mixture. In this respect picrasmin differs from the other two isomers.

Action of Acetic Anhydride and Sodium Acetate upon Picrasmin.—A solution of 1 g. of picrasmin in an acetylating mixture of 8 cc. of acetic anhydride and 0.25 g. of anhydrous sodium acetate was boiled for one and one-half hours. Most of the anhydride was then removed by distillation, and the resulting mass was treated with water. The product that separated soon crystallized and yielded 0.8 g. of material with a melting poing of 200–205°.

The crude crystals were dissolved in boiling methanol and allowed to crystallize. They yielded 220 mg. of needles and boat-shaped plates, which melted at 255°. Recrystallization did not alter the melting point. The substance was identified as dehydroquassin by comparison with an authentic sample from quassin as to melting point, mixed melting point, and optical crystallographic properties.

The mother liquors from the first crystallization were diluted with two volumes of water, which caused the crystallization of a quantity of impure starting material. Purification of this from 35% methanol gave unchanged picrasmin and a small quantity of dehydroquassin. The former was identified by its melting point and mixed melting point.

Summary

Evidence has been presented to show that picrasmin, the bitter constituent of the wood of *Picrasma excelsa*, is an isomer of quassin and neoquassin, and hence has the molecular formula $C_{22}H_{30}O_6$. It is optically active and contains two methoxyl groups.

A method for the preparation of this material is described and some of its reactions are compared with those of quassin. The great similarity between the reactions of picrasmin and quassin indicates that the two materials are structurally very much alike. A summary of the reactions recorded for picrasmin is presented diagrammatically.

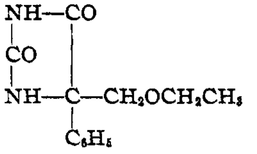
WASHINGTON, D. C. RECEIVED MARCH 14, 1938

[CONTRIBUTION NO. 131 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of Compounds with Hypnotic Properties. II. Phenoxymethylhydantoins[1,2]

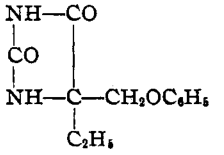
BY WILLIAM B. WHITNEY[3] WITH HENRY R. HENZE

Research in the field of synthetic drugs possessing potency as hypnotics has demonstrated that the compounds showing most promise are of a type in which fat-soluble alkyl groups are attached to a water-soluble nucleus such as barbituric acid.[4] Since hydantoin is closely related to barbituric acid in structure and solubility in water, and inasmuch as the hydantoin nucleus can be substituted similarly by alkyl groups, the fact that certain alkylated (or arylated) hydantoins produce narcosis is not surprising. However, most of these derivatives are not sufficiently potent and for the remainder the margin of safety between the effective and lethal doses is not sufficient to warrant their use. In hopes of improving this factor of safety, alkoxymethyl groups were used as substituents in a previous investigation.[5] By utilization of this ether linkage, substituted in the methyl group which is attached to the 5-position of the hydantoin nucleus, it was expected that much of the narcotic effect produced when methyl is substituted by a higher alkyl might be retained, but that the toxicity of the compound might be diminished. In at least two instances it was found that compounds with definite narcotic action were thus produced. As all of the hydantoins prepared in this previous investigation were, with the single exception of ethoxymethylphenylhydantoin (I), alkoxymethyl alkylhydantoins, it was of interest to continue the study by synthesizing and testing pharmacologically a series of the aryloxy analogs. Especially should the synthesis of phenoxymethylethylhydantoin (II) be desirable, since from its evaluation might be acquired data relating to the effect of position isomerism upon hypnotic activity.



$$\begin{array}{lll}\mathrm{NH}{-}\mathrm{CO} & & \\ | \qquad\ | & & \\ \mathrm{CO} \quad\ | & & \\ | \qquad\ | & & \\ \mathrm{NH}{-}\mathrm{C}{-}\mathrm{CH_2OCH_2CH_3} & & \\ \qquad\ | & & \\ \qquad \mathrm{C_6H_5} & & \end{array}$$

I



$$\begin{array}{lll}\mathrm{NH}{-}\mathrm{CO} & & \\ | \qquad\ | & & \\ \mathrm{CO} \quad\ | & & \\ | \qquad\ | & & \\ \mathrm{NH}{-}\mathrm{C}{-}\mathrm{CH_2OC_6H_5} & & \\ \qquad\ | & & \\ \qquad \mathrm{C_2H_5} & & \end{array}$$

II

It was to be anticipated that the synthesis of 5,5-aryloxymethyl alkyl (or aryl) hydantoins would

---

[1] From a dissertation presented by Wm. B. Whitney to the Faculty of the Graduate School of the University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1937.

[2] Presented before the Division of Organic Chemistry at the 95th meeting of the American Chemical Society, April 18 to 21, 1938, at Dallas, Texas.

[3] Present address, Department of Chemistry, North Texas Agricultural College, Arlington, Texas.

[4] Tabern and Shelberg, THIS JOURNAL, **55**, 328 (1933).

[5] Rigler with Henze, *ibid.*, **58**, 474 (1936).

TABLE I

PHENOXYMETHYL KETONES, $C_6H_5{-}O{-}CH_2{-}CO{-}R$

—R	B. p., °C. (corr.)	Mm.	Yield, %	d^{20}_4	n^{20}_D	Mol. ref.		Carbon, %		Hydrogen, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
—CH_3	110–112	12	16	1.0903	1.5228	41.82	42.06	71.96	71.80	6.72	7.02
—CH_2CH_3	98–100	5	62	1.0740	1.5201	46.43	46.47	73.13	73.42	7.37	7.24
—n-C_3H_7	112	4	64	1.0490	1.5148	51.05	51.18	74.11	74.07	7.92	8.06
—n-C_4H_9	130	4	46	1.0192	1.5068	55.67	55.76	74.95	75.48	8.39	8.61
—s-C_4H_9	117	4	28	1.0283	1.5065	55.67	55.56	74.95	75.05	8.39	8.57
—n-C_5H_{11}	153	10	41	1.0025	1.4960	60.29	60.07	75.68	75.52	8.78	9.01
—iso-C_5H_{11}	140	10	24	1.0067	1.5035	60.29	60.58	75.68	75.55	8.78	8.66
—C_6H_5	187	8	45	[a]				79.21	79.06	5.71	5.74

[a] Phenoxymethyl phenyl ketone, m. p. 74° (corr.).

be effected readily from the appropriate ketones by action of potassium cyanide and ammonium carbonate.[6] However, the method for preparing alkoxymethyl alkyl (or aryl) ketones through the chain of reactions

Aldehyde + Alcohol + Hydrogen chloride $\longrightarrow$
Chloro ether $\longrightarrow$ Cyano ether $\longrightarrow$ Alkoxy ketone

is not adaptable to production of aryloxy ketones since phenols cannot replace alcohols in the chloro ether synthesis. The phenoxyacetonitrile, required for conversion into the phenoxy ketones by means of the Grignard reaction, was obtained by dehydration of phenoxyacetamide. Since no phenoxymethyl alkyl ketones other than the phenoxymethyl-methyl[7] and ethyl ketones[8] had been prepared previously, the seven phenoxy ketones synthesized in the course of this study were purified carefully so that their more important physical properties could be determined; from the vapor pressure data for these new keto ethers the latent heats of vaporization have been calculated.

The phenoxymethyl alkyl (or phenyl) ketones were converted into the corresponding 5-phenoxymethyl-5-alkyl(or phenyl) hydantoins. Since the N-methylhydantoins are now attracting attention in the patent literature,[9] it was of interest to prepare one example of this type, namely, 1,3,5-trimethyl-5-phenoxymethylhydantoin. A report of the pharmacological testing of these nine new hydantoins, all of which show some hypnotic activity, will be made elsewhere.

Experimental

Phenoxyacetone.[7]—Attempts to prepare phenoxyacetone by interaction of phenol and chloroacetone in aqueous sodium hydroxide solution produced only a black resin. This aryloxy ketone was obtained by dissolving 47.2 g. (0.5 mole) of phenol in 300 cc. of dry toluene, adding 11.5 g. (0.5 mole) of sodium and warming until the metal dissolved; subsequently the addition of 46.3 g. (0.5 mole) of chloroacetone caused appreciable darkening of the mixture and separation of sodium chloride. Removal of the toluene by distillation and of the salt by filtration permitted fractionation of the residue; the fraction boiling at 110–12° (corr.) at 12 mm.[10] weighed 12 g.; yield 16%; d^{20}_4 1.0903; n^{20}_D 1.5228; *MR* calcd., 41.82; *MR* found, 42.06.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.96; H, 6.72. Found: C, 71.80; H, 7.02.

Phenoxyacetone Semicarbazone: white solid, recrystallized from 50% alcohol, m. p. 176° (corr.).[11] *Anal.* Calcd. for $C_{10}H_{13}N_3O_2$: N, 20.28. Found: N, 20.07.

Preparation of Phenoxymethyl Alkyl or Phenyl Ketones.—The method used by Blaise and Picard[8] for the production of phenoxymethyl ethyl ketone, from interaction of phenoxyacetyl chloride and zinc ethyl iodide, was investigated, but the chief products of reaction were phenyl phenoxyacetate and phenoxymethyldiethylcarbinol. In another attempt to prepare the aryloxy ketone, from interaction of ethylmagnesium bromide and phenoxyacetamide, the tertiary alcohol was the main product recognized. However, the desired ketone and its analogs were obtained by action of the appropriate Grignard reagent on phenoxyacetonitrile. The latter was prepared best from chloroacetic acid with intermediate formation of phenoxyacetic acid $\longrightarrow$ phenoxyacetyl chloride $\longrightarrow$ phenoxyacetamide $\longrightarrow$ phenoxyacetonitrile (over-all yield 40.5%).

Phenoxyacetonitrile.—B. p. 128° (17 mm.); d^{20}_4 1.0991; n^{20}_D 1.5246; *M*R calcd., 37.00; *M*R found, 37.06.

Anal. Calcd. for C_8H_7NO: N, 10.52. Found: N, 10.59.

In synthesizing the homologs of phenoxyacetone, one part (0.2–0.4 mole) of the appropriate alkyl (or phenyl) bromide was diluted with 100 cc. of anhydrous ether and added to 1.05 parts of magnesium turnings in order to prepare the Grignard reagent. To the latter was added one part of phenoxyacetonitrile mixed with 100 cc. of dry ether. The reaction product was warmed gently for one hour, cooled in an ice-bath and decomposed with ice-cold, 10% hydrochloric acid. After separation and drying over anhydrous calcium chloride, the phenoxy ketone was freed from ether and fractionated.

The density and molecular refractivities of the phenoxy ketones were determined at 20°. The values for these

---

(6) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(7) (a) Stoermer, *Ber.*, **28**, 1253 (1895); (b) *Ann.*, **312**, 273 (1900); Stoermer and Wehln, *Ber.*, **35**, 3553 note (1902).

(8) Blaise and Picard, *Ann. chim. phys.*, [8] **26**, 274 (1912).

(9) Swiss Patents 166,004, 169,509, 176,827, 177,411, 179,690, 179,691, 179,692, 181,175, 181,176, 191,343.

(10) Stoermer,[7a] reports b. p. 229–230° (uncorr.).

(11) Stoermer[7b] reports m. p. 173°.

physical properties, together with the molecular refractivities calculated from them, and the data from the analysis of the ketones are tabulated in Table I.

Semicarbazones were prepared from the eight ketones synthesized during this study and all solidified readily except that of the *s*-butyl member of the series; analysis of the liquid semicarbazone of the *s*-butyl ketone indicates that its failure to solidify may be due to the presence of impurities. The melting points of the semicarbazones of the phenoxymethyl ketones are listed, together with certain analytical data, in Table II.

TABLE II

SEMICARBAZONES OF PHENOXYMETHYL KETONES

$C_6H_5—O—CH_2—C(R)=NNHCONH_2$

—R	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found
$—CH_3$	176	20.28	20.07
$—C_2H_5$	101.5[a]	19.00	19.14
—*n*-C_3H_7	108.5	17.87	18.15
—*n*-C_4H_9	76	16.86	16.95
—*s*-C_4H_9	Liquid	16.86	(15.00)
—*n*-C_5H_{11}	87.5–88.0	15.96	16.04
—iso-C_5H_{11}	83.5–84.0	15.96	15.58
$—C_6H_5$	187.0–187.5	15.64	15.27

[a] Blaise and Picard[8] report m. p. 102° (uncorr.).

Vapor pressure measurements of phenoxyacetonitrile and the phenoxymethyl alkyl ketones prepared during this investigation were made by the method described by Smith and Menzies.[12] The apparatus consisted of an isoteniscope, bath with stirrer, pressure regulating system and manometer. Preliminary trials were made using phenoxymethyl methyl and ethyl ketones, recording the vapor pressures at 5° intervals. When these data were plotted, using the logarithm of the vapor pressure and the reciprocal of the absolute temperature, the graphs approximated closely to a linear relationship. Hence, for the other liquids the vapor pressures were measured at 20° intervals. In order to determine whether the highest temperatures used were causing decomposition, the bath was cooled and the vapor pressures at lower temperatures were redetermined for each compound. In all cases, except that of the phenoxymethyl *n*-amyl ketone, the two values for the vapor pressure at the lower temperature agreed very well.

TABLE III

VALUES FOR LATENT HEAT OF VAPORIZATION AND FOR YOUNG'S EQUATION CONSTANTS FOR PHENOXYMETHYL KETONES AND PHENOXYACETONITRILE

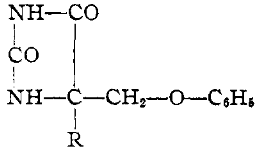
Phenoxymethyl ketone	ΔH	A	B
Methyl	13,360	55,900	8.85
Ethyl	13,690	57,300	8.66
n-Propyl	13,910	58,200	8.63
n-Butyl	14,080	58,900	8.57
s-Butyl	13,580	56,800	8.40
n-Amyl	14,220	59,500	6.68
Isoamyl	14,410	60,300	8.67
Phenoxyacetonitrile	13,740	57,500	8.73

From the data for vapor pressures, values of A and B in Young's[13] equation, $\log_{10} \text{mm.} = -0.05223\ A/T + B$, were calculated and recorded. Also, from the equation $\Delta H = 2.303 \times 1.987 \times 0.05223\ A$, ΔH was determined. The values for A, B and ΔH are tabulated in Table III.

Synthesis of 5-Phenoxymethyl-5-alkyl or -5-Phenylhydantoins.—Following the method of Bucherer and Lieb[6] the appropriate phenoxymethyl ketone (1 mole) was added to a mixture of potassium cyanide (1.3 moles), ammonium carbonate (3 moles), and 250 cc. of 50% alcohol in a flask, equipped with an air condenser, immersed for ten hours in a water-bath maintained at a temperature between 55 and 60°. The temperature was then raised to 90° and maintained there for three hours. The contents of the flask were acidified and cooled causing the hydantoin to precipitate. After removing the precipitate by filtration it was dissolved in alcohol and treated with Norite; by the addition of water, certain hydantoins were reprecipitated in the form of lustrous plates, while others separated from solution as chalky powder. The hydantoins are all very soluble in 95% alcohol and in acetone, and moderately soluble in 50% alcohol and in water, the solubility in the latter decreasing with an increase in molecular weight. The data for the melting points and percentage yields and analytical results of the 5-phenoxymethyl-5-alkyl or -5-phenylhydantoins are included in Table IV.

TABLE IV

5-PHENOXYMETHYL-5-ALKYL OR PHENYLHYDANTOINS



—R	M. p., °C. (corr.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$—CH_3$	147	66	59.97	59.65	5.50	5.63	12.73	12.81
$—C_2H_5$	176	41	61.50	61.60	6.02	6.05	11.97	12.28
—*n*-C_3H_7	149	51	62.87	62.57	6.50	6.63	11.28	11.30
—*n*-C_4H_9	162	76	64.10	63.74	6.92	6.89	10.68	10.30
—*s*-C_4H_9	195	39	64.10	63.75	6.92	7.22	10.68	10.50
—*n*-C_5H_{11}	166	69	65.18	65.18	7.30	7.38	10.19	10.00
—*i*-C_5H_{11}	181.5	29	65.18	64.92	7.30	7.54	10.19	10.40
$—C_6H_5$	181	95	68.08	68.00	5.00	5.13	9.93	10.01

Methylation of 5-Phenoxymethyl-5-methylhydantoin.—Three grams (0.02 mole) of this hydantoin was dissolved in 10 cc. of absolute ethyl alcohol and 1.15 g. (0.05 mole) of metallic sodium was added slowly. The solution was then treated with 6.3 g. (0.05 mole) of dimethyl sulfate and the mixture was maintained at 50° for one hour. On acidification and dilution with water, oily globules separated which solidified after standing for eight days. Recrystallization from dilute alcohol yielded the 1,3,5-trimethyl-5-phenoxymethylhydantoin as colorless crystals softening at 76° and melting at 81–83° (corr.).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.87; H, 6.50; N, 11.28. Found: C, 63.10; H, 6.71; N, 11.03.

Summary

1. Five new phenoxymethyl alkyl ketones and

---

[12] Smith and Menzies, THIS JOURNAL, **32**, 1434–1447 (1910); *Ann. Physik*, **33**, 979–988 (1910).

[13] "International Critical Tables," New York, 1928, Vol. III, p. 215.

one new phenoxymethyl aryl ketone have been prepared. Phenoxymethyl methyl and ethyl ketones, previously reported in the literature, have been resynthesized in a higher degree of purity and more adequately characterized.

2. The method of Blaise and Picard was shown to be unsatisfactory for the production of these phenoxymethyl alkyl ketones and a better procedure was developed.

3. Determinations of vapor pressures were made for phenoxyacetonitrile and the phenoxymethyl alkyl ketones at selected temperatures. These data have been recorded in both graphic and tabular form and used to determine the values *A* and *B* in Young's vapor pressure equation. These constants were then employed to calculate the latent heat of vaporization of the respective compounds.

4. Eight 5,5-disubstituted hydantoins of the new aryloxy-alkyl type have been prepared.

5. N-Methylation of one of these hydantoins, to form 1,3,5-trimethyl-5-phenoxymethylhydantoin, was effected.

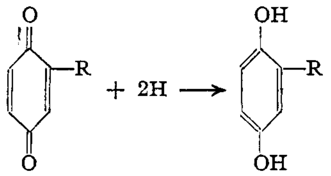
AUSTIN, TEXAS RECEIVED MARCH 12, 1938

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Relative Oxidation–Reduction Reactivities of Ketones and Aldehydes and Applications in Synthesis[1]

BY HOMER ADKINS AND FRED W. COX

Clark, Conant, Fieser and others have shown the relationship of structure to the oxidation–reduction potentials for many ketones of the quinone type. They used an electrochemical method which depends upon the determination of the potential at a platinum electrode immersed in a mixture of the quinone and the corresponding hydroquinone.



Since this procedure is not applicable to the common ketones, a method has been sought in this Laboratory whereby the relative reducing power of various alcohols and the oxidizing power of the corresponding ketones could be determined. Because the ordinary ketones cannot be measured against their alcohols by the electrochemical method, it seemed necessary to equilibrate one ketone against another and thus secure a measure of their relative oxidation–reduction reactivities. Several years ago attempts were made to set up equilibrium in the systems of the type

$$R_2CO + R'_2CHOH \longleftrightarrow R_2CHOH + R'_2C{=}O$$

but reaction could be attained only at relatively high temperatures over such catalysts as nickel or copper–chromium oxide and under conditions where side reactions occurred.

Recently it has been found possible to establish equilibrium at 40 to 100° without side reactions through the use of aluminum *t*-butoxide. At the same time the usefulness of the polarograph as a means of determining the concentrations of ketones in a mixture has become evident[2] so that it has been used in the analysis of the equilibrium mixtures. Incidentally the polarograph enables independent measurements to be made of the reduction potential of a number of ketones and aldehydes.

Our experimental results will be discussed in four sections: first, the use of a polarograph as a means of determining directly the reduction potential of a ketone or aldehyde; second, the use of the polarograph as a means of determining the concentrations of two ketones in a mixture; third, the determination of relative oxidation–reduction reactivities by direct equilibration of two ketones; and, fourth, some practical applications of these methods to synthetic organic chemistry.

Reduction Potentials as Determined with a Polarograph.—A discussion of reduction potentials determined with a polarograph requires first a consideration of the method of determination. When a polarogram is made upon a solution of certain aldehydes and ketones a "break" in the curve is shown, which is characteristic of the compound.

---

(1) This investigation was supported in part by the Wisconsin Alumni Research Foundation.

(2) Borcherdt, Meloche and Adkins, THIS JOURNAL, 59, 2171 (1937).