sistent, and this disagreeable odor becomes more acute with continued exposure to the compound or its vapors. Some individuals appear to have an idiosyncrasy toward the vapor of organic mercurials, and are distinctly more affected than others.

Summary

Some improvements in the preparation of mercury dialkyls from mercuric chloride and the Grignard reagent make this synthesis the best for such compounds on a laboratory scale.

Miscellaneous observations have been reported on the stability, physiological action and behavior toward magnesium halides of mercury dialkyls and mercury diphenyl.

AMES, IOWA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME]

AMINO-ALCOHOLS. II. HOMOLOGS AND ANALOGS OF PHENYLPROPANOLAMINE

BY WALTER H. HARTUNG, JAMES C. MUNCH, W. ALLAN DECKERT AND FRANK CROSSLEY

RECEIVED MAY 1, 1930 PUBLISHED AUGUST 5, 1930

The preparation of phenylpropanolamine and its *p*-methyl derivative by reduction of the corresponding oximino ketones has been described.[1] By employing the same technique, it has been possible to prepare other members of the arylalkanolamine series from phenylethanolamine to phenyloctanolamine. Diphenylethanolamine was prepared by the catalytic reduction of benzoin oxime, both the α- and β-oximes yielding the amino-alcohol melting at 165°.

Procedure

The higher intermediate oximino ketones were prepared according to the method already described for isonitrosopropiophenone and its *p*-methyl derivative, with uniformly good results, although the longer the alkyl side chain, the poorer the yields of purified isonitroso ketone. The lower yields are probably caused by complications attending isolation of the product rather than by incomplete nitrosation, for in no case was it possible to recover unchanged ketone.

Isonitroso-acetophenone was best obtained according to the directions of Claisen and Manasse[2] by allowing butyl nitrite and acetophenone to react in an absolute alcoholic solution containing sodium ethoxide. The method which gave such excellent results with propiophenone and its higher homologs gave very poor yields with acetophenone—6 to 12%.

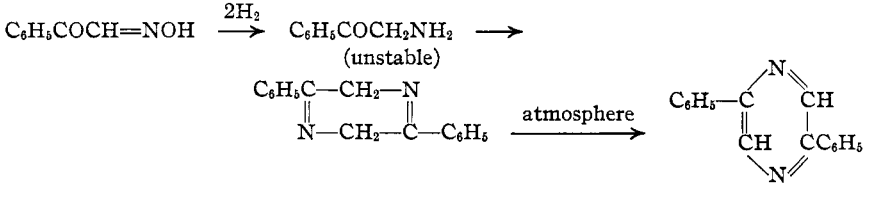
[1] Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929).

[2] Claisen and Manasse, *Ber.*, **20**, 2194 (1887).

Alpha- and β-benzoin oximes were prepared and separated according to the directions of Werner and Detscheff.[3]

The conversion of the oximino ketones, by means of palladium, into the corresponding amino-alcohols by hydrogenation in absolute alcoholic solution containing three equivalents of hydrogen chloride has already been described in connection with the preparation of phenylpropanolamine.[1] This process served equally well for the reduction of the higher homologs and of the benzoin oximes. The products were obtained as their hydrochlorides, from which the free bases could be isolated. The yields were good.

Isonitroso-acetophenone, however, was not so readily reduced to phenylethanolamine, for in only one instance was it possible to go directly from oximino ketone to amino-alcohol; in all other attempts the reduction stopped at the amino ketone stage; this intermediate product was then isolated as hydrochloride and further reduced in aqueous solution by means of fresh catalyst to the desired amino alcohol. When isonitroso-acetophenone was reduced in the absence of hydrogen chloride a product was obtained which after removal of the catalyst and allowing the alcoholic filtrate to stand exposed to the atmosphere melted at 195–196° and corresponded with the diphenylpyrazine described by Braun and Meyer.[4] The formation of this compound may readily be accounted for in the following manner



for Gabriel[5] has pointed out how free amino ketones spontaneously form dihydropyrazines and how readily these are in turn oxidized to the stable pyrazine derivatives.

Pharmacological

All of these compounds are of physiological interest by virtue of their relation to ephedrine and ephedrine-like substances. In the first paper it was pointed out that the pharmacodynamic activity of primary amino-alcohols of the type $ArCHOHCHRNH_2$ merited a more detailed study, and since then Chen and his co-workers,[6] have justified this prediction by showing that primary amino derivatives of the sympathomimetric type are, in general, more potent as pressors than the corresponding methylamino

[3] Werner and Detscheff, *Ber.*, **38,** 72 (1905).

[4] Braun and Meyer. *ibid.*, **21,** 19 and 1269 (1888).

[5] Gabriel, *ibid.*, **41,** 1143 (1908).

[6] Chen, Wu and Henriksen, *J. Pharmacol.*, **36,** 363 (1929).

derivatives; thus Chen[7] points out that *dl*-phenylpropanolamine is a stronger pressor than *dl*-phenylpropanol-methylamine (*dl*-ephedrine). Our present interest in compounds of the ephedrine and adrenaline type has been centered chiefly on the primary rather than on the methylated amines.

The compounds prepared and studied are given in Table I. Since a more complete pharmacological report will be published elsewhere, a brief review of the hypertensive properties will suffice here. Phenylethanolamine (I) has already been somewhat extensively investigated.[8] The physiological action of phenylpropanolamine and its *p*-methyl derivative (II and III) has already been described;[1,9] a correction should, however, be made as to the pressor activity of *p*-tolylpropanolamine, which has been found since our previous paper to be about three-fifths as active as phenylpropanolamine. Phenylbutanolamine (IV) has been investigated by Chen, Wu and Henriksen,[6] and found to possess comparatively very low activity on decerebrate cats, which observation has been confirmed by our results on anesthetized dogs. Phenylhexanolamine hydrochloride (VII) administered intravenously to an anesthetized dog in doses of 10 mg./kg. caused a marked fall in blood pressure, that persisted for about thirty minutes and was followed by a gradual rise which after several hours reached a new level as much above as the fall was below normal. The remaining members of the series show no pressor effect within the range of doses thus far tried.

TABLE I

PHARMACOLOGICAL DATA

	Amino-alcohol $ArCHOHCH(NH_2)R$		Minimum lethal dose of hydrochloride, mg./kg.	
	Ar =	R =	Subcutaneous to guinea pigs	Intravenous to rabbits
I	C_6H_5	H	1000	90[b]
II[a]	C_6H_5	CH_3	600	75
III[a]	$C_6H_4Me(p)$	CH_3	175	33
IV	C_6H_5	C_2H_5	250	60
V	$C_6H_4Me(p)$	C_2H_5	150	25
VI	C_6H_5	$C_3H_7(n)$	300	40
VII	C_6H_5	$C_4H_9(n)$	250	20
VIII	C_6H_5	$C_6H_{13}(n)$	450	10
IX	C_6H_5	C_6H_5	450	60

[a] Repeated for comparison. [b] Alles, *J. Pharmacol.*, **32**, 121 (1927), gives this dose as 30 mg./kg.

From these results it appears that pressor activity is associated with compounds having the general formula ArCHOHCHRNH—, but this activity is exerted at its best when the side chain contains two or three carbons.

[7] Chen, Ref. 6, p. 394.

[8] *Cf.* Gordon, *J. Am. Pharm. Assn.*, **17**, 1195 (1928), and bibliography; Tainter, *J. Pharmacol.*, **36**, 29 (1929).

[9] See also Chen, *ibid.*, **36**, 394 (1929).

If to phenylpropanolamine (II) a methyl is added to the amino group (ephedrine) or to the aromatic nucleus (III), its pressor activity is modified but not destroyed, whereas by adding the methyl to the end of the side chain (IV), this potency has been so diminished as practically to be eliminated. The peculiar behavior of phenylhexanolamine is being further investigated.

Considering the series as a whole, the most striking fact is the ability of the organism to respond so readily and characteristically to what the chemist may ordinarily consider as correspondingly minor changes. All the members of this series contain substantially the same chemically active groupings and give essentially the same type of reactions, yet the organism is capable of responding readily to a change in molecular structure which could, by purely chemical means, be substantiated only with the greatest effort and difficulty. The explanation for such selectivity on the part of an organism in a series of this kind would be most desirable and an invaluable contribution to our present limited and confused knowledge of the relationship between physiological activity and chemical structure.

A survey of the toxicities reveals no parallelism between the two methods of determination. There is, however, a remarkable regularity of increase in the toxicity on intravenous administration of the phenylalkanolamines with increase in length of the side chain. Another striking fact is the much greater toxicity of the *p*-tolyl derivatives (III and V) as compared with the corresponding phenyl products (II and IV), which lends support to the observation of de Burnaga Sanchez[10] that *p*-methylephedrine is about 20% more toxic than ephedrine.

Experimental

The ketones were all prepared by the Friedel–Crafts reaction from the appropriate acid chloride and benzene or, in the case of the tolyl ketones, toluene. All, with one exception, are described in Beilstein.

Octanophenone (phenyl heptyl ketone) is a liquid, having an odor characteristic of the series, which boils at 140–145° (5 mm.) or 150–153° (7 mm.); it forms a semicarbazone which may be recrystallized from benzene–ligroin mixture and melts at 125.0–125.5°.

The isonitroso ketones, with analyses, are given in Table II.

TABLE II
ISONITROSOKETONES

Oximino ketone	Yield, %	M. p., °C.	Nitrogen, % Found (Kjeldahl) I	II	Calcd.
Isonitrosobutyrophenone[a]	50	49	8.03	7.98	7.91
p-Methylisonitrosobutyrophenone	50	78	7.53	7.56	7.33
Isonitrosopentanophenone	69	69	7.49	....	7.33
Isonitrosohexanophenone	55–60	53–54	7.07	7.05	6.83
Isonitroso-octanophenone	25	38.5	5.88	5.83	6.0

[a] This compound was isolated but not purified by Müller and v. Pechmann, *Ber.*, **22**, 2131 (1889).

[10] De Burnaga Sanchez, *Bull. soc. chim.*, [4] **45**, 284 (1929).

Table III contains a summary of the data obtained on the amino-alcohols.

TABLE III

AMINO-ALCOHOLS

No.	Amino-alcohol	M. p., °C.	Nitrogen, % Found	(Kjeldahl)	Calcd.
1	Phenylbutanolamine[a]	80.5–81.0	..	..	..
2	*p*-Tolylbutanolamine	85.0	7.77	7.89	7.82
3	Phenylpentanolamine[a]	70–71	..	..	..
4	Phenylhexanolamine[a]	72.0–72.5	..	..	..
5	Phenyloctanolamine[b]	79	..	..	..

HYDROCHLORIDE

No.	M. p., °C.	Chlorine, % Found, (AgCl) I	II	Calcd.
1	242	17.59	17.60	17.59
2	255	16.32	16.42	16.47
3	222	16.56	16.76	16.47
4	197.5–198.0	15.61	...	15.54
5	157.5	13.77	13.45	13.79

[a] These products were prepared by Tiffeneau and Lévy [*Bull. soc. chim.*, [4] **37**, 1247 (1925); *Compt. rend.*, **183**, 969 (1926)], according to the method

$$C_6H_5CHOHCN \text{ (or } C_6H_5CHOHCONH_2) \xrightarrow{RMgX} C_6H_5CHOHCOR \xrightarrow{H_2NOH}$$

$$C_6H_5CHOHCR{=}NOH \xrightarrow{H_2} C_6H_5CHOHCHRNH_2$$

and they give the following melting points: phenylbutanolamine, 76–78°; phenylpentanolamine, 70–72°; phenylhexanolamine, 65–66°. They did not describe the hydrochlorides. [b] Phenylheptanolamine was prepared but not analyzed; the following information is appended for reference and convenience. Isonitrosoheptanophenone, m. p. 33°; phenylheptanolamine base, m. p. 62.5°, hydrochloride, m. p. 181.0–181.5°.

Diphenylethanolamine may be prepared from benzoin oxime by means of sodium and absolute alcohol[11] but that method gives relatively low yields and the product contains some isodiphenylethanolamine. The catalytic reduction of both α- and β-benzoin oximes gave quantitative yields of pure diphenylethanolamine, isolated as hydrochloride, the salt melting at 235°, and the base at 165°.[12]

Summary

1. The reduction of oximino ketones to the corresponding amino-alcohols by catalytic means has been extended.

2. It has been shown that in this series pressor activity is associated with compounds having the general formula $ArCHOHCHRNH_2$, but that this activity is more intimately connected with ethane and propane derivatives.

3. Phenylhexanolamine caused a fall in blood pressure that was followed by a gradual rise which after several hours reached above normal.

[11] Polonowski, *Ber.*, **21**, 488 (1888).

[12] *Cf.* Beilstein, 3d ed., Vol. II, p. 1078.

4. The toxicities, as determined by intravenous injection to rabbits, show a regular increase as the length of the side chain increases.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

THE ACTION OF THE HALOGEN HYDRINS AND OF ETHYLENE OXIDE ON THE THIOUREAS

BY JOHN F. OLIN AND F. B. DAINS

RECEIVED MAY 2, 1930 PUBLISHED AUGUST 5, 1930

The basis of this investigation was the observation that thiocarbanilide could be desulfurized with ethylene chlorohydrin, as follows. The thiourea was boiled with the chlorohydrin, giving a partial yield of diphenylurea which could be increased to 60% by heating the reaction product with alcoholic potassium hydroxide, thus completing the hydrolysis of the intermediate thio ether, $C_6H_5NHC(NC_6H_5)SCH_2CH_2OH$.

In order to throw more light on these results, which are analogous to the desulfurizing effect of chloro-acetic acid, the action of the chlorohydrins on thioureas and mono- and disubstituted thioureas was studied.

The results show that the primary product is a thio ether which can be isolated in many cases as the halogen hydride salt. These thio ethers are hydrolyzed with great ease, yielding a mixture of decomposition products.

When the hydroxyl of the hydrin is replaced by an ether or ester grouping, the compound is more stable. In the unsubstituted γ-thio ethers the NH and NH_2 groups react readily with acyl chlorides, yielding diacyl derivatives of the type $RCONHC(NCOR)CH_2CH_2OH(R)$, and with phenyl isocyanate, ethers of thiocarbonyl-diurea, $(R)HOCH_2CH_2SCNH\text{-}CONHC_6H_5(NCONHC_6H_5)$.

Ethylene oxide was found to add to the C–SH groups, giving ethers, $RNHC(NR)SCH_2CH_2OH$, which in the case of thiocarban lide could be isolated; in other instances only the hydrolysis products were identified.

Experimental

Ethylene Chlorohydrin and Thiourea. Oxyethylthiourea Hydrochloride, $HOCH_2\text{-}CH_2SC(NH)NH_2$.—When the molar mixture is heated for thirty minutes, allowing the temperature to rise slowly from 90 to 105° and no higher, no precipitation of ammonium chloride occurs. The resulting product is a heavy oil soluble in alcohol and acetone but not in other organic solvents. Cold dry ether precipitated the hydrochloride which crystallized from butyl alcohol in slender needles melting at 111° and which probably had been obtained by Schatzmann,[1] though no melting point was given

Anal. Calcd. for $C_3H_8N_2OSHCl$: N, 17.90. Found: N, 17.87.

All efforts to close the ring, thus forming the simple thiazolidine $SC(NH)NHCH_2CH_2$

[1] Schatzmann, *Ann.*, **261**, 1 (1891).