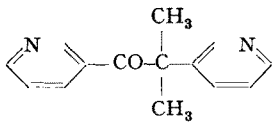
Summary

Intravenous administration of iodoacetate (20 mg/kg) produces in cats a transient miosis. This is shown to be a reflex constriction elicited by an excitatory action of iodoacetate on the retina.

New Amphenone Analogs as Adrenocortical Inhibitors

The synthesis of Amphenone B [3,3-di(p-aminophenyl)-butanone-2-dihydrochloride] by ALLEN and CORWIN[1], with subsequent elucidation of its structure[2] and biological activities[3], led to attempts to obtain a compound which would retain the inhibitory effect of Amphenone B on the secretion of adrenal cortical hormones, but lack some of its other actions. As a result of these investigations, a number of pinacones were synthesized which inhibited adrenal function but differed in other important ways from Amphenone B. The one most thoroughly studied has been 2-methyl-1,2-bis-(3-pyridyl)-1-propanone (Su 4885), which is the subject of this report.

The pinacone is prepared by first performing a bimolecular cathodic reduction on 3-acetylpyridine in a 1 N potassium hydroxide medium at a mercury cathode and a reference potential of – 2·4 volts vs. S.C.E. The isolated pinacol[4] is rearranged by treatment with concentrated sulphuric acid to yield Su 4885, m.p. 50–51°, the structural formula of which is:



Biological Actions

(*A*) *Dogs.*—Both the free base and the ditartrate of Su 4885 were tested for adrenal-inhibiting activity by administration, either intravenously, *per os* or intragastrically, into dogs under Nembutal anesthesia in acute experiments of 2–4 h duration. In each case a cannula was inserted in the lumbo-adrenal vein in a fashion similar to that of HUME and NELSON[5]. At intervals, the entire blood flow through the adrenal vein was collected for two-minute periods and the 17-OH corticoid content measured by a modification of the method of SILBER and BUSCH[6]. Using the various routes of administration in 19 dogs, doses of 10 to 300 mg/kg of either the free base or ditartrate caused in each case a fall in adrenal vein corticoids ranging from 25% to nearly 100% below pretreatment control values. The effects lasted from 1 to more than 4 h. A dose-response curve has not been established but the results suggest that increasing amounts both enhance and prolong the activity. 5 mg/kg intravenously of Su 4885 ditartrate reduced adrenal vein corticoids in 2 of 3 dogs; presumably this approximates the minimal effective dose.

In toxicology studies, the free base of Su 4885 was given orally twice per day to 2 dogs for 4 weeks in doses gradually increased to 200 mg/kg/day, and to 4 dogs for one week (200 mg/kg/day—equivalent to 2·3 times this amount of Su 4885 ditartrate). Adrenal insufficiency was not apparent but there was some ataxia, salivation and depression.

Terminal values for plasma sodium and potassium were in normal ranges but in these 6 treated dogs, terminal adrenal vein corticoids taken 2 h after the last dose of the drug were reduced as indicated in the Table.

An increase in adrenal weight of approximately 50% occurred over control values. This distinguishes the effects of Su 4885 from the adrenolytic action of the insecticide DDD [2,2-bis(para-chlorophenyl)-1,1-dichloroethane] which causes adrenal atrophy in dogs[7] and also suggests that the compound acts directly on the adrenal rather than by suppression of ACTH release. In contrast to Amphenone B and other closely related compounds, Su 4885 did not reduce adrenal blood flow while reducing corticoid secretion.

(*B*) *Rats.*—The effects of Su 4885 ditartrate were sharply distinguished from those of amphenone B by the absence of some amphenone-like actions in rats. In doses of 160 to 320 mg/kg, given either acutely or for 5 day periods by stomach tube, it did not cause adrenal, thyroid or hepatic hypertrophy, natriuresis after a hypotonic saline load, growth inhibition or anesthetic effects. In equimolar doses amphenone B has all of these actions. Su 4885 ditartrate, however, increased the sensitivity to insulin. 2 units/kg of regular insulin, given subcutaneously to 7 rats which had received 300 mg/kg of Su 4885 b.i.d. orally, resulted in convulsions and in a mean decrease of 87% in fasting blood sugar. 17 insulin-treated control animals showed a 25% fall in blood sugar, and no convulsions. The mechanism of this effect is undetermined.

(*C*) *In vitro.*—Su 4885 ditartrate suppressed the output of Silber-Porter reacting steroids when applied *in vitro* with ACTH to rat, guinea pig, or dog adrenal slices at a concentration of 200 mg/l. Under similar conditions Amphenone B acts on the rat but not the guinea pig adrenals. Paper chromatograms of steroid fractions indicated that production of all reducing steroids was blocked by Su 4885. A dose-response curve for rat adrenals showed that 50% inhibition was achieved with approximately 50 mg/l (0·095 mM).

[1] M. J. ALLEN and A. H. CORWIN, J. Amer. chem. Soc. *72*, 117 (1950).

[2] W. L. BENCZE and M. J. ALLEN, J. organ. Chem. *22*, 352 (1957). – J. KORMAN and E. C. OLSON, J. organ. Chem. *22*, 870 (1957).

[3] M. J. ALLEN, R. HERTZ, and W. W. TULLNER, Proc. Soc. exp. Biol. Med. *74*, 632 (1950). – R. HERTZ, M. J. ALLEN, and W. W. TULLNER, Proc. Soc. exp. Biol. Med. *75*, 627 (1950). – R. HERTZ, W. W. TULLNER, and M. J. ALLEN, Proc. Soc. exp. Biol. Med. *77*, 480 (1951). – R. HERTZ, M. J. ALLEN, W. W. TULLNER, and B. B. WESTFALL, Proc. Soc. exp. Biol. Med. *79*, 42 (1952). – A. E. HEMING, D. E. HOLTKAMP, J. F. KERWIN, L. F. MANSOR, and J. G. DECANAY, Proc. Soc. exp. Biol. Med. *80*, 154 (1952). – J. R. HOGNESS, R. H. WILLIAMS, and M. LANCE, Proc. Soc. exp. Biol. Med. *79*, 43 (1952). – R. HERTZ, W. W. TULLNER, J. A. SCHRICKER, F. G. DHYSE, and L. F. HALLMAN, *Recent Progress in Hormone Research*, vol. 11 (New York 1955), p. 119. – W. W. TULLNER, M. M. GRAFF, and R. HERTZ, Endocrinology *58*, 802 (1956). – R. HERTZ, J. A. PITTMAN, and M. M. GRAFF, J. clin. Endocrinol. Metab. *16*, 705 (1956). – G. W. THORN, A. E. RENOLD, A. GOLDFIEN, D. H. NELSON, W. J. REDDY, and R. HERTZ, New England J. Med. *254*, 547 (1956). – A. E. RENOLD, J. CRABBE, L. HERNANDO-AVENDANO, D. H. NELSON, E. J. ROSS, K. EMERSON, Jr., and G. W. THORN, New England J. Med. *256*, 16 (1957). – R. S. MACH and A. F. MÜLLER, Schweiz. med. Wschr. Supplement *14*, 406 (1957).

[4] M. J. ALLEN, J. organ. Chem. *15*, 435 (1950),

[5] D. M. HUME and D. H. NELSON, *Surgical Forum* (10th), Clin. Congress Amer. College Surgeons (Philadelphia, 1955).

[6] R. H. SILBER and R. D. BUSCH, J. clin. Endocrinol. Metab. *16*, 1333 (1956).

[7] J. NICHOLS and H. L. SHEEHAN, Endocrinology *51*, 362 (1952).

	No. Dogs	Hydrocortisone Equivalents	
		μg/ml	μg/2 min
Normal $\pm$ S. D. with Conf. limits, P = 0·01 . .	86	3·6 $\pm$ 1·8 (4·12 — 3·12)	14·0 $\pm$ 6·5 (15·81 — 12·15)
Su 4885 $\pm$ S. D. with Conf. limits, P = 0,01 . .	6	1·1 $\pm$ 0·8 (2·37 — 0)	4·6 $\pm$ 2·9 (9·44 — 0)

(*D*) *Other Endocrine Actions.*—Su 4885 (free base-subcutaneous) was not progestational at 50 mg/kg/day when tested according to the Clauberg technique in rabbits. Neither did it affect the weights of seminal vesicles, testes or uteri in rats in doses of 30–130 mg/kg when given orally or subcutaneously for 3–5 days.

J. J. CHART, H. SHEPPARD, M. J. ALLEN, W. L. BENCZE, and R. GAUNT

Research Department, CIBA Pharmaceutical Products Inc., Summit (N. J.), December 24, 1957.

Zusammenfassung

2-Methyl-1,2-bis-(3-pyridyl)-1-propanon (Su 4885) hemmt beim Hund die Ausscheidung von 17-OH-Steroiden aus den Nebennieren und hemmt *in vitro* ähnlich wie Amphenon den ACTH-Effekt auf Ratten-, Meerschweinchen- und Hunde-Nebennieren. *In situ* bei der Ratte hat es jedoch keine Amphenon-Wirkung, von dem es sich auch sonst unterscheidet.

Stress Response of Leucocytes in Hypothyroid Rats

The relations between adrenal and thyroid glands occupy an important place in the hormonal regulations of the organism. The great part of them has the character of antagonistic influence on various functions[1]. However, the intimate relationship between these two glands remains on the whole unresolved.

We examined the influence of thyroid on the regulation of nonspecific stress response of leucocytes in rats by means of competitive inhibition of thyroid function. In distinction from the majority of experiments using thyroidectomy or strumigen feeding, we applied low doses of dried thyroid gland in order to cause hypofunction of the thyroid gland. Each of a group of white rats, males (n = 30), was given a daily dose of 20 mg dried thyroid gland (Thyreoidin SPOFA). The mean weight of this group (210 g) fell to 180 g after 36 days feeding. The mortality was 10%. The feeding by thyroid gland was stopped on the 37th day and the rats were kept for the next 7 days on normal food. During this period, the weight reached the level of the control non-treated group (n = 30) kept on normal diet. On the 8th day after the stopping of thyroid feeding, 6 of treated animals and 8 of the control group were killed and the thyroid, thymus and spleen were examined histologically. At the same time the leucocytes number and differential count were determined. The histological examination of thyroid in the treated group revealed the lowering and occasionnally the degeneration of follicular epithelium (Fig. 1 and 2). The histological picture of the thymus and the spleen were essentially the same as in the control group. In the peripheral blood, no important differences were found in the total number of leucocytes (M = 8500), neutrophils (M = 3000), lymphocytes (M = 5500) and eosinophils (M = 370).

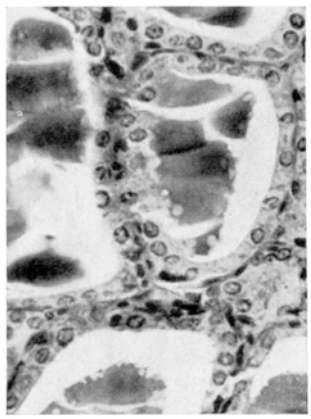


Fig. 1.—Thyroid of the control non-stressed rat. × 340.

The rest of the treated and control animals was given the intramuscular formaldehyde injection (0·5 ml 4%) and the animals were killed after 3 h (2 + 2), 6 h (2 + 2), 12 h (2 + 2), 24 h, (8 + 8) and 48 h (8 + 8). The blood leucocytes, thymus, and spleen were examined. The graphs illustrate the changes of neutrophils, lymphocytes and eosinophils. The stress deviations of the mean values are expressed in % of the mean initial value (= 100%) of the non-stressed animals. The statistical significance of the differences in the course of the stress response was determined by T test from the differences of the absolute values.

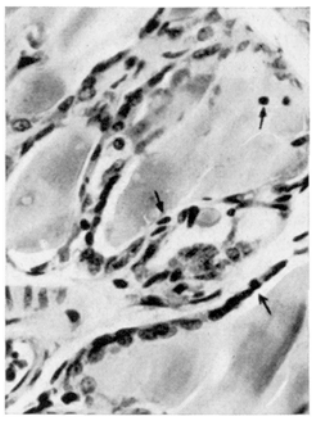


Fig. 2.—Thyroid of the non-stressed rat from the group feeded on thyroid gland before the beginning of the experiment. Follicular epithelium is lowered and occasionally degenerated (→). × 340.

Figure 3 shows the changes of neutrophils, and Figure 4 the changes of lymphocytes and eosinophils during the stress. The stressed control animals exhibit the changes typical for Selye's alarm reaction. The group with thyroid

[1] A. ALBERT, Ann. Rev. Physiol. *14*, 481 (1952).