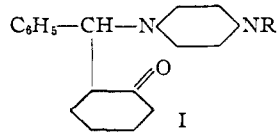
The Addition of Secondary Amines to Some α-Benzal Ketones

BY RICHARD BALTZLY, EMIL LORZ, PETER B. RUSSELL AND FRANCES M. SMITH

RECEIVED AUGUST 23, 1954

The addition of a number of secondary amines to cyclic and open-chain analogs of benzalcyclohexanone has been studied. In these systems the steric requirements of the amine appear to be quite critical, only cyclic amines and methyl secondary amines adding well. Ease of addition also can be correlated to some extent to recent theories of ring strain.

Monoquaternary salts of hexahydrobenzhydrylpiperazines exhibit marked spasmolytic action of an atropine-like nature.[1] Since the obvious preparation of the ditertiary amines (*e.g.*, N-hexahydrobenzhydryl-N′-methylpiperazine), required as precursors, through reaction of the appropriate halide and an N′-alkylpiperazine is rather unsatisfactory, an alternative preparation was sought. A possible route was seen in the addition of an alkylpiperazine to benzalcyclohexanone which should afford an amino ketone I possessing the desired carbon skeleton. Conversion of I to desired compounds of



I

physiological interest has been accomplished and will be the subject of a separate communication.

During the exploratory stage of this work it was found that the addition of amines to the benzalcyclohexanone system was influenced markedly by various factors, largely steric in character, and a study of these factors appeared to have some general interest. Accordingly a variety of secondary amines were allowed to act on benzalcyclohexanone and the addition of certain of these amines to various other cyclic and non-cyclic α-benzal ketones was also studied.

The results of these experiments are shown in Tables I and II. The general procedure was to mix the amine and unsaturated ketone, close the flask and allow the mixture to stand at room temperature. The reaction mixtures tended to become more viscous and to acquire brownish colors, and these changes had an inverse relationship. In certain cases after one to three days the reaction mixture solidified. In these cases excellent yields were obtained and little color developed. In other experiments, especially with diethylamine, the color deepened greatly, the viscosity was unaltered and the yields were extremely poor.

TABLE I

ADDITION OF VARIOUS SECONDARY BASES TO BENZALCYCLOHEXANONE

Base	Yield,[a] %	Base	Yield, %
Piperidine	80–90[a]	1,2,5-Trimethylpiperazine	0–3[d]
N-Methylpiperazine	80–90[a]	Pyrrolidine	70[c]
N-Ethylpiperazine	60[b]	Dimethylamine	40[c,e]
Morpholine	50[c]	Benzylmethylamine	35[c]
2-Methylpiperidine	0[d]	Diethylamine	1–5[d]

[a] Isolated as crystalline ketone. [b] Estimated as basic fraction after reduction. Crystalline aminoalcohols separated. [c] Estimated by reduction to give a non-crystalline but analytically pure mixture of aminoalcohols. [d] Estimated as crude basic fraction after reduction. [e] Carried out in ether.

It seemed likely that the color arose through de-aldolization followed by subsequent recondensation. It was found that when styryl isopropyl and *t*-butyl ketones, in which further condensation is impossible or at least unlikely, were compared with benzalacetone, the two former compounds showed no increase in color while benzalacetone showed some. The yields in the three condensations were quite similar. It seems probable therefore that the development of color may arise from de-aldolization and recondensation, but that it does not necessarily indicate a great diminution of yield. In the case of the cyclopentanone derivatives, however, the rather intense color is accompanied by a poor yield.

(1) R. Baltzly, W. S. Ide, E. Lorz and P. B. Russell, in preparation.

TABLE II

ADDITIONS TO VARIOUS KETONES

Ketone	Yield,[2] %	Ketone	Yield,[2] %
Base, N-methylpiperazine		Base, piperidine	
Benzalcyclopentanone	20[a]	Benzalcyclopentanone	0–16[d]
Benzalcyclohexanone	80–90[b]	Benzalcyclohexanone	80–90[b]
o-Chlorobenzalcyclohexanone	30[a]	Benzalacetone	73[e]
m-Methoxybenzalcyclohexanone	60[a]	Benzal diethyl ketone	15[d]
Benzalcycloheptanone	70[b,c]	Styryl isopropyl ketone	66[e]
		Styryl *t*-butyl ketone	64[e]

[a] Estimated by reduction to crystalline alcohols. [b] Yield of crystalline ketone. [c] A similar yield of crystalline ketone was obtained when N-ethylpiperazine was used. [d] Estimated as crude basic fraction after reduction only. [e] Estimated by reduction to non-crystalline but analytically pure oil.

Three main factors could be expected to influence the course of the addition: (1) the nature of the base, (2) the nature of the aliphatic or alicyclic portion of the unsaturated ketone and (3) substitution in the aromatic ring of the unsaturated ketone. This last factor has not been investigated systematically and may be complicated through steric involvement with (2).

(1) **The Nature of the Base.**—The results shown in Table I point clearly to a marked steric influence. Dimethylamine and benzylmethylamine added fairly well. Cyclic amines added well unless a methyl group was adjacent to the nitrogen (2-methylpiperidine and 1,2,5-trimethylpiperazine). Diethylamine added poorly or not at all.

The basicity of the amine appears to have little relation to the yield. On the assumption that the reverse reaction is initiated by removal of a proton from the α-position it would be expected that the rates of both forward and reverse reactions would have a close relationship to base strength and that the position of the equilibrium might therefore be independent of basicity. In the absence of kinetic data, qualitative observations must be only tentative. However, two parallel additions to benzalcyclohexanone of piperidine and methylpiperazine appeared to proceed at nearly the same rate.[3]

(2) **The Nature of the Unsaturated Ketone.**—In Table II are shown the yields obtained by addition of piperidine and of methylpiperazine to a variety of unsaturated ketones. Since these two amines appear very similar (in respect to this reaction, at least), the two partial lists may be regarded as supplementary. That some parallelism might be expected for other amines is shown by the fact that diethylamine adds as poorly to benzalacetone as it does to benzalcyclohexanone. That this parallelism is only approximate appears from the tolerably successful addition of pyrrolidine to benzalcyclopentanone (45–55% yield) as compared to the poor results shown in Table II for that ketone.

It is evident that additions to the system Ph-CH=CH·COR are reasonably successful without much regard to the nature of R. Benzal diethyl ketone, (the open-chain analog of the benzalcycloalkanones) however, is rather unreceptive. Among the benzalcycloalkanones, ring size is fairly critical.

Some pertinent information may be derived from the absorption spectra of these ketones for which data are shown in Table III.

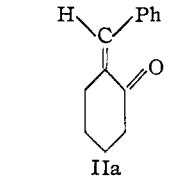
TABLE III

ABSORPTION DATA ON UNSATURATED KETONES DISSOLVED IN ETHANOL

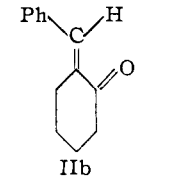
Compound	λ_{max}, Å.	$E_{max.}$
Benzalcyclopentanone	2980[a]	22,600
Benzalcyclohexanone	2900[a]	18,000
o-Chlorobenzalcyclohexanone	2720	12,500
Benzalcycloheptanone	2850	15,000
Benzalacetone	2870[b]	25,000
Styryl isopropyl ketone	2900	26,000
Styryl *t*-butyl ketone	2910	22,000
Benzal diethyl ketone	2750	21,000

[a] H. S. French and L. Wiley, THIS JOURNAL, 71, 3702 (1949), give essentially the same λ_{max} but somewhat lower intensities. [b] T. M. Lowry, H. Moureu and C. A. H. MacConkey, *J. Chem. Soc.*, 3167 (1928), give essentially the same values for this compound.

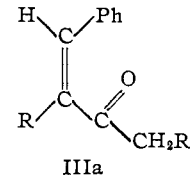
A ketone such as benzalcyclohexanone or benzalacetone can exist in *cis* and *trans* forms IIa and b and IIIa and b. *trans*-Benzalacetone absorbs at a longer wave length and with a greater intensity than does the *cis* form.[4] Comparison of benzalace-



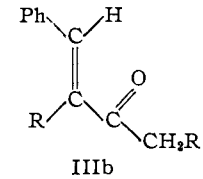
IIa



IIb



IIIa



IIIb

(2) The yields shown are not entirely comparable. The reactions were allowed to proceed from 3 to 14 days with the object of obtaining maximal yields. It is probable that the longer periods were not always essential. A more important point relates to the estimation of yield. All the best results corresponded to the formation of crystalline aminoketones and the yields reported in those cases are obviously *minimal*. Where no product crystallized, the entire reaction mixture was reduced by an excess of lithium aluminum hydride, and the yield shown is calculated from the weight of the crude fraction soluble in dilute acid and insoluble in water. Experiments in which crystalline aminoketone was so reduced showed that the reduction is essentially quantitative. However, the yields calculated on this basis are obviously *maximal*. The deviations from this source are probably not serious with the better and middle yields but may be with the very poor yields, some of which may have been zero since the products were not homogeneous and were not further identified. The fact that the *minimal* yields of crystalline product were the highest obtained may be related to the fact that the addition is reversible, but proceeds to substantial completion when the product crystallizes. It would be difficult to account for the difference in yields in the additions of N-methyl- and N-ethylpiperazine to benzalcyclohexanone on any fundamental basis. In the case of benzalcycloheptanone where the aminoketones from both N-methyl- and N-ethylpiperazine separate in crystalline form, the yields are almost the same. The obvious corollary is that yields of 60–70% correspond to the equilibrium of the addition reaction in uncomplicated cases, better yields having no necessary relationship to the equilibrium. The lower yield (40%) from dimethylamine and benzalcyclohexanone therefore could be due to the presence of solvent and resultant lower concentrations of reactants.

(3) In each reaction 0.03 mole of ketone and 0.045 mole of amine were employed. The two reaction mixtures increased in viscosity to comparable extents and both solidified to magmas of crystals when seeded 2.5 hours after mixing.

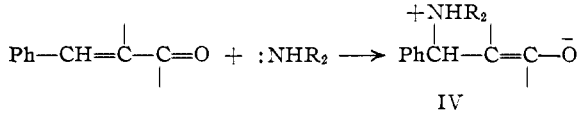
(4) B. Eistert and E. Merkel, *Chem. Ber.*, **86**, 904 (1953). See also R. E. Lutz and co-workers, THIS JOURNAL, **72**, 4090, 4300 (1950).

tone (known to be *trans*-III (R = H)) with benzal diethyl ketone (Table III) suggests that this latter compound is the *cis* form (IIIa, R = CH_3). The *cis* form is probably the more stable since in the *trans* there is possibility of interference between the phenyl and methyl groups. The low yields obtained on addition of amines to benzal diethyl ketone may be an indication that only the *trans* form adds well.

Most of the cyclic compounds would appear to belong to the *trans* series, IIb. Here the small changes in intensity and wave length of absorption probably arise from the difficulty of forcing the conjugated system into a planar form in the excited state.[5] Benzalcyclopentanone, which even in the non-excited state must be planar, therefore absorbs at the longest wave length and with the greatest intensity. The cyclohexanone and cycloheptanone derivatives have increasingly puckered rings and in them more energy must be expended to achieve planar excited states. They consequently absorb at shorter wave lengths and with lower intensity.

The influence of aromatic substitution has not been studied adequately. Available data suggest that *o*-chlorobenzalcyclohexanone belongs to the *cis* series. With methylpiperazine it gives a poor yield of addition product. This is in line with the conclusions reached above from a study of benzal diethyl ketone.

The reaction with amines is probably governed by kindred considerations but here the geometry of transition states rather than of spectroscopically excited states is under consideration. In the addition reactions it is to be presumed that the base first attacks the β-carbon atom

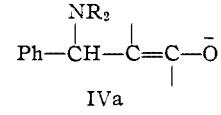


IV

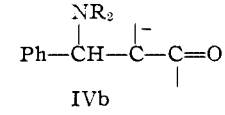
leading to a transition state approximated by IV. This attack ought to be rate determining since a mere prototropy will suffice to convert IV to the final aminoketone.

The reverse reaction should be initiated by removal of an α-proton followed by secession of NHR_2 or $\bar{N}R_2$ (dependent on whether the aminoketone existed previously as free base or as conjugate acid). The rate of the reverse reaction could be dependent on either or both of these steps. The position of the equilibrium ought to be dependent on thermodynamic considerations and on the *relative* rates of forward and reverse reactions but not on their absolute magnitudes.

In the cyclic compounds, the transition state IV possesses an endocyclic double bond. The change from a system with two exocyclic double bonds to one with *one* endocyclic double bond would be expected to be favored in a six-membered ring and opposed in a five-membered ring compound. On this basis one might expect the forward reaction to be considerably more rapid with benzalcyclohexanone than with benzalcyclopentanone. It could be argued that the reverse reaction ought to be accelerated also,[6,7] however, this need not be the case. A number of forms can be derived from the aminoketone type by abstraction of an α-proton. One of these is, of course, IV, but IVa and IVb also are possible. In general, IVa would be expected to predominate over IVb but not in the cyclopentane



IVa

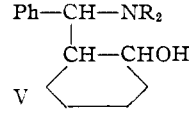


IVb

series.[8] If the transition state for the reverse reaction is a resonance hybrid to which IVb makes a large contribution, we should have a system in which the reverse reaction could proceed at a fair rate corresponding to an unfavorable equilibrium for addition and the observed low yield. It seems unlikely that crowding in the adducts is of much importance. This crowding must inevitably increase from benzalcyclopentanone to benzalcycloheptanone but respectable yields were obtained in this last case despite an apparently slow addition.

It has been mentioned that the aminoketones are reduced smoothly to the aminoalcohols in good yield with lithium aluminum hydride in ether. Sodium trimethoxy borohydride and sodium borohydride also effect the reduction but at a slower rate and some unsaturated starting material, or the corresponding unsaturated alcohol, is obtained. Attempts to reduce the addition compound of N-methylpiperazine and benzalcyclohexanone with aluminum isopropoxide resulted in the formation of a good yield of 2-benzalcyclohexanol. Attempts to carry out the same reduction by the aid of Adams catalyst resulted in hydrogenolysis to give benzylcyclohexanone. The Wolff–Kishner reduction on the semicarbazone gave only neutral material.

Aminoketones such as I have two points of asymmetry and could exist as two pairs of enantiomers while the aminoalcohols, such as V, can have twice that number of isomers. The benzalcyclohexanone



V

adducts derived from piperidine and N-methylpiperazine were obtained in good yield and were apparently homogeneous, whereas the corresponding aminoalcohols in each case could be entirely separated into two pure bases. This suggests that under the conditions of the additions, the hydrogen alpha to the carbonyl in I is sufficiently labile that a less stable isomer can be epimerized readily to a more stable form.

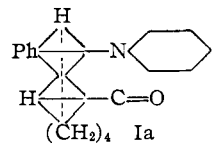
Fisher–Hirschfelder models of I are rather cramped, but of the two diastereomeric forms Ia and Ib the former is less badly crowded. The model of Ia permits rotation of the phenyl group about its bonding axis by about 30° and of the piperidine

(5) E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature*, **173**, 117 (1954).

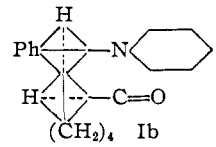
(6) A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 2533 (1928).

(7) F. P. Price and L. P. Hammett, THIS JOURNAL, **63**, 2387 (1941).

(8) Ethyl cyclopentanonecarboxylate is at once more acidic than ethyl cyclohexanonecarboxylate and less enolized; W. Dieckmann, *Ber.*, **55**, 2470 (1922). See other references in H. C. Brown, J. H. Brewster and H. Schechter, THIS JOURNAL, **76**, 467 (1954).



Ia



Ib

radical by about 80°. In Ib the corresponding angles of free rotation are about 5 and 30°, respectively. Analogous models derived from 2-methylpiperidine cannot be constructed at all. In the aminoalcohols V these configurations are presumably unchanged and the multiplied isomerism depends on the *cis* or *trans* position of the hydroxyl group.[9]

While it is entirely reasonable that in a reversible reaction of this sort the configuration at the carbon alpha to the carbonyl should be regularly determined by the configuration at the benzylic carbon atom, it is of course realized that a definite *assignment* of configuration to these positions is not justified by the examination of models alone. Chemical evidence will be presented[9] as to the relationship in the aminoalcohols of the configurations at the two asymmetric atoms of the cyclohexane ring.

Experimental

α-Benzalcycloheptanone.—Cycloheptanone (100 g.) and benzaldehyde (60 g., $^2/_3$ mol) were added to a solution of potassium hydroxide (20 g.) in water (350 ml.). The mixture was refluxed for three hours and after cooling the oily layer was extracted with ether. The ethereal solution was washed with dilute sulfuric acid and then with water. The ether was dried and evaporated. The residue was distilled *in vacuo*. Forerunnings passed over up to 150° at 15 mm. (*ca.* 10 g.). The pressure was then decreased and the main fraction (100 g.) boiled at 130–135° (0.1 mm.). The material solidified on scratching. After recrystallization from pentane it formed colorless prisms, m.p. 45°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.0. Found: C, 84.2; H, 8.3.

The material gave a semicarbazone which melted at 174–175° dec. after recrystallization from aqueous methanol.

Anal. Calcd. for $C_{15}H_{19}ON_3$: C, 70.3; H, 7.1. Found: C, 70.0; H, 7.4.

***m*-Methoxybenzalcyclohexanone.**[10]—*m*-Methoxybenzaldehyde (68 g., 0.5 mole) and cyclohexanone (150 g., 1.5 moles) were refluxed for 4 hours with a solution of potassium hydroxide (25 g.) in water (500 ml.). The product was worked up as in the previous example; it boiled at 160–162° at 1.0 mm. (50.5 g.); on cooling it solidified, m.p. 21–23°. The compound was not obtained analytically pure. Found: C, 76.5; H, 7.6. Calcd. for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4.

***o*-Chlorobenzalcyclohexanone.**—Cyclohexanone (95 g., 1 mol) and *o*-chlorobenzaldehyde (46 g., 0.33 mol) were stirred with a solution of sodium hydroxide (19.8 g.) in water (4.55 l.) for 17 hr. The solution was then acidified by the addition of acetic acid (*ca.* 27 ml.) and after stirring for a further 6.5 hours was extracted with ether. The ethereal solution was washed well with water, dried and the ether evaporated. The main fraction (51 g.) boiled at 110–120° at 10 mm. After recrystallization from pentane it formed pale yellow prisms, m.p. 70–71°.

Anal. Calcd. for $C_{13}H_{13}OCl$: C, 70.7; H, 5.9. Found: C, 71.0; H, 6.1.

Benzal diethyl ketone,[11] styryl isopropyl ketone,[12] styryl *t*-butyl ketone[13] and benzalcyclopentanone[14] were prepared by the literature methods. Benzalacetone was obtained from Eastman Kodak Co. and distilled once before use.

Addition of Piperidine to Benzalcyclohexanone. 2-(α-N-Piperidinobenzyl)-cyclohexanone.—Benzalcyclohexanone (37.2 g.) and piperidine (20 ml.) were mixed and warmed on a steam-bath until homogeneous. The mixture was allowed to stand overnight and the next day the solid material (48 g., 85%) was filtered off and washed with pentane. After recrystallization from ether–pentane it melted at 125–126°.

Anal. Calcd. for $C_{18}H_{25}ON$: C, 79.7; H, 9.2. Found: C, 80.0; H, 9.2.

With semicarbazide hydrochloride in sodium acetate solution it gave a semicarbazone, m.p. 203–205° dec.

Anal. Calcd. for $C_{19}H_{28}N_4O$: C, 69.5; H, 8.5. Found: C, 69.6; H, 8.7.

2-(α-N'-Methyl-N-piperazinobenzyl)-cyclohexanone was obtained in a similar manner from N-methylpiperazine and benzalcyclohexanone in 83% yield. After recrystallization from ether–pentane it melted at 116–117°.

Anal. Calcd. for $C_{18}H_{26}ON_2$: C, 75.5; H, 9.1. Found: C, 75.4; H, 9.2.

2-(α-N'-Methyl-N-piperazinobenzyl)-cycloheptanone was prepared in a similar manner from N-methylpiperazine and benzalcycloheptanone. Over some two weeks a 70–75% yield of the ketone was obtained. After recrystallization from ether the aminoketone melted at 156–157°.

Anal. Calcd. for $C_{19}H_{28}ON_2$: C, 76.0; H, 9.3. Found: C, 76.2; H, 9.0.

The corresponding N'-ethyl compound crystallized from ether, m.p. 124°.

Anal. Calcd. for $C_{20}H_{30}ON_2$: C, 76.4; H, 9.6. Found: C, 76.8; H, 9.5.

We did not consider it advisable to expend effort in crystallizing aminoketones that did not crystallize spontaneously. Those members of the series that were obtained as solids could be crystallized from ether, petroleum ether or mixtures thereof and even from methanol if rapidly manipulated. On the other hand, a specimen of 2-(α-N'-methyl-N-piperazinobenzyl)-cyclohexanone when crystallized from methanol and allowed to stand overnight in contact with its mother liquors was found to have redissolved and was no longer recoverable. It is to be presumed that the addition had been reversed and that under the alkaline conditions the elements of methanol had added to the unsaturated ketone.

Attempts to prepare crystalline salts of the same compound gave poor recoveries of analytically impure material. It was therefore felt that extended operations in the liquid phase were to be avoided. The poor results from the two *slow* reductions described below further support this course. The lithium aluminum hydride reduction is presumably nearly instantaneous.

Catalytic Reduction of 2-(α-Piperidinobenzyl)-cyclohexanone.—The aminoketone (5.4 g., 0.02 mole) was dissolved in methanol (50 ml.) containing acetic acid (1.2 mols). To this was added Adams platinum oxide and the mixture shaken under hydrogen. After 45 min. 1 mol of hydrogen had been absorbed and the rate of absorption was very low. The product was separated into neutral and basic fractions. The neutral fraction weighed 4.0 g. and gave a semicarbazone, m.p. 167–168°, identical with the semicarbazone of 2-benzylcyclohexanone.[15]

Meerwein–Ponndorf Reduction of 2-(α-N'-Methyl-N-piperazinobenzyl)-cyclohexanone.—The aminoketone (13.5 g., $^1/_{20}$ mole) was added to aluminum isopropoxide (40 g.) in dry isopropyl alcohol (300 ml.) and the solution refluxed until no more acetone was evolved. The solvent was then evaporated and the residue made strongly acid. After extraction with ether a neutral fraction (8.0 g.) was obtained. This neutral material melted at 63° and was identical in every respect with 2-benzalcyclohexanol.[15]

Reduction of 2-(α-N-Piperidinobenzyl)-cyclohexanone with Lithium Aluminum Hydride.—The hydride (3.8 g.) was stirred with ether (150 ml.) and to this solution was added during 1 hour a solution of the aminoketone (27 g.)

(9) P. B. Russell and R. Baltzly, THIS JOURNAL, **77**, 629 (1955).

(10) The proportions and method used in this preparation give 60–70% yields for benzalcyclohexanone. The steam distillation recommended in earlier preparations is inadvisable except with very small preparations since it prolongs excessively the exposure to an alkaline medium.

(11) D. Vorländer, *Ann.*, **294**, 296 (1896).

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(15) P. B. Russell, *J. Chem. Soc.*, 1771 (1954).

TABLE IV

AMINOALCOHOLS FROM THE REDUCTION OF AMINOKETONES WITH LITHIUM ALUMINUM HYDRIDE

Aminoalcohol	Yield, % (Total)	M.p. or b.p., °C. (mm.)	Formula	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.
2-(α-N-Piperidinobenzyl)-cyclohexanol[a]	95–100	*cis* 93–94[c]	$C_{18}H_{27}ON$	78.9	79.1	10.1	9.9
		trans 111–112		78.8		10.1	
2-(α-N'-Methyl-N-piperazinobenzyl)-cyclohexanol[a]	95–100	*cis* 154	$C_{18}H_{28}ON_2$	75.1	75.0	10.2	9.7
		trans 101–102		74.9		9.9	
2-(α-N'-Ethyl-N-piperazinobenzyl)-cyclohexanol[b]	60	*cis* 131	$C_{19}H_{30}ON_2$	75.9	75.5	9.7	9.9
		trans 104		75.7		9.6	
2-(α-N'-Methyl-N-piperazino-*m*-methoxybenzyl)[b]-cyclohexanol	60	*cis* 163	$C_{19}H_{30}O_2N_2$	71.7	71.7	9.4	9.4
2-(α-N' Methyl-N-piperazino-*o*-chlorobenzyl)[b]-cyclohexanol	30	*trans* 148	$C_{18}H_{27}ON_2Cl$	67.2	67.0	8.4	8.4
2-(α-N'-Methyl-N-piperazinobenzyl)-cyclopentanol[b]	20	*cis* 139[d]	$C_{17}H_{26}ON_2$	74.3	74.5	9.0	9.5
		trans 80		74.9		9.0	
2-(α-N'-Methyl-N-piperazinobenzyl)-cycloheptanol[a]	95–100	*cis* 103	$C_{19}H_{30}ON_2$	75.7	75.5	9.6	9.9
		trans 147–148		75.8		9.5	
2-(α-N'-Ethyl-N-piperazinobenzyl)-cycloheptanol[a]	95–100	*trans* 137	$C_{20}H_{32}ON_2$	75.8	75.9	10.1	10.1
2-(α-N-Morpholinobenzyl)-cyclohexanol[b]	50	100–103 (0.1)	$C_{17}H_{25}O_2N$	74.6	74.7	9.2	9.2
2-(α-N-Pyrrolidinobenzyl)-cyclohexanol[b]	70	90–93 (0.2)	$C_{17}H_{25}ON$	78.5	78.8	9.5	9.7
2-(α-Dimethylaminobenzyl)-cyclohexanol[b]	40	75–80 (0.2)	$C_{15}H_{23}ON$	77.6	77.3	10.1	9.9
2-(α-Benzylmethylaminobenzyl)-cyclohexanol[b]	35	100–105 (0.2)	$C_{21}H_{27}ON$	82.0	81.6	9.1	8.7
4-Phenyl-4-N-piperidinobutan-2-ol[b]	73	65–70 (0.2)	$C_{15}H_{23}ON$	77.3	77.3	10.3	9.9
4-Phenyl-4-N-piperidino-2,2-dimethylpentan-3-ol[b]	64	78–80 (0.2)	$C_{18}H_{29}ON$	78.8	78.5	10.3	10.5
4-Phenyl-4-N-piperidino-2-methylpentan-3-ol[b]	66	75–80 (0.2)	$C_{17}H_{27}ON$	77.9	78.2	10.0	10.3

[a] By reduction of crystalline ketone. [b] By reduction of non-crystalline addition product. [c] The designations of configuration made in this column are supported by other investigations in these laboratories. See Russell and Baltzly ref. 9. [d] Assignment of configurations tentative.

in ether (200 ml.). When all the ketone had been added the solution was refluxed for 3 to 3.5 hours. After cooling, the excess reagent was decomposed by the addition of excess water (*ca.* 25 ml.). The ethereal solution was decanted from the solid material and then extracted three times with 2 *N* hydrochloric acid solution. The acid extract was basified and the precipitated oil extracted with ether. After the solution had been well washed with water it was dried. Removal of the ether gave a mixture of crystalline stereoisomeric alcohols (26 g.). This crystalline mixture was separated into two forms, as will be described[9] in the following publication: the *cis* form, m.p. 93–94° (*ca.* 20–25%), and the *trans* form, m.p. 111–112° (75–80%).

Anal. Calcd. for $C_{18}H_{27}ON$: C, 79.1; H, 9.9. Found (m.p. 93–94°): C, 78.9; H, 10.1. (M.p. 111–112°): C, 78.8; H, 10.1.

Lithium aluminum hydride reduction of the other crystalline ketones gave rise in general to a mixture of isomeric crystalline aminoalcohols from which it usually was possible to recover both forms. These reductions are listed in Table IV.

Reduction of the Non-crystalline Addition Product of Morpholine and Benzalcyclohexanone.—This is an example which indicates the method of obtaining the percentage yields in most of the additions reported in Tables I and II. The ketone (18.6 g.) was mixed with dry morpholine (8.7 g.) and the mixture warmed until homogeneous. After standing for one week no crystalline product was obtained although the material was quite viscous. The mixture therefore was dissolved in ether (100 ml.) and added dropwise to a suspension of lithium aluminum hydride (3.8 g.) in ether (150 ml.). The excess reagent was decomposed eventually as described above. The ether layer was extracted with 2 *N* hydrochloric acid (3 × 100 ml.) and the ethereal solution washed with water and dried. On removal of the ether the neutral fraction (9.0 g., *ca.* 50%) was obtained as a pale yellow oil. On scratching it solidified and after recrystallization from pentane it melted at 63°. This melting point was not depressed on admixture with an authentic sample of 2-benzalcyclohexanol.[15] The acid solution was basified and the oil extracted with ether; the ethereal solution was washed with water and dried. Removal of the ether gave a basic oil (14 g., *ca.* 50%) which could not be crystallized. On distillation it boiled at 100–103° (2×10^{-3} mm.).

Anal. Calcd. for $C_{17}H_{25}O_2N$: C, 74.2; H, 9.1. Found: C, 74.6; H, 9.2.

The non-crystalline aminoalcohols from other reductions are reported in Table IV.

Ultraviolet absorption spectra were measured on a Beckman model DU quartz spectrophotometer. The solutions were at a concentration of 10 mg./l. in ethanol (cell length 10 mm.).

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