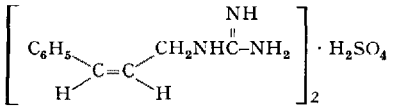
Hypotensive Activity of *cis*-Cinnamyl Guanidine Sulfate

The *cis* and *trans* isomers of cinnamyl guanidine sulfate were found to possess hypotensive activity in animals, the *cis* form (Su-13,686) being more active than the *trans*:



Su-13,686

Su-13,686 was orally active with a rapid onset of action in normotensive anesthetized and unanesthetized dogs and in unanesthetized renal hypertensive dogs; in anesthetized cats it also produced a hypotensive response. In the anesthetized dogs doses of 2.5 and 7.9 mg/kg, injected into a loop of the small intestine produced a 31 and 50 mm decrease in mean arterial blood pressure. The pressor responses produced by injected l-epinephrine and l-norepinephrine were augmented, while the pressor response produced by injected amphetamine was inhibited or greatly decreased.

The oral administration of 7.9 mg/kg to unanesthetized normotensive dogs for two weeks produced a 20 to 40 mm decrease in mean arterial pressure, while the oral administration of 2.0 mg/kg of Su-13,686 to unanesthetized renal hypertensive dogs produced a 31 mm decrease in mean arterial pressure. The drug appeared to be more effective in the renal hypertensive dog than in the normotensive dog.

In normotensive dogs anesthetized with barbital sodium, Su-13,686 produced a significant increase in coronary and renal blood flow. Cardiac output was not altered.

This compound differs from guanethidine[1] in that it is more potent, manifests a more rapid onset and shorter duration of action and produces less cumulation.

The available pharmacological evidence indicates that Su-13,686 produces its hypotensive effect by some degree of blockade of the post-ganglionic sympathetic fibers.

The *trans*-cinnamylamine was prepared by Gabriel synthesis from the commercially available *trans*-cinnamyl chloride according to the method of GENSLER and ROCKETT[2], b.p. 71–74°/mm; hydrochloride, m.p. 246 to 250°; calculated for $C_9H_{11}N \cdot HCl$: C 63.70, H 7.12, N 8.24; found: C 63.51, H 7.11, N 8.21. Reaction of the free amine with 2-methylthiopseudourea sulfate gave *trans*-cinnamyl guanidine sulfate, which was recrystallized from aqueous ethanol and melted with decomposition at 248 to 251°; calculated for $(C_{10}H_{13}N_3)_2 \cdot H_2SO_4$: C 53.62, H 6.30, N 18.76; found: C 53.62, H 6.36, N 18.52.

To prepare the corresponding *cis*-compound, 1-chloro-3-phenyl-2-propyne[3] which was obtained from 3-phenyl-2-propyn-1-ol[4], was allowed to react with potassium phthalimide to give the N-(3-phenyl-2-propynyl)-phthalimide, m.p. 158–160°; calculated for $C_{17}H_{11}NO_2$: C 78.23, H 4.25, N 5.37; found: C 78.22, H 4.14, N 5.32. LINDLAR[5] palladium-lead catalyst reduction of the phthalimide gave the N-*cis*-cinnamyl phthalimide which was recrystallized from aqueous ethanol, m.p. 110–111°; calculated for $C_{17}H_{13}NO_2$: C 77.63, H 4.98, N 5.33; found: C 77.46, H 4.84, N 5.23. Hydrazinolysis of this material gave *cis*-cinnamylamine, b.p. 104–105°/12 mm; hydrochloride m.p. 177–178°; calculated for $C_9H_{11}N \cdot HCl$: C 63.70, H 7.12, N 8.24; found: C 64.12, H 7.11, N 8.51. Reaction of the free *cis*-cinnamylamine with 2-methylthiopseudourea sulfate gave *cis*-cinnamyl guanidine sulfate which was recrystallized from butanol and water and melted with decomposition at 149–151°; calculated for $(C_{10}H_{13}N_3)_2 \cdot H_2SO_4$: C 53.62, H 6.30, N 18.76; found: C 53.86, H 6.36, N 18.87. IR-spectra served to confirm the *cis* and *trans* isomerism of the aforedescribed compounds.

Zusammenfassung. Es wird die Synthese und Pharmakologie eines neuen blutdrucksenkenden Mittels, *cis*-Cinnamyl-guanidinsulfat, beschrieben.

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Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit (New Jersey USA), June 14, 1965.

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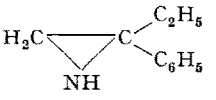
Mutagenic Action of 2-Ethyl-2-phenyl-ethyleneimine

Since the discovery of the mutagenic effect of mustard gas[1] and allied compounds, a large number of chemical compounds have been systematically tested for their mutagenic properties in different laboratories of the world[2–4].

In this laboratory, a derivative of ethyleneimine, 2-ethyl-2-phenylethyleneimine (Figure), was recently tried on barley (*Hordeum vulgare*), and some of the results obtained are presented below. 2-Ethyl-2-phenylethyleneimine is a liquid at room temperature and is practically insoluble in water, but a temporary emulsion is obtained when shaken vigorously.



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Dry seeds of a local 6-rowed variety of barley (Malda) were soaked in emulsions of 2-ethyl-2-phenylethyleneimine in water at concentrations shown in Table I. The pH was kept at about 7.5. Duration of treatments varied from 5 to nearly 7 h at about 23°–25°C. Controls were treated only with distilled water. Details of the effects of the different treatments on germination and survivability are given in Table I.

Seeds were washed in water and sown treatment-wise in small plots in the field. The average number of tillers per plant in the treated and control plants is given in Table II.

Sterility counts were not directly made; however, it was observed that when scoring for mutants in the M_2 generation, the ($5^0/_{00}$) treated plants showed a decrease in the total number of plants germinating from the M_1 spikes as compared to those germinating from the control spikes. Thus the mean number of M_2 plants per M_1 spikes has been found to be 36.7 (M_2) plants per (M_1) spike in the ($5^0/_{00}$) treatment, whereas in the control the corresponding figure was 40.1 plants per spike, indicating an increase in sterility as a result of treatment by the chemical.

Scoring of chlorophyll mutants were made in the usual manner on M_2 seedlings, from M_1 spikes growing on wet sand at about 25°C (Table III).

The frequency of chlorophyll mutation (given here only for the $5^0/_{00}$ treatment) was found to be 3.2% when based on spike progenies and 1.84% when calculated from M_2 seedlings. The corresponding figures for the untreated control were approximately 0.3% and 0.1% respectively. All the 12 mutants in the control belonged to the 'maculata' class, which is grouped here (Table IV) under the heading 'others'.

Table I. Treatments given and their effect on germination and survivability

Concentration used in $^0/_{00}$ in water	Time of treatment	No. of seeds treated and sown	No. of seeds germinated	No. of plants surviving till maturity
3	6 h 45 m	100	91 (91%)	88 (88%)
5	6 h 20 m	100	83 (83%)	83 (83%)
Control (a)	6 h 20 m	100	88 (88%)	88 (88%)
7	5 h	144	6 (4.2%)	1 (0.7%)
Control (b)	5 h	144	119 (82.6%)	113 (78.5%)

Table II. Average number of tillers per plant (M_1 generation) after different treatments. (Spacing between rows 45 cm; between plants 21 cm)

Treatment	Mean no. of tillers/plant
$3^0/_{00}$	10.80 ± 4.6
$5^0/_{00}$	11.47 ± 3.9
Control (a)	10.29 ± 4.8
$7^0/_{00}$	–
Control (b)	11.92 ± 5.0

The frequency of the different classes of chlorophyll mutants in the treatment that were found amongst the 482 plants scored is given in Table IV.

There seems to be a higher proportion of *xantha* mutants (18%) and a lower proportion of *albina* mutants (10.4%) occurring after treatment with the chemical as compared to X-rays; also the highest proportion of mutants that occurred in any class belonged to the viridis type (57.9%), which is not unusual after treatment with chemicals of this nature[4,5].

In spite of its comparative stability, the usefulness of this chemical is greatly limited, as is shown by the fact that a drastic lethal effect was found to occur when a slightly higher concentration ($7^0/_{00}$) was used (Table I). The reason for this is not clear, but this same effect (i.e. a sudden sharp increase in lethality following a slight increase in concentration above a critical dose) has also been observed in other plant species treated with the same chemical (e.g. in jute).

Table III. Frequencies of mutation

Treatment	No. of M_1 spikes	Total no. of M_2 plants	No. of M_2 mutants	Mutation frequency (spike progeny)	Mutation frequency (M_2 seedlings)
Control	307	12,314	12	0.3%	0.097% (= 0.1%)
$5^0/_{00}$	716	26,256	482	5.2%	1.84%

Table IV

Viridis	*Albina*	*Xantha*	Others	Total
57.9%	10.4%	18%	13.7%	(482)

Zusammenfassung. Die Wirkung von 2-Äthyl-2-phenyläthylenimin auf die Induktion von Chlorophyllmutanten bei der Gerste wurde beschrieben. Nach Behandlung mit dem Agens ($5^0/_{00}$ in Wasser) war die Mutationsfrequenz 5,2% für die Ährennachkommenschaften. Die maximale Anzahl Mutanten gehörte zur Viridisklasse (57,9%). Bei höheren Konzentrationen wurde ein beträchtlicher Letaleffekt beobachtet.

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Bose Institute, Calcutta (India), May 3, 1965.

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