Brit. J. Pharmacol. (1953), 8, 22.

SOME MORPHINE-LIKE PROPERTIES OF (±)-*CYCLO*HEXYLOXY-*ALPHA*-PHENYLETHYLAMINES

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(RECEIVED JULY 1, 1952)

Analgesic activity has been reported in a wide range of arylalkylamines, mainly derivatives of β-phenylethylamine (Fellows and Ullyot, 1951). The moderate degree of activity of *m*- and *p-cyclo*hexyloxy-α-phenylethylamine described below was of interest because of the close chemical resemblance to the antipyretic analgesic, phenacetin (*p*-ethoxyacetanilide). This activity might be related either to the antipyretics or to the opiates. Information on this point was sought in their general pharmacology, since it has been found empirically that analgesics, other than the antipyretics, show qualitative similarity over a range of pharmacological properties in spite of gross dissimilarity in chemical structure. For comparison, three closely related amines, *m*- and *p-iso*propyloxy-, and *p*-ethoxy-α-phenylethylamine, which are not analgesic, have been examined.

RESULTS

The amines were given intraperitoneally (unless otherwise stated) as the hydrochlorides, which form stable neutral aqueous solutions.

Acute Toxicity.—Groups of 10 to 15 male albino mice were used at each dose level. Large doses induced convulsions of mixed type. The *cyclo*hexyl ethers caused violent, predominantly tonic convulsions with marked opisthotonos, after an initial phase of excitability with the Straub sign, but the *iso*propyl and ethyl ethers induced predominantly clonic convulsions with no Straub sign. Death was apparently due to respiratory failure. The LD50 and limits of confidence (Table I) were calculated as described by Emmens (1948).

Analgesic Activity.—The mean % elevation of reaction threshold, 30 minutes after injection, was assessed by Thorp's (1946) modification of the method of D'Amour and Smith (1941). Three groups of eight albino rats received the drug, saline, and morphine on alternate days. The *m*- and *p-cyclo*hexyl ethers gave linear log.-dose response curves, $y=200x-190$ and $y=138x-133$ respectively, where $y=\%$ elevation in reaction threshold and $x=$log. dose. Doses equivalent to morphine (4 mg./kg.) were respectively 11.5 and 13.5 mg./kg. The *iso*propyl and ethyl ethers were inactive at 20 mg./kg. Time-action curves (in a more sensitive strain of rats) showed that the maximal response to morphine was reached later than that to the *cyclo*hexyl ethers; the latter caused a sharp rise to a maximum in 10 to 20 minutes, followed by a rapid fall in reaction threshold. Averaged data from several curves are summarized in Table II. (The *m-cyclo*hexyl ether was not examined fully because of its pronounced tendency to produce local necrosis.) The *p-cyclo*hexyl ether was quite inactive subcutaneously, probably owing to failure of absorption, since the injection site slowly hardened and sloughed (cf. s.c. toxicity). Depressant activity was not measured, but it was noted in these tests that there was depression of spontaneous movement following the injection. This was especially marked after the *p-cyclo*hexyl ether. The depression outlasted anal-

TABLE I

ACUTE TOXICITIES OF ALKOXY α-PHENYLETHYLAMINE HYDROCHLORIDES IN MICE

Structure R′ R —CH(NH$_2$)CH$_3$		Hydrochloride	LD50 mg./kg. (Limits of confidence in parentheses		
R	R′	m.p.	i.p.	i.v.	s.c. (abdomen)
H	O C_6H_{11}*	—	117 (110–125)	54 (50–60)	388 (303–496)
H	O C_3H_7†	86°	132 (123–142)	—	—
O C_6H_{11}*	H	180°	170 (160–180)	58 (49–69)	>800‡
O C_3H_7†	H	122°	178 (170–187)	—	—
O C_2H_5	H	204°	180 (168–193)	—	—

* C_6H_{11}=*cyclo*hexyl. † C_3H_7=*iso*propyl. ‡ 20% mortality at 800 mg./kg.

TABLE II

COMPARISON OF THE MAXIMUM ANALGESIC ACTIVITY AND DURATION OF EFFECT, IN RATS, OF *p-CYCLO*HEXYLOXY-α-PHENYLETHYLAMINE HYDROCHLORIDE AND MORPHINE SULPHATE AFTER INTRAPERITONEAL INJECTION

Drug	Dose mg./kg.	No. of Rats	Mean % Elevation of Reaction Threshold*		Mean Peak Time* (min.)	Duration (approx.) (min.)
			At Peak	At 30 Min.		
Morphine sulphate	4	6	60 (20–106)	43 (9–60)	36 (20–60)	80
	5	6	150 (90–293)	44 (11–105)	65 (40–95)	130
p-cyclo-Hexyloxy-α-phenyl-ethyl-amine HCl	5	6	122 (78–172)	0	5	15
	10	6	147 (95–236)	45 (0–153)	15 (8–25)	40
	15	7	222 (120–331)	60 (0–177)	11 (7–20)	50
m-cyclo-Hexyloxy-α-phenyl-ethyl-amine HCl	10	3	130 (103–164)	85 (46–136)	17 (15–20)	40

* Range in parenthesis.

gesic activity of both *cyclo*hexyl ethers by about one hour.

Tolerance to the Analgesic Response.—Six rats were injected daily for four weeks (except Sundays) with the *p-cyclo*hexyl ether (15 mg./kg.). The analgesic response was measured weekly.

TABLE III

THE EFFECT OF CONTINUED DOSAGE (15 MG./KG. I.P.) ON THE ANALGESIC ACTIVITY OF *p-CYCLO*HEXYLOXY-α-PHENYLETHYLAMINE HCl IN RATS

Mean of 4 rats. Ranges are given in parentheses. The "normal" threshold is proportional to the heat delivered by the lamp.

Time (weeks)	Wt. (g.)	"Normal" Threshold	Max. % Elevation of Reaction Threshold
0	368	63 (58–72)	296 (192–353)
1	359	88 (69–132)	179 (30–300)
2	328	114 (72–144)	164 (14–274)
3	344	117 (100–144)	60 (0–100)
4	334	123 (79–156)	61 (17–52)

One rat died of infection and another was rejected because of sluggish reactions. The averaged data for the remainder are summarized in Table III. Complete tolerance to the drug was not established during four weeks, and the observed reduction in % elevation of reaction threshold is due in some measure to the progressive rise in "normal" threshold. There was little alteration in duration of effect or in the time taken to reach the peak response, but whereas the animals initially showed strong depression after the daily dose, two weeks later this was replaced by a short phase of excitability followed by mild depression. No abstinence syndrome was observed on cessation of dosage and the animals remained healthy for some weeks.

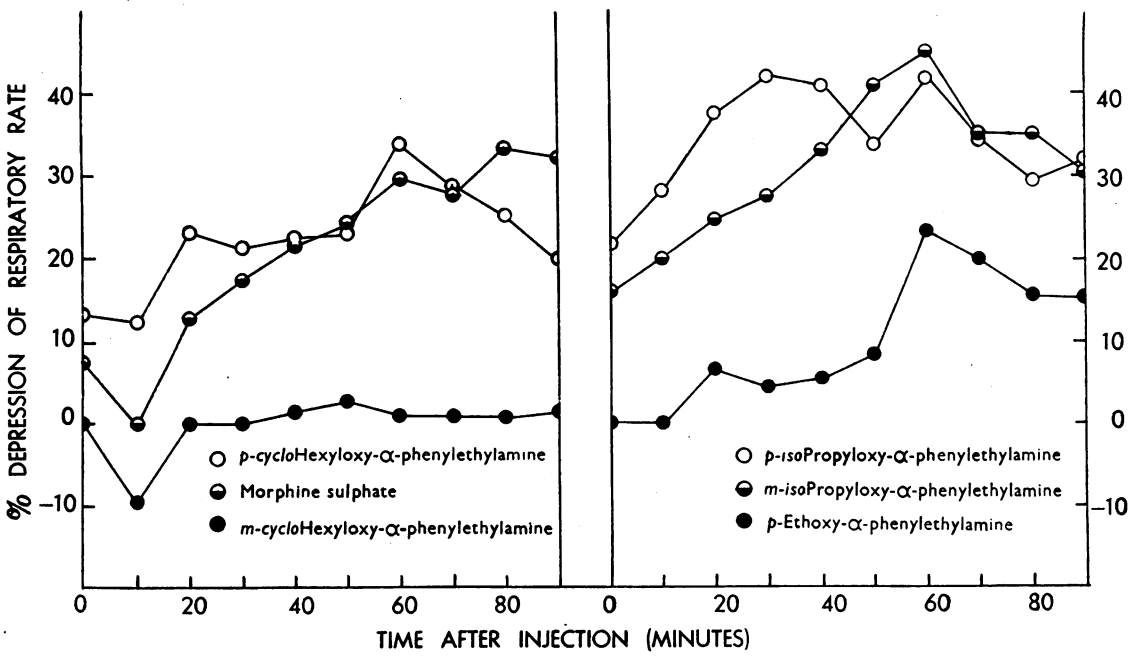

FIG. 1.—Rats, urethane 1 g./kg. The depression of respiratory rate by α-phenylethylamines (20 mg./kg.) and morphine (5 mg./kg.) after intraperitoneal injection. The ordinates represent the mean percentage increase in the time taken for 25 breaths in eight rats compared to a similar group receiving saline. The curves do not start at a common point owing to the large variation in respiratory rate in individual rats; the rate of the controls is taken as zero.

Respiratory Depression.—The rate of respiration has been measured by recording chest movements by a thread and lever writing on a kymograph drum. Urethane (1 g./kg. i.p.) was used to immobilize the animals. In eight controls there was no depression of rate for the first hour. Eight rats were used for each amine (except the *p*-ethoxy ether; five) and the mean depressions of rate are plotted in Fig. 1. The *iso*propyl ethers were most active and gave strong depression lasting about 90 minutes.

Blood Sugar.—No significant effect could be recorded in groups of five rats after a dose of the amines (20 mg./kg.) or morphine (10 mg./kg.), determinations being made at half-hourly intervals, on blood drawn from the tail tip, by the method of Nelson (1944) and the single copper reagent of Somogyi (1945). Rabbits similarly gave no significant response. There was considerable difficulty in obtaining rat blood after the *p-cyclo*hexyl ether.

Body Temperature.—The rectal temperatures of groups of five rats were taken at intervals of 15 minutes after injection. A short training period was given on each of two days before the experiment. Saline gave small insignificant rises in temperature, whereas the amines (20 mg./kg.) and morphine (5 mg./kg.) consistently gave a fall 30 minutes after injection lasting two hours. Significant falls of 1–1.5° C. were obtained with both *cyclo*hexyl ethers ($P=0.01$) and with morphine ($P=0.05$). The significance of the falls due to the *iso*propyl and ethyl ethers was lower ($P=0.1$). The falls in temperature after the *cyclo*hexyl ethers and morphine were significant during the phase of maximal respiratory depression (which occurred much later than the analgesic maximum). There was no such correlation with the *iso*propyl ethers in spite of their powerful effect on respiration.

Blood Pressure.—The method of Crawford and Outschoorn (1951) for the rat was followed except that the vagi were not cut and the tail vein was found to be more convenient for injection. Similar results were obtained for each drug in two or more animals. Saline gave no response. The *cyclo*hexyl ethers (0.5–1 mg.), like morphine, produced an immediate fall of blood pressure of 10–20 mm. Hg, followed by a secondary rise. The fall in blood pressure was transitory and some degree of acute tolerance to subsequent doses was shown. Similar responses were obtained in the spinal cat. The *p-cyclo*hexyl ether produced a temporary apnoea at the same time as the rapid fall. The ethyl ether (1 mg.) produced an immediate transient rise in blood pressure of approximately 10 mm. Hg. The *iso*propyl ethers (0.5–1 mg.) had no immediate effect, but after some five minutes sudden rises in blood pressure, often paroxysmal, occurred, followed usually by death of the animal.

Smooth Muscle.—The spasm of rat duodenum in Tyrode (25 c.c.) due to acetylcholine (1 μg.) was not appreciably affected by the *iso*propyl and ethyl ethers. The *cyclo*hexyl ethers had slight activity at 400 μg., whereas pethidine completely relaxed the muscle at 100 μg.

Discussion

Antipyretics give poor responses in analgesic assays using a heat stimulus (Smith, D'Amour, and D'Amour, 1943; Birren, Schapiro, and Miller, 1950), but the analgesic activity of aminopyrine by these methods is greater than that of its less basic analogue, phenazone. This suggested that the strongly basic nature of the alkoxy α-phenylethylamines might account for their activity in assays where phenacetin gives poor results. However, the pharmacological similarity between morphine and *m-* and *p-cyclo*hexyloxy α-phenylethylamine (Table IV), emphasized by the contrasting

Table IV

COMPARATIVE PHARMACOLOGY OF MORPHINE AND ALKOXY-α-PHENYLETHYLAMINES

Drug	Analgesic Activity (Heat Stimulus)	Nature of Convulsant Activity	Straub Sign (Mice)	Respiratory Depression	Blood Pressure	Body Temp. Reduction
Morphine	+++	Tonic	+	++	Fall	+
p-cyclo-Hexyloxy-	++	Tonic	+	+	Fall	++
m-cyclo-Hexyloxy-	++	Tonic	+	−	Fall	+
p-iso-Propyloxy-	−	Clonic	±	++	Rise	±
m-iso-Propyloxy-	−	Clonic	−	++	Rise	±
p-Ethoxy-	−	Clonic	−	+	Rise	±

Column 1 indicates the etherifying group of α-phenylethylamine.

behaviour of the closely related *iso*propyl ethers, suggests that the mode of action of the *cyclo*hexyl ethers resembles that of morphine rather than the antipyretics. Similar qualitative concordance of properties has been described for pethidine (Yonkman, 1948) and amidone (Thorp, 1949; Scott and Chen, 1946; Chen, 1948), in spite of little discernible structural resemblance. The relatively inert nature of *p*-ethoxy α-phenylethylamine, structurally analogous to phenacetin, stresses the dissimilarity to the antipyretics. In contrast to

β-phenylethylamines, few α-phenylethylamines have been found to be analgesic. Like pethidine and amidone, *m-cyclo*hexyloxy α-phenylethylamine shows a formal resemblance to structures present in the morphine molecule.

Morphine has influence on the whole cerebrospinal axis. It might be expected that morphine or morphine-like drugs would show some difference in the time taken to reach peak responses for different effects which are mediated at different levels in this axis. In these experiments an attempt to standardize conditions with respect to the animal used, the dose employed, and route of administration was made to see if any such dissociation occurred. It was found that the peak analgesic response occurred appreciably before the peak of respiratory depression or reduction in body temperature. These two properties showed correlation in time in morphine and the *cyclo*hexyl ethers but not in the *iso*propyl ethers. It is generally assumed that the respiratory effects of morphine are mediated in the respiratory centres of the brain, whereas there is evidence that the responses used in heat stimulus assays are mediated by spinal reflexes. Spinal animals give the same type of response as intact animals (Bonnycastle and Leonard, 1950; Houde and Wikler, 1951; Irwin, Houde, Bennett, Hendershot, and Seevers, 1951). The observed dissociation in time fulfils expectation, but the reason can only form the subject of speculation.

Two generalizations have emerged from recent work on analgesics with which the results with the *cyclo*hexyl ethers agree. The assay of potency of analgesics by measurement of spinal reflex depression in animals, by dulling of experimental pain in man, and by relief of pain in clinical conditions give broadly parallel results. These methods probably involve distinct neuronal pathways. Secondly, analgesics show similar qualitative behaviour in properties unrelated to pain perception. These generalizations hold good although there is no real chemical relationship between the different classes of analgesic. It seems reasonable to assume either that analgesics act on the same type of structure common to various parts of the central nervous system—e.g., Wikler (1950) suggests internuncial neurones—or that they act on physiological mechanisms common to different structures in the central nervous system.

Summary

1. *m-* and *p-cyclo*Hexyloxy-α-phenylethylamine show qualitative similarity to morphine in analgesic activity, respiratory depression, effect on body temperature and blood pressure. No consistent response was obtained for blood sugar changes.

2. *m-* and *p-iso*Propyloxy- and *p*-ethoxy-α-phenylethylamine have no analgesic activity and, apart from respiratory depression their pharmacological properties are different from those of the *cyclo*hexyl ethers and morphine.

3. Evidence was obtained to show that the analgesic effect of the *cyclo*hexyloxy-α-phenylethylamines is more nearly related to that of morphine, amidone, and pethidine than to the chemically analogous antipyretic and analgesic phenacetin.

Part of this work was carried out in the Department of Pharmacology, University of Leeds, during tenure of a Beit Memorial Fellowship for Medical Research. The author thanks Professor W. A. Bain, F.R.S.E., for his encouragement, Dr. P. Hey for guidance in pharmacological technique, and Miss R. Brown for technical assistance. Part of the work was aided by a grant from the Research Fund of the Bethlem Royal and Maudsley Hospitals.

References

Birren, J. E., Schapiro, H. B., and Miller, J. H. (1950). *J. Pharmacol.*, **100**, 67.

Bonnycastle, D. D., and Leonard, C. S. (1950). Ibid., **100**, 141.

Chen, K. K. (1948). *Ann. N.Y. Acad. Sci.*, **51**, 83.

Crawford, T. B. B., and Outschoorn, A. S. (1951). *Brit. J. Pharmacol.*, **6**, 8.

D'Amour, F. E., and Smith, D. L. (1941). *J. Pharmacol.*, **72**, 74.

Emmens, C. W. (1948). *Principles of Biological Assay*, pp. 150–159. London: Chapman and Hall.

Fellows, E. S., and Ullyot, G. E. (1951). *Medicinal Chemistry*, vol. I, p. 390. New York: John Wiley and Sons.

Houde, R. W., and Wikler, A. (1951). *J. Pharmacol.*, **103**, 236.

Irwin, S., Houde, R. W., Bennett, R. D., Hendershot, L. C., and Seevers, M. H. (1951). Ibid., **101**, 132.

Nelson, N. (1944). *J. biol. Chem.*, **153**, 375.

Scott, C. C., and Chen, K. K. (1946). *J. Pharmacol.*, **87**, 63.

Smith, D. L., D'Amour, M. C., and D'Amour, F. E. (1943). Ibid., **77**, 184.

Somogyi, M. (1945). *J. biol. Chem.*, **160**, 61.

Thorp, R. H. (1946). *Brit. J. Pharmacol.*, **1**, 113.

—— (1949). Ibid., **4**, 98.

Wikler, A. (1950). *Pharmacol. Rev.*, **2**, 435.

Yonkman, F. F. (1948). *Ann. N.Y. Acad. Sci.*, **51**, 59.