(*Rome*), **54**, 745(1964); through *Chem. Abstr.*, **62**, 1541 (1965).
(90) Decombe, J., *Compt. Rend.*, **196**, 866(1933); *ibid.*, **197**, 258(1933).
(91) Dalgliesh, C. E., *J. Am. Chem. Soc.*, **71**, 1697(1947).
(92) Balasubramanian, M., and Baliah, V., *J. Chem. Soc.*, **1954**, 1844.
(93) Chodroff, S., and Whitmore, W. F., *J. Am. Chem. Soc.*, **72**, 1073(1950).
(94) Balasubramanian, M., and Baliah, V., *J. Indian Chem. Soc.*, **32**, 493(1955); through *Chem. Abstr.*, **50**, 10042 (1956).
(95) Balasubramanian, M., Baliah, V., and Rangarajan, T., *J. Chem. Soc.*, **1955**, 3296.
(96) Baliah, V., and Seshapathirao, M., *J. Org. Chem.*, **24**, 867(1959).
(97) Nobles, W. L., and Thompson, B. B., *J. Pharm. Sci.*, **54**, 576(1965).
(98) *Ibid.*, **54**, 709(1965).
(99) Larramona, H., and Tchoubar, B., *Bull. Soc. Chim., France*, **1953**, C53.
(100) Walker, J. F., "Formaldehyde," A.C.S. Monograph No. 98, 2nd ed., Reinhold Publishing Co., New York, N. Y., 1953.
(101) Walker, J. F., and Chadwick, A. F., *Ind. Eng. Chem.*, **39**, 974(1947).
(102) Britton, S. B., Caldwell, H. C., and Nobles, W. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 644(1954).
(103) Barney, A. L., U. S. pat. 2,641,594(June 9, 1953); through *Chem. Abstr.*, **47**, 11805(1953).
(104) Kötz, A., *Ber.*, **33**, 1120(1900).
(105) Evans, E. M., and Hookway, H. T., U. S. pat. 2,543,237(February 27, 1951); through *Chem. Abstr.*, **45**, 4485(1951).

Keyphrases

Mannich reaction—review
Mechanism, technology—Mannich reaction
Condensation, Mannich reaction—mechanism
Decomposition reactions—Mannich bases
Reversibility—Mannich reaction
Formaldehyde source—Mannich reaction

Research Articles

Electrolyte Alterations in Vascular Smooth Muscle and Hypotensive Activity of a New Chalcone Derivative

By GERALD P. SHERMAN, ELIAS W. PACKMAN, and G. VICTOR ROSSI

Chalcone R-2803 [2-(2-dimethylaminoethoxy)-3′,4′,5′-trimethoxy chalcone hydrochloride] is an effective and long-acting depressor agent when administered intravenously and orally to dogs and rats. In the intact animal, R-2803 is essentially devoid of adrenolytic or ganglioplegic activity. Cross-circulation studies indicate that R-2803 does not possess central hypotensive activity. A direct action at the vascular level is demonstrated by inhibition of norepinephrine- and angiotensin-induced contractions of isolated aortic muscle. Single intravenous doses increase the sodium and potassium content of rabbit aorta, but decrease serum sodium and potassium values, reflecting an apparent shift in the equilibrium of electrolytes between blood and vascular tissue. Although a decrease in hypotensive activity is not observed after administration of R-2803 for 3 days, the electrolyte changes are less than those observed after single intravenous doses. An equidepressor dose of hesperidin methyl chalcone produces similar elevations of aortic sodium and potassium levels. The electrolyte alterations are not a consequence of blood pressure reduction as evidenced by failure of other hypotensive agents to alter aortic electrolyte balance. Sodium and potassium changes in vascular muscle may play a role in the initial phase of the hypotensive effect of the chalcones.

PHARMACOLOGIC EVALUATION by Rossi and Packman (1) of 14 chalcone derivatives synthesized by Packman and Rubin (2) indicated 2-(2-dimethylaminoethoxy) chalcone to be the most active hypotensive compound in the series. Further modification of this molecule by Packman (3) resulted in a derivative, 2-(2-dimethylaminoethoxy)-3′,4′,5′-trimethoxy chalcone hydrochloride (compound R-2803), characterized by greater depressor potency and extended duration of action.

Based primarily on studies on isolated intestinal smooth muscle, Riedesel and Combs (4) postulated that hesperidin methyl chalcone, which

Received November 13, 1967, from the Department of Biological Sciences, Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104
Accepted for publication December 27, 1967.
This study was supported in part by a research grant from Wm. H. Rorer, Inc., Fort Washington, Pa.
The authors wish to thank Dr. Joseph P. Buckley, Chairman of the Department of Pharmacology, University of Pittsburgh School of Pharmacy, for permission to report the results of cross-circulation studies performed in his laboratories. The authors also wish to thank Mr. Richard Kostrzewa for performance of the spasmolytic assays with aortic tissue.

possesses blood pressure reducing activity, inhibits potassium efflux thus preventing effective depolarization of the muscle membrane. Preliminary investigations conducted with chalcone R-2803, including spasmolytic activity *in vitro* and effect on regional perfusion rate *in situ*, suggested an action directly at the level of vascular smooth muscle. This report characterizes the depressor activity of chalcone R-2803 in experimental animals and examines the possible relationship between the blood pressure reducing effect of chalcones and alterations in the electrolyte composition of vascular tissue.

EXPERIMENTAL

Hypotensive Activity in Anesthetized Dogs—Blood pressure was monitored in 20 male and 17 female mongrel dogs (9–18 Kg.), anesthetized with allobarbital[1]–urethan (0.6 ml./Kg., intravenously), by coupling a femoral arterial cannula *via* a photoelectric transducer to a physiograph (E & M Instrument Co., Houston, Texas). In this series of experiments all drugs were administered intravenously. The intensity and duration of the hypotensive response to 5, 10, and 20 mg./Kg. of chalcone R-2803 were determined, and the effect of prior administration of 10 mg./Kg. of R-2803 was evaluated on the pressor or depressor response to: bilateral occlusion (30 sec.) of the common carotid arteries, electrical stimulation (30 v., 120 p.p.s. for 15 sec.) of the central and peripheral stumps of the severed vagus nerve, epinephrine (25–50 mcg.), norepinephrine (5–10 mcg.), acetylcholine (5–10 mcg.), dimethylphenylpiperazinium (12.5 mcg.), 5-hydroxytryptamine (250 mcg.), and angiotensin amide (10 mcg.).

Three dog cross-circulation pairs were prepared according to the procedure detailed by Bickerton and Buckley (5). Compound R-2803 was administered into the arterial inflow to the recipient's head, and subsequently into the recipient's femoral vein in doses of 1 and 5 mg./Kg.

Hypotensive Activity in Unanesthetized Dogs—The hypotensive effect of 10 and 20 mg./Kg. of R-2803, administered orally in gelatin capsules, was evaluated in 2 male and 2 female unanesthetized mongrel dogs (7–11 Kg.). Femoral arterial systolic and diastolic pressures were monitored externally by means of an automatic cuff inflation pump functioning in conjunction with an electrosphygmograph which provides a system for continuous recording of occluding cuff pressure and superimposed Korotkoff sounds.

Hypotensive Activity in Unanesthetized Rats—The depressor response to oral administration of 20 mg./Kg. of R-2803 was determined in unanesthetized normotensive and experimental hypertensive male Sprague-Dawley rats (150–190 Gm.). Sustained elevated blood pressure (*i.e.*, systolic pressure in excess of 170 mm. Hg) was induced by extirpation of the left kidney and replacement of drinking water by 2% saline solution. Caudal arterial pressure was estimated indirectly by means of an electrosphygmographic system.

Effect on Contraction of Rabbit Aortic Spirals In Vitro—Spiral strips prepared, according to the procedure described by Furchgott (6), from the descending thoracic aorta of male New Zealand white rabbits (1–2 Kg.) were suspended in Krebs-bicarbonate solution at 37.5°, aerated with 95% O_2 + 5% CO_2, and arranged for kymographic recording of contractions. The concentration of *l*-norepinephrine bitartrate required to elicit a submaximal response was determined individually for each muscle preparation, after which the extent of inhibition of norepinephrine-induced contraction was evaluated with concentrations of R-2803 ranging from 1.67 to 20 mcg./ml. This assay procedure was repeated with other aortic strips using angiotensin amide as the spasmogenic stimulus.

Sodium and Potassium Levels in Rabbit Aorta—Analyses of the sodium and potassium content were performed with aortic tissue samples obtained from male New Zealand white rabbits (1–2 Kg.) 2 hr. after intravenous administration of: R-2803 (10 mg./Kg.), hesperidin methyl chalcone (40 mg./Kg.), mecamylamine (5 mg./Kg.), guanethidine (15 mg./Kg.), chlorothiazide (100 mg./Kg.), and normal saline (volumes equal to injected solution of the experimental drugs). The descending thoracic and abdominal aorta was excised from animals sacrificed by air embolism; the tissue was rinsed in deionized water, trimmed of fat and connective tissue, weighed and ashed (600°, 12–14 hr.). Sodium and potassium concentrations were determined by means of a Perkin-Elmer 303 atomic absorption spectrophotometer, and results expressed in terms of meq./Kg. wet weight of tissue.

RESULTS

Hypotensive Activity in Anesthetized Dogs—Reduction of systolic and diastolic pressure was apparent within 60 sec. after intravenous injection of 5 mg./Kg. of chalcone R-2803 in anesthetized dogs. Blood pressure decreased progressively and attained a hypotensive plateau within 60–90 min. (Fig. 1). A dose-response relationship was evident with the 5, 10, and 20 mg./Kg. dosage range examined.

The chalcone had a more pronounced effect on diastolic than on systolic blood pressure. There was

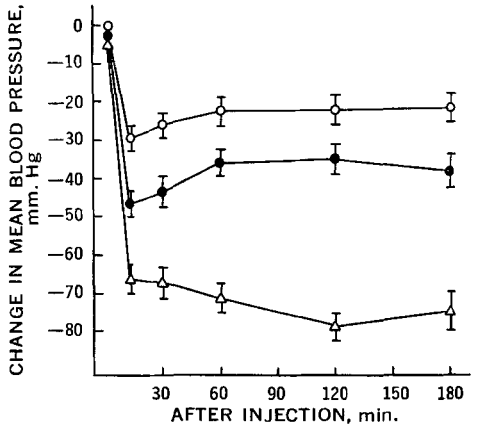

Fig. 1—Reduction of mean blood pressure in anesthetized dogs after intravenous injection of chalcone R-2803. Key: ○, 5 mg./Kg. (N = 3); ●, 10 mg./Kg. (N = 4); △, 20 mg./Kg. (N = 3). Vertical bars indicate standard errors of the mean.

[1] Dial, Ciba Pharmaceutical Co., Morris Plains, N. J.

little change in heart rate and no apparent alteration in the electrocardiogram. A short period of hyperpnea occurred following intravenous administration of the chalcone.

In no case was there a substantial return to pretreatment pressure levels after 3 hr. (arbitrary termination of most assays in this series), and the blood pressure remained depressed 6 hr. after drug administration in those experiments ($N = 5$) conducted for an extended time period. There were no detectable differences in the depressor response to intravenous administration of 10 mg./Kg. of R-2803 in nonpretreated dogs ($N = 4$) and in dogs ($N = 3$) pretreated with 3 daily intraperitoneal injections of 10 mg./Kg. of the chalcone.

A moderate additional reduction in blood pressure (Δ 20 mm. Hg) occurred when the position of anesthetized dogs administered 10 mg./Kg. of R-2803 intravenously, and secured to a tilt table, was abruptly changed from the horizontal plane to an angle of 60°. In contrast, this postural change elicited a further marked reduction in pressure (Δ 50 mm. Hg) in dogs injected intravenously with 15 mg./Kg. of phenoxybenzamine.

Intravenous injection of 10 mg./Kg. of R-2803 partially blocked the carotid occlusion pressor reflex and the responses to electrical stimulation of the central and peripheral ends of the severed vagus nerve, but did not significantly alter the characteristic pressor or depressor effects of epinephrine, norepinephrine, acetylcholine, dimethylphenylpiperazinium, 5-hydroxytryptamine, and angiotensin.

Administration of the antihistaminic compound chlorpheniramine (6 mg./Kg., intravenously) 30 min. prior to intravenous injection of 5, 10, and 20 mg./Kg. of R-2803 in anesthetized dogs ($N = 3$, 4, 3, respectively) decreased by 26–42% the extent, but did not significantly affect the duration of the hypotensive activity of the chalcone. Pretreatment, intravenously, of anesthetized dogs with 150 mcg. of the histamine-releasing agent 48/80 ($N = 3$), or 150 mg. of the antiserotonin agent cyproheptadine ($N = 3$) did not alter the intensity or duration of the depressor response to intravenous injection of 10 mg./Kg. of R-2803.

Administration of R-2803 [1 mg./Kg. ($N = 1$) and 5 mg./Kg. ($N = 2$)] into the arterial inflow to the recipient's head in cross-circulation preparations reduced blood pressure in the donor dog but did not elicit a hypotensive response in the recipient animal. However, administration of the chalcone into the arterial inflow resulted in a marked reduction in perfusion pressure to the recipient's head, indicative of cerebral vascular dilation.

Hypotensive Activity in Unanesthetized Dogs—Blood pressure reduction was detectable within 30 min. after oral administration of 10 and 20 mg./Kg. of R-2803 to unanesthetized dogs; the maximal response was evident within 2 hr. (Fig. 2). The extent of blood pressure reduction following oral administration of 20 mg./Kg. was approximately equivalent to that produced by intravenous injection of 10 mg./Kg. of the chalcone. In those animals monitored for an 8-hr. period after oral administration, the blood pressure had not returned to the predrug level at the termination of the assay.

That the anesthetic employed in a previous phase of this study had no appreciable effect on the depressor response was evidenced by the lack of a significant difference between the hypotensive activity of the chalcone (10 and 20 mg./Kg., orally) in unanesthetized dogs and in dogs anesthetized (allobarbital–urethan) immediately following administration of R-2803.

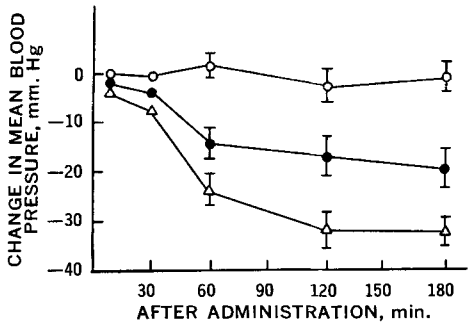

Fig. 2—Reduction of mean blood pressure in unanesthetized dogs after oral administration of chalcone R-2803. Key: ○, placebo capsule (N = 4); ●, 10 mg./Kg. (N = 5); △, 20 mg./Kg. (N = 5). Vertical bars indicate standard errors of the mean.

Hypotensive Activity in Unanesthetized Rats—Oral administration of 20 mg./Kg. of R-2803 produced essentially the same degree and duration of blood pressure reduction in normotensive rats and in renal hypertensive rats (Fig. 3). Although the extent of depressor activity following oral administration of R-2803 in unanesthetized rats was comparable to that observed in unanesthetized dogs, the duration of blood pressure reduction was considerably shorter in the rat (approximately 2.5 hr.) than in the dog (exceeding 6 hr.).

Inhibition of Contraction of Rabbit Aortic Spiral In Vitro—With reference to blocking the contractile response of isolated spiral strips of rabbit aorta to norepinephrine, the ED_{50} concentration of R-2803 was found to be 3.2 mcg./ml. ($N = 22$). A concentration of 20 mcg./ml. of R-2803 reduced angiotensin-induced contractions of aortic smooth muscle by approximately 30% ($N = 8$). It was not possible, however, to determine an ED_{50} value for angiotensin-antagonism inasmuch as concentrations of chalcone in excess of 20 mcg./ml. elicited contracture in aortic strips previously exposed to angiotensin.

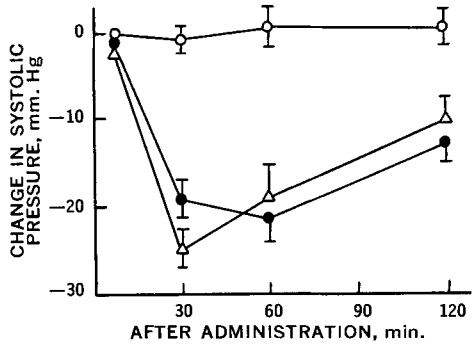

Fig. 3—Reduction of systolic blood pressure in unanesthetized rats after oral administration of chalcone R-2803. Key: ○, saline administration in normotensive rats (N = 2); ●, 20 mg./Kg. in normotensive rats (N = 12); △, 20 mg./Kg. in hypertensive rats (N = 11). Vertical bars indicate standard errors of the mean.

TABLE I—MEAN SODIUM AND POTASSIUM LEVELS IN RABBIT AORTA AND SERUM 2 HR. AFTER INTRAVENOUS ADMINISTRATION OF VARIOUS HYPOTENSIVE AGENTS

Treatment	Dose mg./Kg.	No. Animals	Sodium meq./Kg. $\bar{X}^a \pm$ S.E.	*P* Value	Potassium meq./Kg. $\bar{X}^a \pm$ S.E.	*P* Value
Aortic Electrolyte Levels						
Control (saline)		32	1.195 ± 0.019		1.178 ± 0.016	
Chalcone R-2803	10	20	1.295 ± 0.024	<0.05	0.642 ± 0.022	<0.001
Hesperidin methyl chalcone	40	20	1.304 ± 0.019	<0.01	0.449 ± 0.026	<0.001
Control (saline)		14	1.176 ± 0.027		0.228 ± 0.025	
Chalcone R-2803[b]	10	17	1.138 ± 0.020	...	0.328 ± 0.018	<0.05
Control (saline)		27	1.229 ± 0.020		0.323 ± 0.015	
Mecamylamine	5	18	1.196 ± 0.022	...	0.245 ± 0.001	<0.01
Guanethidine	15	17	1.177 ± 0.024	...	0.353 ± 0.017	...
Control (saline)		5	1.246 ± 0.042		0.204 ± 0.025	
Chlorothiazide	100	6	1.188 ± 0.033	...	0.287 ± 0.021	...
Serum Electrolyte Levels						
Control (saline)		14	2.125 ± 0.713		0.816 ± 0.052	
Chalcone R-2803	10	14	2.078 ± 0.580	<0.05	0.705 ± 0.036	<0.05

[a] Mean logarithmic values ± standard error. [b] Pretreatment with R-2803, 10 mg./Kg., intraperitoneally in single doses for 3 days and sacrified 2 hr. after administration of R-2803, 10 mg./Kg., intravenously.

Sodium and Potassium Levels in Rabbit Aorta—Chalcone R-2803 (10 mg./Kg., intravenously) increased aortic sodium and potassium levels, and decreased the serum concentration of these electrolytes (Table I). The aortic potassium elevation following intravenous administration of R-2803 was less in rabbits pretreated with the chalcone (10 mg./Kg./day, intraperitoneally, for 3 days) than in those animals which received only the single intravenous injection.

An approximate equidepressor dose (40 mg./Kg., intravenously) of hesperidin methyl chalcone produced alterations in aortic sodium and potassium values similar to those obtained with R-2803.

With the exception of a decreased potassium level following treatment with mecamylamine, the intravenous administration of mecamylamine (5 mg./Kg.), guanethidine (15 mg./Kg.), and chlorothiazide (100 mg./Kg.) did not elicit significant changes in the sodium or potassium content of aortic tissue.

DISCUSSION

Chalcone R-2803 [2-(2-dimethylaminoethoxy)-3′,4′,5′-trimethoxy chalcone HCl] was found to be an effective and long-acting depressor agent when administered intravenously to anesthetized normotensive dogs, and orally to unanesthetized normotensive dogs, normotensive and hypertensive rats. Prolonged moderate reductions in arterial pressure were consistently obtained following intravenous injection of 5–10 mg./Kg., and oral administration of 10–20 mg./Kg. of the chalcone in dogs.

In the intact animal, R-2803 does not possess significant ganglionic blocking or alpha-adrenergic blocking activity. Cross-circulation studies with R-2803 did not reveal any basis for a central mechanism of hypotensive action. A direct action at the vascular level was indicated by an increase in the regional perfusion rate *in situ*, and inhibition of the contractile effect of norepinephrine and angiotensin on isolated aortic smooth muscle.

The possibility of histamine release as a component of the hypotensive action was explored by comparing the blood pressure patterns following intravenous administration of R-2803 in anesthetized saline-pretreated (control) dogs, in dogs pretreated with an effective histamine-blocking dose of chlorpheniramine, and in dogs administered repeated doses of compound 48/80 until the onset of refractoriness. Chlorpheniramine appreciably diminished the degree of blood pressure reduction at all dosage levels of R-2803 examined, but did not consistently affect the duration of the depressor response. No comparable inhibition of the hypotensive action of R-2803 was observed in dogs pretreated with compound 48/80. These latter results may be considered inconclusive inasmuch as there is no definitive method for determining the completeness of histamine depletion in the intact animal, although Slomka and Goth (7) have proposed that refractoriness to subsequent doses of 48/80 is indicative of depletion of available histamine stores. It has frequently been noted that the histamine release which occurs with the peak blood levels resulting from the intravenous injection of certain drugs may not occur or may be less apparent following the relatively slow absorption of the same drugs from the gastrointestinal tract. However, the hypotensive response to intraduodenal administration of R-2803 was also diminished in dogs pretreated with chlorpheniramine. Partial reduction rather than complete abolition by chlorpheniramine of the hypotensive response suggests that histamine release may contribute to, but cannot completely account for, the blood pressure reducing effect of R-2803.

Correlations among the ionic and bioelectric properties of smooth muscle provide a foundation for the proposed roles of altered electrolyte composition of the vascular tree in the increased peripheral resistance characteristic of essential hypertension, and in the mechanism of action of certain blood pressure reducing agents. Su and Bevan (8) have suggested that intracellular antagonism of potassium may be involved in the reduction of arteriolar tone produced by the alpha-adrenergic blocking agents, phenoxybenzamine and SY-14 [*N*-(2-chloroethyl)-*N*-ethyl-1-naphthalenethylamine HCl]. It has been theorized that the gradient of sodium and/or potassium ions existing between the intracellular and extracellular spaces is related to inherent vascular responsiveness and that the thiazides may elicit their hypotensive effect by altering these electrolyte gradients (9).

This basic hypothesis remains plausible although the thiazides have not been found to alter the concentration of sodium in the plasma of hypertensive patients (10), or the sodium content of the arterial walls of experimental animals (11).

The studies with intestinal smooth muscle conducted by Riedesel and Combs (4) on the basis of which they postulated that hesperidin methyl chalcone inhibits potassium efflux, and our observations that chalcone R-2803 increased regional perfusion rate and decreased the reactivity of isolated aortic smooth muscle to norepinephrine and angiotensin, prompted an investigation of the effect of R-2803 on the electrolyte composition of vascular tissue. Single intravenous hypotensive doses of R-2803 increased the sodium and potassium content of rabbit aorta and decreased the serum sodium and potassium levels. These data may reflect a shift in the equilibrium of electrolytes between blood and vascular muscle, *i.e.*, alterations in the intracellular/extracellular gradients of sodium and potassium ions. An approximate equidepressor dose of hesperidin methyl chalcone, which was about one-fourth as potent as R-2803 on a milligram basis, produced similar changes in aortic sodium and potassium levels.

The electrolyte alterations in vascular muscle following administration of R-2803 and hesperidin methyl chalcone are apparently not a consequence of the blood pressure reduction as evidenced by the failure of other potent hypotensive agents (*i.e.*, mecamylamine, guanethidine, and chlorothiazide) to similarly alter the aortic electrolyte concentrations.

Sodium and potassium imbalances in vascular smooth muscle may play a role in the initial phases of the hypotensive action of the chalcones, with the inhibition of potassium efflux preventing effective depolarization of the muscle membrane. However, due possibly to compensatory mechanisms, the electrolyte concentrations in vascular tissue revert toward normal levels within a time period during which refractoriness to the blood pressure reducing effect does not develop.

REFERENCES

(1) Rossi, G. V., and Packman, E. W., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 640(1958).
(2) Packman, A. M., and Rubin, N., *Am. J. Pharm.*, **134**, 35(1962).
(3) Packman, A. M., Wm. H. Rorer, Inc., Fort Washington, Pa., personal communication.
(4) Riedesel, C. C., and Combs, A., presented to the Scientific Section, American Pharmaceutical Association, New York meeting, August 1964.
(5) Bickerton, R. K., and Buckley, J. P., *Proc. Soc. Exptl. Biol. Med.*, **106**, 834(1961).
(6) Furchgott, R. F., *Methods Med. Res.*, **8**, 177(1960).
(7) Slomka, M. B., and Goth, A., *Proc. Soc. Exptl. Biol. Med.*, **93**, 30(1962).
(8) Su, C., and Bevan, J. A., *Federation Proc.*, **22**, 308 (1963).
(9) Brest, A. N., and Moyer, J. H., "Recent Advances in Hypertension," Lea and Febiger, Philadelphia, Pa., 1961, p. 250.
(10) Winer, B. M., *Circulation*, **23**, 211(1961).
(11) Tobian, L., *Ann. Rev. Pharmacol.*, **7**, 399(1967).

Keyphrases

Chalcone derivatives—pharmacological activity
Depressor activity—chalcone R-2803
Hypotensive activity—chalcone R-2803
Norepinephrine activity—antagonized
Angiotensin activity—antagonized
Electrolyte changes—smooth muscle, blood

Cyclic α,β-Unsaturated Ketones Related to Ethacrynic Acid

By JOHN G. TOPLISS and LEROY M. KONZELMAN

2-Carboxymethoxy-8,9-dihydro-6-methyl-5*H*-benzocyclohepten-5-one and 5-carboxymethoxy-2-methylindone, which are structurally related to ethacrynic acid, have been synthesized and the acute renal excretory response to intravenous injections of the compounds in the anesthetized dog has been evaluated. Only marginal activity, compared to ethacrynic acid, was observed.

THE DISCOVERY of a new class of diuretic agents, α,β-unsaturated ketone derivatives of aryloxyacetic acids of the general structure I, was reported by Schultz *et al.* in 1962 (1). Subsequently, pharmacological and clinical reports (2) have appeared on a compound in this series, ethacrynic acid (II).

The authors were interested in determining the effect on diuretic activity of the incorporation of the α,β-unsaturated ketonic function in a ring system in compounds of this general structural type. Consequently, it was decided to synthe-

Received October 19, 1967, from the Medicinal Chemical Research Department, Schering Corporation, Bloomfield, NJ 07003
Accepted for publication December 15, 1967.
The authors thank Dr. N. Sperber for his interest and encouragement.