of the glycol is proved by periodate titration, and by permanganate oxidation to benzene-o-acetic-propionic acid. Phthaldehyde condenses with aryloxyacetones to yield aryl ethers of 4,5-benztropolone.

Amines Related to 2,5-Dimethoxyphenethylamine. V. 2,5-Dihydroxy and 2-Methoxy-5-hydroxy Derivatives[1]

BY RICHARD BALTZLY,* JOHANNES S. BUCK[2] AND WALTER S. IDE

Interest in the 2,5-dialkoxylated type of pressor was first aroused by the study of the properties of 2,5-dimethoxyphenethylmethylamine.[3] This substance was at that time unique as being the only ring-alkoxylated pressor of considerable potency.[4] It was also unusual as possessing considerable activity when given orally. Whereas ordinarily the hydroxy pressors are far more potent than their ethers, 2,5-dihydroxyphenethylmethylamine was of about the same potency as its dimethyl ether and its action was shorter.[4]

When a more extended series of 2,5-dialkoxyphenethylamines[5] had been prepared, comparison was sought between two other members and their demethylated analogs. Demethylation of 2,5-dimethoxyphenethylamine and of β-(2,5-dimethoxyphenyl)-isopropylamine afforded the corresponding dihydroxy compounds of which only the first could be obtained crystalline. Both were tested, the latter as a solution of the crude prepara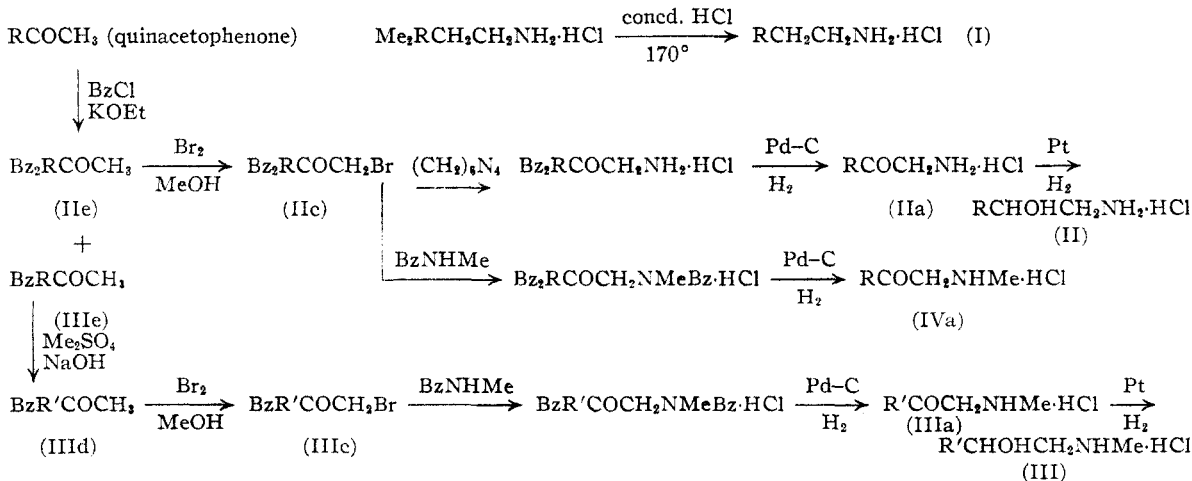tion, and gave results similar to those previously reported by Hjort[4] although 2,5-dihydroxyphenethylamine[5a] was somewhat superior to its N-methyl derivative and resembled closely the dimethoxy pressors. Oral activity was, however, largely absent.

It later became apparent that optimal activity was to be expected only with an hydroxyl group in the side chain.[6] We decided to attempt preparation of further 2,5-dihydroxy types, but as extreme experimental difficulties were anticipated (since these are derivatives of hydroquinone) it seemed best to prepare a few specimens for test and only to complete the series if preliminary results gave promise that the effort would be rewarded.

The scheme of synthesis followed is outlined in Chart I. Use of quinacetophenone as starting material gave access also to derivatives of the 2-methoxy-5-hydroxy type and operations in that series were carried out in parallel. Observations from various laboratories, confirmed and sum-

CHART I

The Roman numerals refer to new substances isolated in pure form: R = 2,5-dihydroxyphenyl; Me₂R = 2,5-dimethoxyphenyl; Bz₂R = 2,5-dibenzyloxyphenyl; BzR = 2-hydroxy-5-benzyloxyphenyl; BzR' = 2-methoxy-5-benzyloxyphenyl; R' = 2-methoxy-5-hydroxyphenyl

RCOCH₃ (quinacetophenone)   Me₂RCH₂CH₂NH₂·HCl $\xrightarrow[170°]{\text{concd. HCl}}$ RCH₂CH₂NH₂·HCl   (I)

Bz₂RCOCH₃ $\xrightarrow[\text{MeOH}]{\text{Br}_2}$ Bz₂RCOCH₂Br   (CH₂)₆N₄   Bz₂RCOCH₂NH₂·HCl $\xrightarrow[\text{H}_2]{\text{Pd–C}}$ RCOCH₂NH₂·HCl $\xrightarrow[\text{H}_2]{\text{Pt}}$

(IIe)   (IIc)   (IIa)   RCHOHCH₂NH₂·HCl
                                                                                              (II)
    +

BzRCOCH₃
                    BzNHMe
(IIIe) $\xrightarrow{}$ Bz₂RCOCH₂NMeBz·HCl $\xrightarrow[\text{H}_2]{\text{Pd–C}}$ RCOCH₂NHMe·HCl
Me₂SO₄   (IVa)
NaOH

BzR'COCH₃ $\xrightarrow[\text{MeOH}]{\text{Br}_2}$ BzR'COCH₂Br $\xrightarrow{\text{BzNHMe}}$ BzR'COCH₂NMeBz·HCl $\xrightarrow[\text{H}_2]{\text{Pd–C}}$ R'COCH₂NHMe·HCl $\xrightarrow[\text{H}_2]{\text{Pt}}$

(IIId)   (IIIc)   (IIIa)
                                                                       R'CHOHCH₂NHMe·HCl
                                                                            (III)

marized by Hjort[4] had been to the effect that in pressors a m-hydroxyl group was especially bene-

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* Harvard University Ph.D. 1931.

(1) This work is part of a joint research carried out in collaboration with a pharmacological group in these laboratories.

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(3) Buck, THIS JOURNAL, **54**, 3661 (1932).

(4) Hjort, J. Pharmacol. Exptl. Therapeut., **52**, 101 (1934).

(5) Baltzly and Buck, THIS JOURNAL, **62**, 161 (1940).

(5a) Neuberger (Biochem. J., **43**, 606 (1948)) has recently reported this substance. His characterization (m. p. 169–170°) is in reasonable agreement with ours.

(6) Hjort, Randall and de Beer, J. Pharmacol. Exptl. Therapeut., **92**, 283 (1948).

<div align="center">

Table I

Physical and Analytical Data of the Compounds of Chart I

</div>

Compound number	M. p. (cor.), °C.	Appearance	Crystallizing solvent	Empirical formula	% Carbon Calcd.	Found	% Hydrogen Calcd.	Found
I	173	Tan micro plates	Ethanol–ether	$C_8H_{12}ClNO_2$	50.65	50.64	6.38	6.22
II	176	Lavender powder	Ethanol	$C_8H_{12}ClNO_3$	46.70	46.21	5.85	6.04
IIa	230 dec.	Fine yellow needles	Ethanol	$C_8H_{10}ClNO_3$	47.16	47.60	4.72	4.84
IIc	100	Silky needles	Heptane	$C_{22}H_{19}BrO_3$	64.22	64.01	4.66	4.81
IIe	81	Plates	Hexane	$C_{22}H_{20}O_3$	79.96	80.05	5.96	6.36
III	199	Prisms	95% EtOH + ether	$C_{10}H_{16}ClNO_3$	51.37	51.28	6.90	6.76
IIIa	224 dec.	Fine yellow needles	Ethanol	$C_{10}H_{14}ClNO_3$	51.82	52.06	6.09	6.14
IIIc	80	Rhombs	Heptane	$C_{16}H_{15}BrO_3$	57.31	57.36	4.51	4.60
IIId	54	Prisms	Hexane	$C_{16}H_{16}O_3$	74.96	74.81	6.29	6.13
IIIe	69.5–70	Yellow needles	Methanol	$C_{15}H_{14}O_3$	74.67	74.41	5.85	6.29
IVa	225 dec.	Yellow crusts	Ethanol	$C_9H_{12}ClNO_3$	49.64	49.86	5.56	5.49

ficial. It was assumed that benzylation of quin-acetophenone would take place first at the 5-hydroxyl. This assumption was justified by the properties of the monobenzyl ether isolated. The 2-hydroxyl was then methylated and the benzyl group removed by hydrogenolysis at a later stage of the synthesis.

In actual operations serious difficulties were encountered only in the last stage. The 2,5-dihydroxy-α-aminoketone hydrochlorides, IIa and IVa, were unexpectedly stable, probably due to chelation. On reduction of the carbonyl group, however, the substances became extremely sensitive. Compound II, β-hydroxy-β-(2,5-dihydroxyphenyl)-ethylamine hydrochloride was isolated but could not be obtained free from color. Its N-methyl derivative did not crystallize and, probably because of that, rapidly decomposed. Compound III, β-hydroxy-β-(2-methoxy-5-hydroxyphenyl)-ethylmethylamine hydrochloride was not abnormally sensitive.

Compounds II and III were tested and exhibited pressor characteristics very similar to those reported[6] for their 2,5-dimethoxy analogs without the side chain hydroxyl group. Both were much inferior to β-hydroxy-β-(2,5-dimethoxyphenyl)-isopropylamine hydrochloride (Compound 839)[6] requiring 3–4 times as large a dose to provoke a 50 mm. rise in blood pressure and one that lasted only twenty to thirty minutes as compared with the two-hour pressure elevation produced by Number 839. The toxicity relationships were relatively favorable (LD₅₀ = about 700 mg./kg. body weight in mice) but it was fairly clear that other substances of this type would not be of outstanding interest and that any results from completing the series would not be proportionate to the effort involved.

Experimental

Physical and analytical data for the new substances prepared are presented in Table I.

Quinacetophenone.—The original directions of Nencki and Schmid[7] lead to poor results. In our hands the yield of product sublimed *in vacuo* by their procedure was 3%. This was increased to about 12% if the reaction mixture,

after complete addition of hydroquinone, was refluxed vigorously for one and one-half hours. A yield of 40% of sublimed material was obtained in one run during which one equivalent of acetic anhydride was added in small portions during this reflux period. The purification of quinacetophenone by recrystallization is accompanied by serious losses. The best procedure was to sublime the crude precipitate at 1-mm. pressure.

Benzylation of Quinacetophenone.—The quinacetophenone was dissolved in ten volumes of 95% ethanol and heated until refluxing was vigorous. Alkali (as 40% sodium hydroxide solution) and benzyl chloride were added in portions to the boiling solution. When 0.2 mole of quinacetophenone, 0.35 mole of benzyl chloride and 0.3 mole of alkali were used, 46% of the starting material was isolated as pure 2-hydroxy-5-benzyloxyacetophenone (IIIe) and 25% as pure 2,5-dibenzyloxyacetophenone (IIe). Use of larger quantities of benzyl chloride and of alkali resulted in larger yields of IIe and smaller of IIIe.

After refluxing two hours the alcohol was evaporated and the residual material partitioned between ether and 10% sodium hydroxide solution. The sodium salt of IIIe has a tendency to precipitate during the extractions. The free phenol, precipitated by acidification, is markedly yellow and gives an intense coloration with alcoholic ferric chloride solution.

When dissolved in sodium hydroxide solution and methylated with dimethyl sulfate (100% excess of alkylating agent and alkali used) on the steam-bath IIIe afforded α-methoxy-5-benzyloxyacetophenone (IIId) in 90% yield.

Preparation of the Bromoketones IIc and IIIc.—Bromination of IIe and IIId in methanol as described by Ardis, Baltzly and Schoen[8] gave 2,5-dibenzyloxy-α-bromoacetophenone (IIc) in 88% yield and 2-methoxy-5-benzyloxy-α-bromoacetophenone in 54% yield. Both were free of 2-hydroxy ketones as shown by negative tests with ferric chloride.

The Aminoketone Hydrochlorides, IIa, IIIa and IVa.—The primary aminoketone hydrochloride IIa was prepared from IIc and hexamethylenetetramine by the conventional method followed by hydrogenation with palladized charcoal to remove the benzyl groups. The intermediate 2,5-dibenzyloxy-α-aminoacetophenone hydrochloride was obtained in crystalline form but contaminated by ammonium chloride that could not be separated by crystallization.[8,9]

The secondary aminoketone hydrochlorides, IIIa and IVa, were prepared by the reaction of benzylmethylamine (2 mols) in ether with the bromoketones IIIc and IIc followed by hydrogenation over palladized charcoal. In both cases the intermediate benzylmethylaminoketone hydrochlorides could not be crystallized. This is not unusual with substances of this type.[9] After the protective benzyl groups had been removed by hydrogenolysis, IIIa and IVa were purified without difficulty.

The Aminoalcohol Hydrochlorides, II and III.—Reduction of IIa, IIIa and IVa with Adams catalyst in 90%

(7) Nencki and Schmid, *J. prakt. Chem.*, II, **23**, 546 (1881).

(8) Ardis, Baltzly and Schoen, This Journal, **68**, 591 (1946).

(9) *Cf.* Ide and Baltzly, *ibid.*, **70**, 1084 (1948).

ethanol proceeded smoothly. The reduction product of IIIa, β-hydroxy-β-(2-methoxy-5-hydroxyphenyl)-ethyl-methylamine hydrochloride, III, was also isolated and purified with ease. The corresponding 2,5-dihydroxy derivative, expected from the reduction of IVa, could not be induced to crystallize. The solutions darkened rapidly and resulted in unmanageable tars. In the case of IIa, the product, β-hydroxy-β-(2,5-dihydroxyphenyl)-ethyl-amine hydrochloride crystallized without difficulty, but could not be obtained free of color although charcoaled repeatedly and crystallized under nitrogen.

2,5-Dihydroxyphenethylamine Hydrochloride (I).—Five grams of 2,5-dimethoxyphenethylamine was dissolved in 35 cc. of concentrated hydrochloric acid and heated at 170° for two hours in a glass bomb. The dark brown solution was evaporated to dryness *in vacuo* giving a dark gum that crystallized overnight. It was crystallized repeatedly from ethanol–ether mixtures with charcoaling,

but could not be obtained in a colorless form although analytically pure.

Demethylation by the same procedure of β-(2,5-di-methoxyphenyl)-isopropylamine[5] gave colored material that could not be induced to crystallize. Samples received preliminary testing in solution.

Summary

1. The preparation of β-hydroxy-β-(2,5-dihy-droxyphenyl)-ethylamine, of 2,5-dihydroxyphene-thylamine and of β-hydroxy-β-(2-methoxy-5-hydroxyphenyl)-ethylmethylamine as their hydrochlorides is described.

2. As pressors these compounds are inferior to the corresponding 2,5-dimethoxy compounds.

Piperidine Derivatives. XXII. The Condensation of 1-Methyl-4-piperidone with Active Methylene Compounds

BY S. M. McELVAIN* AND ROBERT E. LYLE, JR.[1]

In paper XVI[2] of this series the Knoevenagel condensation of 1-benzyl-4-piperidone and 1-benzoyl-3-ethyl-4-piperidone with cyanoacetic ester to the corresponding piperidylidene compounds (I and II) in the presence of ammonium acetate[3] was reported. The piperidylidene derivative II was hydrogenated and then converted to *dl*-ethyl cincholoiponate. Later, 1-benzoyl-4-piperidone was similarly condensed with cyano-acetic ester.[4] The resulting compound (III) was found to add hydrogen cyanide readily, but with phenylmagnesium bromide there was obtained only a magnesium enolate, from which III was recovered.

CN—C—COOC₂H₅   CNCX
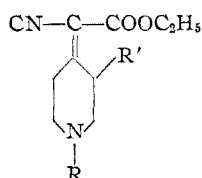
I, R = C₆H₅CH₂, R′ = H   IV, X = COOC₂H₅
II, R = C₆H₅CO, R′ = C₂H₅   V, X = CN
III, R = C₆H₅CO, R′ = H   VI, X = C₆H₅

In extending these studies to 1-methyl-4-piperidone, it now has been found that this piperidone condenses readily (within one hour) with cyanoacetic ester in the presence of ammonium acetate to yield IV, which was isolated as the hydrochloride in 95% yield. The free base IV slowly polymerizes on standing to a solid, m. p. 234–235°, that shows the same analyses as IV. Malononitrile condenses quite rapidly (fifteen

minutes) with the piperidone, and the hydro-chloride of V was isolated in 98% yield. The free base V polymerizes immediately on liberation from its salt.

In contrast to the above nitriles, such active methylene compounds as diacetylmethane, aceto-acetic ester and malonic ester undergo no condensation with 1-methyl-4-piperidone in the presence of ammonium acetate. From each of these attempted reactions the piperidone was recovered unchanged. These results show that at least one of the activating groups of an active methylene compound must be a cyano group if a condensation with the piperidone in the presence of ammonium acetate is to be successful.

Recently, Anker and Cook[5] described the condensation of this piperidone with phenylaceto-nitrile to VI in 52% yield in the presence of sodium methoxide; VI was reported to be a liquid, b. p. 150° (0.5 mm.). Repetition of this work in this Laboratory gave a 94% yield of the hydro-chloride of VI. The free base (VI) could be readily purified by distillation after extraction from the reaction mixture. It boils at 144–148° (0.4 mm.) together with a small amount of phenylacetamide resulting from the hydration of the nitrile by the water formed in the condensation. After separation of the amide (ether insolubility), VI was obtained as a crystalline solid, m. p. 55–56.5°.

In view of these results the sodium methoxide-catalyzed condensation of the piperidone with those active methylene compounds that had failed to react in the presence of ammonium acetate was attempted. In no case could a simple piperidylidene compound be obtained; usually a complex mixture of products resulted, but with

(1) Wisconsin Alumni Research Foundation Research Assistant, 1948–1949.

(2) Stork and McElvain, THIS JOURNAL, **68**, 1053 (1946).

(3) Cope, *et al.*, *ibid.*, **63**, 3452 (1941).

(4) McElvain and McMahon, *ibid.*, **71**, 901 (1949).

(5) Anker and Cook, *J. Chem. Soc.*, **806** (1948).