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ACKNOWLEDGMENTS AND ADDRESSES

Received March 30, 1970, from the *Department of Pharmaceutical Chemistry, College of Pharmacy, Rutgers—The State University, Newark, NJ 07104*

Accepted for publication January 8, 1971.

This paper is abstracted from a portion of the dissertation submitted by Richard W. Janssen to the Graduate School, Rutgers—The State University, New Brunswick, N. J., in partial fulfillment of Doctor of Philosophy degree requirements.

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Chemistry and Pharmacological Evaluation of 1-Phenyl-2-propanols and 1-Phenyl-2-propanones

CHARLES F. BARFKNECHT, ROBERT V. SMITH, DAVID E. NICHOLS, JAMES L. LESENEY, JOHN P. LONG, and JAMES A. ENGELBRECHT

Abstract □ Various ring-methoxylated 1-phenyl-2-propanols and 1-phenyl-2-propanones were synthesized and pharmacologically evaluated. Most compounds had depressantlike activity. The ketones were readily reduced by rabbit liver microsomes. No reductase activity was found in rat and mouse liver preparations. Partition coefficients were determined, and a linear correlation between LRA_{50}'s (loss of righting ability in 50% of the mice) and partition coefficients was observed for six of the compounds investigated.

Keyphrases □ 1-Phenyl-2-propanols, 1-phenyl-2-propanones, derivatives—synthesis, pharmacological evaluation as psychotomimetic agents □ Partition coefficients—1-phenyl-2-propanols, 1-phenyl-2-propanones, derivatives □ Structure–activity relationships—1-phenyl-2-propanols, 1-phenyl-2-propanones, derivatives □ TLC—identification □ GLC—analysis

In the study of psychotomimetic agents, the identity of active chemical species has been the subject of controversy. Harley-Mason *et al.* (1) suggested that the hallucinogenic action of mescaline was caused by a metabolite. Goldstein *et al.* (2) isolated 3,4,5-trimethoxyphenylethanol (I) as a product of mescaline metabolism. When I was injected into rabbits, a mescalinelike effect was observed. They proposed that the corresponding aldehyde, 3,4,5-trimethoxyphenylacetaldehyde (II), was the "active" intermediate.

Since methoxylated amphetamines are psychotomimetics related to, and generally more potent than, mescaline (3), it was decided that the oxygen analogs of methoxylated amphetamines, namely 1-phenyl-2-propanols (III) and 1-phenyl-2-propanones (IV), be synthesized and their pharmacology examined. Recent studies on the metabolism of amphetamine revealed that significant amounts of IV*a* are excreted by rabbits, while small amounts are excreted by man (4).

Initial studies were conducted on 1-(3,4-dimethoxyphenyl)-2-propanol (III*c*), which was found to have an immediate, but short-lived, depressantlike effect on a conditioned avoidance response in the rat (5). Encouraged by this action, a systematic study of the series was begun. The effects of ring methoxylation on potency, metabolism, and partition coefficients are reported here.

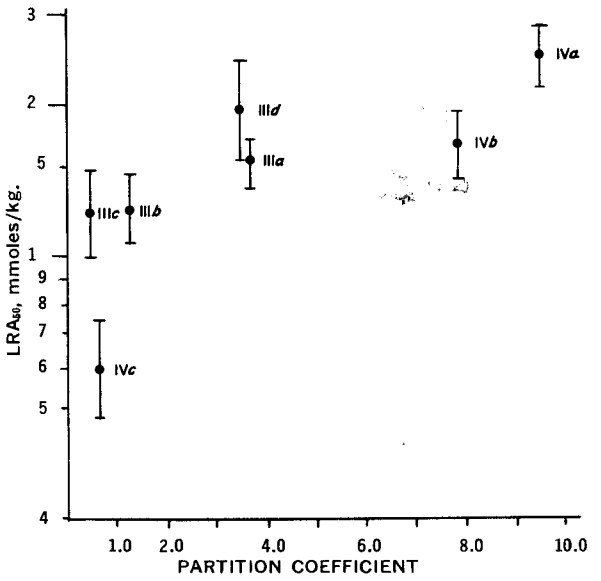
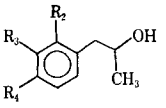
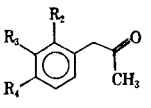


Figure 1—*Plot of* LRA_{50}*'s* versus *partition coefficients. For* n = 6 *(excluding IVc), the correlation coefficient = 0.84.*



III



IV

Table I—Pharmacological Data on 1-Phenyl-2-propanols and 1-Phenyl-2-propanones

Compound	R_2	R_3	R_4	LD_{50}, mg./kg.	LRA_{50}, mg./kg.	LRA_{50}, mmoles/kg.	Salivation	Onset, min.	Ataxia	Hyperactivity
III*a*	H	H	H	520 (423–640)[a]	215 (182–233)	1.58	No	<3	Yes, then sedation	No
III*b*	OCH_3	OCH_3	H	580 (518–650)	240 (205–281)	1.22	Perfuse, 100–300 None >300	<3	Yes	No
III*c*	H	OCH_3	OCH_3	650 (551–767)	240 (198–290)	1.22	No	<3	Yes	No
III*d*	H	H	OCH_3	820 (738–920)	320 (254–367)	1.93	No	<3	Yes	No
IV*a*	H	H	H	540 (486–599)	330 (289–376)	2.46	No	<3	Yes, then sedation	No
IV*b*[b]	OCH_3	OCH_3	H	740 (649–844)	320 (274–374)	1.65	Slight, 100–200 Perfuse, 300–400	<3	No, immediate sedation	No
IV*c*[b]	H	OCH_3	OCH_3	670 (520–724)	115 (93–143)	0.59	No	<3	Yes	No
IV*d*[b]	H	H	OCH_3	560 (483–649)	—[c]	—	No	<3	Tremors	Yes

[a] 95% fiducial limits. [b] Prepared according to the method of R. V. Heinzelman, in "Organic Syntheses," coll. vol. IV, Wiley, New York, N. Y., 1963, p. 573. [c] Effective only at toxic doses.

RESULTS AND DISCUSSION

1-Phenyl-2-propanols and 1-phenyl-2-propanones were synthesized according to literature methods. New compounds (III*b* and III*d*) were prepared by analogous routes. The results of the pharmacological testing are summarized in Table I. Most compounds had depressantlike activity. The data indicate that the 3,4-dimethoxyketone (IV*c*) is the most potent compound. Animals dosed with the LRA_{50}'s (loss of righting ability in 50% of the mice) exhibited varying refractivity to noxious stimuli (footpad and tail clamps). Deaths were apparently due to respiratory depression. Compound IV*d* demonstrated activity different from the remainder of the series and was the only compound showing hyperactivity associated with ataxia.

Compounds IV*a–c* were found to be readily reduced by the 10,000-g supernatant of rabbit liver (Table II); reversal of this reaction was not observed at pH 7.4. When similarly incubated with mouse and rat liver preparations, reductase or oxidase activity was not detected. Analogous results with substituted acetophenones were reported by Culp and McMahon (6).

The partition studies were patterned after those of Hansch *et al.* (7) and Quintana (8). The partition coefficients determined were of the relative order of magnitude expected for the compounds used (8). Interestingly, a plot of LRA_{50}'s (mmoles/kg.) *versus* partition coefficients (Fig. 1) was linear, with a correlation coefficient of 0.84 for III*a–d* and IV*a–b*.

Table II—Physical Properties of 1-Phenyl-2-propanols and 1-Phenyl-2-propanones and *In Vitro* Reduction of Ketones

Compound	Retention[a,b] Time, min.	R_f	$\lambda_{max.}$ (ϵ)[c]	Partition Coefficients	Rate of Reduction[d], μmoles/g. liver/hr.
III*a*	8.8	0.47	259 (188)	3.67	—
III*b*	4.8	0.45	272 (1230)	1.27	—
III*c*	8.0	0.35	277 (2740)	0.26	—
III*d*	—	—	278 (1810)	3.48	—
IV*a*	4.4	0.61	260 (232)	9.45	14.2
IV*b*	3.6	0.63	275 (1370)	7.85	14.8
IV*c*	5.6	0.52	281 (3410)	0.67	15.7
IV*d*	—	—	279 (1820)	6.73	—

[a] Column temperature at 115° for III*a* and IV*a*; 180° for III*b–c* and IV*b–c*; retention times relative to solvent front. [b] III*a–c* chromatographed as their acetates. [c] Maxima used in partition studies. [d] With rabbit liver, 10,000-g supernatant only.

The experiments performed were not capable of discerning whether the effects observed were central and/or peripheral in origin. However, the apparent depressant activity of these compounds is interesting in light of the work of Moffett *et al.* (9) with the phenone congeners of III and IV. They reported that 3′,4′,5′-trimethoxyacetophenone had some tranquilizer effect in schizophrenic patients, while 3,4-dihydroxyphenylcyclopentylketone received clinical study as a tranquilizer. Recently, the sleep-inducing properties of tryptophol and its 5-hydroxy and 5-methoxy analogs were reported by Feldstein *et al.* (10). They suggested that their compounds might be involved in sleep regulation. From the data reported here, it would appear that the depressant action of arylalkyl alcohols and the corresponding ketones may be a more general property of this class of compounds than previously implied.

Further studies on the structure–activity relationships and the mechanism of action of these systems are in progress.

EXPERIMENTAL

Materials—With the exception of III*b* and III*d*, all compounds were previously reported in the literature. Samples were prepared by the literature methods and had physical properties that agreed with the published values.

1-(2,3-Dimethoxyphenyl)-2-propanol (*III*b)—Compound III*b* was synthesized in essentially quantitative yield by sodium borohydride reduction of IV*b* and purification by distillation, b.p. 97°/0.25 mm.

Anal.—Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.19; H, 8.26.

1-(p-Methoxyphenyl)-2-propanol (*III*d)—Compound III*d* was synthesized in essentially quantitative yield by a route analogous to that used for III*b*, b.p. 95°/0.1 mm.

Anal.—Calcd. for $C_{10}H_{14}O_2$: C, 72.12; H, 8.44. Found: C, 72.11; H, 8.37.

Sodium NADP[1], dipotassium glucose-6-phosphate[1], and glucose-6-phosphate dehydrogenase[1] were used as purchased. New Zealand rabbit livers[2] and livers from mature male albino mice and Holtzman rats were used for the preparation of 10,000-g supernatant in 0.25 *M* sucrose (1 ml. ≡ 0.5 g. liver) after the method of Lu and Coon (11). All solvents and reagents were analytical reagent grade.

Methods—*Liver Incubations*—In the standard procedure, 5 μmoles of phenylpropanone or phenylpropanol in 0.5 ml. of 0.2 *M* Tris–HCl buffer, pH 7.4, was mixed with 2.5 ml. of 10,000-g liver supernatant, 1 μmole NADP, 5 μmoles glucose-6-phosphate, and 2

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Pel-Freez, Rogers, Ark.

units glucose-6-phosphate dehydrogenase. Control mixtures were prepared in the same way but with liver preparation which had been boiled for 1 min. A blank mixture was also prepared in like manner but without substrate. The liver mixtures were incubated at 37° for 1 hr.; each mixture was quenched by boiling. The incubated mixtures were extracted with 3 × 1 ml. of ethyl acetate; after drying over anhydrous Na_2SO_4, the ethyl acetate extracts were reduced to dryness and then treated as indicated under GLC. For TLC, *n*-heptane extracts of the ethyl acetate residues were used.

TLC—Plates of 250-μ silica gel GF_{254} were used throughout with the following solvent system: benzene–ethyl acetate, 1:1 v/v; development was 10 cm. Detection was *via* fluorescence quenching in 254-nm. radiation. Attempts to locate phenolic metabolites were with diazotized sulfanilic acid of Axelrod and Pulliam (12).

GLC—A Hewlett-Packard 5750B gas chromatograph, equipped with 3% OV-17 on Gas Chrom Q (100/120 mesh) column (6 mm. i.d. × 180 cm.), was used with 60 ml./min. carrier gas flow and the column temperatures listed in Table II. Phenylpropanols were chromatographed as their acetates following reaction of 10–20 mg. of them in 0.05 ml. of pyridine–acetic anhydride (1:1) for 1 hr. at room temperature.

Partition Studies—UV spectra were recorded with a Beckman DK-2 spectrophotometer. Phenylpropanone derivative, 1–5 mg., dissolved in 25 ml. of *n*-heptane was shaken vigorously for 1.5 hr. with 25 ml. of citrate phosphate buffer (pH 7.0) at 25.0 ± 0.1°. The heptane layer was dried over anhydrous Na_2SO_4, diluted to 50 ml. in a volumetric flask with *n*-heptane, and compared to standard solutions at the maxima indicated in Table I with a Gilford model 240 spectrophotometer.

Pharmacological Evaluation—All compounds were administered as suspensions in less than 1% polysorbate 80. Graded doses were administered intraperitoneally to Swiss-Webster male mice weighing 25–30 g. Groups of 10 mice at each dose level were observed, and the gross effects were recorded. Loss of righting ability was considered positive in animals that could not right themselves for a period of at least 30 sec. The loss of righting ability dose (LRA_{50}) and the lethal dose (LD_{50}) were calculated by the method of Litchfield and Wilcoxon (13).

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 2, 1970, from the *Division of Medicinal Chemistry, College of Pharmacy and Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, IA 52240*

Accepted for publication January 8, 1971.

This work was supported in part by U. S. Public Health Service Grant MS-01396. The technical assistance of V. D. Reif is gratefully acknowledged.

NMR Studies on Enolization of 1-*p*-Chlorophenyl-1-hydroxy-2-propanone

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Abstract □ NMR spectroscopy was used to study the enolization of 1-*p*-chlorophenyl-1-hydroxy-2-propanone. At 55°, chloroform solutions of this material gave an equilibrium mixture consisting of the starting material, the enol form, and a third material. This third component was isolated and identified by spectral data as 3,6-bis-(*p* - chlorophenyl) - 1,4 - dimethyl - 2,5,7 - trioxabicyclo - [2,2,1]-heptane. The equilibrium mixture was found to contain 70% of the starting material and 30% of the two reaction products.

Keyphrases □ 1-*p*-Chlorophenyl-1-hydroxy-2-propanone—enolization followed by NMR, characterization of equilibrium mixture □ 3,6-Bis(*p*-chlorophenyl)-1,4-dimethyl-2,5,7-trioxabicyclo-[2,2,1]-heptane—isolation, identification from enolization of 1-*p*-chlorophenyl-1-hydroxy-2-propanone □ NMR spectroscopy—enolization of 1-*p*-chlorophenyl-1-hydroxy-2-propanone

In studies on 1-*p*-chlorophenyl-1-hydroxy-2-propanone, it became necessary to determine if enolization occurred and, if so, to what extent, under what set of conditions, and with what products, if any, being formed. NMR was the analytical method of choice because it was capable of following both the disappearance of the starting material and the appearance of the reaction products as they formed. NMR has been shown to be a valuable analytical tool in the study of reactions and reaction mechanisms (1, 2).

EXPERIMENTAL

All NMR spectra were recorded on a Jeolco C60H spectrometer equipped with a variable-temperature probe. Deuterated chloroform was used as the solvent. Chemical shifts were measured relative to tetramethylsilane.

IR spectra were recorded between 4000–625 $cm.^{-1}$ on a Perkin-Elmer model 21 spectrometer with a sodium chloride prism.

NMR Spectra—A sample of Compound I was dissolved in deuterated chloroform and transferred to an NMR sample tube. The tube was flushed with nitrogen and sealed, and an NMR spectrum was immediately run on the sample. After this spectrum was obtained, the sealed sample tube was placed in a constant-temperature bath set at 55°. The sample was withdrawn at selected intervals, and the NMR spectrum was recorded and integrated.

Isolation of Compound III—The solution containing Compounds I, II, and III was streaked onto 0.5-mm. thick silica gel GF plates. The plates, 20 × 20 cm. (8 × 8 in.), were developed in benzene