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The Comparative Cardiovascular Effects of Substituted Cyclohexane Derivatives

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THE COMPARATIVE CARDIOVASCULAR EFFECTS OF
SUBSTITUTED CYCLOHEXANE DERIVATIVES

BY

JOHN CHARLES SMITH, JR.

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
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OF

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ABSTRACT

The trans-2-o-tolyl, cis-2-o-tolyl, trans-2-p-tolyl and cis-2-p-tolyl derivatives of cyclohexylamine hydrochloride and six other cyclohexane derivatives were tested for their effects on intact anesthetized rats, isolated rat atria, isolated guinea pig hearts, isolated guinea pig intestines, and intact anesthetized cats. Most of these compounds produced effects on the cardiovascular system and on the small intestine in varying degrees.

Trans-2-o-tolylcyclohexylamine hydrochloride was the most potent of the cyclohexylamine series tested. Of the six other compounds tested, 2-o-tolylcyclohexan-2-one (#204) was the most potent in its cardiovascular effects.

Studies indicate that trans-2-o-tolylcyclohexylamine hydrochloride does not produce toxic effects in doses which elicit its cardiovascular actions.

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I. INTRODUCTION

Previous studies have shown that cyclohexane and cyclohexanol derivatives actively affect the cardiovascular system. Cyclohexane and cyclohexanol derivatives have been shown to be capable of producing cardioplegia in dogs undergoing cardiopulmonary bypass. Correlations were shown by Smookler (1962) between the isomer of cyclohexanol and its degree of activity.

New cyclohexylamine hydrochloride derivatives of cyclohexane were prepared to test this class of compounds on the cardiovascular system, to determine the existence of structure-activity relationships, and to assess their ability to produce cardioplegia. These compounds were also tested for their effects on isolated smooth muscle to determine the presence of other actions by this series.

II. REVIEW OF THE LITERATURE

During the past few years the cyclohexane group has been included in a number of compounds which have been investigated for their possible use as drugs. Cyclohexane and its many derivatives have been extensively investigated for industrial use. However, few of these compounds have been tested for pharmacological actions.

Huitric et al. (1959) reported that trans-2-o-tolylcyclohexanol produced mechanical arrest in the hearts of experimental animals. Nelson et al. (1959) also investigated this compound and reported similar findings.

Snookler and DeFoe (1962) extensively investigated cyclohexane and substituted 2-aryl derivatives of cyclohexanol and found that these compounds actively affect the cardiovascular system. The compounds tested were shown to be capable of lowering the blood pressure of intact rats and depressing myocardial contractility of isolated and intact hearts. Substitution of chlorophenyl or tolyl groups in the 2-aryl position of the cyclohexanol moiety was found to increase the hypotensive effect from six to forty times. All in the series except cis-2-o-tolyl and cis-2-o-chlorophenylcyclohexanol produced cardiac arrest of isolated perfused guinea pig hearts. Once again, the substitution of these groups increased the cardio-inhibitory activity of cyclohexanol from four to twenty times. Trans-2-o derivatives were the most active on the isolated guinea pig hearts. Atrial studies conducted showed that the depressant action of trans-2-o-tolylcyclohexanol was antagonized by calcium.

Unpublished work of Smookler (1961) showed that trans-2-*p*-tolylcyclohexanol and trans-2-*p*-chlorophenylcyclohexanol also produced cardioplegia in dogs undergoing cardiopulmonary bypass. In some of these experiments, the normal heart beat returned following the arrest.

Other compounds containing the cyclohexyl group have been investigated. Greifenstein et al. (1958) studied 1-(1-phenylcyclohexyl)piperidine hydrochloride (Sernyl) for use in anesthesia. When given intravenously to human patients, the substance produced good analgesia but did not relax muscles. When doses larger than normal were given, convulsions occurred initially. The blood pressure and the respiration both increased slightly.

Lear et al. (1959) have tested *n*-ethyl-1-phenylcyclohexylamine monohydrochloride (cyclohexamine) and Sernyl clinically as analgesic agents for use in major surgery and found that they produce blockade of sensory impulses without producing sleep. However, psychic disturbances resulted following the use of Sernyl. Neither compound depressed blood pressure or respiration. The site of action of these drugs was not found. Cardiac rhythm was unaffected. Also, there was an increase in salivation.

Luby et al. (1959) studied the psychic effects of 1-(1-phenylcyclohexyl)piperidine monohydrochloride and found that the drug produced a psychopathology similar in nature to primary symptoms of the schizophrenic process.

The two derivatives, 1-(1-phenylcyclohexyl)piperidine

monohydrochloride and n-ethyl-1-phenylcyclohexylamine monohydrochloride have been studied by Adey and Dunlop (1960). These compounds were found to interfere with a learned approach in a T-maze situation for periods of up to twenty-four hours following interperitoneal injection in cats. Electroencephalograph records show that an interference with discharge from the hippocampal structures was produced during the period in which these derivatives were active.

III THE INVESTIGATION

A. OBJECTIVES

Substituted cyclohexylamine hydrochloride derivatives and miscellaneous cyclohexane derivatives have been recently synthesized. No reports were found in the literature of their actions, and this investigation was undertaken to determine their effects on the cardiovascular system and on other systems, and to determine whether structure activity relations can be established for the 2-aryl isomers of cyclohexylamine hydrochloride.

This investigation includes:

1. The screening of the compounds for their effects on the animals or tissues used.
2. The attempt to determine mechanisms by which these compounds produce their effects.

B. THE COMPOUNDS

The compounds used have been prepared by Dr. Alain C. Haitric of the Department of Pharmaceutical Chemistry, University of Washington, College of Pharmacy, Seattle, Washington. The cyclohexylamine hydrochloride salts (Fig. 1) are readily soluble and aqueous solutions of these derivatives were used throughout the investigation. All the other compounds (Fig. 2) were soluble in polyethyleneglycol (PEG) 400. The polyethyleneglycol solutions of

Fig. 1 Cyclohexylamine derivatives

Fig. 2 Miscellaneous cyclohexane derivative

Fig. 1 - CYCLOHEXYLAMINE HYDROCHLORIDE DERIVATIVES

R

Fig. 2 - MISCELLANEOUS CYCLOHEXANE DERIVATIVES

CYCLOHEXANONE

2-o-TOLYL

2-p-TOLYL

2-o-TOLYL CYCLOHEXEN-2-ONE

2-o-TOLYL CYCLOHEX-4-EN-1-OL

ETHYL-2-(p-TOLYL-1-HYDROXY)
CYCLOHEXYL ACETATE

these compounds were used throughout the investigation.

C. ANIMALS USED

1. Rats - Albino rats of the Wistar (MW-2) strain were employed in part in the investigation.
2. Guinea pigs - The guinea pigs were of a heterogenous group.
3. Cats - The Cats were of a heterogenous group.

D. EXPERIMENTAL PROCEDURES AND RESULTS

This investigation was divided into five sections:

1. The effects of the cyclohexylamine derivatives on the blood pressure of intact anesthetized rats and cats.
2. The effects of all of the compounds on isolated guinea pig atria.
3. The effects of all of the derivatives on isolated perfused guinea pig hearts.
4. The effects of all of the derivatives on isolated small intestinal strips.

1. Effects of Substituted Cyclohexylamine Hydrochloride Products on the Blood Pressure of Rats and Cats

a. Experimental Procedures

The blood pressure of male albino rats was recorded using direct cannulation of the carotid artery. A mercury manometer, connected via a fluid bridge of sodium chloride 0.9 per cent to the cannula, was utilized. Recordings were made by a glass writing lever on smoked kymograph paper. The cannula was filled with heparin to prevent the blood from clotting.

The animals were anesthetized with sodium pentobarbital, 35 mg./kg. (IP). The trachea was cannulated to allow unobstructed respiration. Injection of the drugs was made into either femoral vein, by a needle permanently secured to the vessel.

When the blood pressure studies were made using cats, the blood pressure was recorded on a physiograph, using a calibrated Statham transducer.

Allowing sufficient recovery from the previous injection, as many as three injections were made into each rat. The usual response was an immediate drop in the blood pressure, often followed by a gradual rise. At least twenty minutes were allowed between injections of the drug to allow the blood pressure to stabilize.

The observations made in these studies include:

1. The per cent drop in blood pressure produced by the compound.

2. The period of time required for the blood pressure to return to 95 per cent of its normal value prior to injection of the drug.

5. Results

The results include the following:

1. The effects of substituted cyclohexylamine hydrochloride derivative on the blood pressure of rats and cats.

(Tables I to V)

2. A comparison of the effects of the several compounds tested on the blood pressures. (Table VI; Fig. 3)

3. A comparison of the effects of selected doses of the various compounds on the blood pressures of the rat and of the cat. (Table VII)

Table I Effects of trans-2-p-tolylcyclohexylamine hydrochloride on the blood pressure of rats

DOSE (mg/kg)	NORMAL BLOOD PRESSURE (mm)	% DROP IN BLOOD PRESSURE	TIME FOR 95% RECOVERY (minutes)
4.0	156.0	33.3	A
6.0	124.0	41.1	53.0
12.0	100.0	52.0	34.0
18.0	106.0	72.2	58.0
24.0	153.0	70.6	30.0
36.0	74.0	B	B

A incomplete recovery obtained

B animal died

Table II Effects of cis-2-p-tolylcyclohexylamine hydrochloride on the blood pressure of rats

DOSE (mg/kg)	NORMAL BLOOD PRESSURE (mm)	% DROP IN BLOOD PRESSURE	TIME FOR 95% RECOVERY (minutes)
6.0	106.0	45.1	A
6.0	117.0	39.3	20.0
12.0	96.0	52.1	20.0
16.0	92.0	54.3	9.0
18.0	104.0	33.6	60.0
18.0	96.0	44.0	3.0
18.0	96.0	B	B
18.0	54.0	B	B
18.0	90.0	37.8	8.0
24.0	98.0	99.0	A
30.0	70.0	B	B

A incomplete recovery obtained

B animal died

Table III Effects of trans-2-(2-tolyl)cyclohexylamine hydrochloride on the blood pressure of rats

DOSE (mg/kg)	NORMAL BLOOD PRESSURE (mm)	% DROP IN BLOOD PRESSURE	TIME FOR 95% RECOVERY (minutes)
3.0	94.0	34.0	8.0
6.0	116.5	48.9	66.0
8.3	105.0	51.4	50.0
9.0	100.0	42.5	33.0
9.0	97.0	40.2	A
9.0	135.0	54.8	A
9.0	79.0	41.8	A
9.0	116.0	B	B
12.0	120.0	76.7	13.0
15.0	98.5	72.0	48.0
18.0	91.0	74.2	B
21.0	112.0	91.1	B

A incomplete recovery obtained

B animal died

Table IV Effects of cis-2-o-tolylcyclohexylamine hydrochloride on the blood pressure of rats

DOSE (mg/kg)	NORMAL BLOOD PRESSURE (mm)	% DROP IN BLOOD PRESSURE	TIME FOR 95% RECOVERY (minutes)
3.0	55.0	54.5	68.0
3.0	97.0	38.2	A
6.0	93.0	28.0	A
9.0	94.0	25.5	80.0
9.0	100.0	51.0	3.0
12.0	69.0	53.6	3.0
15.0	95.0	44.2	3.0
15.0	90.0	37.8	A
18.0	148.0	56.8	B
18.0	108.0	38.0	A
18.0	90.0	42.2	40.0
21.0	95.0	37.9	16.0
21.0	111.0	73.9	80.0
24.0	111.0	72.9	90.0
27.0	89.0	75.3	A
30.0	102.0	B	B
33.0	67.0	95.6	A

A incomplete recovery obtained

B animal died

Table V Effects of substituted cyclohexylamine hydrochloride derivatives on the blood pressure of cats

DERIVATIVE OF CYCLOHEXYLAMINE HYDROCHLORIDE	DOSE (mg/kg)	NORMAL BLOOD PRESSURE (mm)	% DEPRESSION IN BLOOD PRESSURE
<u>trans</u> -2- <u>o</u> -tolyl	6.0	122.5	53.5
<u>trans</u> -2- <u>o</u> -tolyl	12.0	140.0	78.6
<u>cis</u> -2- <u>o</u> -tolyl	12.0	140.0	67.9
<u>trans</u> -2- <u>p</u> -tolyl	12.0	140.0	A
<u>cis</u> -2- <u>p</u> -tolyl	12.0	140.0	65.2

A animal died 1 minute after injection

Table VI A comparison of the ED_{50} (hypotensive) of substituted cyclohexylamine hydrochloride derivatives tested on the blood pressure of rats

CYCLOHEXYLAMINE HYDROCHLORIDE DERIVATIVE	CALCULATED ED_{50} ^a (mg/kg)
<u>trans</u> -2- <u>o</u> -tolyl	6.3
<u>cis</u> -2- <u>o</u> -tolyl	10.3
<u>trans</u> -2- <u>p</u> -tolyl	9.0
<u>cis</u> -2- <u>p</u> -tolyl	9.0

a. calculated by the method of Litchfield and Wilcoxon (1949)

Fig. 3 A comparison of the hypotensive effects produced by substituted cyclohexylamine hydrochloride derivatives in rats.

A- trans-2-o-tolylcyclohexylamine hydrochloride
 B- cis-2-o-tolylcyclohexylamine hydrochloride

C- trans-2-p-tolylcyclohexylamine hydrochloride
 D- cis-2-p-tolylcyclohexylamine hydrochloride

Table VII A comparison of the effects of substituted cyclohexylamine hydrochloride derivatives on the blood pressure of rats and cats

CYCLOHEXYLAMINE HYDROCHLORIDE DERIVATIVE	DOSE (mg/kg)	% DEPRESSION PRODUCED IN RATS	% DEPRESSION PRODUCED IN CATS
<u>trans</u> -2- <u>o</u> -tolyl	6.0	48.9	53.5
<u>trans</u> -2- <u>o</u> -tolyl	12.0	76.7	78.6
<u>cis</u> -2- <u>o</u> -tolyl	12.0	53.6	67.9
<u>trans</u> -2- <u>p</u> -tolyl	12.0	52.0	A
<u>cis</u> -2- <u>p</u> -tolyl	12.0	52.1	65.2

A animal died during injection of this dose

2. Effects of Substituted Cyclohexylamine Hydrochloride Products and Miscellaneous Substituted Cyclohexane Products on the Isolated Guinea Pig Heart

a. Experimental Procedures

Guinea pigs of both sexes weighing between 0.442 and 1.000 Kg were sacrificed by cervical dislocation. The ribs were cut, the thoracic cavity was opened and the aorta was mobilized. A glass cannula was then secured to the aorta and a few milliliters of warm perfusate was injected into the cannula to remove all residual blood in the coronary vessels. The heart was then removed from the animal. All surrounding tissue was removed and the heart was placed into the perfusion chamber.

The perfusion chamber was of the Anderson-Craver type.^a The water in the outer jacket was maintained at 37.5° C by a recycling pump which contained a heating unit. The perfusion fluid was introduced at a constant rate maintained by air pressure to the inner coil leading to the cannula containing the heart. The perfusion fluid was recycled, except after the injection of a drug when at least 30 ml. was withdrawn to insure removal of the drug. The temperature of the perfusion chamber was always maintained at 37.5° C.

After the preparation had stabilized, a hook was passed through the apex of the heart. A thread

a. Metro Industries, Long Island City, N. Y.

connected the hook via a pulley system to a myograph, where recordings were made on a physiograph.^a

The perfusion fluid used for all the experiments was that recommended by Chenoweth and Koelle (1946) with one modification. Magnesium chloride was replaced with an equivalent amount of magnesium sulfate, in order to reduce the chloride ion content which will facilitate contractions.

A stock solution containing all of the ingredients, except the dextrose and sodium bicarbonate was prepared. The latter two were added on the day that the required amounts of the perfusion solution were prepared. The perfusion solution was aerated using 95 per cent oxygen and 5 per cent carbon dioxide.

Injections of the drug were made into a special outlet from the perfusion chamber. Each injection was immediately followed with an injection of 1.5 ml. (the calculated volume of the special injection spiral) of perfusate to insure complete administration of the drug.

The drugs which were dissolved in the polyethyleneglycol 400 were all administered in 0.25 ml. of that solvent. Control doses of 0.25 ml. of polyethyleneglycol 400 were administered and the effects were recorded.

Each preparation was tested from one to five times depending on the recovery from the previous dose. At least twenty minutes was allowed between injections to allow the preparation to stabilize sufficiently.

a. E & M Instrument Co. Houston, Texas

Drug activity was measured by the following parameters:

1. The change in the amplitude of contraction.
2. The change in the rate of the heart.
3. The time to return to 50 per cent of the normal contraction.

b. Results

The results include the following:

1. The effects of substituted cyclohexylamine hydrochloride derivatives on the isolated guinea pig heart. (Tables VIII to XI)
2. The effects of miscellaneous substituted cyclohexane derivatives and the polyethyleneglycol 400 control dose. (Tables XII to XVII)
3. The comparative effects of the substituted cyclohexylamine hydrochloride derivatives on the isolated guinea pig heart. (Table XVIII)
4. The comparative effects of the miscellaneous substituted cyclohexane derivatives on the isolated guinea pig heart. (Table XIX)

Table VIII Effects of trans-2-p-tolylcyclohexylamine hydrochloride on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.19	14.0	-57.1	116.0	+6.9	2.0
0.38	28.0	-96.4	124.0	+6.9	A
0.57	11.0	-59.1	114.0	F	6.5
0.95	13.0	-76.9	108.0	F	11.0

A. recovery incomplete

F. fibrillation occurred

Table IX Effects of cis-2-p-tolylcyclohexylamine hydrochloride on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.48	24.0	-75.0	142.0	F	A
1.20	25.5	-100.0	128.0	-100.0	A
2.40	30.0	-100.0	132.0	-100.0	4.25

A. recovery incomplete

F. fibrillation occurred

Table X Effects of trans-2-o-tolylcyclohexylamine hydrochloride on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.38	27.5	- 94.5	90.0	- 2.2	A
0.38	34.0	- 92.6	96.0	+4.2	A
0.95	30.0	- 50.0	148.0	- 10.8	A
1.90	33.5	- 94.0	108.0	- 7.4	A
3.80	29.5	- 100.0	80.0	- 100.0	A

A. recovery incomplete

Table XI Effects of cis-2-o-tolylcyclohexylamine hydrochloride on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.63	51.0	-72.5	99.0	-11.1	1.67
1.26	20.0	-85.0 B	108.0	- 8.3	A
2.52	40.0	+100.0	152.0	+36.8	A
2.52	24.0	- 97.9	104.0	-30.8	4.25

A. recovery incomplete

B. stimulation followed the depression

Table XII Effects of polyethyleneglycol 400 on the
isolated guinea pig heart

DOSE (ml.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.25	28.0	-60.7	102.0	-2.0	3.16
0.25	32.0	-59.4	96.0	+20.8	2.40
0.25	28.0	-53.6	128.0	-15.6	3.0
0.25	23.0	-43.5	104.0	-7.7	A

A. recovery incomplete

Table XIII Effects of 2-p-methylphenylcyclohexanone (#202)
on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
3.14	9.3	-67.7	102.0	-4.9	2.75
4.32	10.0	-95.0	66.0	+9.1	4.67
4.32	49.0	-87.8	129.0	-25.6	3.50
5.40	36.0	-100.0	117.0	-100.0	A
5.40	24.0	-100.0	112.0	-100.0	7.33

A. recovery incomplete

Table XIV Effects of 2-o-methylphenylcyclohexanone (#203)
on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
2.06	17.0	-64.7	126.0	-7.9	1.5
4.11	21.0	-100.0	75.0	-100.0	A
6.17	25.5	-100.0	116.0	-100.0	A
8.22	17.5	F	114.0	F	A
10.27	11.0	-100.0	102.0	-100.0	A

A. recovery incomplete

F. fibrillation occurred

Table XV Effects of 2-o- tolylcyclohexen-2-one (#204)
on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
0.75	19.0	-47.4	102.0	+2.0	A
1.12	24.5	-57.1	105.0	-4.8	1.67
1.50	31.0	-48.3	114.0	-5.3	A
1.87	21.0	-85.7	111.0	-5.4	A

A. recovery incomplete

Table XVI Effects of 2-g-tolylcyclohex-4-en-1-ol (#205)
on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
1.95	25.0	-36.0	105.0	-4.8	A
2.875	25.0	-40.0	108.0	-19.8	A
3.90	33.0	-57.9	84.0	-3.0	2.33
3.90	38.0	-93.9	66.0	-4.8	4.40
4.825	13.5	-55.6	90.0	-16.7	4.75

A. recovery incomplete

Table XVII Effects of ethyl-2-(~~2~~-tolyl-1-hydroxy) cyclohexyl-
acetate (#206) on the isolated guinea pig heart

DOSE (mg.)	NORMAL AMPLITUDE (mm)	AMPLITUDE % CHANGE	NORMAL RATE (per minute)	RATE % CHANGE	TIME OF 50% RETURN (minutes)
1.52	29.0	-37.9	108.0	+7.4	A
1.52	39.0	-51.3	118.0	+1.7	A
2.20	13.0	-96.2	114.0	+12.3	A
3.04	44.0	-56.8	124.0	0.0	0.75
3.80	36.5	-63.0	123.0	-2.4	A

A. recovery incomplete

TABLE XVIII The comparative effects of substituted cyclohexylamine hydrochloride derivatives on the isolated guinea pig heart

CYCLOHEXYLAMINE DERIVATIVE	MINIMUM DOSE USED WHICH PRODUCED 100% DEPRESSION OF HEART (Cardiac Arrest) (mg.)
<u>trans</u> -2-p-tolyl	A
<u>cis</u> -2-p-tolyl	1.20
<u>trans</u> -2-o-tolyl	3.80
<u>cis</u> -2-o-tolyl	A

A. Compound did not produce 100% depression of the heart.

Table XIX Comparative effects of the miscellaneous substituted cyclohexane derivatives on the isolated guinea pig heart

COMPOUND	MINIMUM DOSE USED WHICH PRODUCED 50% DEPRESSION OF THE HEART (mg.)
2- <u>p</u> -tolylcyclohexanone (#202)	3.14
2- <u>o</u> -tolylcyclohexanone (#203)	2.06
2- <u>o</u> -tolylcyclohexen-2-one (#204)	1.12
2- <u>o</u> -tolylcyclohex-4-en-1-ol (#205)	3.90
ethyl-2-(<u>p</u> -tolyl-1-hydroxy) cyclohexyl- acetate (#206)	1.52

3. Effects of Substituted Cyclohexylamine Hydrochloride
Derivatives and Miscellaneous Substituted Cyclohexane
Derivatives on the Isolated Rat Atria

a. Experimental Procedures

Albino rats were sacrificed with a sharp blow to the head. The thoracic cavity was exposed and the heart was quickly removed and immersed in warm perfusate. The ventricles were gently compressed to remove blood remaining in the chambers. The atria were separated from the ventricles and extraneous tissue was removed.

The atria were placed in a 70 ml. tissue bath (Magnus) maintained at 32° C. A hook from the aeration tube anchored the tissue at one end. The other end of the tissue was attached to a hook which was connected via thread to a myograph. Recordings were made on a Physiograph.^a

The perfusion solution employed was the same as that used for the isolated guinea pig hearts. Air was gently bubbled through the perfusion solution in the tissue bath.

The preparation was allowed to stabilize for at least fifteen minutes before the first test was made. When and if the tissue recovered adequately, one to four tests were conducted on each tissue preparation. Drugs were administered from a syringe directly into the tissue chamber. All doses of the drug dissolved in polyethyleneglycol 400 contained 0.25 ml. of that solvent. Control studies, using 0.25 ml. of

a. S & M Instrument Co., Houston, Texas

polyethyleneglycol 400 alone were carried out.

Three minutes after the injection was made, the perfusion fluid was removed. Following two washings, fresh warm perfusion fluid was then added to the tissue chamber. The changes produced by the drug usually persisted through the entire three minute test period until washing. Several studies allowing a five minute period of drug action prior to washing were also made. Only one dose was tested in each preparation of the five minute studies.

b. Results

The results include the following:

- (1) Effects of substituted cyclohexylamine hydrochloride derivatives on the isolated rat atria. (Table XX to XXIII; Fig. 4)
- (2) Effects of miscellaneous substituted cyclohexane derivatives on the isolated rat atria. (Table XXIV to XXIX; Fig. 5)
- (3) The comparative effects of substituted cyclohexylamine hydrochloride derivatives on the isolated rat atria. (Table XXX)

Table XX Effects of trans-2-p-tolylcyclohexylamine hydrochloride on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
1.9	+45.0	-26.7
1.9	0.0	0.0
3.8	+83.8	0.0
3.8	+57.7	-7.9
5.7	+50.0	-50.7

Table XXI Effects of cis-2-p-tolylcyclohexylamine hydrochloride on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
1.2	+77.8	-25.0
2.4	+7.4	-26.9
4.8	-42.9	-21.9
4.8	-30.4	-36.8

Table XXII Effects of trans-2-o-tolylcyclohexylamine hydrochloride on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
0.19	+11.1	-20.0
3.8	+50.0	-61.2
7.6	+45.0	-53.5

Table XXIII Effects of cis-2-p-tolylcyclohexylamine hydrochloride on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
0.63	+37.5	-17.2
0.63	+64.9	-14.9
0.63	+102.9	-22.5
1.26	+58.3	-46.3
1.26	+33.3	-27.5
1.26	-3.2	-4.6
1.26	+3.3	-2.7
2.52	+177.8	-45.5

TIME IN SECONDS

Fig. 4 THE EFFECT OF 2-o-TOLYLCYCLOHEXEN-2-one (#204) (1.13 mg)
ON ISOLATED RAT ATRIA.

TIME IN SECONDS

Fig. 5 THE EFFECT OF ETHYL-2-p-TOLYL-1-HYDROXYCYCLOHEXYLACETATE
(#206) (3.8 mg) ON ISOLATED RAT ATRIA.

Table XXIV Effects of polyethyleneglycol 400 on the isolated
rat atria

DOSE (ml.)	AMPLITUDE % CHANGE	RATE % CHANGE
0.25	+15.6	-1.9
0.25	+23.3	-52.5
0.25	+17.8	-5.6
0.25	+16.4	+7.7

Table XXV Effects of 2-p-methylphenylcyclohexanone (#202)
on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
3.14	+3.7	-8.3
4.32	+10.9	0.0
4.32	+25.0	+47.2*
4.32	+4.8	-20.6
5.4	+25.0	+5.8*

* increase

Table XXVI Effects of 2-o-methylphenylcyclohexanone (#203)
on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
4.11	+23.3	-16.0
6.17	+24.1	-9.5
8.22	-23.1	-33.3
10.27	0.0	-42.9

Table XXVII Effects of 2-g-tolylcyclohexen-2-one (#204) on
the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
0.75	+16.3	-5.9
1.13	+75.4	-9.1
1.30	+30.8	-8.3
1.30	+29.2	-8.9
1.50	+170.5	-14.3

Table XXVIII Effects of 2-g-tolylcyclohex-4-en-1-ol (#205)
on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
1.95	+42.9	-18.2
2.88	+22.4	-2.2
3.9	+5.3	-17.1
4.83	+6.4	-14.2

Table XXIX Effects of ethyl-2(p-tolyl-1-hydroxy) cyclohexyl-
acetate (#206) on the isolated rat atria

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE
1.52	+4.3	-11.0
2.28	+29.2	-25.0
3.04	+42.9	-29.4
3.80	+43.4	-30.6
3.90	+43.2	-37.0

Table XXX A comparison of the five minute effects of substituted cyclohexylamine hydrochloride derivatives on the rat atria

CYCLOHEXYLAMINE HYDROCHLORIDE DERIVATIVE	DOSE (mg.)	TIME FOR ONSET OF ACTION (seconds)	AMPLITUDE % CHANGE	RATE % CHANGE
<u>trans</u> -2-p-tolyl	1.9	100	+18.4	0.0
<u>cis</u> -2-p-tolyl	1.9	180	0.0	-43.1
<u>trans</u> -2-o-tolyl	1.9	120	+55.0	-68.2
<u>cis</u> -2-o-tolyl	1.9	120	+34.6	-48.2

4. Effects of Substituted Cyclohexylamine Hydrochloride and Miscellaneous Cyclohexane Derivatives on Isolated Guinea Pig Intestinal Strips

a. Experimental Procedures

Guinea pigs were sacrificed with a sharp blow to the base of the skull. The abdomen was quickly opened and the intestinal tissues were exposed. The upper portion of the small intestine, including the duodenum, was removed and immediately placed in warm perfusion solution which had air bubbling gently through it. Then a few ml. of the fluid was forced through the lumen of the tissue to remove any particles present.

A 3 cm. section of the intestine was then obtained and placed in a 75 ml tissue bath (Magna). The temperature was maintained at 37.5°C throughout the experiment.

The perfusion solution employed was the same as that used for the isolated guinea pig hearts. Air was gently bubbled through the perfusing fluid throughout the experiment.

The tissue section was anchored at the bottom to a hook connected to the bubbling tube. The other end of the intestinal strip was held by a hook and thread which lead to a myograph. Recordings were made on a Physiograph.^a

The four cyclohexylamine hydrochloride salts and two of the miscellaneous cyclohexane derivatives were tested for their action on isolated small intestines. The salts were water soluble; the other two were dissolved in 1.00 ml. of

a. E and S Instrument Co. Houston, Texas

polyethyleneglycol 400. Control experiments were also run to determine the effects of 1.00 ml. polyethyleneglycol 400 alone. The drugs were injected directly into the solution in the inner jacket.

The drugs were allowed to act for a three minute period. Following three successive washes, fresh solution was then added. If the tissue recovered sufficiently, it was used for up to three trials before being replaced with a new strip.

The measures of drug activity include the following:

1. The change in the amplitude of contraction of the tissue.
2. The change in the rate of contraction of the intestinal strip.
3. The change in the tone of the tissue strip.
4. The time needed for the tone of the tissue to return to normal.

b. Results

The results include the following:

- (1) The tone did not return to normal in any of the experiments except once with 4.06 mg of ethyl-2-(p-tolyl-1-hydroxy) cyclohexylacetate (#206).
- (2) The effects of substituted cyclohexylamine hydrochloride derivatives on the isolated guinea pig small intestines. (Tables XXXI to XXXIV: Figs. 6 to 7)
- (3) The effects of polyethyleneglycol 400 and miscellaneous substituted cyclohexane derivatives on the isolated guinea pig small intestines. (Tables XXXV to XXXVII)

Table XXXI Effects of trans-2-p-tolylcyclohexylamine
hydrochloride on the isolated guinea pig
small intestine

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE	TONE CHANGE (mm.)
0.105	+358.3	+5.9	0.0
0.315	+33.3	+20.0	0.0
0.524	+25.0	+60.0	0.0
2.097	+100.0	+225.0	-6.0

Table XXXII Effects of cis-2-p-tolylcyclohexylamine hydrochloride on the isolated guinea pig small intestine

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE	TONE CHANGE (mm.)
0.24	-100.0	-100.0	0.0
0.24	-100.0	-100.0	-10.0 ^a
0.48	-100.0	-100.0	-10.0
0.48	-100.0	-100.0	0.0
1.20	-100.0	-100.0	-20.0
2.40	+25.0	+11.1	-20.0 ^b

a. Baseline stimulated to +25.0 mm., then depressed.

b. Baseline stimulated to +39.0 mm., then depressed.

Table XXXIII Effects of trans-2-o-tolylcyclohexylamine hydrochloride on the isolated guinea pig small intestine

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE	TONE CHANGE (mm.)
0.25	+33.3	-28.6	0.0
0.50	+27.3	-44.4	-5.0
0.99	+70.8	0.0	-2.0
0.99	-50.0	+500.0	-5.0
1.98	+168.8	+10.0	-7.0
1.98	+30.6	+8.3	-15.0

Table XXXIV Effects of cis-2-o-tolylcyclohexylamine hydrochloride on the isolated guinea pig small intestine

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE	STONE CHANGE (mm.)
0.22	+20.0	-19.4	0.0
0.56	+24.0	0.0	0.0
0.56	+18.0	+16.7	0.0
1.11	+6.0	-35.0	0.0
1.11	-55.0	-84.6	0.0
2.22	+22.9	+66.7	-12.0

Table XXXV : Effects of polyethyleneglycol 400 on the
isolated guinea pig small intestine

DOSE (ml.)	AMPLITUDE % CHANGE	RATE % CHANGE	STONE CHANGE (mm.)
1.0	-100.0	-100.0	-9.0

**Table XXXVII Effects of ethyl-2-(p-tolyl-1-hydroxy) cyclohexyl-
acetate (#206) on the isolated guinea pig small
intestine**

DOSE (mg.)	AMPLITUDE % CHANGE	RATE % CHANGE	TOPE CHANGE (mm.)
4.06	+133.3	+75.0	+33.0 ^a
4.06	+27.3	-12.5	-36.0
4.06	0.0	+6.7	+10.0
8.13	-67.2	-3.4	0.0
8.13	+84.6	-47.1	-22.0

a. Baseline returned to normal level after 2 minutes 5 seconds.

Fig. 6 THE EFFECT OF trans-2-o-TOLYLCYCLOHEXYLAMINE HYDROCHLORIDE (1.98 mg) ON ISOLATED GUINEA PIG INTESTINE.

Fig. 7 THE EFFECT OF cis-2-p-TOLYLCYCLOHEXYLAMINE HYDROCHLORIDE (0.48 mg) ON ISOLATED GUINEA PIG INTESTINE.

IV DISCUSSION

Preliminary investigations by Huitric et al. (1958) and Nelson et al. (1958) and a more extensive investigation by Sackler and DeFoe (1962) have shown that 2-aryl substituted cyclohexanol compounds produce effects on the cardiovascular system. Cis and trans isomers of 2-o-tolyl-, 2-o-chlorophenyl- and 2-o-chlorophenylcyclohexanol were tested for their actions on isolated guinea pig hearts and found to depress the heart in varying degrees with some producing cardioplegia. It was found that the trans-2-o-tolyl substitution on the 2-aryl position of the cyclohexanol molecule produced the greatest effects on the blood pressure of intact rats and isolated guinea pig hearts. In all cases, the trans isomer was more potent than its corresponding cis isomer. The tolyl derivatives were apparently less toxic than the chlorophenyl derivatives, as the latter usually prevented the tissues studied from recovering their normal levels.

A series of substituted cyclohexylamine hydrochloride derivatives and other miscellaneous cyclohexane derivatives were synthesized by Huitric. The structure of these compounds is shown on Tables 1-2. They were tested for their effects on the blood pressure of intact cats and rats, on isolated guinea pig hearts, on isolated rat atria and on isolated guinea pig small intestines.

The blood pressure studies were undertaken to ascertain their gross effects on the blood pressure. Only the cyclohexylamine hydrochloride derivatives were studied in

this portion of the experiments as the others were not water soluble. All the compounds studied produced an immediate drop in the blood pressure which lasted for varying lengths of time. The amount of depression produced seemed to vary with the dose of the compound administered. The trans-2-p-tolyl derivative of cyclohexylamine hydrochloride had the most potent effects on the blood pressure of the rat. Cis-2-p-tolylcyclohexylamine hydrochloride was the least potent of the series, and the cis and trans isomers of 2-p tolyl were about equal in their effects. Similar effects were observed on the blood pressure of the cat. (Table VII)

It has been observed in these studies that when increasing the dose above the level producing a 45 to 55% response, a lower degree of depression was obtained than previously obtained using a lower dose. This can be seen in Table II where the response to 18.0 mg. of the drug produced less depression than at 12.0 and 16.0 mg. This might indicate a compensating mechanism coming into effect at this level of depression. In no case in the studies on intact rats was the blood pressure reduced in an amount between 56.8 and 70.6%. (Table I to Table IV) It is possible that a compensating mechanism is affecting the response to these drugs at these dose levels.

When death occurred during these blood pressure studies, it was often observed that the respiration ceased before the heart stopped beating. Sometimes artificial respiration was able to prevent the death of the animal, despite the effects of the drug.

All the compounds were tested for their actions on

isolated guinea pig hearts. The presence of a limited quantity of the drugs prevented more extensive testing of the compounds in some of these studies. From Tables VIII to XI, it can be seen that the trans isomers of tolylcyclohexylamine hydrochloride were more potent than the corresponding cis-isomers in their ability to depress the amplitude of contractions. The effects on the rate of the heart were mixed, some stimulating and some producing depression. The rate usually was not affected to a great degree except in high doses where the contractions were almost totally depressed. It might appear that the rate is little affected directly but only through the effects on the amplitude of contractions. It seems that the S-A node is not the site of action of this series.

Of the miscellaneous cyclohexane derivatives, 2-o-tolyl-cyclohexan-2-one (#204) was the most depressant, while 2-o-tolyl-cyclohex-4-en-1-ol (#205) was the least effective on the amplitude. All produced effects on the amplitude in varying degrees in excess of that produced by polyethyleneglycol 400 alone. (Table XII) It is not known whether the depression produced by the polyethyleneglycol 400 and by the cyclohexane derivatives is by the same mechanism or through a separate action. The effects on the rate were varied, some producing an increase and some a decrease. When the amplitude was totally depressed, the rate also ceased completely.

Studies on the rat atria showed that the cyclohexylamine hydrochloride derivatives increased the amplitude of contractions while decreasing the rate. Inconsistencies occurred among the p-tolyl derivatives which produced a depression rather than a stimulation of the amplitude. In these studies, it was shown

that once again the trans-2-o-tolyl derivative was most potent of this series and the cis-2-p-tolyl derivative least potent. The trans isomer was more potent than the corresponding cis isomer. The trans-2-p-tolyl derivative had no effect on the rate in most of the experiments. The trans-2-o-tolyl compound had the greatest effect on the rate. (Table XXII)

The miscellaneous cyclohexane derivatives all increased the amplitude of the atria contractions and decreased the rate. The effects did not vary with the dose and often a large dose had little effect. This may have been due to an actual depressant effect by the drug which overcame the stimulating effects on the amplitude of the polyethyleneglycol 400 solvent. 2-o-tolylcyclohexen-2-one (#204) was the most potent (Table XXVII) and 2-o-tolylcyclohexanone (#203) and 2-p-tolylcyclohexanone (#202) were the least effective. (Tables XXV-XXVI)

In order to determine the effects on smooth muscle, some of the compounds were then tested on guinea pig small intestine. The four members of the cyclohexylamine hydrochloride series were tested, and all increased the amplitude except the cis-2-p-tolyl derivative which greatly decreased the amplitude of contractions to total depression. (Table XXXII) The effects on the rate were variable and inconsistent. trans-2-o-Tolylcyclohexylamine was the most potent, (Table XXXIII), and the cis-2-o-tolyl derivative was the least potent (Table XXXIV). The cis-2-p-tolyl compound was apparently toxic and totally depressed the tissue. The change in tone was measured in terms of the change in the baseline. The trans-2-o-tolyl derivative depressed the tone while the cis-2-o-tolyl and the trans-2-p-tolyl derivatives usually did not alter the baseline. cis-2-p-Tolylcyclo-

hexylamine hydrochloride depressed the baseline.

Ethyl-2-(p-tolyl-1-hydroxy)cyclohexylacetate (#206) usually stimulated the amplitude and depressed the rate (Table XXXVII). 2-p-tolylcyclohexanone (#202) apparently had little effect on the rate or amplitude which was not due to the depressant action of the polyethyleneglycol 400 solvent (Table XXXVI).

From these experiments it appears that the cyclohexylamine hydrochloride derivatives affect the tissue tested in a manner similar to that of parasympathetic stimulation. The actions elicited were a stimulation of intestinal contractions and a depression of the amplitude of cardiac contractions and an overall hypotensive effect on the blood pressure. A few studies were made in cats in which during the peak of the hypotensive action of the cyclohexylamine hydrochloride derivatives vagal stimulation was affected. No additional lowering of blood pressure resulted from this procedure. The carotid sinus reflexes remained intact during the depressant effects of the compounds. It is conceivable that these compounds may produce their actions by involving mechanisms of the parasympathetic nervous system. Further research in this direction might be feasible.

V. SUMMARY

The cis and trans-2-p-tolyl and the cis and trans-2-p-tolyl derivatives of cyclohexylamine hydrochloride and other miscellaneous cyclohexane derivatives were tested for various pharmacological actions. The tests included blood pressure studies on intact rats and cats, experiments on isolated guinea pig hearts, studies using isolated rat atria and tests on isolated guinea pig small intestines. These compounds were found to actively affect the cardiovascular system and the smooth muscle tissue tested.

Due to the limited water solubility of the miscellaneous cyclohexane compounds, only the four cyclohexylamine hydrochloride derivatives were studied on intact rats and cats for their gross blood pressure effects. All produced an immediate drop in blood pressure, the hypotensive effect varying with the dose administered. Of the cyclohexylamine series tested, the trans-2-p-tolyl derivative was the most potent and cis-2-p-tolyl was the least active. Both the cis and the trans-2-p-tolyl derivatives produced similar hypotensive effects at the dosages tested. These results were obtained in the blood pressure studies of both the rat and cat. No appreciable differences were obtained in the responses of the animals of these two different species to the compounds tested.

All the compounds were tested for their actions on isolated guinea pig hearts. Of the cyclohexylamine hydrochloride series, the trans isomers were more potent than their corresponding cis isomers. The amplitude is more susceptible

to the depressant action of these compounds than the rate.

2-o-tolylcyclohexen-2-one (#204) was the most potent of the miscellaneous cyclohexane derivatives studied. 2-o-Tolylcyclohex-4-en-1-ol (#205) possessed the least amount of activity on the isolated heart.

The trans-2-o-tolyl isomer of cyclohexylamine hydrochloride was the most potent of its series in affecting the rat atria. The cis-2-p-tolyl derivative was the least potent. The usual response was an increase in the amplitude of contractions.

Within the group of miscellaneous compounds tested, 2-o-tolylcyclohexen-2-one (#204) was the most potent in its action on the rat atria. 2-o-tolyl and 2-p-tolylcyclohexanone (#202, #203) were the least active on the rat atria.

trans-2-o-Tolylcyclohexylamine hydrochloride produced the greatest amount of stimulation to the small intestinal strips. The cis-2-p-tolyl derivative was exceptional to the other members of this series since it depressed the intestine.

Ethyl-2-(p-tolyl-1-hydroxy) cyclohexylacetate (#206) stimulated the small intestine while 2-p-tolylcyclohexanone (#202) had little effect.

VI. CONCLUSIONS

1. trans-2-o-tolyl-, cis-2-o-tolyl-, trans-2-p-tolyl- and cis-2-p-tolylcyclohexylamine hydrochloride are capable of depressing myocardial contractility and producing a hypotensive effect. They stimulate isolated atria and small intestine.
2. The trans-2-o-tolyl position appears to be the most active in this series. The cis isomers were never more active than the trans isomers in this series.
3. 2-o-tolylcyclohexen-2-one (#204) was the most active of the miscellaneous cyclohexane derivatives tested.

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