growth hormone or prolactin with doses as high as 200 and 500 μg. The presence of ICSH activity in the FSH preparation used is borne out by the reports of others.‡ The problem of LH or ICSH activity in preparations of FSH is a topic of much discussion(10). Woods and Simpson(11) have recently stated, "No follicle stimulant of natural origin (pituitaries of any species, menopause or castrate serum or urine) is known which did not at some relatively low multiple of the minimal dose for follicle-development also show uterine stimulation and luteinization or interstitial cell stimulation."

Summary. Experiments have been reported which indicate that a measurement of Zn^{65} uptake by the dorsolateral prostate of the hypophysectomized rat is a sensitive and specific bioassay for ICSH activity.

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Received August 30, 1960. P.S.E.B.M., 1960, v105.

Endocrine Effects of Sulfoxone and of Two Nitriles as Compared with Amphenone.* (26132)

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Amphenone (3, 3-bis-(p-aminophenyl)-butanone-2), has been shown to exert marked endocrine effects on intact mammals through inhibition of formation of adrenal cortical and thyroid hormones by those glands and by a direct effect on the genital tract of the female(1). Because of the report of endocrine changes in patients treated with a sulfone(2) and because of the structural resemblance of the "parent sulfone" diaminodiphenylsulfone (DDS) to amphenone, it was decided to test the disodium formaldehyde sulfoxylate derivative of 4, 4′ diaminodiphenylsulfone (sulfoxone, "Diasone",® Abbott Pharmaceutical Co.) for such actions. Two steroid analogues bearing some structural resemblance to amphenone were also tested: 2, 3-bis-(p-hydroxyphenyl)-valeronitrile (SC-3402 of the G. D. Searle Co.), and 2, 3-bis-(p-hydroxyphenyl)-proprionitrile (Searle SC-4473). The formulae are given in Fig. 1.

Methods. The intact rats were immature females from 23 to 28 days of age obtained from the Holtzman Co., Madison, Wisc. Ovariectomies were performed on a group of these rats at this age one week before beginning drug administration. The hypophysectomized rats were adults of a Sprague-Dawley strain from the Hormone Assay Labs., Chicago, Ill. They had been hypophysectomized about 2 months prior

* We would like to acknowledge the kind gifts of nitriles from G. D. Searle Co., Chicago, Ill.; sulfoxone from Abbott Labs., North Chicago, Ill.; and amphenone from Upjohn Co., Kalamazoo, Mich.

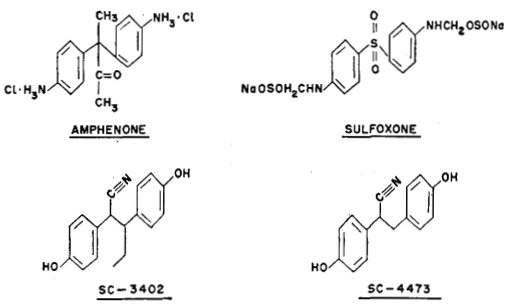

FIG. 1.

to beginning of experiment. The diet was Purina Lab Chow, and all controls were pair-fed. Experiments lasted 5 days each, except those with SC-4473 in the intact animals and in the ovariectomized animals which lasted 7 days. All substances were given in doses of 20 or 40 mg/100 g of body weight according to the weight as determined every other day. The sulfoxone and amphenone were administered in aqueous solutions by daily subcutaneous injections. SC-3402 and SC-4473 were suspended in corn oil and administered by stomach tube daily. Controls received the vehicles only. The day following the last day of experiment (the day after the 5th or 7th day of treatment) the animals were sacrificed, autopsied, and organ weights determined on a Roller-Smith torsion balance. Because of the close similarity of body weights in the test animals as compared with those of the controls, no allometric corrections were made. Statistical methods were those of Fisher(3). The sellar regions of the hypophysectomized animals were examined with a hand lens at autopsy for gross evidence of pituitary remnants, which were not found in any of the animals.

Results. Mean organ weights, expressed as mg/100 g of body weight, are presented in the table with standard deviations, an estimate of the significance of the differences between test and control values, and an expression of maximum change control value in per cent. As expected, administration of amphenone was followed by an increase in size of adrenals (68%), thyroids (77%), and uteri (62%), and by thymolysis and possibly a slight increase in ovarian size. None of the other substances showed an adrenomegalic effect similar to that seen with amphenone, and sulfoxone appeared inert by these measurements except for a decrease in ovarian and uterine weight on the lower dose, of no statistical significance. There were small changes in the ovarian, uterine, and thyroid weights of the SC-3402 animals. The SC-4473-treated rats showed marked enlargement of the uteri and ovaries with striking thymolysis. The uterine and thymic changes persisted in the hypophysectomized and the spayed groups.

Discussion. The absence of significant adrenal enlargement in the sulfoxone-treated rats is not surprising, considering that patients have been treated for leprosy for prolonged periods of time with this drug without signs of adrenal dysfunction. Possibly administration by the oral route might bring about some effects, since hydrolysis to the "parent sulfone" DDS is said to occur in the gastrointestinal tract. However, sulfones which are more active when administered orally may also be effective parenterally(4). While no adrenomegaly occurred with either of the nitriles, the marked changes in uterus and thymus, persisting in the hypophysectomized and ovariectomized animals, indicate that SC-4473 is markedly estrogenic. This property is of particular interest, since these represent the first nitriles to be shown to possess estrogenic activity. However, in our experiments the valeronitrile is inactive in contrast to the previous findings(5,6). This discrepancy might be due to species or strain differences, route or duration of administration, or dose, larger doses having been used in the present work. Uterine response in rats has not been previously reported for either nitrile. The adrenomegalic response previously noted was reported in intact male rats and was absent in hypophysectomized males suggesting that this may be similar to the response seen with other estrogens(7). The ovarian enlargement seen with SC-4473 also resembles the estrogenic effect seen in conjunction with gonadotropins and might be expected to disappear with larger doses, although uterine response was marked and the rats

TABLE I. Organ Weights as mg/100 g Animal.

	Dose, mg/100 g	No. animals	Mean body wt, g	Adrenals		Thyroid		Ovaries		Thymus		Uterus	
				Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Controls		5	79.6	35.9	3.6	9.0	1.8	53.9	12.0	369	45.4	123	33.0
Amphenone B	20	5	69.0	60.3	14.8	15.9	2.6	62.3	8.1	154	40.1	199	35.8
Max change				+68%†		+77%†		+16%		−58%‡		+62%‡	
Controls		10	91.0	33.0	2.3	7.5	.9	49.3	9.1	324	54.3	126	25.8
Sulfoxone	20	7	88.5	33.8	4.0	7.2	1.7	33.7	3.4	322	26.4	101	26.9
"	40	7	90.2	34.1	2.8	8.1	.6	41.4	9.0	292	78.7	129	41.7
Max change								−32%				−20%	
Controls		10	101.6	32.7	3.8	12.0	1.5	53.9	10.4	316	43.8	163	20.1
SC-3402	20	7	99.8	32.8	4.7	9.7	1.9	55.0	4.0	331	28.8	177	49.7
"	40	7	101.2	29.1	3.4	8.8	1.9	61.9	5.7	312	29.8	135	17.5
Max change						−27%†		+15%				−17%	
Controls		9	81.6	38.7	4.1	10.7	2.3	43.2	5.2	350	71.8	114	25.8
SC-4473	20	7	70.2	39.5	3.2	10.5	2.2	83.0	8.4	202	47.8	274	50.1
"	40	7	67.8	39.4	2.9	11.6	1.5	81.2	11.8	167	23.0	383	70.7
Max change								+92%‡		−52%‡		+236%‡	
Hypox controls		5	165.6	26.2	2.1	6.9	.8	36.2	7.1	162	51.8	85	13.0
" SC-4473	20	5	171.2	27.8	4.4	7.6	.9	39.3	5.9	120	35.6	267	113.5
Max change										−26%		+214%*	
Ovarx. controls		5	130.1	38.0	6.4	10.0	1.3			264	54.0	43.6	8.3
" SC-4473	20	5	121.3	36.9	10.1	9.0	1.1			250	51.3	110.6	27.4
" "	40	5	127.7	35.0	4.9	8.5	1.5			209	39.8	157.0	70.8
Max change										−26%		+260%‡	

* $P < .05$ † $P < .01$ ‡ $P < .001$

quite young(8). An estrogenic response might be expected from the structural similarity of these compounds with the stilbestrols.

The reduction in thyroid weight seen with SC-3402 is unusual and may be related to the large thyroid size of the control animals in that particular lot. Likewise, the decreased ovarian and uterine weight in the rats on the lower dose of sulfoxone was not sustained with larger doses and is probably of no biological significance.

Summary. A sulfone, sulfoxone, and 2 nitrile steroid analogues, SC-3402 and SC-4473, have been tested in female rats for endocrine effects and compared with amphenone for reference. None of the 3 substances caused adrenal enlargement similar to that seen in the amphenone-treated animals. SC-4473 was markedly estrogenic. This substance represents the first nitrile to be shown to possess estrogenic activity in the rat.

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Received Sept. 1, 1960. P.S.E.B.M., 1960, v105.

Serum Thrombotic Accelerator (STA) Activity: Its Relation to the First Phase of Clotting.* (26133)

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Normal mammalian serum, in striking contrast to plasma, induces thrombosis in areas of vascular stasis essentially devoid of endothelial injury(1,2). The activity of the moiety in serum responsible for this phenomenon (serum thrombotic accelerator, or STA activity) is mediated through the intrinsic clotting system and is demonstrable only in serum prepared from blood initially rich in Hageman factor (HF), plasma thromboplastin antecedent (PTA), and Factor IX (PTC)(3). The present report further characterizes the relationship between STA activity and these factors.†

Methods and materials. STA activity of human and hen serum was measured in the rabbit by a previously described assay using a standard dose of 1.32 ml/kg(5). When STA activity was measured in the hen using hen and normal human serum, doses as high as 2.64 ml/kg were employed. The amount of thrombus formed was scored on a scale from 0 to 4; a score of 0 represented no clot; a score of 1, a few macroscopic strands of fibrin; a score of 2, several small thrombi; a score of 3, two or more large thrombi; and a score of 4, or complete thrombosis, represented a single thrombus forming a cast of the isolated segment(5).

* This study was supported by research grants from Nat. Heart Inst., and by a grant-in-aid from Am. Heart Assn.

† Presented in part before Am. Physiol. Soc. April 12, 1960, Chicago, Ill.(4).