The formation of isoxazolines from α,β-unsaturated ketones has been shown not to proceed through an oxime as an intermediary and has been shown inferentially to proceed through a complex dimolecular 1,4-addition process.

BUFFALO, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME, INC.]

AMINO ALCOHOLS. VII. PHENOLIC ARYLPROPANOLAMINES

BY WALTER H. HARTUNG, JAMES C. MUNCH, ELLIS MILLER AND FRANK CROSSLEY

Studies on compounds that produce a rise in blood pressure, i. e., with ephedrine, epinephrine, tyramine and related substances, indicate that certain pharmacological effects are unquestionably associated with definite elemental groups in the structure of the active molecule. For example, it has been established that: (1) the optimum skeleton for pressor activity is found in compounds having a phenyl and an amino group (or a substituted amino group) attached to adjacent carbons of an aliphatic chain.[1] (2) Compounds containing two or three carbons in the aliphatic chain possess maximum pressor activity.[2] (3) Compounds with the three-carbon side chain are active on the blood pressure after oral administration.[2b,1c,3] (4) A secondary alcoholic hydroxyl attached to the carbon bearing the phenyl serves to detoxicate very markedly and perhaps to increase the activity of the molecule.[2a,1c,1a,4] (5) Primary amines tend to be more active and less toxic than the corresponding methylated secondary amines, and if the amino group is further methylated or if the size of the alkyl is increased, there is a corresponding decrease in activity and increase in toxicity.[2a,5]

These conclusions are based chiefly on results obtained from compounds in which the aromatic nucleus of the molecule is a phenyl group. A most significant difference, however, between the structure of epinephrine (I) and ephedrine (II) is that the former has two hydroxyls substituted in the phenyl portion, and these contribute very substantially toward its characteristic action. It was in order to determine more specifically the effect of phenolic groups in molecules of this type that the synthesis of a series of hydroxyaryl derivatives and their pharmacological study was undertaken, and to confine as nearly as possible any change in activity solely to phenolic

[1] (a) Barger and Dale, J. Physiol., 41, 19 (1910); (b) Hasama, Arch. exptl. Path. Pharmakol., 153, 165 (1930); (c) Hartung and Munch, THIS JOURNAL, 53, 1875 (1931).

[2] (a) Chen, Wu and Henriksen, J. Pharmacol., 36, 363 (1929); (b) Hartung, Munch Deckert and Crossley, THIS JOURNAL, 52, 3317 (1930).

[3] Piness, Miller and Alles, J. Am. Med. Assn., 94, 790 (1930).

[4] Tainter, Quart. J. Pharm. Pharmacol., 3, 584 (1930).

[5] Curtis, J. Pharmacol., 35, 321 (1929).

CHOHCH₂
    |
  NHCH₃
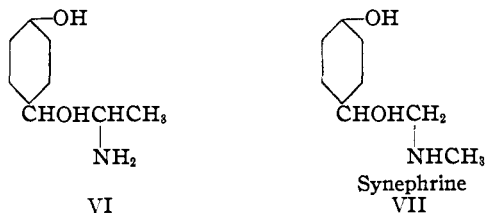Epinephrine
I

CHOHCHCH₃
      |
    NHCH₃
Ephedrine
II
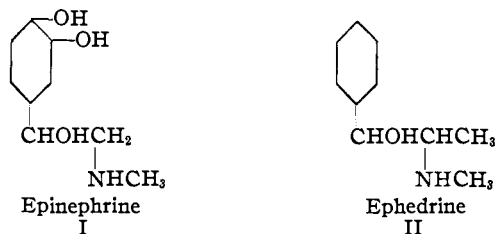
substitution, only derivatives of phenyl-1-amino-2-propanol-1 were prepared.

At the time this work was begun relatively little was known about the specific action of phenolic hydroxyls. Barger and Dale[1a] had studied a limited number, among them the monohydroxy-β-phenylethylamines. They found the ortho derivative (III) no more active than β-phenylethylamine itself; the meta (IV) and para (V) compounds were equally active, and about five times more potent than β-phenylethylamine.

CH₂CH₂NH₂
III

CH₂CH₂NH₂
IV

CH₂CH₂NH₂
Tyramine
V
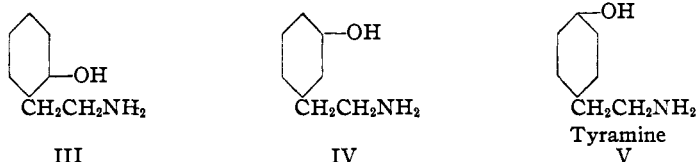
Chen, Wu and Henriksen,[2a] from their experience with epinephrine and the conclusion of Barger and Dale, ascribe an "intensifying" effect to the phenolic groups and they ventured the prediction that p-hydroxyphenyl-1-amino-2-propanol-1 (VI) would possess the characteristic action of ephe-

CHOHCHCH₃
      |
     NH₂
VI

CHOHCH₂
    |
   NHCH₃
Synephrine
VII

drine combined with some of the intense action of epinephrine. Actually the compound does possess the prolonged action of ephedrine and is a stronger pressor.[6] In the meantime Tainter has reported that only those compounds with a catechol nucleus are truly "sympathicotropic," whereas synephrine (VII)—sympatol in Germany—which is epinephrine minus the m-phenolic group, is not sympathicotropic.[7]
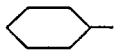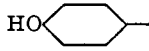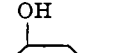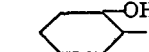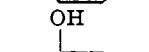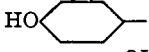
The compounds prepared for our studies are given in Table I, along with

[6] (a) p-Hydroxyphenylpropanolamine was described by the authors before the Organic Section at the Columbus Meeting (April, 1929) of the American Chemical Society.   (b) Chen, *J. Pharmacol.*, **36**, 394 (1929).

[7] Tainter, *ibid.*, **40**, 23, 43 (1930).

data on toxicity and comparative pressor activity. Epinephrine and phenylpropanolamine are included for comparison.
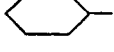
TABLE I

PHENOLIC DERIVATIVES OF PHENYLPROPANOLAMINE

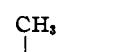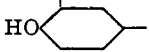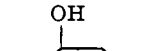|	ArCHOHCHCH₃ NH₃ Ar =	M. L. D. of HCl salt mg./kg., intravenous to rabbits	Relative pressor potency[a] C₆H₄CHOHCH-(NH₂)CH₃ = 1	Remarks
1	(phenyl)	75	1	Equals ephedrine
2	HO—⟨phenyl⟩— (OH)	100–125	1.5	Potentiates epinephrine[b]
3	(phenyl with OH)	16	3	No potentiation of epinephrine observed
4	—OH / OH (phenyl)	40	Less than 1	Impure, see below
5	HO—⟨phenyl⟩— (OH)	11	12 or more	......
6	HO—⟨phenyl⟩—OH (OH)	12	Comparatively inactive[c]	Depressor at higher doses. Impure
7	CH₃ HO—⟨phenyl⟩— (OH)	20	2	See note a, Table IV
8	CH₃—⟨phenyl⟩—	90	2	No potentiation of epinephrine observed
9	l-Epinephrine (U. S. P. X)	0.10	150	......
10	—OCH₃ (phenyl)	25	1	Potentiation of epinephrine absent up to 0.35 mg./kg.
11	CH₃O—⟨phenyl⟩—	35	0.5	Potentiates epinephrine
12	CH₃O—⟨phenyl⟩—OCH₃	21	1	Potentiates epinephrine, large dose gives primary fall followed by rise

[a] These values are only approximations. [b] Munch and Hartung, J. Am. Pharm. Assn., 19, 356 (1930). [c] Boruttau, Chem.-Ztg., 36, 1111 (through Chem. Abst., 8, 2152 (1914)), described 2,4-dihydroxyphenylethanolamine as having little circulatory effect, even in large doses.

Since a more detailed report of the pharmacology of the whole series will be published later, only general observations will be discussed here. p-Hydroxyphenylpropanolamine (No. 2) is markedly superior to phenyl-propanolamine in that it is more active and less toxic than phenylpropanol-amine (No. 1).[6b]   The m-hydroxy derivative (No. 3) caused an agreeable surprise, for it is at least twice as active as the p-isomer, which is quite

different from what one might have been led to expect from the results of Barger and Dale.

3,4-Dihydroxyphenylpropanolamine (No. 5) is of particular interest because of its isomerism with epinephrine; it may be considered as derived from epinephrine by shifting the methyl from the N atom to extend the side chain to three carbons. The compound is not new.[8] The levo form is two to three times as active as the racemic form;[9] Tiffeneau[10] found the *l*-form thirty times as active as the *d*-compound and 60–75% as active as *l*-adrenaline. Bierry, Rathery and Leving[11] reported that its hyperglycemic effects are similar to those of adrenaline. Our tests have thus far been conducted with the racemic form as synthesized. Since it contains two asymmetric carbons it is theoretically capable of existing in six stereo-isomeric forms, just as does ephedrine. When administered intravenously to an anesthetized dog it produced a blood pressure tracing indistinguishable from that of epinephrine except as to dosage; it is about a twelfth as active and a hundredth as toxic as *l*-epinephrine. Given orally to a dog it produced a marked and sustained rise in blood pressure, thus demonstrating again the effect of the three-carbon side chain.[12]

The *o*-phenolic compounds (Nos. 4 and 5) were obtained in an impure form and consequently the physiological results obtained with them are probably of only qualitative rather than quantitative value; but the fact that No. 4 is weaker than No. 1 and that No. 6 is weaker than No. 2 agrees with the observation of Barger and Dale that the introduction of an *o*-hydroxyl group (IX) into adrenalone (VIII) decreases the activity.

OH

OH

COCH₂NHCH₃

Adrenalone
VIII

IX
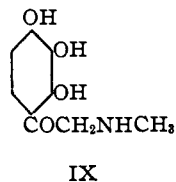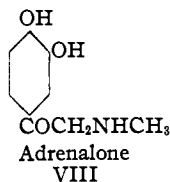
As might be expected, the simultaneous introduction of a *p*-methyl group (No. 8) counteracts, at least to some extent, the enhancement of pressor activity produced by the *m*-hydroxyl; but since the *p*-methyl alone increases very markedly the toxicity of the phenylalkanolamines[2b,13]

[8] German Patent 216,640, *Friedländer*, 9, 1032 (1908–1910); German Patent 254,438, *ibid.*, 11, 1017 (1912–1914).

[9] German Patent 269,327, *ibid.*, 11, 1019 (1912–1914).

[10] Tiffeneau, *Compt. rend.*, 161, 36 (1915); *Paris Medical*, 10, 390–394 (1920).

[11] Bierry, Rathery and Leving, *Compt. rend. soc. biol.*, 88, 3 (1923).

[12] The synthesis and behavior of 3,4-dihydroxyphenylpropanolamine were described before the Medicinal Chemistry Section at the Atlanta Meeting (April, 1930) of the American Chemical Society.

[13] (a) Hartung and Munch, THIS JOURNAL, 51, 2262 (1929); (b) de Burnaga Sanchez, *Bull. soc. chim.*, [4] 45, 284 (1929).

and the *m*-hydroxyl alone (No. 3) does so even more, the very low, in fact decreased, toxicity of the molecule resulting from their simultaneous introduction into phenylpropanolamine was most unexpected. The effect of *m*-methyl substitution (No. 7) is being further investigated.

It might be mentioned, in passing, that with none of the active phenolic compounds was tachyphylaxia observed; that is, unlike ephedrine or phenylpropanolamine, the second or third doses showed no diminishing effect on the rise in blood pressure produced.

The methyl ether derivatives are all pressors. Since these possess elements of structure present in mescaline (X), the active principle of peyote or mescal button, they will be examined to determine whether they produce an analogous intoxicating action on the cerebellum.

Mescaline
X
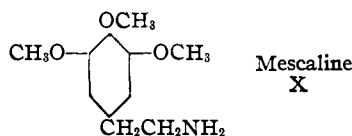
Procedure

Except for the *o*-phenolic compounds (Nos. 4 and 6), which will be discussed later, all the products were prepared after the manner already described for the synthesis of simple phenyl- and tolylalkanolamines.[13a,2b] The appropriate phenolic propiophenone was nitrosated by means of butyl nitrite and the resulting oximino ketone reduced by means of palladium on charcoal. The nitrosation of the *m*- and *p*-phenolic ketones offered no particular difficulty and the yields of the purified intermediates were satisfactory. While the reduction was carried out as already described, it was found that phenolic compounds, or their ethers, first went to the corresponding amino ketone and this could, in aqueous solution and with fresh catalyst, be further reduced to the desired amino alcohol.

Preparation of Ketones

o- and *p*-Hydroxypropiophenones.—The directions of Goldzweig and Kaiser[14] resulted in the formation of *p*-hydroxypropiophenone but in very low yields. For the preparation of larger amounts a modification of the Fries reaction[15] was found most satisfactory, resulting in good yields of a mixture of the *o*- and *p*-isomers. Phenyl propionate was prepared by adding slowly 293 g. of thionyl chloride (2.46 moles) to a mixture of 178 g. of propionic acid (2.4 moles) and 225 g. of phenol (2.4 moles); since the reaction is endothermic a low flame was used. After all the thionyl chloride was added the reaction mixture was slowly warmed until the evolution of gas had practically ceased and the liquid was then distilled. In this manner 290 g. of ester, b. p. 200–210°, was obtained, a yield of 81%. This product was then subjected to rearrangement.

To a suspension of 454 g. of aluminum chloride (3.4 moles) in 500 ml. of carbon bisulfide was slowly added 404 g. of phenyl propionate (2.7 moles); the mixture was

14 Goldzweig and Kaiser, *J. prakt. Chem.*, [2] **43**, 86 (1891).

15 *Cf.* Cox, THIS JOURNAL, **49**, 1028 (1927).

gently refluxed on an oil-bath until the evolution of hydrogen chloride had practically ceased; the carbon bisulfide was then distilled off and the residue heated at 135–140° until no more gas was given off, usually one and one-half to two hours. The solid was then allowed to cool and the aluminum complex decomposed by the addition of excess dilute hydrochloric acid (1:1), whereupon a black oil collected at the surface; after standing for some time a large portion of this crystallized and could be removed by filtration. After recrystallizing from dilute alcohol the solid melted at 147°; obtained, 185 g. or 45.8%; a second recrystallization gave product with maximum melting point at 148°. The non-crystalline or oily portion was taken up in alkaline solution to remove non-phenolic product; the alkaline extract was acidified, the o-propionylphenol removed, dried and distilled, b. p. 110–115° at 6 mm.; obtained, 134 g. or 33.2%. Both these products are described in Beilstein, 4th ed., Vol. VIII, p. 102.

The oxime of o-propionylphenol was prepared in the regular manner and recrystallized from high-boiling ligroin; the white crystals melted at 94° (corr.). Found: N (Kjeldahl), 8.40, 8.47. Calcd. for $C_9H_{11}O_2N$: N, 8.49.

(3-Methyl-4-hydroxyphenyl)-ethyl Ketone.—o-Tolyl propionate was prepared from o-cresol and propionic acid after the manner described for phenyl propionate. From 270 g. of o-cresol (2.5 moles), 190 g. of propionic acid (2.5 moles) and 300 g. of thionyl chloride (2.5+ moles) was obtained 243 g. of product boiling at 220–227°, a yield of 60%. This ester was rearranged according to the procedure given for the preparation of the propionylphenols. The oil resulting from the decomposition of the aluminum complex was distilled and divided into three fractions: (1) boiling up to 110° at 6 mm., mostly o-cresol; (2) boiling up to 140° at 3 mm., presumably (2-hydroxy-3-methylphenyl)ethyl ketone; (3) boiling at 190–195° at 12 mm. and weighing 105 g. This last fraction solidified and after crystallization from benzene melted at 86.5° (corr.). This product was (3-methyl-4-hydroxyphenyl)-ethyl ketone (for the correctness of the positions, see later under isonitroso ketones).

Propionylocatechol was prepared according to the directions of Rosenmund and Lohfert.[16]

Propionylresorcinol has been described by Johnson and Lane.[17]

m-Hydroxypropiophenone was obtained by diazotizing m-aminopropiophenone. Propiophenone treated with fuming nitric acid[18] gave m-nitropropiophenone in yields of 27–50%. After recrystallization from 70% alcohol it melted at 97°.[19] An oily by-product, boiling at 153–160° at 7–10 mm., was also obtained; this was undoubtedly o-nitropropiophenone.

Reduction of the m-nitro compound with tin and hydrochloric acid resulted in the formation of the amine in yields of 63–69%, distilling at 115–120° (5–7 mm.). The hydrochloride was precipitated from an ethereal solution of the base by the addition of an absolute alcoholic solution of hydrogen chloride, m. p. 202.5°.[20] Eighty-five grams of the amine was dissolved in excess hydrochloric acid, the solution cooled to +6° and a cold solution of sodium nitrite slowly added until a positive test for free nitrous acid was obtained with potassium iodide–starch paper; the solution was allowed to come slowly to room temperature, stand overnight and the next morning was gently warmed; the product that collected at the surface was removed, dissolved in dilute alkali to remove

[16] Rosenmund and Lohfert, *Ber.*, **61**, 2601 (1928).

[17] Johnson and Lane, THIS JOURNAL, **43**, 2571 (1921).

[18] Hartung and Munch, *ibid.*, **51**, 2571 (1929).

[19] Beilstein, 4th ed., Vol. VII, p. 302, gives m. p. 98°.

[20] Comanducci and Pescitelli, *Gazz. chim. ital.*, **36**, II, 787 (1906); *Chem. Centr.*, I, 1034 (1907), describe m-aminopropiophenone and give the melting point of the hydrochloride as 170°.

non-phenolic bodies and again liberated by the addition of acid; after recrystallization from water or benzene it began to sinter at 79° and melt at 82° (corr.); obtained, 65.4 g., a yield of 76%.

(3-Hydroxy-4-methylphenyl)-ethyl ketone was prepared by the diazotization of (3-amino-4-methylphenyl)-ethyl ketone, which has already been described,[18] and the diazotization was carried out as described above. The product melted at 123°.

p-Methoxypropiophenone was best prepared by the Friedel–Crafts reaction from propionyl chloride and anisole, using excess anisole as solvent. By taking 8 moles of anisole, 1.3 moles of aluminum chloride and 1 mole of propionyl chloride, it was possible to obtain 0.74 mole of ketone. This obviates the formation of large amounts of 1,1-di-p-methoxyphenylpropene-1, which is obtained when carbon bisulfide is taken as solvent.[21] p-Methoxypropiophenone is described in Beilstein, 4th ed., Vol. VIII, p. 103.

o-Methoxypropiophenone was prepared by Fischer and Slimmer[22] from zinc diethyl and o-methoxybenzoyl chloride. We obtained it by methylating o-propionylphenol. Two hundred and ten g. of o-propionylphenol (1.4 moles), 73 g. of sodium hydroxide (1.8 moles) and 221 g. of dimethyl sulfate (1.75 moles) resulted in the formation of 211 g. of the ether, a yield of 92%. The product boiled at 137° at 16.5 mm. The etherification was carried out according to the directions of Hiers and Hager for the preparation of anisole.[23]

2,4-Dimethoxypropiophenone was prepared by methylating propionylresorcinol. The formation of this compound is of particular interest in view of the fact that Twiss[24] was unable to obtain the dimethyl ether of caproylresorcinol. The following procedure was used. In a flask, provided with stirrer and reflux condenser, were placed 196.5 g. of propionylresorcinol (1.18 moles), 500 ml. of methyl alcohol and 540 g. of dimethyl sulfate (4.3 moles); the mixture was cooled by an ice-bath to +10°, and to the stirred solution was slowly added a solution of 215 g. of sodium hydroxide (5.35 moles) in 325 ml. of water, keeping the reaction mixture cool the while. After the alkali was added the cooling bath was replaced by a water-bath and the stirred solution slowly warmed for about three hours; after standing overnight, the mixture was diluted with excess water and the product removed; it distilled at 180° at 20 mm., and after recrystallization from ligroin the white granular crystals melted at 83°; it gave no coloration with ferric chloride; obtained, 205 g., a yield of 89%.

Isonitroso Ketones.—The isonitroso ketones were prepared substantially according to the method described for the preparation of isonitrosopropiophenone. The phenolic ketone was dissolved, or if it did not dissolve it was suspended, in the requisite amount of ether, hydrogen chloride was bubbled through the stirred solution and an equimolar quantity of freshly distilled butyl nitrite was slowly added. The isolation was, except for the variations indicated, carried out in the following manner. After completion of the nitrosation reaction the ethereal solution was extracted with dilute alkali and the alkaline extract slowly stirred into concentrated hydrochloric acid containing ice. The crystals which separated out, consisting of nitrosated and unchanged phenol, were removed and dried.

[21] Gattermann, Ber., 22, 1130 (1889); Gattermann, Ehrhardt and Maisch, ibid., 23, 1203 (1890); Klages, ibid., 35, 2263 (1902).

[22] Fischer and Slimmer, ibid., 36, 2585 (1903).

[23] Hiers and Hager, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1929, Vol. IX, p. 13.

[24] Twiss, THIS JOURNAL, 48, 2206 (1926).

The purification, fortunately, is not difficult, for the oximino ketones are relatively insoluble in boiling benzene and the unchanged ketone may usually be completely removed by two extractions. Purification at this stage is necessary to insure pure products later on. The benzene-insoluble substance may be further purified by recrystallization from water. In the case of the ethers there is, naturally, no possibility for contamination by non-nitrosated material.

The experimental data on the various oximino ketones are summarized in Table II. It should be emphasized, in passing, that every attempt to prepare an isonitroso derivative of a ketone bearing a phenolic hydroxyl in the ortho position has been unsuccessful.

TABLE II

OXIMINO KETONES

ARCOCCH$_3$ NOH AR =	Yield, %	M. p. (corr.), °C.	Formula	Nitrogen analysis Calcd.	Found (Kjeldahl)
1 p-HOC$_6$H$_4$-[a]	36–52[b]	184.5	C$_9$H$_9$O$_2$N	7.81	7.87, 8.00
2 m-HOC$_6$H$_4$-	38	138	C$_9$H$_9$O$_2$N	7.81	7.72
3 p-HO-m-CH$_3$C$_6$H$_3$-[c]	72[d]	188.5–189.0	C$_{10}$H$_{11}$O$_2$N	7.25	7.13
4 p-CH$_3$-m-HOC$_6$H$_3$-	56	158.5[e]	C$_{10}$H$_{11}$O$_2$N	7.25	6.89, 6.96
5 p,m-(HO)$_2$C$_6$H$_3$-[f]	25	217 (dec.)	C$_9$H$_9$O$_4$N	7.18	7.14, 7.10
6 p-CH$_3$OC$_6$H$_4$-	72	131	C$_{10}$H$_{11}$O$_2$N	7.25	7.50, 7.32
7 o-CH$_3$OC$_6$H$_4$-	41[g]	132	C$_{10}$H$_{11}$O$_2$N	7.25	7.38
8 o,p-(CH$_3$O)$_2$C$_6$H$_3$-	90	110.5	C$_{11}$H$_{13}$O$_4$N	6.27	6.39

[a] Fusion with sodium hydroxide gave p-hydroxybenzoic acid, m. p. 208° (uncorr.), thus proving that the oximino group did not enter the aromatic nucleus.

[b] If allowance is made for recovered p-hydroxypropiophenone the yield is over 60%.

[c] Fusion with 60% potassium hydroxide gave 3-methyl-4-hydroxybenzoic acid, m. p. 174.5° (corr.). This proves that the isonitroso group did not enter the ring, and also establishes the position of the substituents in the original ketone.

[d] Allowing for recovery of unchanged ketone.

[e] Recrystallized from 25% alcohol.

[f] The nitrosation was carried out in the regular manner; about ninety minutes after all the BuNO$_2$ was added the ethereal reaction solution was slowly poured into about two and a half volumes of warm water; the remaining ether was evaporated on a water-bath, while the non-volatile portion dissolved in the water; the aqueous solution was boiled with decolorizing charcoal, filtered and chilled; the product which settled out was extracted with boiling benzene to remove unchanged ketone and the benzene-insoluble portion recrystallized from water.

[g] In the ethereal solution after nitrosation was found an appreciable amount of o-hydroxypropiophenone, identified by its oxime. This indicates that demethylation also took place.

Amino Ketones.—The reduction of the respective isonitroso ketones was carried out in the manner already described.[13a,25] The absorption of hydrogen practically stopped, however, when two moles were taken up. The catalyst was removed, the solvent removed by evaporation *in vacuo*

[25] Hartung, THIS JOURNAL, **50**, 3370 (1928); **53**, 2248 (1931).

over sulfuric acid and a mixture of calcium chloride and soda lime, and the product was isolated as its hydrochloride salt. All reduced Fehling's solution, and all formed red, decomposing or effervescing melts, characteristic of the hydrochlorides of amino ketones. The individual compounds are described in Table III.

TABLE III
HYDROCHLORIDE SALTS OF AMINO KETONES

	ARCOCHCH₃ NH₂·HCl AR =	M. p. (corr.), °C.	Formula	Caled. Cl	Caled. N	Found Cl as AgCl	N (Kjeldahl)
1	p-HOC₆H₄-ᵃ	219	C₉H₁₁O₂NHCl	17.58	6.95	17.62 17.63	6.97 7.12
2	m-HOC₆H₄-ᵇ	177ᶜ	C₉H₁₁O₂NHCl	17.58	..	17.52 17.53	
3	p-HO-m-CH₃C₆H₃-ᵇ	184.5ᶜ	C₁₀H₁₃O₂NHCl	16.46	..	16.78 16.79	
4	p-CH₃-m-HOC₆H₃-ᵈ	145ᵉ	C₁₀H₁₃O₂NHCl	...	6.51		6.82
5	p,m-(HO)₂C₆H₃-ᵃ,ᶠ	233	C₉H₁₁O₃NHCl	...	6.44		6.27
6	p-CH₃OC₆H₄-ᵃ	226	C₁₀H₁₃O₂NHCl	16.45	6.50	16.53 16.53	6.56 6.51
7	o-CH₃OC₆H₄-ᵃ	112	C₁₀H₁₃O₂NHCl	16.45	..	16.57	
8	p,o-(CH₃O)₂C₆H₃-ᵃ	178–180	C₁₁H₁₅O₃NHCl	14.43	5.71	14.10 14.33	5.62

ᵃ Recrystallized from absolute alcohol.

ᵇ Forced out of absolute alcoholic solution with ether.

ᶜ Began to sinter at 170°.

ᵈ Forced out of sec.-butyl alcohol with isopropyl ether.

ᵉ Began to sinter at 100°, bubbles began to appear at 130–132° and an actively effervescing melt formed at 145°.

ᶠ This product has been prepared previously [German Patent 216,640, Friedländer, 9, 1032 (1908–1910)]. It was obtained by hydrolyzing and demethylating the product isolated from a Friedel–Crafts reaction between catechol dimethyl ether and α-phthalimidopropionyl chloride. It is described as melting at 240°.

Aminoalcohols.—By subjecting the aminoketone salts, in aqueous solution, to further reduction with fresh catalyst the corresponding aminoalcohols were obtained. These are described as their hydrochloride salts in Table IV.
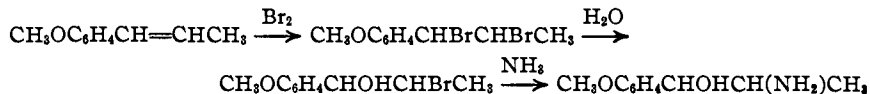
TABLE IV
AMINOALCOHOL HYDROCHLORIDES

	ARCHOHCHCH₃ NH₂·HCl AR =	M. p. (corr.), °C.	Formula	Caled. Cl	Caled. N	Found Cl (as AgCl)	N (Kjeldahl)
1	p-HOC₆H₄-	206.5	C₉H₁₁O₂N·HCl	17.41	6.88	17.38 17.38	6.94 7.15
2	m-HOC₆H₄-	182	C₉H₁₁O₂N·HCl		6.88		6.66
3	p-HO-m-CH₃C₆H₃-ᵃ						
4	p-CH₃-m-HOC₆H₃-	222	C₁₀H₁₅O₂N·HCl	16.29		16.63	
5	p,m-(HO)₂C₆H₃-ᵇ	176	C₉H₁₃O₃N·HCl	16.15	6.38	15.97 15.98	6.38
6	p-CH₃OC₆H₄-ᶜ	216.5	C₁₀H₁₅O₂N·HCl	16.29	6.41	16.44 16.39	6.47 6.56
7	o-CH₃OC₆H₄-ᵈ	245 (dec.)	C₁₀H₁₅O₂N·HCl	16.29		16.52	
8	p,o-(CH₃O)₂C₆H₃-	219	C₁₁H₁₇O₃N·HCl	14.37		14.59	

ᵃ This product is very hygroscopic; even after drying for days over phosphoric anhydride no definite melting material could be obtained, and with the facilities available samples for analysis could not be weighed out without taking up moisture. But since the intermediates were established and the reduction followed the proper course, there can be no doubt as to the identity of the product.

ᵇ This compound, also obtained by the catalytic reduction of the corresponding amino ketone, has been described as melting at 95° [German Patent 254,438, Fried-

länder, **11**, 1017 (1912–1914)]. It is very hygroscopic and thus far no solvent has been found from which it may be recrystallized. It was isolated from aqueous solution by drying finally over phosphorus pentoxide at 5 mm. for two or three weeks.
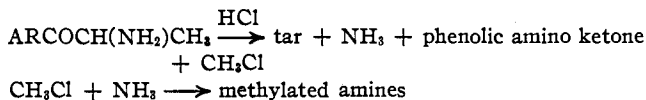
^{c} The free base after recrystallization from water melted at 120.5° (corr.). A compound of the same structure is described by Read and Reid [*J. Chem. Soc.*, 1487 (1928)] and was prepared by them as follows

$$CH_3OC_6H_4CH{=}CHCH_3 \xrightarrow{Br_2} CH_3OC_6H_4CHBrCHBrCH_3 \xrightarrow{H_2O}$$

$$CH_3OC_6H_4CHOHCHBrCH_3 \xrightarrow{NH_3} CH_3OC_6H_4CHOHCH(NH_2)CH_3$$

Their free base melted at 84° and the hydrochloride at 182°. In a private communication Professor John Read agreed that our respective products are stereoisomeric. Such syntheses are not unknown [*cf.* Späth and Göhring, *Monatsh.*, **41**, 319 (1920); Manske and Johnson, THIS JOURNAL, **51**, 580 (1929)].

^{d} The free base recrystallized from benzene–ligroin, 1:1, began to sinter at 67° and melted at 75° (corr.).

Ortho-Phenolic Compounds.—As already pointed out, the *o*-phenolic aminoalcohols, *o*-hydroxyphenylpropanolamine and 2,4-dihydroxyphenyl-propanolamine (Nos. 4 and 6, Table I) could not be obtained by reducing the corresponding isonitroso ketone, for in every attempt to prepare these desired intermediates from a ketone bearing an *o*-hydroxyl in the nucleus, no trace of the oximino derivative could be found; a reaction did apparently take place, but its direction was not determined. Consequently the compounds sought had to be prepared in another manner, which consisted in demethylating *o*-methoxyphenyl α-aminoethyl ketone and 2,4-dimethoxyphenyl α-aminoethyl ketone (Nos. 7 and 8, Table III), respectively, and reducing further the resulting phenolic amino ketones. This procedure, however, still leaves much to be desired. During the demethylation considerable tar formed, particularly with the dimethyl compound, and the resulting product was not analytically pure. The impurity was soluble in absolute alcohol, and it may be some amine salt, formed conceivably in the following manner

$$ARCOCH(NH_2)CH_3 \xrightarrow{HCl} tar + NH_3 + \text{phenolic amino ketone}$$
$$+ CH_3Cl$$
$$CH_3Cl + NH_3 \longrightarrow \text{methylated amines}$$

The correctness of this supposition was not determined, for too little product was obtained to permit repeated crystallization for maximum purity. Instead, the product as recrystallized from absolute alcohol was reduced catalytically and in each instance the theoretical amount of hydrogen was taken up before reduction ceased. This fact, coupled with the observation that the compounds are physiologically active, is the basis for believing that the ones sought were obtained, at least in part.

o-Hydroxyphenyl α-Aminoethyl Ketone.—Six grams of the hydrochloride of *o*-methoxyphenyl α-aminoethyl ketone was heated with 35 ml. of concentrated hydrochloric acid in a closed tube at about 150° for seventy-five to ninety minutes; consider-

able pressure developed; the tube was opened and the contents evaporated to dryness on the steam-bath. The solid residue was taken up in absolute alcohol, insoluble material removed and the solution diluted with isopropyl ether. From three such runs 10 g. of product was obtained; the gray crystals formed the characteristic red, decomposing melt at 223.5–224.0° (corr.), were readily soluble in water, reduced Fehling's solution, and gave a deep mahogany color with ferric chloride. The analysis gave 8.86% N and 20.63% Cl; calculated for $C_9H_{11}O_2N \cdot HCl$: N, 6.95; and Cl, 17.59.

o-Hydroxyphenylpropanolamine.—The amino ketone salt described above was dissolved in water, 10.6 g. in 100 ml., and shaken with the catalyst in an atmosphere of hydrogen until no more hydrogen was taken up—1290 ml. of hydrogen was taken up in 690 minutes, calcd., 1245 ml. The product was isolated by evaporating the solvent *in vacuo;* the residual white crystals, with a pinkish crust, sintered to a yellow mass at 225–227° but did not melt completely at 250°; they did not reduce Fehling's solution and gave a violet coloration with ferric chloride. The product contained 22.7% Cl; after recrystallization from alcohol the chlorine content was reduced to 20.65%. Calcd. for $C_9H_{13}O_2N \cdot HCl$: Cl, 17.41. On the basis of the analysis the product used in pharmacological testing is considered as 89% pure.

2,4-Dihydroxyphenyl α-Aminoethyl Ketone.—The 2,4-dimethoxyphenyl α-aminoethyl ketone was demethylated in the manner already described, and the product was similarly isolated. The yield, however, was smaller, 24%, and the amount of tar greater. After purification, the red-brown crystals formed a slowly effervescing melt at 176° (corr.), reduced Fehling's solution and gave a deep brown coloration with ferric chloride. Found: N, 7.38. Calcd. for $C_9H_{11}O_3N \cdot HCl$: N, 6.89.

2,4-Dihydroxyphenylpropanolamine.—The phenolic amino ketone salt, 3.4 g., reduced in the regular manner, resulted in the formation of white crystals which gave a violet-blue color with ferric chloride and a doubtful reaction with Fehling's solution; after recrystallization from absolute alcohol the crystals slowly darkened at 190°, darkened more rapidly at 225° and formed a red decomposing mass at 249° (corr.). Calcd. for $C_9H_{13}O_3N \cdot HCl$: Cl, 15.44. Found: Cl, 18.49. The product was considered as 92% pure.

Addenda.—Since this paper was written, work on similar compounds and some identical with those described above has been published. Kuschinsky[26] found that racemic *m*-sympatol (I), synthesized by Legerlotz, is 4–5 times more active than is the *l-p*-sympatol (II).

Ehrhart found *m*-hydroxyephedrine more active than the *p*-hydroxy isomer.[27] Schaumann in a much more extended pharmacological report on hydroxyephedrines and hydroxy-nor-ephedrines substantially confirms our observations, although he says nothing about the oral activity of the 3,4-dihydroxy derivatives.[28]

OH

OH—

CHOHCH₂NHCH₃
I

CHOHCH₂NHCH₃
II
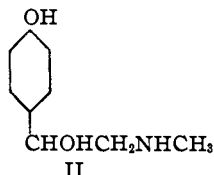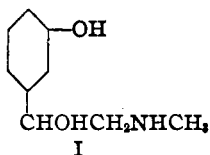
[26] Kuschinsky, *Arch. Exptl. Path. Pharmakol.*, **156**, 306 (1930).
[27] Ehrhart, *Metallbörse*, **20**, 1800 (1930).
[28] Schaumann, *Arch. Exptl. Path. Pharmakol.*, **160**, 127 (1931).

Summary

1. The synthesis of various phenolic derivatives of phenylpropanol-amine has been described.

2. A preliminary report on their physiological activity has been included. It has been found that: (a) the p-hydroxyl group increases pressor activity and decreases toxicity to rabbits. (b) Contrary to expectations, the m-hydroxyl increases activity at least twice as much as does the p-isomer. It also increases toxicity. (c) The phenolic group introduced into the o-position decreases the activity and probably increases the toxicity. (d) The m,p-dihydroxy derivative is most active and produces an action resembling very strikingly that of epinephrine. Since it has three carbons in the side chain it is also active after oral administration. The two hydroxyls have increased the activity to a greater extent than the toxicity. (e) It is not safe to predict the toxicity of a compound obtained by the introduction, simultaneously, of more than one group (Nos. 7 and 8, Table I).

PHILADELPHIA, PENNSYLVANIA

THE COMPOSITION OF CHERRY GUM

BY C. L. BUTLER AND LEONARD H. CRETCHER

In a recent paper on the composition of gum arabic[1] the authors pointed out the unsatisfactory state of our knowledge of substances such as pectins, plant gums, mucilages, hemicelluloses and algins, which may be described generically as acid polysaccharides. Numerous papers dealing with the identification of the sugars in these substances have been published over a period of many years. The problem of the acidic nucleus in gums was long ago attacked by O'Sullivan.[2] After hydrolysis of gums arabic, gedda and tragacanth, he isolated the barium salt of a stable organic acid to which, after analysis he assigned the formula $C_{23}H_{38}O_{22}$. Later, Robinson[3] obtained an acid of similar composition from the gum of *Cochlospermum Gossypium*. Until quite recently, it has been generally accepted, on the basis of O'Sullivan's work, that the acidic nucleus of gums is a complex organic molecule of unknown constitution containing twenty-three carbon atoms in combination with hydrogen and oxygen in the ratio indicated above.

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[1] Butler and Cretcher, THIS JOURNAL, **51**, 1519 (1929).

[2] O'Sullivan, *J. Chem. Soc.*, **45**, 41 (1884); *ibid.*, **59**, 1029 (1891); *ibid.*, **79**, 1164 (1901).

[3] Robinson, *ibid.*, **89**, 1496 (1906).