Brit. J. Pharmacol. (1953), 8, 2.

ANALGESIC AND OTHER PROPERTIES OF 3 : 3-DITHIENYLALKENYLAMINES

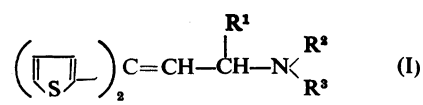
BY

A. F. GREEN

From the Wellcome Research Laboratories, Langley Court, Beckenham, Kent

(RECEIVED AUGUST 18, 1951)

Several 3:3-diphenylallylamines (Adamson, 1949) have shown moderate atropine-like, antihistamine, and local anaesthetic properties (White, Green, and Hudson, 1951). A number of allied series have also been investigated, among them dithienylalkenylamines (I) (Adamson, 1950).



(I)

These have been shown to have similar properties, but some are also powerful analgesics (Adamson and Green, 1950) and will be described in greater detail.

METHODS

Analgesia.—The pain thresholds of groups of 10 or more 3- to 4-week-old rats were measured 30 minutes after subcutaneous injection of the analgesics, at each of two or more dose levels, by the heat and pressure methods described by Green and Young (1951). Activities relative to that of morphine, tested on the same occasion, were estimated from the regression lines relating log-dose and the probit of the proportion of animals in the group whose pain thresholds were at least twice that of a control group injected with saline.

In rabbits pain thresholds were measured with a simple analgesiometer constructed from a 20 ml. "Record" type syringe by soldering a brass wedge to the knob of the piston. The piston was lubricated with vaseline and set at the 20 ml. mark, after which the syringe was sealed with an occluded needle mount. Holding the barrel, pressure was applied to the forelimb of the rabbit through the brass wedge until an avoidance reaction was produced. When this occurred the volume of air in the syringe was recorded. The pressure in cm. of mercury was calculated from Boyle's law. The proportion of animals failing to respond to a pressure of 114 cm. of mercury, 60 minutes after subcutaneous injection of an analgesic, was used to calculate the ratios of activity, by probit analysis.

The results shown in Table II were obtained by injecting each compound at doses of 1, 3, and 9 mg./kg. into groups of 10 rabbits. The regression of the probit response on log-dose had a mean slope for all the drugs of 2.5, and the ED50 of morphine sulphate was approximately 2 mg./kg.

The syringe analgesiometer was also used on dogs. It was applied to the tip of each ear and to the skin of the foreleg over the radius. The proportion of dogs with a 100% increase in pain threshold was used as a basis of comparison. Durations of analgesia were determined by repetition of the test at half-hourly intervals up to two to three hours and hourly thereafter. The dogs were rarely used for more than one experiment; about 5% were rejected because their initial pain thresholds were too high.

Breathing.—Relative activity in causing a depression of respiratory movement was estimated in rats and rabbits from the relationship of dose to frequency of respiration. The latter was determined by recording the pressure changes in a tambour held against the belly of the animal. The minute volume was determined in unanaesthetized rabbits at rest by applying a face mask and recording the mean rate of air flow (Gaddum, 1941).

Temperature changes in the rabbit were measured by a thermocouple in the rectum connected to a recording galvanometer.

Antihistamine action was determined on guinea-pig ileum *in vitro* using the procedure described by White, Green, and Hudson (1951). Each of two concentrations of the compound and of mepyramine (the standard) was tested on spasm induced by histamine in each of four strips of ileum in random order, by adding them to the organ bath immediately after the effect of histamine had reached its peak. Relative activities were estimated from the mean percentage relaxation after three minutes.

Atropine-like activity was determined on isolated rabbit ileum, the procedure being the same as for antihistamine action but using carbachol 2.5×10^{-7} to cause contraction of the muscle, and atropine sulphate as the standard of comparison. Mydriatic action was determined from the pupil diameters of groups of 10 mice, 30 minutes after intraperitoneal injection (Ing, Dawes, and Wajda, 1945).

RESULTS

Fig. 1 shows the results of a preliminary exploration of the analgesic, atropine-like, and

antihistamine effects of the hydrochlorides of the dithienylalkenylamines (I). The tops of the columns indicate, on a logarithmic scale of ordinates, the activity found. The lower end of each column is the level below which no attempt was made to measure activity, and where no activity was observed a horizontal line is drawn in the chart. The black columns indicate the ratio of the analgesic activity of each compound to

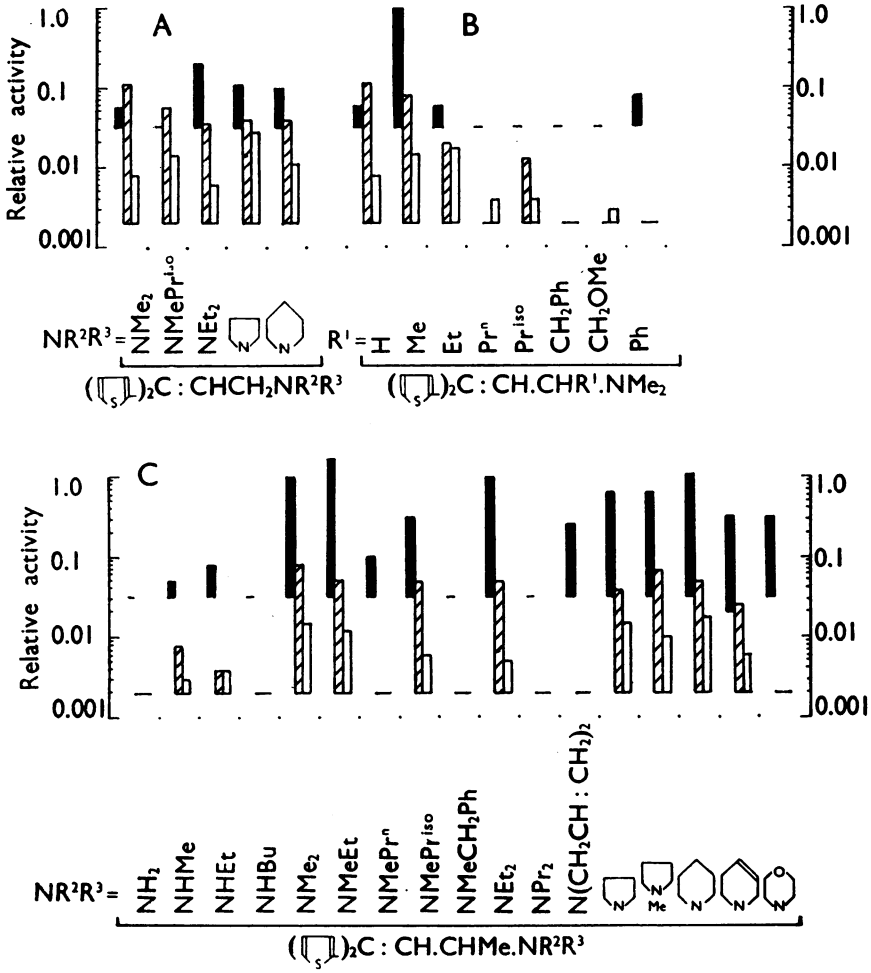


FIG. 1.—Relative activities of the dithienylalkenylamine hydrochlorides (I). The upper ends of the columns give the activity found. The lower ends are the levels below which no activities were measured, and when the activity of a compound did not exceed this a horizontal line is drawn. Black columns: analgesic activity in rats, morphine sulphate = 1·0. Cross-hatched columns: carbachol antagonism in isolated rabbit ileum, atropine sulphate = 1·0. Clear columns: antihistamine action in isolated guinea-pig ileum, mepyramine = 1·0.

that of morphine sulphate in the rat by the pressure method; the cross-hatched show the ratio of antagonism of carbachol on the rabbit intestine to that produced by atropine; and the clear columns the ratio of antihistamine action on guinea-pig ileum to that of mepyramine. Fig. 1A shows the activities of a number of dithienylallylamines (I, $R^1=H$) with varying substituents on the amino group (NR^2R^3); Fig. 1B the effect of varying the substituent R^1 when NR^2R^3 is dimethylamino; and Fig. 1C the effect of varying the amino substituent in dithienylbutenylamines (I, $R^1=Me$).

Variation of the substituent R^1 has a marked effect on analgesic activity, which is far greater where R^1 is methyl (butenylamine series) than where R^1 is hydrogen (allylamines) or any other substituent. Variation of R^1 has a smaller effect on atropine-like and antihistamine activities, which are approximately the same for the allylamine and butenylamine series. Fig. 1B indicates that, where NR^2R^3 is dimethylamino, antagonism to carbachol is greater when R^1 is hydrogen and antihistamine action when R^1 is ethyl.

Each of the activities is influenced by variation of the amino group NR^2R^3. The most active analgesic is the ethylmethylamino butenylamine, with an activity 1.7 times that of morphine sulphate.

Compounds with similar amino substituents (dimethylamino, diethylamino, pyrrolidino, and piperidino) are also powerful analgesics, but the activity decreases with reduction or increase in the dimensions of the amino substituents. In general, amino substituents favouring analgesic activity also favour carbachol and histamine antagonism, but to different degrees and with some notable exceptions (e.g. morpholino and diallylamino).

Those compounds with the greatest antagonistic action to carbachol caused in large doses marked mydriasis in mice, but they were only about 0.005 times as active as atropine. Local anaesthetic activity on the rabbit cornea equivalent to or greater than that of cocaine was shown by some substances ; they caused damage to the cornea and were not investigated further.

Five of the analgesics in the series were selected for further study. They are the butenylamine hydrochlorides (I, $R^1 = Me$) with NR^2R^3 as NMe_2, NMeEt, NEt_2, pyrrolidino, or piperidino, whose laboratory code numbers, used by others (Keele, 1952 ; Eddy and Leimbach, 1953), are respectively 338C48, 1C50, 191C49, 268C49, and 127C49. They will be referred to below by their amino substituents.

Analgesia.—The slopes of the regression lines relating the dose of the thienyl compounds to their analgesic effect (probit response) were not significantly different from that of morphine in any of the several tests using the pressure method which, when analysed, gave the relative potencies shown in Table I. By the heat method the activities of the ethylmethylamino and pyrrolidino compounds were, respectively, 1.0 (limits, p=0.95, 0.7–1.6) and 0.37 (0.26–0.55) times that of morphine sulphate. These values are less than those obtained by the pressure method (Table I). A similar difference in the potency ratios of pethidine: morphine by the two methods has been reported previously (Green and Young, 1951). The activities of the ethylmethylamino and pyrrolidino compounds when estimated from the probit of rats showing complete insensitivity to pressure stimuli were not significantly different from those obtained with smaller pressure stimuli.

TABLE I

ANALGESIC ACTIVITIES OF DITHIENYLBUTENYLAMINES (I, R^1=Me) IN THE RAT

The weighted mean values of several tests in which thresholds to pressure were determined 30 minutes after subcutaneous injection

Amino Group	Number of Tests	Activity Ratio, Morphine Sulphate=1·0	
		Mean	Limits of Error, p=0·95
Dimethylamino ..	4	1·07	0·91–1·25
Ethylmethylamino ..	4	1·7	1·54–1·87
Diethylamino ..	2	1·0	0·83–1·10
Pyrrolidino	5	0·7	0·62–0·78
Piperidino	2	1·1	0·97–1·30

Estimates of the analgesic activities of three of the compounds *in rabbits* are shown in Table II. Although the limits of error are wider than those obtained in rats, the ratios are substantially the same.

TABLE II

ANALGESIC ACTIVITIES OF DITHIENYLBUTENYLAMINES (I, R^1=Me) IN THE RABBIT, ONE HOUR AFTER SUBCUTANEOUS INJECTION

Thirty rabbits used for each compound

Amino Group	Activity Ratio, Morphine Sulphate=1·0	
	Mean	Limits of Error, p=0·95
Dimethylamino ..	0·78	0·38–1·6
Diethylamino ..	0·96	0·48–1·9
Piperidino	0·95	0·49–1·8

In dogs the ratios of the analgesic activities of the thienyl compounds to that of morphine are very much smaller than those found in rodents. Table III shows the results obtained in tests using two or more doses of each compound.

TABLE III

ANALGESIA IN DOGS INJECTED SUBCUTANEOUSLY

Activities relative to morphine sulphate calculated from (*a*) proportion of dogs showing a 100% rise in pain threshold and (*b*) the duration of this rise. Limits of error for p=0·95 in brackets

Compound	No. of Dogs Used	Activity Ratio	
		(*a*) From Proportion	(*b*) From Duration
Dithienylbutenylamines:			
Dimethylamino-	20	0·15 (0·08–0·27)	0·13 (0·07–0·24)
Ethylmethylamino-	22	0·31 (0·18–0·54)	0·38 (0·20–0·72)
Diethylamino- ..	41	0·19 (0·12–0·31)	0·23 (0·13–0·39)
Pyrrolidino- ..	22	0·11 (0·06–0·21)	0·10 (0·05–0·19)
Piperidino- ..	18	0·12 (0·07–0·20)	0·077 (0·04–0·15)
Pethidine hydrochloride	20	0·074 (0·044–0·13)	0·05 (0·026–0·097)
Morphine sulphate	33	[1·0]	[1·0]

The slopes of the regression of the probit of animals showing a 100% elevation in threshold on log-dose were homogeneous (p=0.3) for all drugs, the overall weighted mean value being 3.34±0.47. This level of analgesia was given in 50% of dogs by 1.04 mg./kg. of morphine sulphate (limits, p=0.95, 0.7–1.5). The slopes relating log-dose and the duration of effect in hours were also homogeneous (p=0.3) with a weighted mean value of 4.15±0.54, and the dose of morphine sulphate required to elevate the pain threshold by 100% for one hour was 1.4 mg./kg. (0.96–2.2). The common slopes were used in estimating the relative activities of the compounds in the table.

The p95 limits are wider in the dog tests than in the rat tests, and this obscures the differentiation.

However, although relative to morphine the thienyl compounds are less active in dogs than in rodents, relative to one another their activities are about the same. The ethylmethylamino compound is the most active of the thienyl analgesics in both rats and dogs. Trial in man (Keele, 1952) indicates that the results in the dog are much closer to the relative potencies in man than those in the rat and rabbit.

The observations that the slopes of the regression lines relating dose and the duration of analgesia in dogs are homogeneous for all the drugs, and that their relative activities are the same when assessed by duration of effect as by the quantal method, indicate that there are no significant differences between their durations of effect.

Higher levels of analgesia were attainable with the thienyl analgesics than with very large doses of morphine sulphate. Doses of 20–40 mg./kg. of the ethylmethylamino or diethylamino compounds, for example, made dogs insensitive to mechanical stimuli (the corneal reflex remained intact).

Only the diethylamino compound has been administered intravenously; 1–5 mg./kg. rapidly caused narcosis lasting five minutes to one hour depending on the dose, followed by a period of reduced sensitivity to pain. Much smaller amounts were required to cause the same level of analgesia by this route than by subcutaneous injection, and the action was more rapid in onset and of shorter duration.

In cats the ethylmethylamino and diethylamino compounds given subcutaneously in doses of 5 to 20 mg./kg. caused analgesia comparable with that due to 0.5 to 2 mg./kg. of morphine. They also produced excitation and mydriasis, but in contrast to morphine the thienyl compounds did not cause vomiting.

Toxic Actions in Mice and Rats.—Several tests in which groups of 10 mice were injected by various routes with doses separated by an interval ratio of 1.5 provided the LD50 estimates shown in Table IV. In the mouse the thienyl compounds cause analgesia, hyperexcitability, mydriasis, and erection of the tail. Respiratory depression was the primary cause of death with subcutaneous administration, but a cardiovascular component may be equally if not more important with intravenous injection.

The subcutaneous toxicity of each of the five thienyl analgesics was determined concurrently with that of amidone in 50–90 g. rats. Table IV shows the LD50 and the toxicity relative to that of amidone in the rat for each compound. The latter estimates have varied less between repeat tests than have the absolute LD50 values. These various thienyl analgesics have 0.4 to 0.8 times the toxicity of amidone. As amidone in our rats has 2.3 times the potency of morphine in the rat analgesic tests (Green and Young, 1951) the analgesic potencies of the five compounds (Table I) range between 0.3 and 0.8 times that of amidone. Thus the toxicity: analgesic ratios are similar to that of amidone. Depending on the dose, the thienyl analgesics caused periods of excitement, respiratory depression, and somnolence. Respiratory depression seemed to be the primary cause of death with subcutaneous injections. Like pethidine, they do not cause rigidity of the abdominal muscles, whereas morphine and amidone do so.

TABLE IV

THE TOXICITIES OF THE DITHIENYLBUTENYLAMINES (I, R^1=Me) IN MICE AND RATS

The limits of error, p=0·95, are shown in brackets

Amino Group	LD50 in Mice		Rats (Subcutaneous)	
	Intravenous mg./kg.	Subcutaneous mg./kg.	LD50 mg./kg.	Relative Toxicity Amidone =1·0
Dimethylamino- ..	16 (13–18)	100 (85–120)	170 (140–220)	0·42 (0·38–0·47)
Ethylmethylamino-	17 (14–20)	94 (61–140)	63 (41–97)	0·58 (0·31–1·1)
Diethylamino- ..	16 (14–18)	81 (72–92)	45 (31–64)	0·81 (0·46–1·4)
Pyrrolidino- ..	25 (22–29)	120 (85–170)	92 (61–140)	0·40 (0·22–0·73)
Piperidino- ..	15 (12–17)	120 (100–140)	95 (77–120)	0·75 (0·67–0·83)

There was no retardation in growth, change in the erythrocyte count, or damage to internal organs (the lungs, livers, spleens, and kidneys were examined histologically by Dr. D. J. Trevan) when subcutaneous doses of 6 mg./kg. of the dimethylamino, diethylamino, or piperidino compound, or 3 mg./kg. of the ethylmethylamino or 10 mg./kg. of the pyrrolidino compound, were injected daily in groups of six rats for two months.

Toxic Actions in Dogs.—The thienyl compounds not only resemble morphine in their analgesic effect but share many of its side-actions. On subcutaneous injection in dogs they cause respiratory depression, preceded occasionally by hyperpnoea, miosis, and sometimes slight salivation. They induce evacuation of the bowel in a small percentage of animals, particularly those with existing diarrhoea, but to a lesser extent than does morphine. Unlike morphine, they do not cause vomiting when administered subcutaneously. Further, the hypnotic action of these compounds is more pronounced, with smoother induction and recovery. The slight salivation and the miosis are eliminated by atropine.

Very large doses have been injected subcutaneously in a few dogs. Prolonged narcosis but no toxic actions were seen with amounts up to 100 mg./kg. of the dimethylamino or pyrrolidino compounds, or with 50 mg./kg. of the ethylmethylamino or diethylamino compounds. However, after 100 mg./kg. of the diethylamino compound the narcosis was accompanied first by tremors and then 70 minutes later by severe clonic convulsions. These were abolished by pentobarbitone sodium (30 mg./kg.) and subsequent recovery was uneventful. Convulsions, controlled by pentobarbitone sodium, have also followed the intravenous injection of 6 to 10 mg./kg. of this compound.

The side-actions of the thienyl analgesics were also examined in dogs under pentobarbitone sodium. Administered intravenously, they caused a sharp temporary fall in blood pressure, of 30 mm. Hg with 0.5 mg./kg. of the diethylamino compound, 50 mm. Hg with 1 mg./kg. of the dimethylamino and piperidino compounds, or with 0.1 mg./kg. of the ethylmethylamino, and 85 mm. Hg with 1 mg./kg. of the pyrrolidino compound. They also caused brief apnoea followed by recovery within 15 to 30 min.; the effect was of shorter duration than that of morphine or amidone at these doses. In experiments in which the tone of the small intestine was recorded with balloons at pressures of 8–15 cm. of water all the thienyl compounds caused intestinal spasm. The minimal effective doses were 0.02 to 0.07 mg./kg. of the dimethylamino, 0.02 mg./kg. of the ethylmethylamino, and 0.03 mg./kg. of the diethylamino compound. Morphine had an effect of equal magnitude at doses varying between 0.0005 and 0.005 mg./kg.

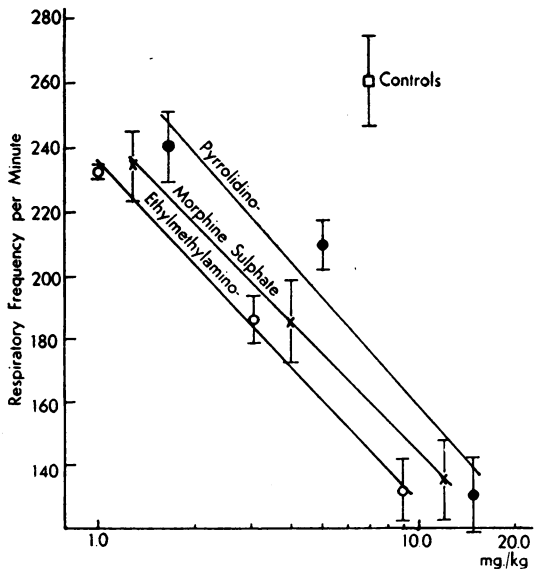


FIG. 2.—Frequency of respiration of rats thirty minutes after subcutaneous injection of dithienylbutenylamines or morphine sulphate. Means for groups of twenty rats with standard errors represented by vertical lines. The nature of the NR^2R^3 group is indicated on the graph.

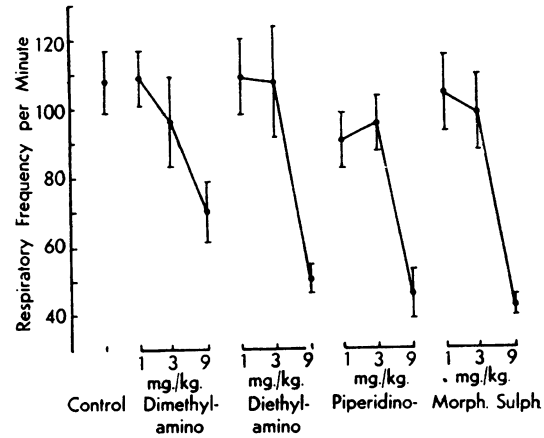


FIG. 3.—Frequency of respiration of rabbits one hour after subcutaneous injection of dithienylbutenylamines (I, R^1=Me) or morphine sulphate. Means for groups of ten rabbits with standard errors represented by vertical lines. The nature of the NR^2R^3 group is indicated below the abscissae.

Administered in gelatine capsules by mouth, doses of 200 mg. of each of the five butenylamines caused vomiting in 50–75% of dogs, usually within 6–30 min., and effected only slight or moderate increases in pain threshold. As an emetic action has not been observed when administered by other routes it seems likely that these drugs have an irritant action on the stomach.

Respiratory Depression.—The mean respiratory frequencies of groups of 20 rats 30 min. after subcutaneous injection are plotted against the dose of the ethylmethylamino and pyrrolidino butenylamines and of morphine in Fig. 2. Deviations from linearity and parallelism were not significant and it was estimated from this data that the ethylmethylamino and pyrrolidino compounds were respectively about 1.3 and 0.7 times as depressant as morphine sulphate. These ratios do not differ significantly from the analgesic ratios in Table I.

In rabbits the magnitude of the respiratory depression caused by the dimethylamino, diethylamino, or piperidino compounds did not differ significantly from that with the same doses of morphine sulphate, whether the effect was estimated from changes in frequency in animals excited to some extent by handling (Fig. 3) or from changes in minute-volume in rabbits at rest

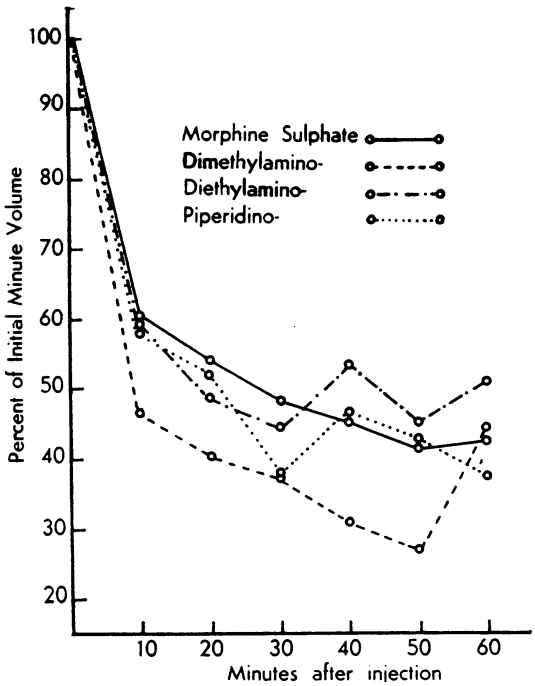


FIG. 4.—The respiratory minute-volume in rabbits as a percentage of initial at intervals following the subcutaneous injection of 2 mg./kg. of dithienylbutenylamines or morphine sulphate. Means for groups of four rabbits. The nature of the NR^2R^3 is indicated on the graph.

(Fig. 4). The depression in minute-volume in rabbits at rest was due mainly, though not entirely, to a reduction in frequency. It was associated with hypnosis, since with this dose (2 mg./kg.), and to a lesser extent with higher dosages, the minute-volume could be largely restored by disturbing the animals.

Temperature.—The thienyl compounds, like morphine, cause a fall in rectal temperature after subcutaneous injection into rabbits at rest (Fig. 5). The temperature depressant activities of the dimethylamino, diethylamino, and piperidino derivatives, relative to that of morphine, approximate to their analgesic potencies in this species. A fall of temperature also occurred on injection of the ethylmethylamino and morpholino analogues. The times taken both for the onset of the maximum fall in temperature and for recovery from each of the thienyl compounds tended to be shorter than those for morphine.

TABLE V

THE ACTIVITIES OF THE OPTICAL ISOMERIDES OF DITHIENYLBUTENYLAMINES (I, R^1 = Me) AS PROPORTIONS OF THOSE OF THE RESPECTIVE RACEMIC MIXTURES

The limits of error, p=0·95, are given in brackets

Amino Group	Isomer [α]$^{20}_{5461}$	*In vitro* Antagonism of		Mydriasis (Mouse)	Analgesia (Rat)
		Carbachol	Histamine		
Dimethyl-amino	*dextro* +118°	1·63 (1·03–2·56)	1·41 (0·96–2·07)	1·18 (1·13–1·23)	1·65 (0·98–2·79)
	laevo −125°	0·89 (0·56–1·39)	0·60 (0·41–0·88)	Not examined	0·27 (0·17–0·44)
Pyrroli-dino	*dextro* +110°	1·13 (0·78–1·66)	1·33 (0·92–1·91)	1·24 (0·92–1·68)	1·51 (1·20–1·91)
	laevo −109°	1·02 (0·70–1·49)	0·81 (0·60–1·10)	0·70 (0·52–0·94)	0·64 (0·50–0·82)

Optical Isomers.—The butenylamine hydrochlorides so far described are racemic mixtures. The component optical isomerides of the dimethylamino and pyrrolidino butenylamines have also been examined. The results of some comparative spasmolytic, antihistamine, mydriatic, and analgesic tests are shown in Table V, where the activity of each isomeride is given in terms of the activity of the respective racemic mixture. Qualitatively the pharmacological properties examined were similar, but the *dextro* isomeride of each compound was

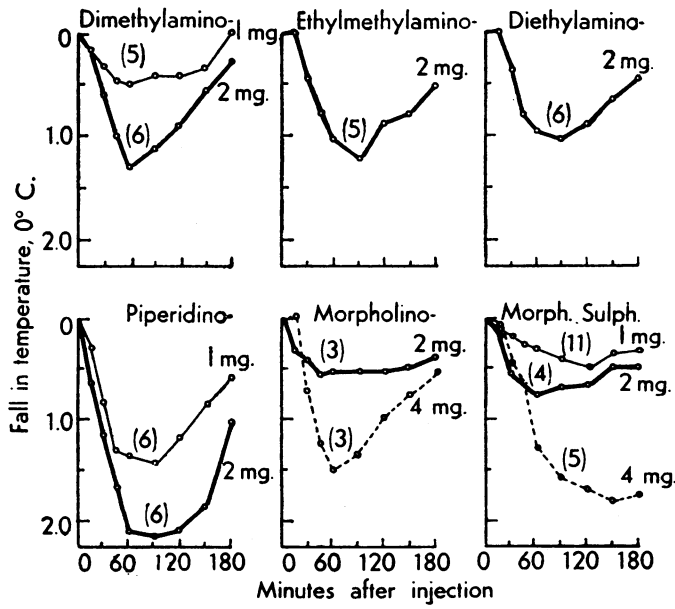


FIG. 5.—The fall in the rectal temperatures of rabbits after subcutaneous injection of dithienylbutenylamines and morphine sulphate. Doses in mg./kg. The number of rabbits in each group is shown in brackets. The nature of the NR^2R^3 group is indicated on the graph.

rather more active than the *laevo* form in most of the tests. The greatest difference observed was in analgesic potency, the *dextro* isomerides of the dimethylamino and pyrrolidino compounds being respectively about six and three times more active. This is in contrast with the finding that the *laevo* isomer is more active than the *dextro* in both amidone (Thorp, Walton, and Ofner, 1947) and in dromoran (Randall and Lehmann, 1950). In a comparative toxicity test where the compounds were injected intravenously in groups of ten mice, there was no significant difference between the toxicities of the pyrrolidino isomers. Estimates of the LD50 of the racemic, *dextro*, and *laevo* isomers were 25 mg./kg. (limits, p=0.95, 22–29), 23 mg./kg. (21–26), and 25 mg./kg. (21–31) respectively. Both the *d* and *l* isomerides of the pyrrolidino compound caused corneal anaesthesia after application of 0.5% solutions to rabbits' eyes.

Discussion

There is a striking resemblance between the action of these dithienylbutenylamines and that of morphine. The slopes of the regression lines relating dose and increase in pain threshold in the rat and rabbit are similar to that of morphine, and similar high levels of analgesia may be attained. The relative analgesic, respiratory, and temperature effects parallel one another and like those of morphine are antagonized by N-allylnormorphine (Green and White, 1952, unpublished findings). Although the behaviour pattern of the mouse, rat, rabbit, cat, and dog injected with these compounds is similar to that after morphine, there are some differences. For example, the ethylmethylamino and pyrrolidino derivatives have a greater effect, relative to morphine, on the "flight" reaction to pressure on the tail of the rat than on the reflex removal of the tail from a source of heat stimulation. Unlike morphine and amidone they do not cause rigidity of the abdomen in rats. Further, these compounds do not cause vomiting on subcutaneous injection in the dog or in the cat. Experiments in anaesthetized dogs and in rats given charcoal meals (Green, unpublished) indicate that in comparable analgesic doses these compounds have a smaller effect than morphine on intestinal activity. A further difference from morphine is shown by the relative activities in different species, since in the rat and the rabbit several members have approximately the same analgesic activity as morphine but are only 0.1 to 0.4 times as potent in the dog and cat.

The dithienylbutenylamines have been tested in man by Keele (1952), who found that they were intermediate in activity between morphine and pethidine. Hence it seems that their relative activities in man and dog are similar. The species differences in sensitivity to analgesics might be due to the species differing in their modes of appreciation and response to pain stimuli; alternatively the thienyl compounds might act at a different site from morphine. Another possibility now being explored is that the thienyl compounds, which are somewhat unstable in solution, may be more readily inactivated or excreted in man, the dog, and cat than in the rabbit and rat.

Many of the differences from morphine displayed by these thienyl compounds are shared by pethidine. For example, relative to morphine, pethidine exhibits an activity by the pressure test in the rat which is relatively higher than that by the radiant heat test (Green and Young, 1951). Pethidine does not cause rigidity of the abdomen; it has a smaller effect than morphine on intestinal propulsion in the rat (Karr, 1947) and the dog (Vaughan Williams and Streeten, 1950). It is only about a fifth as active in man and the dog as it is in the rat. In these respects the actions of amidone more closely resemble those of morphine. It is therefore possible that the thienyl compounds and pethidine have a similar mode of analgesic action, which is in some respects different from that of morphine and amidone.

Summary

1. Powerful analgesic properties and some atropine-like, antihistamine, and local anaesthetic properties have been found in a series of 3:3-dithienylalkenylamines.

2. 3-Dimethylamino, 3-ethylmethylamino, 3-diethylamino, 3-pyrrolidino, and 3-piperidino-1:1-di-2′-thienylbut-1-ene hydrochloride show activities varying between 0.6 and 1.7 times that of morphine sulphate in rats and rabbits, and between 0.1 and 0.4 times that of morphine in dogs and cats. The ethylmethylamino compound is the most active. Compared with morphine, their respiratory and temperature depressant activities are proportional to their analgesic potencies, but they seem to have less effect on the bowel. In this and other respects they and pethidine have a similar type of action, differing from that of morphine and amidone.

3. The *dextro* isomerides of the dimethylamino and pyrrolidino compounds exhibited greater analgesic, antihistamine, and atropine-like properties than the *laevo* isomerides.

The author is indebted to Drs. D. W. Adamson, J. W. Trevan, and A. C. White and Mr. P. A. Young for much useful advice, and to Messrs. J. B. Attlesey and J. A. Calnan and Mesdames I. Carter, E. D. R. Dann, and E. Stacey for valuable technical assistance.

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