The results show that mefruside does possess renal hemodynamic properties but that they are not similar to the renal hemodynamic properties of furosemide. Furosemide decreases renal vascular resistance and thereby enhances renal blood flow (2–5). In contrast, mefruside (10 mg./kg. i.v.) increases renal vascular resistance and thereby decreases renal blood flow. The effect of mefruside on renal blood flow is more like that of the thiazide agents which also increase renal vascular resistance and decrease renal blood flow (2, 8).

REFERENCES

(1) K. Meng and G. Kroneberg, *Arzneim.-Forsch.*, **17**, 659(1967).

(2) J. B. Hook, A. H. Blatt, M. J. Brody, and H. E. Williamson, *J. Pharmacol. Exp. Ther.*, **154**, 667(1966).

(3) J. H. Ludens, J. B. Hook, M. J. Brody, and H. E. Williamson, *ibid.*, **163**, 456(1968).

(4) C. Vorburger, A. M. Harvey, and R. L. Malvin, *Arch. Pharmakol. Exp. Pathol.*, **261**, 346(1968).

(5) J. H. Ludens and H. E. Williamson, *Fed. Proc.*, **28**, 739(1969).

(6) G. E. Schreiner, *Proc. Soc. Exp. Biol. Med.*, **74**, 117(1950).

(7) G. W. Snedecor, "Statistical Methods," 5th ed., Iowa State College Press, Ames, Iowa, 1956, p. 49.

(8) S. Cassin and B. Vogh, *Proc. Soc. Exp. Biol. Med.*, **122**, 970 (1966).

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1-(3,4-Dimethoxyphenyl)-2-propanol Effect on Conditioned Avoidance Response in the Rat

C. F. BARFKNECHT, J. M. MILES, and J. L. LESENEY

Abstract □ The compound, 1-(3,4-dimethoxyphenyl)-2-propanol, was found to prolong latency times initially in a conditioned avoidance response test in rats. It was found to be a CNS depressant in mice. The structural implications of this action, plus the relationship between 1-(3,4-dimethoxyphenyl)-2-propanol and psychotomimetic amphetamines, are discussed.

Keyphrases □ 1-(3,4-Dimethoxyphenyl)-2-propanol—effect on conditioned avoidance response, rat □ Psychotomimetic agents—3,4-dimethoxyamphetamine oxygen analog, pharmacological screening

The literature contains a report indicating that the oxygen analog of mescaline, namely, 3,4,5-trimethoxyphenylethanol (TE), may be psychotomimetic (1). TE was isolated as a product of mescaline metabolism. When it was injected intravenously into rabbits, a mild mescalinelike action was observed.

In structure–activity relationship studies on mescaline, certain methoxylated amphetamines were found to be more potent than mescaline (2). If conversion from β-phenylethylamine to phenylisopropylamine can enhance the potency of psychotomimetics, then a similar logic possibly could be applied to the oxygen analogs of these psychotomimetics. One could anticipate that any mescalinelike actions would be more pronounced in 1-phenyl-2-propanols than in 2-phenylethanols. This paper reports the results of a study on the effect of 1-(3,4-dimethoxyphenyl)-2-propanol (DP), which is the oxygen analog of the psychotomimetic agent 3,4-dimethoxyamphetamine, on conditioned avoidance response (CAR) in the rat.

RESULTS AND DISCUSSION

Although the synthesis of DP was reported in the literature (3), no pharmacological information on the compound could be found. Initially the effect of DP on CAR in rats was studied. The evaluation of drug action on CAR has been exploited widely. This technique has been especially valuable for the evaluation of psychotomimetics (4).

To determine whether DP is producing an effect similar to mescaline or 3,4-dimethoxyamphetamine (3,4-DMA), the effects of these drugs at various dosages on a running response in conditioned male rats were determined. Each drug was given in three dosage levels ("effective dose," one quarter the effective dose, and four times the effective dose) to groups of six rats. Figures 1 and 2 show the mean reaction time for each trial during the drug sessions for each dosage level of mescaline and 3,4-DMA. That the profile of 3,4-DMA is not completely analogous to mescaline may be due to the amphetamine structure present in 3,4-DMA. CNS stimulation caused by amphetamine would be expected to counteract the increased reaction times. Figure 3 shows the enhanced performance caused by amphetamine sulfate relative to placebo. The lower dose was more effective.

Since 3,4-DMA is expected to be a poorer stimulant than amphetamine itself (*i.e.*, require a much larger dose to cause the same effect), the greatest variation from the mescaline profile would be expected at the higher doses. The large variation between reaction times of adjacent trials is observed in both mescaline and 3,4-DMA, which suggests that this is a characteristic feature of the behavior disruption caused by these agents.

Figure 4 shows the effects of DP. The overall profile of the drug session is substantially different from any of the other drugs tested. When it became clear that DP was different, it was subjected to a more conventional pharmacological screening. In mice intraperitoneally it was a CNS depressant [ED_{50}(sleep) = 150 mg./kg; LD_{50} = 650 mg./kg.] (5). This pharmacological action of DP is not unexpected in light of the report that acetophenones and other phenones and their corresponding alcohols exhibit depressant effects (6). Thus, DP may be viewed as a structural isomer of these phenones and alcohols.

The data presented here suggest that a reevaluation of the pharmacological effects of TE is required.[1] A detailed study of the structure–activity relationships and the mechanism of action of ring-substituted phenyl-2-propanols, phenyl-2-propanones, and chemi-

[1] Preliminary, unpublished studies indicate that TE has a CNS-depressant effect, ED_{50}(sleep) > 650 mg./kg. i.p. in mice.

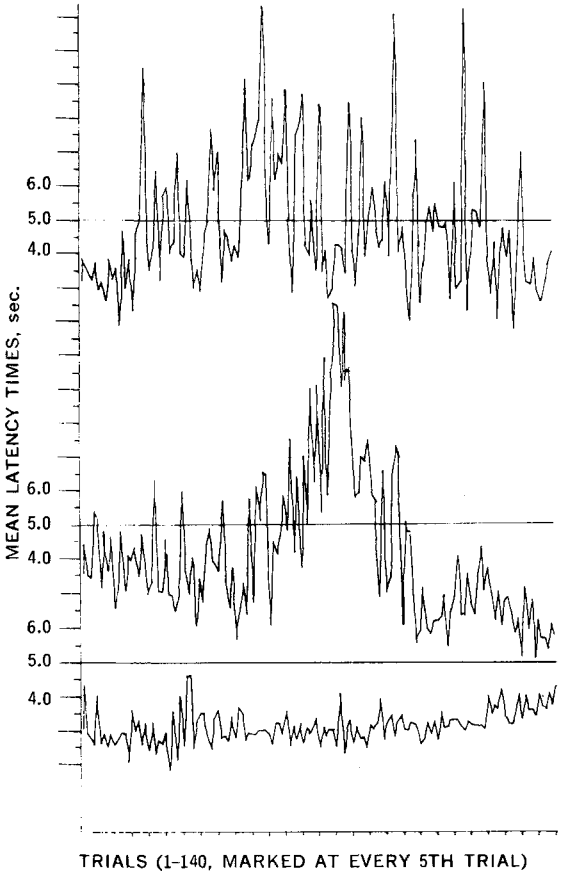

Figure 1—*Effect of mescaline hydrochloride on CAR. Doses (bottom to top) were 6.3, 25, and 100 mg./kg., respectively. The horizontal lines at 5.0 sec. for each dose separate avoidance (<5 sec.) and non-avoidance (>5 sec.) of shock.*

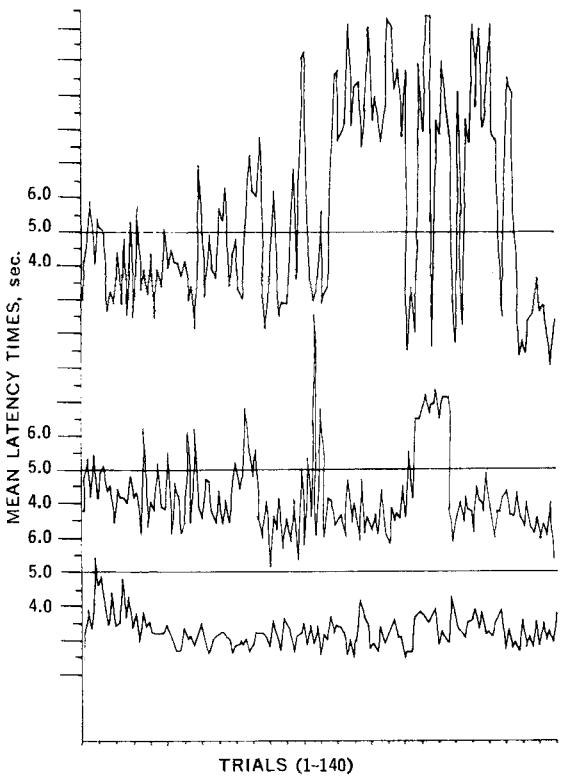

Figure 2—*Effect of 3,4-dimethoxyamphetamine hydrochloride on CAR. Doses (bottom to top) were 3.1, 12.5, and 50 mg./kg., respectively.*

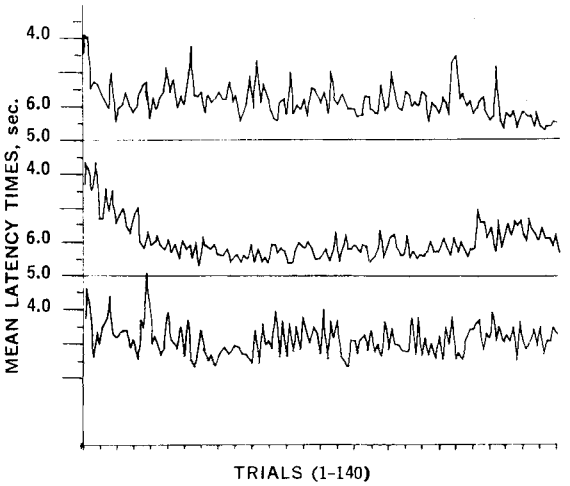

Figure 3—*Effect of placebo (0.9% saline solution, bottom) and dextroamphetamine sulfate at 1 and 4 mg./kg., respectively, on CAR.*

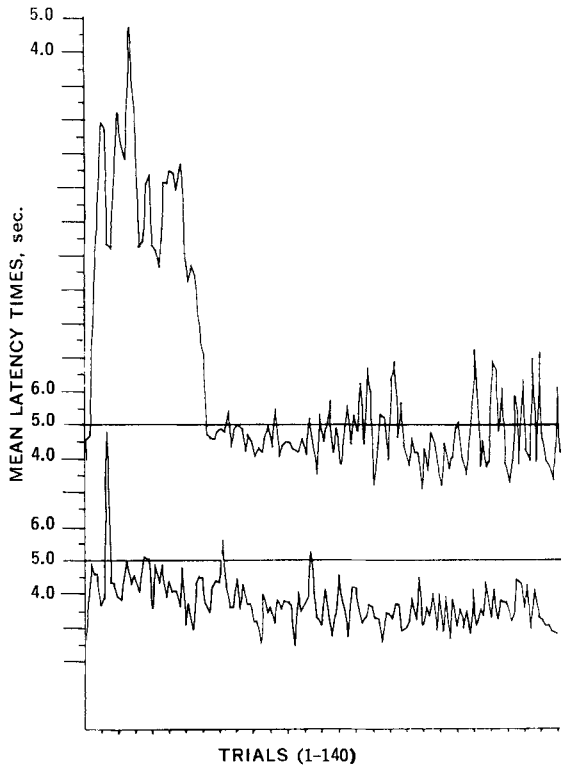

Figure 4—*Effect of 1-(3,4-dimethoxyphenyl)-2-propanol at 3.1 and 12.5 mg./kg., respectively, on CAR.*

cally related compounds is underway and will be the subject of a future communication.

EXPERIMENTAL

An A-584 automatic shuttlebox system[2] was used to measure a running response in male, 70–100-day-old, hooded rats.

Training—Each animal was required to cross from one side to the other in response to a conditioned stimulus (a buzzer, 5 sec.). At the end of this time, the unconditioned stimulus (electric shock, 1.0 mamp., maximum time = 15 sec.) was administered if the animal had failed to cross. The trial ended when the animal made the cross or when a total of 20 sec. had elapsed. After a 40-sec. intertrial interval, the sequence was repeated. Each rat received 20 trials per day until

[2] Lafayette Instrument Co., Lafayette, Ind.

it attained 90% avoidance of unconditioned stimulus on that day or until it had received 200 trials. Rats failing to reach the criterion were discarded. Those attaining 90% avoidance were dosed with drugs (randomly selected) the following day.

Drug Session—The day following attainment of criterion the rat was injected with a saline solution of a drug intraperitoneally and immediately placed in the shuttlebox. A series of 140 trials was given, and the data (escape or avoidance and reaction time) were automatically recorded. With the exception of extremely unruly subjects, the rats were completely isolated during the entire drug session. After the drug day, the rats were discarded.

Some animals died during the drug sessions with mescaline hydrochloride at 25 mg./kg. (after Trials 77, 87, and 97) and at 100 mg./kg. (after Trials 60, 61, and 68), and with 3,4-DMA hydrochloride at 12.5 mg./kg. (after Trial 53) and at 50 mg./kg. (after Trials 66, 67, and 73). The animals were not considered in the computation of mean reaction times after death.

REFERENCES

(1) M. Goldstein, A. L. Friedhoff, S. Pomerantz, C. Simmons, and J. F. Contrera, *J. Neurochem.*, **6**, 253(1961); A. L. Friedhoff and M. Goldstein, *Ann. N. Y. Acad. Sci.*, **96**, 5(1962).

(2) J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Jr., *Nature*, **216**, 128(1967); A. T. Shulgin, T. Sargent, and C. Naranjo, *ibid.*, **221**, 537(1969).

(3) A. A. Chuksarrova, L. L. Serguva, and N. N. Sharygina, *Izv. Akad. Nauk SSSR*, **1959**, 2219; E. Adler and J. Morton, *Acta Chem. Scand.*, **15**, 357(1961).

(4) J. R. Smythies, E. A. Sykes, and C. P. Lord, *Psychopharmacologia*, **9**, 434(1966); J. R. Smythies, R. J. Bradley, V. S. Johnston, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **10**, 379 (1967).

(5) J. P. Long, personal communication.

(6) R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178(1964) and previous references cited therein.

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COMMUNICATIONS

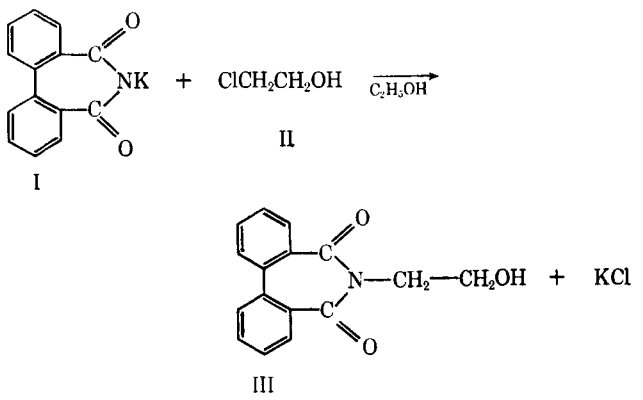
Preparation of Ethyl Diphenamate in Ethanol Using Potassium Diphenimide and 2-Chloroethanol

Keyphrases ☐ Ethyl diphenamate—synthesis ☐ *N*-(2-Hydroxyethyl)-diphenimide synthesis—literature correction ☐ NMR spectroscopy—structure

Sir:

The preparation of *N*-(2-hydroxyethyl)-diphenimide (III, Scheme I) was reported in 1952 by Demers and Jenkins (1). The approach taken in preparing this compound involved the reaction of potassium diphenimide (I) with 2-chloroethanol (II) in ethanol (1). Since this route of synthesis had been used successfully by Moore and Rapala (2) in the preparation of a series of dialkylaminoalkyl phthalimide derivatives, it appeared unlikely that a product other than that reported (III) would be obtained. Elemental nitrogen analysis of Compound III reported by these workers was well within experimental error.

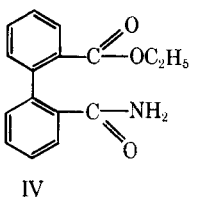
In 1963, Jenkins *et al.* (3) reported that during the attempted synthesis of a series of dialkylaminoalkyl diphenimide hydrochloride salts, using a similar procedure to that reported by Demers and Jenkins (1), the corresponding hydrochloride salts of ethyl diphenamate were formed rather than the diphenimide derivatives. The similar chemical nature of the alkylating species in these reactions prompted us to repeat



Scheme I

the work of Demers and Jenkins to determine if Compound III had actually been obtained.

The results of our work, which we report at this time, shows that Demers and Jenkins did not prepare *N*-(2-hydroxyethyl)-diphenimide (III) as reported but instead obtained ethyl diphenamate (IV).



IV

Identification of Compound IV was established as follows: (*a*) an NMR spectrum showed peaks at 6.83–8.00 δ (m, 8, Ar), 6.08 δ (b.s., NH_2), 4.09 δ (q, CH_2),