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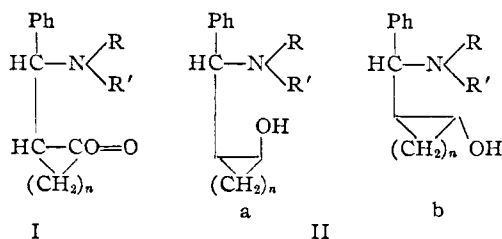
On the Configuration of the Epimeric 2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclohexanols and Related Compounds

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RECEIVED AUGUST 23, 1954

The crystalline aminoalcohol obtained by lithium aluminum hydride reduction of 2-( $\alpha$ -N'-methylpiperazinobenzyl)-cyclohexanone has been separated into two pure bases. These differ in the *cis* and *trans* position of the hydroxyl and amino-benzyl groups. The lower melting base forms a tosyl ester from which an unsaturated derivative is obtained with potassium *t*-butoxide. This unsaturated compound is smoothly hydrogenated catalytically to the known N-hexahydrobenzhydryl-N'-methylpiperazine. The higher melting aminoalcohol reacts with tosyl chloride to give directly an unsaturated derivative which suffers hydrogenolysis in the presence of platinum and is consequently believed to be allylic. On the basis of these reactions the high melting alcohol is assigned the *cis* configuration and the low melting, the *trans*. The configurations of a number of related compounds have been correlated with these.

In the preceding paper<sup>1</sup> it was mentioned that the reduction of a 2-( $\alpha$ -aminobenzyl)-cycloalkanone (I) with lithium aluminum hydride gave a mixture of epimeric 2-( $\alpha$ -aminobenzyl)-cycloalkanols IIa and b. The present paper deals with the isolation of these isomers in a pure state and with their configurations.

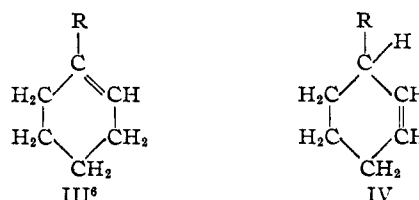


Reduction of 2-( $\alpha$ -N'-methyl-N-piperazinobenzyl)-cyclohexanone with the mixed hydride gave a crystalline mixture of epimeric alcohols in high yield. Fractional crystallization from ether and ether-pentane separated this mixture into its two components. The less soluble isomer melted at 157° and was obtained in about 20% yield while the more soluble melted at 101° and constituted some 80% of the product.

It was hoped that the configuration of these two compounds could be established by their conversion to the known *cis*- and *trans*-2-benzylcyclohexanols.<sup>2</sup> Since these compounds are effectively  $\alpha$ -substituted benzylamines, it was believed that this cleavage could be achieved by catalytic hydrogenolysis.<sup>3,4</sup> These speculations however could not be reduced to practice and other proofs of configuration were sought.

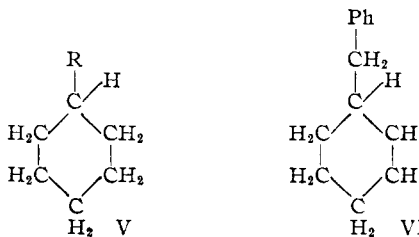
The isomer, m.p. 101°, gave with tosyl chloride<sup>5</sup> in pyridine an ester, m.p. 119°. This tosylate yielded a compound C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>, m.p. 85°, on heating with potassium *t*-butoxide or with 2,6-lutidine. This compound can have either of the structures III or IV.

On hydrogenation with Adams catalyst  $\alpha$ -N'-methyl-N-piperazinobenzylcyclohexane (N-hexahydrobenzhydryl-N'-methylpiperazine, V), m.p. 72–73°, was obtained. This compound was prepared

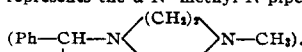


by two alternative routes; one consisted of the reduction of the tosylate, m.p. 119°, with lithium aluminum hydride,<sup>7,8</sup> the other the reaction of hexahydrobenzhydryl chloride with methylpiperazine.<sup>9</sup>

The tosylation of the isomer, m.p. 157°, under similar conditions proceeded somewhat differently. If the reaction was stopped after a short time (24 hr.) some starting alcohol was isolated, but longer reaction times gave an oil, C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>, isomeric with the 85° melting compound. Consequently, this also is represented by one of the structures III or IV. The formation of this unsaturated compound is explained most readily as proceeding *via* a tosyl ester that undergoes elimination very rapidly. The formation of this tosylate is slower than the formation of the ester of m.p. 119°. These facts suggest that the alcohol, m.p. 157°, is the *cis* epimer and that the unsaturated compound C<sub>18</sub>H<sub>26</sub>N<sub>2</sub> is the isomer III. Independent proof of this last postulate was obtained: the oily isomer C<sub>18</sub>H<sub>26</sub>N<sub>2</sub> on catalytic reduction with Adams catalyst underwent hydrogenolysis to give a neutral compound, probably benzylcyclohexane (VI). Since neither the saturated compound V nor the epimeric alcohols undergo hydrogenolysis, it is evident that



(6) In formulas III, IV, V, VII, VIII, IX, X and XI the group R represents the  $\alpha$ -N'-methyl-N-piperazinobenzyl radical



(1) R. Baltzly, E. Lorz, P. B. Russell and F. M. Smith, *THIS JOURNAL*, **77**, 624 (1955).

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

(3) R. Baltzly and P. B. Russell, *THIS JOURNAL*, **75**, 5598 (1953).

(4) H. Dahn, *et al.*, *Helv. Chim. Acta*, **35**, 1162, 1348, 2117 (1952).

(5) In this paper the *p*-toluenesulfonyl radical will be referred to as "tosyl" throughout.

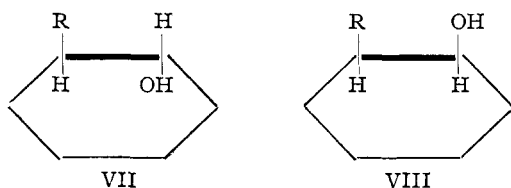
(7) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(8) J. Strating and H. J. Backer, *Rec. trav. chim.*, **69**, 638 (1950).

(9) R. Baltzly, S. DuBreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1949).

some other group in addition to the phenyl group is influencing the  $\alpha$ -(benzylic)-carbon atom. The double bond in the allylic position in III is admirably situated to provide this influence.<sup>10</sup> If the oily isomer has the structure III then the 85° melting compound must have structure IV.

Since the unsaturated compound IV is obtained pure and in good yield by elimination of *p*-toluenesulfonic acid from the 119° tosylate with bases, it follows that this elimination is essentially unilateral. Because such eliminations are known to involve hydrogen atoms at adjacent carbon atoms *trans* to the ester group,<sup>11,12</sup> it follows that the hydroxyl and the substituted benzyl residue must be *trans* to one another in the original alcohol, m.p. 101° (VII). As previously mentioned the rapid elimination in the direction indicated by the Saytzeff rule is characteristic of *cis*-alcohols, thus the 157° isomer is VIII.



The teachings of the above example may be applied to the determination of the configuration of other pairs of alcohols. Thus of the two alcohols, m.p. 104 and 131°, obtained by the reduction of crude 2-( $\alpha$ -N'-ethyl-N-piperazinobenzyl)-cyclohexanone, the lower melting isomer gave a tosylate, m.p. 120°, the higher melting isomer, on the other hand, gave an unsaturated compound on treatment with tosyl chloride in pyridine. The 104° isomer is thus the *trans*, while the 131° is the *cis* epimer. The single crystalline 2-( $\alpha$ -N'-methyl-N-piperazino-*m*-methoxybenzyl)-cyclohexanol, obtained by the reduction of the crude ketone, is assumed to be a *cis* compound since on treatment with tosyl chloride in pyridine an unsaturated compound was obtained. 2-( $\alpha$ -N'-Methyl-N-piperazino-*o*-chlorobenzyl)-cyclohexanone yielded only one crystalline alcohol on reduction. This, with tosyl chloride in pyridine, gave an ester and is therefore assigned the *trans* configuration.

2-( $\alpha$ -N-Piperidinobenzyl)-cyclohexanone gave a quantitative yield of crystalline material on reduction with lithium aluminum hydride.<sup>1</sup> By crystallization from hexane this material was separated into one pure isomer, m.p. 111–112°, and a crystalline material, m.p. 83–85°. The melting point of this last material was not changed by repeated crystallization and it was at first thought to be a second pure isomer. The alcohol, m.p. 111–112°, gave, with tosyl chloride in pyridine, a tosylate, m.p. 142°, in excellent yield. The 83–85° melt-

ing material on tosylation gave a poor (40%) yield of the same tosylate; it was therefore not homogeneous. Chromatography on alumina separated the 83–85° material into two pure compounds: one melting at 111°, the most mobile, was identical with the 111–112° isomer, while the other, removed from the column with ether but not hexane, melted at 93°. The original 83–85° melting material appeared to be an approximately equimolecular mixture of these two forms. The original mixture of epimeric compounds contained about 80% of the higher melting compound.

The tosylate, m.p. 142°, of the higher melting isomer gave an unsaturated compound, with loss of the elements of *p*-toluenesulfonic acid, on treatment with potassium *t*-butoxide. This on catalytic reduction yielded  $\alpha$ -N-piperidinobenzylcyclohexane identical with that prepared from the original tosylate by reduction with lithium aluminum hydride. It is believed that the 112° compound is a *trans* isomer. The 93° melting isomer was not esterified by tosyl chloride in pyridine, which might be expected if this is a *cis*-alcohol. Experience gained in the N-methylpiperazino series suggested that the presence of a strong tertiary base might aid tosylation. Accordingly the tosylation was carried out in the presence of triethylamine. A second tosylate, m.p. 129–130°, was isolated in small yield together with some alcohol and unsaturated compound.<sup>13</sup> Reduction of this isomer with lithium aluminum hydride gave  $\alpha$ -N-piperidinobenzylcyclohexane identical with the material prepared from the 142° tosylate by the same method.

It is worthy of note that in the piperidino compounds the *trans* isomer melts somewhat higher than the *cis*, while in the N-alkylpiperazino series this order is reversed. Further, in the latter series the difference in melting points is unexpectedly large (40–50°), and the *cis* isomer has a low solubility in hexane and in ether.

Information regarding the properties of isomers of the cyclohexane series cannot be applied rigidly to ring systems with a different number of carbon atoms. Thus although 2-( $\alpha$ -N'-methyl-N-piperazinobenzyl)-cyclopentanone gave two alcohols, m.p. 80 and 139°, on reduction, neither of these com-

(10) The removal of an oxygen or nitrogen in the allylic position to a double bond by hydrogenolysis has not been examined in a truly systematic manner as far as we are aware. There are, however, several examples to be found in the literature: R. Adams and E. F. Rogers, *THIS JOURNAL*, **63**, 537 (1941); D. H. Marrian, P. B. Russell, A. R. Todd and W. S. Waring, *J. Chem. Soc.*, 1365 (1947); I. Marszak and A. Marszak-Fleury, *Bull. soc. chim. France*, [5] **17**, 1305 (1950).

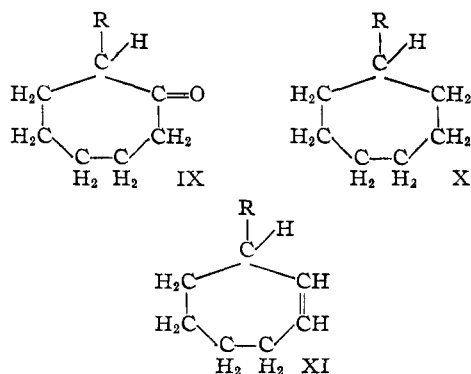
(11) W. Hüchel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940).

(12) P. D. Bartlett, in Gilman's "Organic Chemistry," Vol. III, John Wiley and Sons, New York, N. Y., 1953, p. 51.

(13) It would appear that base serves two functions here: to facilitate the tosylation and to initiate elimination through withdrawal of a proton. Little is known as to the mechanism of reactions of alcohols with sulfonyl chlorides. Pyridine generally has been regarded as merely a convenient solvent for sulfonations that also neutralizes the acid released in the reaction. More direct action is also possible perhaps through conversion of the alcohol to an anion. A point that troubled us initially is that the basicity of the nitrogen in the piperidino alcohols is not likely to be less than that of either nitrogen in the piperazine analogs. We are now of the opinion that (in these situations) steric availability may outweigh considerable disparity in abstract "basicity" (i.e., basicity measured against small detached acids). This result with the tosylation of the *cis*-piperidino alcohol suggests that not only is the far nitrogen of the piperazino alcohols more effective than the nitrogen of the piperidino alcohol and that of triethylamine in forming the tosylate, but also in the elimination therefrom. In models it can be seen that the tertiary proton that is readily removed in the piperazino series is completely shielded from a nitrogen in the benzylic position. Thus participation by this nitrogen within the same molecule will be impossible and approach of a similar nitrogen in a separate molecule is greatly hindered. Approach by the further nitrogen of a different molecule of the piperazino series should be much easier and, in particular, should be easier than approach by triethylamine (which was a convenient base for the experiment but perhaps not too fortunate a choice).

pounds gave a pure tosylate or a pure unsaturated compound on treatment with tosyl chloride in pyridine. By analogy with the melting points of compounds VII and VIII, of the cyclohexane series, the 80° melting isomer is tentatively called the *trans* and the 139° isomer the *cis*. Poor yields have not allowed a further investigation of this epimeric pair.

Reduction of the crystalline 2-( $\alpha$ -N'-methyl-N-piperazinobenzyl)-cycloheptanone (IX), gave mainly an alcohol, m.p. 147–148°. By repeated fractional crystallization a small quantity (*ca.* 5%) of a second alcohol, m.p. 103°, was isolated. The alcohol, m.p. 147–148°, on tosylation in the usual manner gave a tosylate, m.p. 133°, together with a considerable quantity of unsaturated compound. The latter on hydrogenation with Adams catalyst gave the saturated compound,  $\alpha$ -N'-methyl-N-piperazinobenzylcycloheptane (X), identical with the product obtained from the lithium aluminum hydride reduction of the tosylate. The unsaturated compound was therefore XI. It was also formed by the action of 2,6-lutidine on the tosylate, m.p. 133°.



By analogy with the corresponding cyclohexane derivatives described above, the alcohol, m.p. 147–148°, is assigned the *trans* configuration. It is obvious that elimination of the elements of *p*-toluenesulfonic acid from the corresponding tosylate, m.p. 133°, proceeds more easily than in the *trans*-cyclohexane series. Since both *cis*- and *trans*-cycloheptane-1,2-diols give boric acid complexes and cyclic isopropylidene compounds (with acetone)<sup>14</sup> it is evident that both configurations permit approximate coplanarity of two adjacent substituents. This line of argument, however, would lead one to predict a  $\Delta^1$ -cycloheptene derivative from both isomers. It may be that co-planar conformations are permitted between the 2- and 3-positions but are barred between the 1- and 2-positions by the bulk of the substituent at 1.

The  $\alpha$ -N'-alkyl-N-piperazinobenzylcycloalkanes and cycloalkenes described above were converted to their monoquaternary salts. Several of these salts were found to have atropine-like spasmolytic activity of quite a high order.<sup>15</sup>

#### Experimental

**Separation of the Epimeric 2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclohexanols.**—The basic fraction from the reduc-

tion of 2-( $\alpha$ -N'-methyl-N-piperazinobenzyl)-cyclohexanone (114.4 g.)<sup>1</sup> was dissolved in ether (*ca.* 150 ml.). On standing in the ice-box, crystals, m.p. 155°, separated. The ether was replaced with pentane and a further quantity of crystals of the same melting point separated (in all, 26.5 g.). The pentane liquors were evaporated to small bulk and on standing yielded a crop of needles (70 g.) melting at 95°. Several more crops of the same melting point were obtained by successive evaporations of solvent. Finally another crop of material, m.p. 154°, was obtained. Recrystallization of the 155° melting material several times from ether raised the melting point to 157°. The low-melting isomer, after several recrystallizations from hexane, melted at 101° (in all, about 80 g.). Before the analyses, which were reported in the earlier paper,<sup>1</sup> both isomers were sublimed at 0.1 mm. and *ca.* 100°.

Separation of other 2-( $\alpha$ -N'-alkyl-N-piperazinobenzyl)-cycloalkanol and related compounds was achieved in a similar manner. The physical constants and analyses of these compounds have been reported previously.<sup>1</sup> Table I gives the proportion of the *cis* and *trans* isomers.

TABLE I

PROPORTIONS OF EPIMERS RESULTING FROM REDUCTION OF 2-( $\alpha$ -AMINOBENZYL)-CYCLOALKANONES WITH LITHIUM ALUMINUM HYDRIDE

Alcohol	<i>trans</i> , %	<i>cis</i> , %
2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclohexanol	75	25
2-( $\alpha$ -N'-Ethyl-N-piperazinobenzyl)-cyclohexanol	78	22
2-( $\alpha$ -N'-Methyl-N-piperazino- <i>m</i> -methoxybenzyl)-cyclohexanol	<sup>a</sup>	25
2-( $\alpha$ -N'-Methyl-N-piperazino- <i>o</i> -chlorobenzyl)-cyclohexanol	60	<sup>a</sup>
2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclopentanol	60	15
2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cycloheptanol	92	5
2-( $\alpha$ -N'-Ethyl-N-piperazinobenzyl)-cycloheptanol	90	<sup>a</sup>
2-( $\alpha$ -N-Piperidinobenzyl)-cyclohexanol	80	20

<sup>a</sup> Not isolated in pure condition.

**The Separation of *cis*- and *trans*-2-( $\alpha$ -N-Piperidinobenzyl)-cyclohexanols.**—The above mixture of alcohols (26 g.), prepared by the reduction of 2-( $\alpha$ -N-piperidinobenzyl)-cyclohexanone,<sup>1</sup> was dissolved in a small amount of hexane and the solution allowed to stand. A crop of crystals (15 g.) separated. The mother liquors were decanted and evaporated to yield a second crop (*ca.* 8 g.) and then two further crops (*ca.* 3 g.) were obtained.

The first fraction gave on recrystallization 11 g. of crystals, m.p. 110–111°. This melting point was not elevated by further recrystallization. The mother liquors deposited crystals, m.p. *ca.* 80°. The second crop gave crystals, m.p. 82–84°, on recrystallization from hexane. The last crop of the original crystallization gave on recrystallization from hexane more 111° melting material.

In all, about 13 g. of the 111° melting compound and 10 g. of the 82–84° melting material were obtained. Recrystallization of 82–84° melting material did not change the melting point.

Tosylation (see below) of the 111° melting compound revealed that this was a pure compound. The 82–84° melting material gave about a 40% yield of the *same* tosylate and therefore was not pure. The components were separated by chromatography.

The 82–84° melting material (2 g.) was dissolved in hexane (25 ml.) and placed on a column of alumina. The chromatogram was developed with hexane. The runnings were collected in 100-ml. portions. The first four fractions all contained material, m.p. 111° (1.1 g.), the fifth fraction contained no solid. Further development with hexane gave nothing. The column was eluted with ether. The ether on evaporation gave prisms, m.p. 90–91° (*ca.* 0.7 g.), and these, after several recrystallizations from Skelly A, formed small needles, m.p. 92–93°.

**Tosylation of the *trans*-2-( $\alpha$ -N-Piperidinobenzyl)-cyclohexanol, M.p. 111°.**—The aminoalcohol (2.7 g.) and tosyl chloride (4 g., *i.e.*, 2.1 mols) were dissolved in dry pyridine (25 ml.). The solution was allowed to stand for 75 hours; at the end of this time it was reddish in color. It was poured onto ice (200 g.) and the mixture made alkaline with sodium carbonate. The oily material was extracted with ether, the ethereal extract was washed many times with water to

(14) P. H. Hermans and C. T. Maan, *Rec. trav. chim.*, **57**, 643 (1938).

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

TABLE II  
 TOSYLATES OF *trans*-2-( $\alpha$ -N'-ALKYLPYPERAZINOBENZYL)-CYCLOALKANOLS

Alcohol	M.p., °C.	Formula	Carbon, %		Hydrogen, %	
			Calcd.	Found	Calcd.	Found
2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclohexanol	119	C <sub>25</sub> H <sub>34</sub> O <sub>2</sub> N <sub>2</sub> S	67.9	67.5	7.7	7.9
2-( $\alpha$ -N'-Ethyl-N-piperazinobenzyl)-cyclohexanol	120	C <sub>26</sub> H <sub>36</sub> O <sub>2</sub> N <sub>2</sub> S	68.4	68.5	7.9	8.0
2-( $\alpha$ -N'-Methyl-N-piperazino- <i>o</i> -chlorobenzyl)-cyclohexanol	129	C <sub>25</sub> H <sub>32</sub> O <sub>2</sub> N <sub>2</sub> SCl	63.0	63.1	6.9	6.9
2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cycloheptanol	133	C <sub>26</sub> H <sub>36</sub> O <sub>2</sub> N <sub>2</sub> S	68.4	68.6	7.9	7.8

remove pyridine and finally dried over sodium sulfate. On evaporation of the ether the ester crystallized. After recrystallization from ether it melted at 141–142° (3.5 g.).

*Anal.* Calcd. for C<sub>25</sub>H<sub>34</sub>O<sub>2</sub>NS: C, 70.3; H, 7.7. Found: C, 70.2; H, 7.7.

**Tosylation of the *cis*-2-( $\alpha$ -N-Piperidinobenzyl)-cyclohexanol, M.p. 93°.**—This *cis*-alcohol was not tosylated under the conditions used for the *trans*, the bulk of the starting material being recovered unchanged.

The alcohol (2.7 g.), triethylamine (1.0 g., 1 mol), pyridine (20 ml.) and tosyl chloride (4 g.) were mixed and allowed to stand. The solution became red almost at once and some crystalline material began to separate. After four days the solution was poured onto ice. The ester was worked up in the manner described above. The residue after removal of the ether yielded small plates which melted at 129–130° after recrystallization from pentane (0.8 g.). The melting point of this isomer was depressed to 115–117° by the isomer, m.p. 141–142°.

*Anal.* Calcd. for C<sub>25</sub>H<sub>34</sub>O<sub>2</sub>NS: C, 70.3; H, 7.7. Found: C, 70.5; H, 7.6.

The residue after removal of the crystalline material gave an oil which appeared to be a mixture of the alcohol and its dehydration product.

The tosylates of the other *trans*-alcohols were prepared by the action of tosyl chloride in pyridine as in the first example. The esters are given in Table II.

**The Action of Tosyl Chloride in Pyridine on 2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cycloheptanol.**—When the aminoalcohol (10 g.) in pyridine (50 ml.) was treated with tosyl chloride (20 g.) the crystalline tosylate described above was isolated in small yield (2 g.). The main bulk of the product was an oil, b.p. 95–100° (0.2 mm.) (7 g.).

*Anal.* Calcd. for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>: C, 80.3; H, 9.9. Found: C, 80.2; H, 9.9.

This oil with ethyl iodide gave a quaternary salt which after recrystallization from acetone-ethyl acetate melted at 177° dec.

*Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>I: C, 57.3; H, 7.5. Found: C, 56.9; H, 7.8.

On reduction, the oily base gave  $\alpha$ -N'-methyl-N-piperidinobenzylcycloheptane, the ethiodide of which was identical with an authentic sample (see below).

The oily material from the tosylation was thus  $\alpha$ -N'-methyl-N-piperazinobenzylcyclohept-2-ene. It was also formed when the tosylate, m.p. 133°, was heated with 2,6-lutidine as described below.

**The Action of Tosyl Chloride and Pyridine on *cis*-2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)-cyclohexanol.**—The alcohol (17 g.), tosyl chloride (34 g.) and pyridine (100 ml.) were allowed to stand. After 24 hours crystals separated. A sample was removed. It was insoluble in organic solvents and soluble in water. These facts together with the analysis, point to its being a salt of the aminoalcohol with *p*-toluenesulfonic acid.

*Anal.* Calcd. for C<sub>25</sub>H<sub>36</sub>O<sub>4</sub>N<sub>2</sub>S: C, 65.2; H, 7.8. Found: C, 65.1; H, 8.1.

This salt was recombined with the pyridine solution and the mixture set aside at room temperature for a further 100 hours. The mixture was then poured onto ice and the solution basified with sodium carbonate. The oil was extracted with ether and the ethereal solution washed many times with water to free it from pyridine. After drying the solvent was removed and the residue distilled. It boiled at 90–95° (0.2 mm.) (11 g.) and was a colorless oil.

*Anal.* Calcd. for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>: C, 80.0; H, 9.6. Found: C, 80.0; H, 9.9.

With ethyl iodide an ethiodide, m.p. 185° dec., was obtained.

*Anal.* Calcd. for C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>I: C, 56.3; H, 7.3. Found: C, 56.3; H, 7.3.

With isopropyl iodide the base gave an isopropiodide, m.p. 189–190° dec.

*Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>I: C, 57.3; H, 7.5. Found: C, 57.2; H, 7.4.

**Hydrogenolysis of the above Base (2-( $\alpha$ -N'-Methyl-N-piperazinobenzyl)cyclohex-1-ene).**—The base (4 g.) was dissolved in methanol (50 ml.) containing acetic acid (1.0 ml.) and Adams catalyst added. The mixture was shaken under hydrogen. When the pressure drop represented the absorption of 2 mols of hydrogen the hydrogenation was stopped. The product was divided into neutral and basic fractions. The neutral fraction weighed 2.5 g. (*i.e.*, the theoretical for complete hydrogenolysis) and there was only a negligible water-insoluble basic fraction.

**$\alpha$ -N'-Ethyl-N-piperazinobenzyl- and  $\alpha$ -N'-Methyl-N-piperazino-*m*-methoxybenzylcyclohex-1-enes.**—These two bases were prepared by treatment of the corresponding *cis*-alcohols with tosyl chloride in pyridine as described above. The former boiled at 63–65° (2 × 10<sup>-3</sup> mm.).

*Anal.* Calcd. for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>: C, 80.3; H, 9.9. Found: C, 80.0; H, 10.0.

It gave an ethiodide, m.p. 211–212° dec.

*Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>I: C, 57.3; H, 7.5. Found: C, 57.0; H, 7.5.

The latter boiled at 70° (0.2 mm.).

*Anal.* Calcd. for C<sub>19</sub>H<sub>28</sub>ON<sub>2</sub>: C, 76.0; H, 9.3. Found: C, 75.9; H, 9.4.

It also gave an ethiodide, m.p. 193–194° dec.

*Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>ON<sub>2</sub>I: C, 55.3; H, 7.2. Found: C, 55.0; H, 7.1.

**$\alpha$ -N-Piperidinobenzylcyclohexane.**—The tosylate of *trans*-2-( $\alpha$ -N-piperidinobenzyl)-cyclohexanol (see above—4.25 g.) was added to a suspension of lithium aluminum hydride (0.9 g.) in dry ether (25 ml.). The solution was refluxed for about 12 hours and then, after cooling, the excess reagent was decomposed by addition of water. The ethereal solution was washed well with water and dried. Removal of the ether gave a colorless oil (2.7 g.) which boiled at 95–100° (0.2 mm.) (bath temp.).

*Anal.* Calcd. for C<sub>15</sub>H<sub>27</sub>N: C, 84.0; H, 10.5. Found: C, 84.0; H, 10.1.

The hydrochloride crystallized from methanol-ether in plates, m.p. 267–268°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>28</sub>NCl: C, 73.6; H, 9.5. Found: C, 73.7; H, 9.6.

Reduction of the tosylate of the *cis*-alcohol in the same manner gave the same product.

**$\alpha$ -N'-Methyl-N-piperazinobenzylcyclohexane** was prepared from the corresponding tosylate by reduction with lithium aluminum hydride as described above. The product, obtained in 75–80% yield, boiled at 95° (0.2 mm.) (bath temp.). The distilled oil crystallized and after recrystallization from pentane, melted at 72–73°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>: C, 79.4; H, 10.3. Found: C, 79.6; H, 9.9.

The base gave an isopropyl iodide, m.p. 195–196° dec., identical with the iodide prepared from an authentic sample.<sup>9</sup>

**$\alpha$ -N'-Methyl-N-piperazinobenzylcycloheptane** was prepared in a similar manner. The oil was converted to the ethiodide which after recrystallization from acetone-ethyl acetate melted at 181° dec.

*Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>I: C, 57.0; H, 7.9. Found: C, 56.8; H, 7.6.

**$\alpha$ -N-Piperidinobenzylcyclohex-2-ene.**—The tosylate of *trans*-2-( $\alpha$ -N-piperidinobenzyl)-cyclohexanol (2.5 g.) was

dissolved in *t*-butyl alcohol (15 ml.) and refluxed with a solution of potassium (1.0 g.) in *t*-butyl alcohol (60 ml.). After about 1 hour a crystalline precipitate (potassium *p*-toluenesulfonate) began to separate. The reflux was continued for 15 hours and then the *t*-butyl alcohol was removed *in vacuo*. The residue was partitioned between water and ether, the ether layer washed well with water and then extracted with 2 *N* hydrochloric acid. Basification of the acid solution gave a colorless oil which boiled at 80° (0.1 mm.) (1.7 g.).

*Anal.* Calcd. for  $C_{18}H_{23}N$ : C, 84.7; H, 9.7. Found: C, 84.7; H, 9.8.

The hydrochloride melted at 248–249° dec.

*Anal.* Calcd. for  $C_{18}H_{26}NCl$ : C, 74.1; H, 8.9. Found: C, 74.4; H, 9.1.

The same compound was obtained when the tosylate was heated with 2,6-lutidine for 48 hours.<sup>16</sup>

Catalytic reduction of the hydrochloride with Adams catalyst gave the hydrochloride of  $\alpha$ -N-piperidinobenzylcyclohexane identical with the previously described sample.

$\alpha$ -N'-Methyl-N-piperazinobenzylcyclohex-2-ene was prepared in an exactly similar manner from the corresponding tosylate both with potassium *t*-butoxide and with 2,6-lutidine. After distillation (b.p. 65–70° ( $2 \times 10^{-3}$  mm.)) it

(16) In these hindered systems the use of a bulky base for the eliminations may not be necessary. In model experiments with cyclohexyl *p*-toluenesulfonate the superiority of *t*-butoxide to methoxide was marked. Diethylaniline and benzyldimethylamine in the absence of solvents did not react cleanly.

One-tenth mole portions of cyclohexyl *p*-toluenesulfonate were refluxed three hours with 0.3 mole of methanolic potassium hydroxide and sodium methoxide and with sodium *t*-butoxide in *t*-butyl alcohol. The reaction mixtures were steam distilled until a boiling point of 100° was reached and the distillates were made up to volume with methanol. Cyclohexene was then estimated by catalytic reduction of aliquots. In the reaction with *t*-butoxide 95% of the calculated quantity of cyclohexene was formed while in the other two cases the yield was 57%.

solidified and melted at 85° after recrystallization from pentane.

*Anal.* Calcd. for  $C_{18}H_{23}N_2$ : C, 80.0; H, 9.6. Found: C, 80.1; H, 9.6.

The ethiodide melted at 180–181° dec.

*Anal.* Calcd. for  $C_{20}H_{21}N_2I$ : C, 56.3; H, 7.3. Found: C, 56.2; H, 7.2.

The isopropyl iodide melted at 217–220° dec.

*Anal.* Calcd. for  $C_{21}H_{23}N_2I$ : C, 57.3; H, 7.5. Found: C, 57.2; H, 7.7.

The ethyl *p*-toluenesulfonate melted at 107–108°.

*Anal.* Calcd. for  $C_{27}H_{30}O_2N_2S$ : C, 68.9; H, 8.1. Found: C, 68.8; H, 8.3.

$\alpha$ -N'-Methyl-N-piperazinobenzyl- and  $\alpha$ -N'-Ethyl-N-piperazinobenzylcyclohept-2-ene were prepared by heating the corresponding tosylates with 2,6-lutidine. The former compound is described above. The latter (prepared from crude tosylate-unsaturated compound mixture) boiled at 85–90° (0.1 mm.).

*Anal.* Calcd. for  $C_{20}H_{23}N_2$ : C, 80.5; H, 10.1. Found: C, 80.3; H, 10.0.

The ethiodide melted at 200° dec.

*Anal.* Calcd. for  $C_{22}H_{25}N_2I$ : C, 58.1; H, 7.7. Found: C, 58.2; H, 7.9.

Hydrogenation of the above base gave  $\alpha$ -N'-ethyl-N-piperazinobenzylcycloheptane, b.p. 85° (0.1 mm.).

*Anal.* Calcd. for  $C_{20}H_{27}N_2$ : C, 80.0; H, 10.7. Found: C, 79.6; H, 10.5.

The ethiodide melted at 160–161°.

*Anal.* Calcd. for  $C_{22}H_{27}N_2I$ : C, 57.9; H, 8.1. Found: C, 58.1; H, 8.4.

The authors wish to thank Mr. S. W. Blackman for the microanalyses reported here.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

## The Preparation of N-Benzyl-3-morpholones and N-Benzyl-3-homomorpholones from N-(Hydroxyalkyl)-chloroacetamides

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RECEIVED AUGUST 27, 1954

The preparation and cyclization of some N-benzyl-N-(2-hydroxyethyl)-chloroacetamides to give N-benzyl-3-morpholone derivatives is described. A one-step process for the formation of the latter from N-benzylethanolamines also is reported. The homologous N-benzyl-3-homomorpholones have been prepared by cyclization of N-benzyl-N-(3-hydroxyalkyl)-chloroacetamides.

As part of our search for amebicidal agents<sup>1</sup> we prepared a series of N-benzyl-N-(2-hydroxyethyl)-chloroacetamides (I) which are listed in

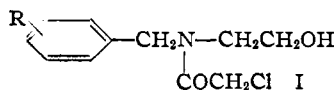
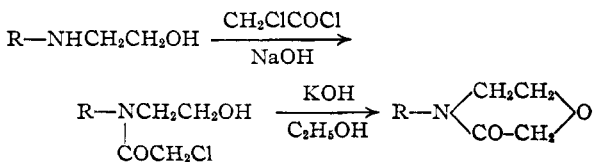


Table I. These compounds were prepared from the appropriate N-benzylethanolamines by acylation with chloroacetyl chloride in the presence of an equivalent amount of dilute sodium hydroxide solution. When tested in hamsters<sup>2</sup> the monochloroacetamides were found to be active but considerably less active than the corresponding dichloroacetamides reported previously.<sup>1</sup> The same was found true for the N-(2,4- and 3,4-dichlorobenzyl)-N-(2-hydroxypropyl)-chloroacetamides.

(1) A. R. Surrey, *THIS JOURNAL*, **76**, 2214 (1954).

(2) We are indebted to Dr. D. A. Berberian for the amebicidal screening.

Since these N-(2-hydroxyalkyl)-chloroacetamides were available, it seemed of interest to see if they could be cyclized to yield 3-morpholones to make them available for biological investigation. It was found that ring-closure could indeed be effected by treatment with alcoholic potassium hydroxide at room temperature. The N-benzyl-3-morpholones prepared by this procedure are reported



in Table II, and the N-(2,4- and 3,4-dichlorobenzyl)-6-methyl-3-morpholones are described in the Experimental part.

Attempts to effect cyclization using potassium carbonate, sodium acetate or triethylamine in