a_i = any chosen value of a in the range present.
a_{io} = the zero time radius of a_i.
C = concentration.
C_s = saturation concentration.
C_o = concentration of bulk of solution.
D = diffusion coefficient.
$f>a_o$ = fraction larger than radius, a_o, at zero time.
$f>a$ = fraction larger than radius, a, at time t.
K = a proportionality constant.
$K' = \frac{4\pi K}{3V_o}$
m = mass of a single particle.
M = total mass of undissolved solid.
M_o = total mass of solid at zero time.
n = number of particles of a given size.
N = total number of particles.
Q = fraction of undissolved solid at time t; M/M_o.
r = radius of imaginary sphere through which diffusion occurs.
t = time.
v = volume of a single particle.
$V_o = \frac{M_o}{\rho}$
v_o = volume of a particle of a_o radius at zero time.
π = 3.1416.
ρ = density.

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Hypotensive Activity of Certain Diquaternarized Ammonium Compounds as Influenced by Administration Route and Anesthesia

By DAVID W. COATES†, JOSEPH P. BUCKLEY, and WILLIAM J. KINNARD

A three-way crossover experimental design demonstrated that urethan anesthesia enhanced the hypotensive responses of certain diquaternarized ammonium compounds in normotensive rats. The test showed that cardiovascular responses were more significant in hypertensive than in normotensive rats. Barbiturate anesthesia potentiated the hypotensive responses of certain of the compounds in normotensive dogs. Intravenous infusion of two of the compounds into anesthetized normotensive dogs produced a maximum hypotensive effect in 2 minutes with no further lowering of the blood pressure as the infusion was continued.

THE INCOMPLETE absorption following the oral administration of bisquaternary ammonium compounds has long been considered one of the main factors contributing to the erratic results produced by these ganglionic blocking agents in the treatment of arterial hypertension, and strong support for this view was provided by the absorption studies of Levine, *et al.* (1), and Schanker, *et al.* (2). Maxwell, *et al.* (3), reported the relative ineffectiveness of chlorisondamine in lowering the blood pressure of unanesthetized normotensive rats and dogs following intravenous administration. Haas and Goldblatt (4) obtained slight pressor responses in mean femoral arterial blood pressure following the intravenous infusion of tetraethylammonium, hexamethonium, pentolinium, chlorisondamine, and mecamylamine in unanesthetized normotensive dogs. However, these same investigators demonstrated a depressor response with pentolinium during an intermediate period of renal hypertension in dogs (5).

This report deals with the attempt to evaluate several bisquaternary ammonium compounds (Fig. 1) for their oral hypotensive activity in unanesthetized normotensive rats and dogs and in unanesthetized renal hypertensive rats. The experiment was designed to allow comparisons between oral and parenteral administration of the compounds to unanesthetized animals and between parenteral administration to unanesthetized and anesthetized animals.

METHOD

Hypotensive Activity in Normotensive Rats.—Normotensive Wistar rats were trained for indirect systolic blood pressure determinations using the photoelectric tensometer.[1] These rats were then divided into five groups of eight animals each. One of the following compounds was assigned to each

[1] Metro Industries.

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TABLE I.—EFFECTS OF CERTAIN HYPOTENSIVE AGENTS ON SYSTOLIC BLOOD PRESSURE OF NORMOTENSIVE RATS

Compound JB	Dose, mg./Kg.	Route of Adm.	Control Blood Pressure,[a] mm. Hg	% of Control Blood Pressure at Time Noted (min.) Following Drug Administration[a] 15	30	60	90	120	150	180	210	240
654	100	oral	118	114	111	110	117	111	116	125	114	119
654	10	i.p.	124	83	103	110	115	117	110	96	105	106
654	10	i.p.[b]	109	80	73	69	76	80	82	84	86	94
643	100	oral	108	91	104	98	98	92	103	98	93	99
643	10	i.p.	113	86	89	101	98	93	94	95	91	102
643	10	i.p.[b]	107	84	80	73	77	84	90	89	93	101
591	250	oral	104	96	97	92	91	91	106	104	97	100
591	25	i.p.	107	86	89	99	96	94	86	93	98	89
591	25	i.p.[b]	101	83	82	84	88	87	99	107	95	97
676	75	oral	124	91	93	92	89	89	92	96	99	99
676	7.5	i.p.	131	96	99	97	98	101	103	106	96	108
676	7.5	i.p.[b]	124	65	65	65	72	73	78	83	75	90
Chlorisondamine	5	oral	115	103	100	106	107	103	104	104	104	106
Chlorisondamine	0.5	i.p.	121	85	94	98	98	98	104	97	98	101
Chlorisondamine	0.5	i.p.[b]	108	71	59	61	64	70	77	87	90	95

[a] Each value in the table represents the mean responses of eight rats. [b] Rats anesthetized with urethan, 1.2 Gm./Kg. i.p.

group: JB 654, JB 643, JB 591, JB 676, or chlorisondamine dimethochloride.[2] The compounds were first administered orally to 24-hr. fasted unanesthetized animals in a dose ten times the selected intraperitoneal dose for that particular compound (6). The oral doses selected were as follows: JB 654, 100 mg./Kg.; JB 643, 100 mg./Kg.; JB 591, 250 mg./Kg.; JB 676, 75 mg./Kg.; and chlorisondamine dimethochloride, 5 mg./Kg. Blood pressures were obtained prior to administration of the compounds and periodically as indicated in Table I. After a recovery period of from 3 to 5 days to allow for full elimination of the compounds, these same unanesthetized groups of rats received the compounds by intraperitoneal injection. Blood pressure determinations were again made over the noted period of time. Following the recovery period, these same groups of rats were anesthetized with urethan, 1.2 Gm./Kg. i.p., and control pressures obtained. The compounds were administered by intraperitoneal injection and the effects on systolic blood pressure determined.

All compounds were administered in the form of freshly prepared solutions in distilled water. The concentrations were held constant for each compound, since it has been shown that the concentration is an important factor in oral absorption (7, 8).

The data were grouped into three sections: results following oral administration, results following intraperitoneal administration in unanesthetized rats, and results following intraperitoneal administration in anesthetized rats. The data were then subjected to an analysis of variance (9) to determine any differences between the actions of the compounds within each of the three sections.[3] The analysis also made it possible to demonstrate any effect time had upon the results obtained.

The data were then regrouped and paired comparisons (10) made between the oral and the intraperitoneal unanesthetized results and the intraperitoneal unanesthetized and intraperitoneal anesthetized results for each compound.[4] The values for the comparisons were obtained by totaling the blood pressure responses, noted as the per cent of the control blood pressure, at each time interval following drug administration and dividing by the number of intervals for each of the eight rats in the groups. This can be termed: the Individual Overall Cardiovascular Response (IOCR). A single figure representative of the entire group was determined by

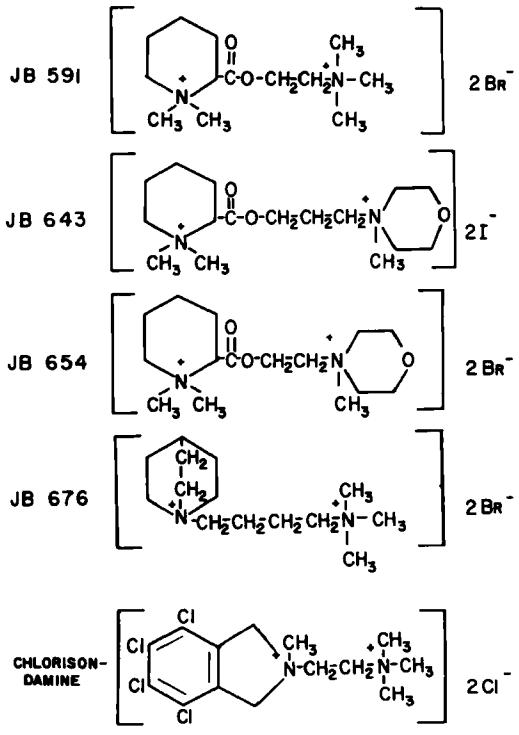

Fig. 1.—Structures of compounds investigated. JB 591 (β-dimethylaminoethyl N-methylpipecolinate dimethobromide), JB 643 (3-morpholinopropyl N-methylpipecolinate dimethoiodide), JB 654 (2-morpholinoethyl N-methylpipecolinate dimethobromide), JB 676 (N-(4-trimethylaminobutyl)-quinuclidinium bromide methobromide), and chlorisondamine (4,5,6,7-tetrachloro-2 (dimethylaminoethyl) isoindoline dimethochloride).

[2] Supplied as Ecolid by Ciba Pharmaceutical Products.
[3] Significance was measured at P = 1%.
[4] Significance was measured at P = 0.05.

TABLE II.—EFFECTS OF CERTAIN HYPOTENSIVE AGENTS ON SYSTOLIC BLOOD PRESSURE OF HYPERTENSIVE RATS

Compound JB	Dose, mg./Kg.	Route of Adm.	Control Blood Pressure,[a] mm. Hg	% of Control Blood Pressure at Time Noted (min.) Following Drug Administration[a] 15	30	60	90	120	150	180	210	240
654	100	oral	185	102	85	80	78	87	89	92	88	99
654	10	i.p.	202	60	68	79	83	99	87	89	94	93
654	10	i.p.[b]	137	40	40	45	44	53	64	67	73	79
643	100	oral	195	84	73	72	71	70	63	68	70	73
643	10	i.p.	185	60	64	71	83	89	92	94	93	94
643	10	i.p.[b]	140	48	45	60	63	76	82	83	86	90
591	250	oral	214	80	86	76	74	78	78	80	80	82
591	25	i.p.	211	51	67	78	73	83	90	80	91	92
591	25	i.p.[b]	181	62	53	60	64	71	73	78	81	82
676	75	oral	210	79	78	75	83	79	87	82	88	91
676	7.5	i.p.	204	89	107	97	108	105	108	108	106	108
676	7.5	i.p.[b]	171	58	61	73	80	82	84	92	95	95
Chlorisondamine	5	oral	200	101	104	104	108	116	117	115	117	115
Chlorisondamine	0.5	i.p.	214	103	83	99	106	106	110	107	107	107
Chlorisondamine	0.5	i.p.[b]	236	44	49	33	46	42	46	56	61	66

[a] Each value in the table represents the mean responses of eight rats. [b] Rats anesthetized with urethan 1.2 Gm./Kg. i.p.

dividing the sum total of the IOCR's by the number of subjects in the group. This was termed: Overall Cardiovascular Response (OCR) for that particular compound and method of administration. An OCR less than 100 indicated hypotensive activity while a figure greater than 100 indicated pressor activity.

Hypotensive Activity in Hypertensive Rats.—Hypertensive rats were prepared using a modification of the method of Freed, *et al.* (11). Four to 6 weeks following the simultaneous unilateral nephrectomy and figure-of-eight ligature of the contralateral kidney, weekly injections of desoxycorticosterone trimethylacetate,[5] 0.25 ml. (6.25 mg.), were initiated. Simultaneously, 1% sodium chloride solution was substituted for drinking water. This regimen was continued until a marked and sustained hypertension was produced, as recorded by the photoelectric tensometer. The rats were divided into five groups of eight animals each, and the identical experimental design as that outlined for normotensive rats was employed.

Hypotensive Activity in Normotensive Dogs.—The systolic blood pressures of unanesthetized mongrel dogs were obtained by the method of Prioli and Winbury (12) using the Infratron unit.[6] The dogs were restrained in a specially constructed animal sling which limited movement but did not completely support the animals. The tail was shaved and the coccygeal artery, located on the ventral surface, used as the site of blood pressure determination. A digital cuff was placed at the base of the tail and the microphone of the Infratron unit secured to the tail beneath the coccygeal artery, distal to the cuff, and so adjusted to obtain the best pulse pattern that could be observed on an oscilloscope. Systolic blood pressure was determined by increasing the cuff pressure until the pulse waves disappeared and then slowly reducing this pressure until the pulse pattern was again evident on the oscilloscope. At this point, the cuff pressure in mm. of Hg was recorded as the systolic blood pressure. The experimental design was identical with that utilized in rats except that the number of animals per group was reduced to four, 35 mg./Kg. i.v. of pentobarbital sodium was utilized as the anesthetic, and the compounds were administered orally in capsule form or intravenously.

Intravenous Infusion of JB 591 and JB 676.—Mongrel dogs were anesthetized with 35 mg./Kg. i.v. of pentobarbital sodium and prepared for direct femoral blood pressure determinations in the usual manner. The contralateral femoral vein was isolated and freed of surrounding fascia. An intravenous drip system[7] was fitted with a 20-gauge hypodermic needle and adjusted to deliver 1 ml./min. of the drug solutions. Aqueous drug solutions were prepared in suitable concentrations so that a previously determined total intravenous dose of JB 676 (7.5 mg./Kg.) or JB 591 (25 mg./Kg.) could be delivered over a 20-min. period. Following a stabilization period of at least 30 minutes, the needle was inserted into the vein and the infusion started. Blood pressure recordings were obtained for the 20-min. infusion period.

RESULTS

Hypotensive Activity in Normotensive Rats.—The effects of the diquaternary ammonium compounds on the blood pressure of normotensive rats are summarized in Table I. The compounds did not produce significant hypotensive effects when administered orally or intraperitoneally to unanesthetized normotensive rats. There was no significant difference between any of the compounds when the IOCR data for oral and intraperitoneal activity were analyzed.

Urethan anesthesia enhanced the hypertensive activity of JB 654, JB 676, and chlorisondamine but did not significantly alter the depressor response to JB 591 and JB 643.

Hypotensive Activity in Hypertensive Rats.—The results obtained following the administration of the compounds to hypertensive rats are summarized in Table II. Most of the compounds were active in unanesthetized hypertensive rats in contrast to their relative inertness in unanesthetized normotensive rats. The analysis of variance demonstrated a difference between the activities of the compounds

[5] Supplied as Percorten by Ciba Pharmaceutical Products.
[6] Medical Electronics Development Co.
[7] Marketed as Venopak by Abbott Laboratories.

when administered orally. The OCR's, expressed in per cent of predrug control blood pressure, suggested the following order of decreasing potency: JB 643, 72%; JB 591, 79%; JB 676, 82%; JB 654, 88%; and chlorisondamine, 112%. The maximum hypotensive effects occurred in approximately 60 minutes with JB 591 and JB 676 and 150 minutes with JB 643. There was a marked difference in the response to certain of the compounds when they were administered intraperitoneally to unanesthetized hypertensive rats. The activities of JB 654, JB 643, and JB 591 were similar, their respective OCR's being 82%, 82%, and 79% of the control blood pressure. JB 676 and chlorisondamine produced slight pressor responses. The maximum mean hypotensive effects of the depressor compounds occurred 15 minutes following drug administration.

Analysis of the data obtained from the intraperitoneal administration of the compounds to anesthetized hypertensive rats showed a difference in the hypotensive activity of the compounds. All the agents were active and the following order of decreasing hypotensive activity was suggested: chlorisondamine and JB 654, 50% and 56% of the control; JB 591 and JB 643, 69% and 72%; and JB 676, 80%. Maximum hypotensive activity occurred within 15 minutes for all the compounds except JB 591, which required 30 minutes.

The results of the paired comparisons between the oral and intraperitoneal routes of administration in unanesthetized animals showed the oral route to be significantly more effective in lowering the blood pressure for JB 643 and JB 676. The intraperitoneal route was more active for JB 654 and chlorisondamine, and there was no significant difference between these two routes of administration with JB 591.

When the data obtained from the intraperitoneal administration of the drugs to unanesthetized and anesthetized rats were compared, urethan anesthesia was found to significantly enhance the hypotensive activity of all compounds in the hypertensive animals.

Hypotensive Activity in Normotensive Dogs.—All the compounds produced some degree of hypotension in normotensive dogs (Table III). However, the differences in activity were not significant regardless of the route of administration. The OCR's, reported in per cent of predrug blood pressure, following oral administration were: JB 654, 75%; JB 643, 83%; JB 591, 89%; JB 676, 88%; and chlorisondamine, 94%. The mean depressor responses were maximal at the termination of the experiment (240 minutes).

The intravenous administration of the compounds to unanesthetized dogs produced the following OCR's: JB 654, 79% of the control pressure; JB 643, 81% of the control; JB 591, 75%. The time at which the maximum mean hypotensive effects occurred varied from 15 minutes for JB 654 to 180 minutes for JB 643. The intravenous administration of the compounds to anesthetized normotensive dogs produced the following OCR's: JB 654, 64%; JB 591, 70%; JB 643, 74%; chlorisondamine, 81%; and JB 676, 84%. Time of maximum depressor activity varied from 15 minutes for JB 654 to 120 minutes for JB 643 and chlorisondamine.

The paired comparison of the data obtained with the compounds administered orally and intravenously to the unanesthetized dogs suggest that JB 676 and chlorisondamine were more effective intravenously and JB 654 more effective orally. No significant differences could be demonstrated between the intravenous or oral activities of JB 591 and JB 643.

Analysis of the data obtained when the compounds were administered intravenously to unanesthetized and anesthetized dogs indicated that the anesthetic augmented the hypotensive effects produced by JB 654, JB 591, and JB 676. The anesthetic did not significantly alter the depressor effect of JB 643 and chlorisondamine.

Intravenous Infusion of JB 591 and JB 676.—The results obtained from the intravenous infusion of JB 676 and JB 591 into anesthetized normotensive dogs are recorded in Table IV. JB 676 produced its maximum effect upon blood pressure within 2 minutes in each of the two dogs receiving this drug. The dose delivered at this time was one-tenth of the

TABLE III.—EFFECTS OF CERTAIN HYPOTENSIVE AGENTS ON SYSTOLIC BLOOD PRESSURE OF NORMOTENSIVE DOGS

Compound JB	Dose, mg./Kg.	Route of Adm.	Control Blood Pressure,[a] mm. Hg	% of Control Blood Pressure at Time Noted (min.) Following Drug Administration[a] 15	30	60	120	180	240
654	100	oral	141	70	75	84	74	75	72
654	10	i.v.	138	75	80	79	79	82	81
654	10	i.v.[b]	138	62	58	63	65	66	67
643	100	oral	134	92	87	83	81	78	76
643	10	i.v.	148	83	82	79	81	79	83
643	10	i.v.[b]	130	72	72	72	71	74	72
591	250	oral	155	88	103	83	84	89	82
591	25	i.v.	143	95	92	87	88	88	87
591	25	i.v.[b]	145	72	65	61	68	68	75
676	75	oral	125	92	88	83	94	87	83
676	7.5	i.v.	122	78	75	78	77	84	87
676	7.5	i.v.[b]	142	78	79	84	88	90	83
Chlorisondamine	5	oral	131	94	100	95	90	92	91
Chlorisondamine	0.5	i.v.	139	83	71	75	75	78	76
Chlorisondamine	0.5	i.v.	128	85	78	75	76	89	79

[a] Each value in the table represents the mean responses of four dogs. [b] Dogs anesthetized with pentobarbital sodium, 35 mg./Kg. i.v.

TABLE IV.—EFFECT OF AN INTRAVENOUS INFUSION OF JB 676 AND JB 591 ON BLOOD PRESSURE OF ANESTHETIZED NORMOTENSIVE DOGS

Compound JB	Control Blood Pressure, mm. Hg	% Drop in Blood Pressure at Time (min.) Following Start of Infusion 2	10	20[a]
676[b]	110	40	31	38
676[b]	180	20	19	19
591[c]	160	25	12	16
591[c]	154	31	30	30

[a] End of infusion period. [b] Infusion rate of 1 ml./min. (0.375 mg./Kg./min.); total dose, 7.5 mg./Kg. in 20 minutes. [c] Infusion rate of 1 ml./min. (1.25 mg./Kg./min.); total dose, 25 mg./Kg. in 20 minutes.

total dose or 0.75 mg./Kg. No further decrease in blood pressure was produced over the 20-minute infusion period.

JB 591 produced similar effects in two dogs. The maximum depressor response occurred in less than 2 minutes. The dose delivered at this time was 2.5 mg./Kg. No further decrease in the blood pressure was realized over the remainder of the infusion period. Total dose given was 25 mg./Kg.

DISCUSSION

The results obtained from the administration of the experimental compounds to unanesthetized normotensive rats and dogs indicate that there is some mechanism present in the normotensive animal which is capable of offsetting the expected hypotensive effects of ganglionic blocking agents. Since these agents are all active in anesthetized animals, the nature of the compensatory mechanism would appear to be central in origin. Most of the compounds were active in unanesthetized hypertensive rats indicating that these restorative mechanisms were reduced in the hypertensive animals but not absent since the compounds were even more active in anesthetized hypertensive rats.

No explanation can be offered for the ineffectiveness of chlorisondamine in unanesthetized hypertensive rats. This finding is similar to the results obtained by Maxwell, *et al.* (3), in studies on unanesthetized normotensive rats. However, when chlorisondamine was administered to these animals under barbiturate anesthesia, the compound produced marked sustained falls in both systolic and diastolic blood pressure. Haas and Goldblatt also studied the effects of various ganglionic blocking agents in normotensive (4) and hypertensive (5) dogs. Infusion of tetramethylammonium, hexamethonium, pentolinium, chlorisondamine, and mecamylamine in unanesthetized normotensive dogs resulted in slight pressor responses in mean femoral blood pressure. Pentolinium infusion produced varying effects in renal hypertensive dogs. They noted that pressor responses were obtained following short (2 to 14 days) and long (50 to 103 weeks) periods of hypertension but a depressor response was obtained during an intermediate period (2 to 19 weeks) of hypertension. It is possible that this same pattern of response to ganglionic blocking agents occurs in hypertensive rats. The hypertensive rats used in this study were prepared at approximately the same time and were possibly tested during this intermediate period. An explanation for the hypotensive activity of the experimental compounds and the ineffectiveness of chlorisondamine may be the possible central hypotensive actions of the former compounds. Although JB 654, JB 643, and JB 676 have not been tested in the cross circulation preparation, they are structurally related to JB 591 (see Fig. 1), which has been reported to produce a centrally evoked depressor response (13).

The results obtained from the intravenous infusion of JB 591 and JB 676 in anesthetized normotensive dogs demonstrated a difficulty which might arise in attempting to estimate oral absorption on the basis of activity produced. One-tenth of the previously employed intravenous doses of these compounds produced a maximum hypotensive effect on blood pressure. The remainder of the dose must, therefore, contribute only to maintaining the duration of this maximum effect. If this is also true of oral absorption, then we cannot estimate oral absorption in excess of the amount necessary to produce maximum effects.

SUMMARY

1. The three-way crossover design in normotensive rats demonstrated no significant hypotensive activity following either oral or intraperitoneal administration of the drugs to unanesthetized animals. Urethan anesthesia enhanced the hypotensive responses of JB 654, JB 676, and chlorisondamine.

2. There was a statistically significant difference between the hypotensive activities of the experimental compounds investigated in a three-way crossover test in hypertensive rats. The order of decreasing hypotensive activity following oral administration was: JB 643, JB 591, JB 676, and JB 654. Chlorisondamine produced a pressor response. JB 654, JB 643, and JB 591 produced approximately equal depressor effects upon intraperitoneal administration to unanesthetized hypertensive rats, JB 676 and chlorisondamine produced pressor effects, JB 643 and JB 676 were more active orally, and JB 654 more effective *via* the intraperitoneal route. JB 591 appeared equally active by either route. Urethan anesthesia increased the hypotensive response of all compounds.

3. All the compounds lowered systolic blood pressure of the normotensive dog regardless of the method of administration. The oral route was more active for JB 654 and the intravenous route was more active for JB 676 and chlorisondamine in unanesthetized dogs. Barbiturate anesthesia enhanced the hypotensive responses of JB 654, JB 591, and JB 676 but not those of JB 643 and chlorisondamine.

4. The intravenous infusion of JB 591 and JB 676 in anesthetized normotensive dogs showed the

maximum hypotensive response to occur within 2 minutes and at a dose one-tenth that previously employed. Continued infusion only served to maintain the hypotensive effect.

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Pharmaceutical Aspects of a *p*-Aminosalicylate Dialdehyde Starch Compound

By JAMES A. CAMPBELL

A compound resulting from the reaction between sodium *p*-aminosalicylate and dialdehyde starch was investigated. The bland taste and slow rate of dissolution of the compound appeared to offer certain advantages in the administration of NaPAS. The compound was subjected to certain *in vitro* and *in vivo* tests to demonstrate the availability of NaPAS.

THE EFFECT of *p*-aminosalicylic acid upon the tubercule bacillus has been known for a number of years. Bernheim (1) in 1941 observed that benzoic and salicylic acids increased the oxygen consumption of the bacillus. Lehmann (2) discovered that the increased oxygen consumption was accompanied by an inhibition in growth and multiplication, and subsequently found that *p*-aminosalicylic acid was the most effective of a group of related compounds.

A number of salts and other derivatives of the acid have been prepared and investigated (3, 4). Particularly well known are the sodium, potassium, and calcium salts. These salts have the advantage of being more soluble than the acid, and are reputed to be less irritating. Aqueous solutions of the sodium salt are more stable on heating than is a solution of the acid.

Foye and Duvall (5) made a comparative study of the *in vivo* antitubercular activity in mice of cupric and ferrous chelates of PAS. Both compounds were found to be active, but the cupric complex possessed a much higher activity than the ferrous complex.

Due to the large dosage level of PAS (2–4 Gm., with a daily average dose of 12–16 Gm.), the unpleasant taste, the irritant action, and other factors, the administration of PAS is sometimes beset with problems. Intolerance manifested by nausea and vomiting is common with average or large doses (6).

The objective in this effort was to prepare and study a derivative of PAS which might have certain advantages in overcoming the problems associated with the administration of PAS. Dialdehyde starch is known to react with amines and compounds containing the amino group, and the resulting compounds are sometimes noted for their unique properties (7). Dialdehyde starch was thus reacted with sodium PAS and the resulting compound was studied.

EXPERIMENTAL

Formation of the Compound.—A 27.4-Gm. quantity (0.141 mole) of dialdehyde starch (90.4% oxidized; 8.6% moisture) and 24.6 Gm. (0.116 mole) of sodium *p*-aminosalicylate dihydrate was slurried in 100 ml. of dry benzene in a 500-ml. three-necked flask equipped with a stirrer, Barret trap, and condenser. During the refluxing and stirring period of 5 hours, 5.0 ml. of water separated in the Barret trap. After cooling the mixture to room temperature, the pale yellow solid was collected, washed with dry benzene and dried to constant weight in a vacuum oven. Subsequent analysis including infrared spectra showed that a linkage between the compounds had taken place. Total nitrogen and free aldehyde content showed that NaPAS had added to half of the available aldehyde groups. Based upon the action of dialdehyde

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