Anal. Calcd. for C_8H_8ClBr: Cl, 16.16. Found: 16.00.

1,3-Xylyl-5-bromo-4-nitrile, $C_6H_2(CH_3)_2BrCN$.—The bromoxylidine was converted into the nitrile by the Gattermann-Sandmeyer reaction. In the distillation with steam the nitrile crystallized in the condenser, from which it was removed with hot alcohol. It crystallized in needles which melted at 86–87°. A by-product appeared in the receiver. It boiled at 205° and was therefore regarded as 5-bromo-1,3-dimethylbenzene.

Anal. Calcd. for C_9H_8BrN: Br, 38.05. Found: 38.00.

1-(5-Bromo-1,3-xylyl-4-azo)-2-naphthol, $C_6H_2(CH_3)_2BrN_2C_{12}H_6OH$.—The bromoxylidine was diazotized and coupled with 2-naphthol in the presence of sodium hydroxide. The crude red precipitate melted at 132°. Recrystallization from a mixture of alcohol and petroleum ether gave rich red needles melting at 136°.

Anal. Calcd. for $C_{18}H_{15}ON_2Br$: Br, 23.50. Found: 23.15.

1-(5-Bromo-1,3-xylyl-4-azo)-4-phenol, $C_6H_2(CH_3)_2BrN_2C_6H_4OH$.—On coupling phenol with diazotized bromoxylidine a dark yellow precipitate formed; weight 3 g. from 2 g. of the xylidine. It was recrystallized from 90% acetic acid, or from a mixture of 3 parts of benzene and 7 parts of alcohol, to give small orange-colored crystals which melt at 166°.

Anal. Calcd. for $C_{14}H_{13}ON_2Br$: Br, 26.20. Found: 26.14.

Summary

1. The preparation of 4-amino-5-bromo-1,3-dimethylbenzene was improved upon.

2. Its hydrochloride and benzoate are described.

3. The methyl and ethyl ethers of the bromoxylenol were prepared.

4. The amino group was replaced by Cl and by CN.

5. Two azo dyes were made by coupling the diazotized bromoxylidine with phenol and with 2-naphthol.

CHAPEL HILL, NORTH CAROLINA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYNTHETIC HOMOLOGS OF *d,l*-EPHEDRINE

BY J. F. HYDE,[1] E. BROWNING[1] AND ROGER ADAMS

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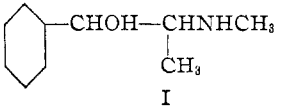
The interesting and important drug, ephedrine (I) has in recent years been brought to the attention of the medical profession and has become widely used chiefly through the brilliant investigations of Dr. K. K. Chen.[2] Although a careful comparison of the pharmacological action of *l*-ephedrine with *d,l*-ephedrine and pseudo-ephedrine has been completed, no study has as yet been made of the comparative values of *l*-ephedrine or *d,l*-ephedrine with a series of homologs, particularly those in which an

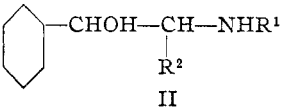
[1] Portions of theses of J. F. Hyde and E. Browning submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Chen and Kao, *J. Am. Pharm. Assocn.*, **15**, 625 (1926). At the end of this article is given a bibliography of chemical, pharmacological and medical articles on ephedrine.

alkyl group other than methyl is found on the nitrogen or on the β-carbon atom from the benzene ring.

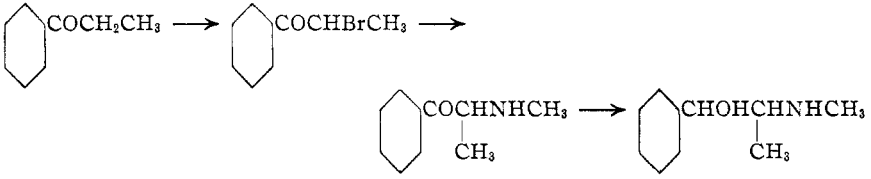


I



II

In this investigation a series of racemic compounds of the general formula (II) has been prepared where R^1 is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl or *n*-amyl, and where R^2 is hydrogen, methyl, ethyl or *n*-propyl. In addition, one or two compounds were made in which both hydrogens of the nitrogen were replaced by alkyl groups. The methods of synthesis of *d,l*-ephedrine have been reviewed in the article of Chen previously referred to and so need not be repeated here. It is sufficient to say that for this work no attempt was made to find the process which might prove the most advantageous from a commercial standpoint, but merely the one which could be used most conveniently in the laboratory for obtaining small quantities of material. The one selected for the preparation of *d,l*-ephedrine and then applied to the preparation of its homologs was first described by Eberhard[3] and later repeated by Fourneau and Kanao[4] and Fourneau and Torres.[5] This consists in the bromination of propiophenone to a bromopropiophenone, condensation with methylamine to form the α-methylaminopropiophenone, and finally reduction to the corresponding amino alcohol. It is reported that if sodium amalgam was used as a reducing agent in the last step, a mixture of *d,l*-ephedrine and pseudo-ephedrine was usually formed. With palladium and hydrogen, however, Eberhard obtained *d,l*-ephedrine.



In this investigation *d,l*-ephedrine was first synthesized and the work carried out by H. A. Graffis. No particular comments are necesssary on the bromination. In the second step, however, the method of purification of the α-methylaminopropiophenone is worthy of mention, since the purity is important for the success of the subsequent reduction. The reaction mixture containing α-methylaminopropiophenone hydrochloride and excess methylamine hydrochloride was evaporated to dryness in a vacuum. The crude mixture obtained was extracted several times with chloroform, which left methylamine hydrochloride insoluble and dissolved

[3] Eberhard, *Arch. Pharm.*, **253**, 62 (1915).

[4] Fourneau and Kanao, *Bull. soc. chim.*, [4] **35**, 614 (1924).

[5] Fourneau and Torres, *Anales soc. españ. fís. quím.*, **23**, 450 (1925).

the amino ketone hydrochloride. The latter was recrystallized and reduced by means of hydrogen and platinum-oxide platinum black to the amino alcohol.

This method of catalytic reduction proved to be an excellent procedure, not only on account of its convenience for the production of amino alcohol but also because apparently just one of the two possible isomeric amino alcohols resulted. The product isolated proved to be exclusively *d,l*-ephedrine, which was essentially pure after one crystallization.

The various homologs in which the alkyl group attached to the β-carbon atom was varied in size were made in the same general manner as that used for ephedrine, except that acetophenone, butyrophenone, valerophenone, etc., were halogenated in place of propiophenone and the subsequent steps carried out with these halogenated products.

In the series in which merely the alkyl group on the nitrogen was varied, the method of isolation of the amino ketones had to be modified because the excess alkylamine hydrochloride was soluble in chloroform. In this case the mixture of the amino ketone and excess of alkyl amine was isolated and the excess of the amine removed by distillation *in vacuo* at room temperature.

Dr. E. C. Kendall of the Mayo Clinic has kindly made tests on the amino ketones and amino alcohols to determine the effect of the compounds on blood sugar. His detailed results will be published elsewhere but it is sufficient to remark here that in the series where the methylamino group remains constant and the alkyl group on the β-carbon atom is varied in size (in formula II, R^1 is methyl and R^2 varies from hydrogen to *n*-propyl) the molecule where the $R^2 = H$ is the most effective, and the increase in blood sugar becomes less as the group is varied from methyl to propyl. On the other hand, if the alkyl group on the β-carbon atom remains a methyl and the alkyl group on the nitrogen is varied in size (in formula II, R^2 is methyl and R^1 varies from methyl to *n*-amyl) the blood sugar steps up with the increase in the number of carbon atoms in the alkyl group. The butyl and amyl derivative cause convulsions and respiratory paralysis following the injection. Those substances in which two hydrogens of the nitrogen were replaced by alkyl groups showed no physiological effect.

The ketones corresponding to the effective alcohols gave essentially the same results as the alcohols in the effect on blood sugar.

The amount of blood sugar increase was dependent to a certain extent on the size of the dose.

The effect of these products on blood pressure was ascertained by Mr. C. Nielsen and assistants of the Abbott Laboratories, North Chicago, Illinois. They report that of the various homologs only one caused any marked rise in blood pressure. It was the homolog of ephedrine in which

the methyl group of the β-carbon atom was replaced by hydrogen. Practically all of the others either caused merely a very slight rise in blood pressure preceded usually by a fall, or else caused a direct fall in blood pressure. The results were not of sufficient regularity to warrant drawing quantitative conclusions concerning this physiological effect.

These compounds are now being studied by Dr. K. K. Chen in order to determine their possible medical value as compared with *l*-ephedrine.

Experimental

Brominated Ketones.—The procedure for the preparation was that of Schmidt,[6] according to which the ketone is brominated in glacial acetic acid.

α-Bromo-*n*-valerophenone.—As this substance has not previously been described in the literature, it may be mentioned that it is a straw-colored liquid boiling at 150° at 2.5 mm.; n_D^{20}, 1.5600; d_4^{20}, 1.3993.

Reaction of the Bromo Ketones with Methylamine.—One-tenth of a mole of the bromo ketone was added drop-wise with vigorous stirring to 0.25 mole of methylamine (in the form of a 30% solution in absolute alcohol) over the required period of time (one hour for bromopropiophenone, seventeen to eighteen hours for α-bromobutyrophenone, twenty-four hours for α-bromovalerophenone). The reaction flask was immersed in ice water during the reaction and stirring was continued for one-half to three-quarters of an hour after the addition of the bromo compound. Cold, concd. hydrochloric acid was then added very slowly along with some finely cracked ice until the mixture was acidic. If it became warm the product turned very dark in color and a larger proportion of tar was produced. At this point the reaction mixture was orange or red due to the presence of some bromo ketone that had not reacted and to the formation of certain tarry by-products. These were extracted with ether from the water layer and the bromo ketone recovered. The water layer was evaporated to dryness *in vacuo*, treated with a little chloroform and evaporated to dryness again to assist in removing the moisture from the rather hard mass. After standing in a vacuum desiccator for a day, the residue was extracted several times with fresh portions of chloroform and each time the insoluble crystals of methylamine hydrochloride were filtered. The chloroform solution was then evaporated until it was very concentrated, and acetone was added to cause the crystallization of the amino ketone hydrochloride. Recrystallization was carried out by dissolving in a small amount of alcohol, filtering, and adding about twice the volume of acetone in small portions.

In the condensation of chloro-acetophenone with methylamine, the reaction was carried out in essentially the same way as the one just described for the bromo ketones except that the chloro-acetophenone was added in the form of a powder and allowed to react with the alcoholic methylamine for a period of five to six hours.

For the preparation of the alkylamino ketones in which a group larger than methyl was attached to the nitrogen, a slightly different procedure was used. A 50% aqueous solution of the amine was cooled down carefully to 5–10° in an ice-bath and previously cooled bromo ketone was added slowly with mechanical stirring in the ratio of 1 mole of bromo ketone to 2 moles of amine. The reaction product was allowed to stand and to come to room temperature and the stirring continued until no layer of unreacted bromo ketone separated upon standing. The reaction mixture was then cooled and an excess of concd. potassium hydroxide solution was added slowly with stirring, the temperature not being permitted to rise above 15–20°. The amino ketone and excess alkylamine separated and were extracted with ether and the ether solution was washed with water.

[6] Schmidt, *Ber.*, **22**, 3251 (1889).

Upon evaporation of the ether and then warming the residue *in vacuo* to a temperature not over 40°, the excess alkylamine was removed. The residual amino ketone was dried with solid potassium hydroxide, taken up in dry ether, cooled thoroughly and dry hydrogen chloride passed in with stirring. In the course of a few minutes the hydrochloride of the amino ketone began to crystallize.

These hydrochlorides were purified by first digesting with hot acetone and filtering. This helped to remove the color. The hydrochlorides were crystallized from ethyl acetate containing a small amount of ethyl alcohol (3–10%, depending upon the product being prepared), or from alcohol by addition of some acetone as described under the crystallization of the amino ketone hydrochlorides.

In the condensation of chloro-acetophenone with *n*-butylamine, the powdered chloro compound was added to 2.5 times the quantity of anhydrous *n*-butylamine over a period of seven hours and stirring continued for three hours more. The reaction flask was cooled well during this time. The reaction product was worked up in the same manner as previously described for the condensation of various amines other than methylamine with the halogenated ketones.

If any decomposition occurred during the formation of the amino ketones, the hydrochlorides invariably separated as oils which crystallized only with great difficulty. In one or two instances it was found possible to vacuum distil the amino ketone base in an atmosphere of nitrogen, but ordinarily this procedure is not to be recommended because some decomposition always takes place.

In condensing bromobutyrophenone with di-*n*-butylamine, the reaction was carried out by adding the bromo ketone to the amine in the proportion of 1 to 3 moles, respectively. Stirring was continued and no attempt was made to cool the reaction mixture. The crystals of di-*n*-butylamine hydrobromide were filtered and washed with ether. The ether solution was worked up as previously described. The hydrochloride separated as a red, sirupy mass. After drying it in a vacuum desiccator, it was dissolved in a little dry acetone and by adding small amounts of ether a solid product was obtained and purified.

TABLE I

SUBSTITUTED α-AMINO PROPIOPHENONES

$C_6H_5COCH(R)NHCH_3$ R =	M. p., °C. HCl salt	Yield, %	Analyses, % Cl Calcd.	Found
H[7]	219	23	...	...
CH_3[2]	176–177	57	...	...
C_2H_5	190–192	33	16.63	16.86
n-C_3H_7	183.5–184.5	39	15.60	15.64
$C_6H_5COCH_2NHC_4H_9(n)$	214–215	35	15.58	15.60
$C_6H_5COCHN(C_4H_9(n))_2CH_2CH_3$	138–140	30	11.32	11.26
$C_6H_5COCH(CH_3)NHR$ R =				
C_2H_5	183	30	16.60	16.60
C_3H_7	180	35	15.59	15.04
iso-C_3H_7[8a]	213–213.5	51	15.59	15.52
n-C_4H_9[8b]	158–159	39	14.68	14.60
n-C_5H_{11}	150	41	13.89	13.64
$C_6H_5COCH(CH_3)N(C_2H_5)_2$	167–168	25	14.68	14.45

[7] Almström, *Ann.*, **409**, 300 (1915); Gabriel, *Ber.*, **47**, 1337 (1914).

[8] (a) B. p. of free base 105–110° at 3 mm.; (b) b. p. of free base 140–142° at 8 mm. with some decomposition.

Reduction of Amino Ketones to Amino Alcohols.—The amino ketones were dissolved in ordinary ethyl alcohol in the proportion of 0.1 mole of ketone to 50–100 cc. of solvent and 0.1 g. of platinum oxide[9] was added. The reductions were carried out under a pressure of 30–40 pounds and the calculated amount of hydrogen was always absorbed. The rate of reduction depended upon the purity of the amino ketone hydrochlorides. In general the time ran from twenty minutes to six hours in the compounds studied. The products were removed from the reaction mixture merely by filtration of the catalyst and evaporation to a concd. solution. They were recrystallized either by dissolving in absolute alcohol and adding acetone to the hot solution to the point where precipitation just started, or from ethyl acetate containing a few per cent. of ethyl alcohol. The products were generally pure after one crystallization and the yields amounted to about 90%.

TABLE II

α-PHENYL β-METHYLAMINO ALKANOLS

$C_6H_5CHOH\overset{R}{\overset{\vert}{C}}HNHCH_3$ R =	M. p., °C. HCl salt	M. p., °C. Base	Analyses, % Cl Calcd.	Found
H[10]	105–106	75–76	18.90	18.79
CH_3[2]	189–190	76–77	...	...
C_2H_5	201–202	89–90	16.46	16.31
n-C_3H_7	224–225	76–77	15.46	15.46
$C_6H_5CHOHCH_2NHC_4H_9(n)$	218–220	58–59	15.46	15.41
$C_6H_5CHOHCHN(C_4H_9(n))_2C_2H_5$	114–116	...	11.32	11.88
$C_6H_5CHOHCH(CH_3)NHR$ R =				
C_2H_5	190–191	...	16.47	16.26
C_3H_7	218	...	15.51	15.38
iso-C_3H_7	193	...	15.51	15.79
n-C_4H_9	220–221	...	14.55	14.43
n-C_5H_{11}	219	...	13.79	13.91
$C_6H_5CHOHCH(CH_3)N(C_2H_5)_2$	205–206	...	14.55	14.46

Summary

A series of homologs of *d,l*-ephedrine has been prepared in which the alkyl group on the nitrogen has been varied from methyl to *n*-amyl; a series in which the alkyl group on the β-carbon has been replaced by H, ethyl and *n*-propyl and two compounds in which the alkyl groups are present on the nitrogen.

Blood sugar is increased as the alkyl group on the nitrogen is made larger; blood sugar is decreased as the alkyl group on the β-carbon is increased in size; the ketones showed a similar action; the dialkylamino compounds produced no physiological action.

The only homolog which gave a dependable increase in blood pressure was the α-phenyl β-methylamino-ethanol.

URBANA, ILLINOIS

[9] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923). See "Organic Syntheses," Vol. VIII, John Wiley and Sons, New York, **1928**, for complete details of apparatus and catalyst.

[10] Barger and Dale, *J. Physiol.*, **41**, 19 (1910).