with reserpine and a β-adrenergic blocking agent (pronethalol or propranolol). In fact, it can be seen that the propranolol plus reserpine pretreated mice have elevated seizure thresholds following the administration of isoproterenol.

The results of this preliminary study suggest the presence of central adrenergic receptors which may be involved in the expression of l.f. EST. This concept is supported by the previous work of Swinyard *et al.* (3, 4), who demonstrated that the threshold for both chemically and electrically induced seizures in mice can be altered by prior administration of epinephrine and norepinephrine. Moreover, Baldessarini and Kopin (13) have recently reported that a marked release of ^{3}H-norepinephrine from rat brain occurs in response to electrical stimulation and Scudder *et al.* (14) have demonstrated the existence of a positive correlation between the level of endogenous brain amines and maximal electroshock seizure latency in mice.

The failure to observe consistently significant alterations in l.f. EST when reserpine or α-mmT were given *per se* may reflect incomplete amine depletion, lack of inhibition of amine biosynthesis (in the case of reserpine), or production of active metabolites from α-mmT, *e.g.*, *m*-hydroxyamphetamine, metaraminol, or *m*-methoxyamphetamine (15). Nevertheless, the results observed with the adrenergic agents employed seem to imply that threshold for low frequency electroshock seizures may be markedly influenced by the degree of drug-induced differential stimulation applied to opposing central adrenergic receptors. In order to substantiate this hypothesis, additional data of a similar nature must be collected for a variety of adrenergic drugs which are known to interact specifically with α and β receptors. Furthermore, the work must be conducted in animals that have been subjected to a more selective inhibition of brain amine biosynthesis than that reported above. Such studies are currently in progress.

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Keyphrases

Adrenergic agent
α-adrenergic blocking agents
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Catecholamine depleting agents
Electroshock, low frequency—seizure threshold effect
Neurotoxicity—adrenergic agents
Fluorometry—brain tissue analysis

Ion-Exchange Resins and Cinchona Alkaloids I. Exchange Equilibria

By S. S. KANHERE, R. S. SHAH, and S. L. BAFNA

The exchange equilibria of four cinchona alkaloid sulfates with sulfonic acid cation-exchange resins of different degrees of cross-linking and particle size have been studied and the results are discussed.

THE AVAILABLE ion-exchange studies with cinchona alkaloids (1–21) do not seem to cover detailed physicochemical studies and hence it should be of interest to undertake such work. This paper summarizes the study of exchange equilibria of four cinchona alkaloid sulfates with styrene divinylbenzene copolymer-based sulfonic acid cation-exchange resins (in hydrogen form) of different degrees of cross-linking (percent nominal divinylbenzene content) and particle size.

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EXPERIMENTAL

Resins (22) and chemicals (23) were from the samples used in earlier work. The stock solution of the alkaloid sulfate (as $Q_2H_2SO_4 \cdot nH_2O$, where Q denotes the alkaloid base) was prepared in distilled water and its concentration in gram equivalents (half the molecular weight of the alkaloid sulfate) per liter was evaluated by sulfate estimation (as barium sulfate).

To study the exchange equilibria of the alkaloid sulfates with the resins, weighed amounts of air-dried resins were placed in contact with suitable volumes of the aqueous sulfate solution of known concentration, in well-stoppered flasks, with frequent shaking at room temperature (~30°). Preliminary work was carried out to find the approximate time within which equilibrium was attained. After sufficiently more time than this (about 4 to 35 days, depending

on X, the relative cross-linking of the resins), the solutions were analyzed for alkaloid sulfate concentration by taking out a known volume from each flask, diluting suitably with distilled water, and measuring the absorbance at the invariant wavelengths (23). The total sulfate in the equilibrium mixture was estimated gravimetrically for each resin and it showed no measurable difference in the initial and equilibrium values. Preliminary work also indicated that the values of P_R at room temperature, 35°, and 45° did not differ significantly; also the lowering of the pH to about 2.5 (by addition of sulfuric acid) did not significantly affect the value of P_R.

RESULTS AND DISCUSSION

The selectivity coefficients for alkali metal ions with resins in hydrogen form in sulfate solution had been studied earlier (22). When calculations were carried out for exchange in solutions of the cinchona alkaloid sulfates studied, with resins in the hydrogen form, the calculated values of P_R (Tables I and II; P_R = 100 times the mole fraction of counter ions in the resin phase at equilibrium) were practically constant for resins of higher degree of cross-linking and varied only to a relatively small extent for resins of lower degrees of cross-linking when P_A was varied.

The results were not measurably different when either the amount of alkaloid sulfate solution was held constant and the amount of added resin varied or when the amount of added resin was held constant and the amount of alkaloid sulfate solution was varied, provided the ratio of the initial concentration (in meq./L.) of the resin to the initial concentration of the alkaloid sulfate was the same. This suggests that the value of the equilibrium constant for the exchange (24–32) of the cation QH^+ is large and the equilibrium $HR + QH^+ \rightleftharpoons RQH + H^+$ is shifted very much to the right. However, all the replaceable hydrogen ions in the resin phase are not accessible for exchange, or the available capacity is only a fraction of the total capacity, probably due to the size of the organic counter ions. It is likely that the marked shift of the equilibrium to the right is aided by the operation of nonexchange interactions (31–33) and that the interactions tend to increase the extent of exchange with increase in $(A)_e$. This may be feasible, to some extent, by further expansion of and/or further separation between some segments in the swollen (34,35) or expanded resin network and should depend on the degree of cross-linking and the extent to which exchange has already occurred. If the further expansion and/or segment separation is sufficient to accommodate some more organic cations by exchange, P_R should increase with increase in $(A)_e$ or decrease in P_A; this is so for lower cross-linked resins in hydrogen form. On the other hand,

TABLE I—EQUILIBRIUM OF AQUEOUS QUININE SULFATE AND QUINIDINE SULFATE WITH SULFONIC ACID CATION-EXCHANGE RESINS

		Quinine Sulfate					Quinidine Sulfate				
Resin	a (mm.)	$(\bar{H})_i$	$(A)_i$	$(\bar{A})_e$	P_A	P_R	$(\bar{H})_i$	$(A)_i$	$(\bar{A})_e$	P_A	P_R
X1	0.215	0.86	2.12	0.47	22.1	54.7	0.85	2.00	0.48	24.0	56.5
		1.69	2.12	0.89	42.0	52.7	1.70	2.00	0.87	43.5	51.2
		2.52	2.12	1.28	60.4	50.9	2.13	2.00	1.05	52.5	49.3
		3.38	2.12	1.69	79.7	50.0	2.92	2.00	1.37	68.5	46.9
		4.22	2.12	2.05	96.7	48.6	3.61	2.00	1.64	82.0	45.4
X2	0.215	0.84	2.12	0.44	20.8	52.7	1.68	2.00	0.90	45.0	53.6
		1.68	2.12	0.86	40.5	51.1	2.14	2.00	1.08	54.0	50.5
		2.49	2.12	1.25	59.0	50.2	3.33	2.00	1.62	81.0	48.6
		3.35	2.12	1.64	77.4	49.0	4.18	2.00	1.93	96.5	46.2
		4.18	2.12	2.01	94.8	48.1	...	...	...	...	...
X4	0.215	0.70	2.07	0.34	16.5	49.1	1.28	2.00	0.61	30.5	47.6
		1.38	2.07	0.69	33.3	49.9	1.98	2.00	0.95	47.5	48.0
		2.77	2.07	1.38	66.7	49.8	2.54	2.00	1.22	61.0	48.0
		3.44	2.07	1.69	81.6	49.1	3.83	2.00	1.80	90.0	47.0
X8	0.215	0.98	2.07	0.39	19.1	40.1	1.38	2.00	0.56	28.0	40.6
		1.46	2.07	0.60	28.8	40.9	1.83	2.00	0.70	35.0	38.1
		2.00	2.07	0.80	38.8	40.2	2.76	2.00	1.05	52.5	38.0
		4.01	2.07	1.56	75.4	39.0	3.64	2.00	1.44	72.0	39.6
X12	0.215	1.44	2.12	0.37	17.3	25.5	2.86	2.00	0.71	35.5	24.8
		2.87	2.12	0.72	34.0	25.1	4.13	2.00	1.02	51.0	24.7
		5.73	2.12	1.48	69.8	25.8	5.72	2.00	1.39	69.5	24.3
		7.16	2.12	1.84	86.8	25.7	7.22	2.00	1.79	89.5	24.8
X16	0.215	2.15	2.12	0.38	18.1	17.8	4.26	2.00	0.73	36.5	17.1
		6.44	2.12	1.17	55.2	18.2	6.39	2.00	1.12	56.0	17.5
		8.64	2.12	1.59	75.0	18.4	7.76	2.00	1.54	77.0	19.8
		10.76	2.12	1.95	92.1	18.1	10.65	2.00	1.78	89.0	16.7
X20	0.215	6.10	2.02	0.33	16.3	5.4	5.53	2.00	0.27	13.5	4.9
		11.19	2.02	0.72	35.5	6.4	8.12	2.00	0.47	23.5	5.8
		...	...	...	...	...	11.10	2.00	0.70	35.0	6.3
IR-120	0.37	2.62	2.02	1.06	52.5	40.5	2.62	2.00	0.95	47.5	36.2
		3.81	2.02	1.54	76.2	40.4	3.84	2.00	1.40	70.0	36.5
		5.00	2.02	1.97	97.5	39.4	5.05	2.00	1.87	93.5	37.1
IR-200	0.37	2.87	2.02	0.90	44.7	31.5	2.89	2.00	0.88	44.0	30.4
		4.29	2.02	1.31	64.9	30.5	4.33	2.00	1.31	65.5	30.3
		5.70	2.02	1.70	84.1	29.8	5.74	2.00	1.68	84.0	29.3
Am-15	0.37	2.65	2.10	0.86	40.9	32.4	2.11	2.00	0.67	33.5	31.8
		3.52	2.10	1.12	53.3	31.8	3.52	2.00	1.09	54.5	31.0
		4.40	2.10	1.39	66.1	31.6	4.34	2.00	1.37	68.5	31.1
		5.29	2.10	1.66	79.0	31.4	5.25	2.00	1.61	80.5	30.7

TABLE II—EQUILIBRIUM OF AQUEOUS CINCHONINE SULFATE AND CINCHONIDINE SULFATE WITH SULFONIC ACID CATION-EXCHANGE RESINS

Resin	a (mm.)	Cinchonine Sulfate					Cinchonidine Sulfate				
		$(\bar{H})_i$	$(A)_i$	$(\bar{A})_e$	P_A	P_R	$(\bar{H})_i$	$(A)_i$	$(\bar{A})_e$	P_A	P_R
X1	0.215	1.35	2.00	0.77	38.5	57.0	1.34	2.18	0.79	36.2	58.9
		1.69	2.00	0.91	45.5	53.8	1.67	2.18	0.94	43.1	56.3
		2.09	2.00	1.08	54.0	51.7	2.31	2.18	1.21	55.1	52.4
		3.39	2.00	1.68	84.0	49.6	2.94	2.18	1.49	68.3	50.7
		4.00	2.00	1.94	97.0	48.5	3.48	2.18	1.74	79.8	50.0
X2	0.215	1.27	2.00	0.72	36.0	56.7	1.26	2.18	0.74	33.9	58.7
		1.59	2.00	0.87	43.5	54.7	1.58	2.18	0.89	40.8	56.3
		1.97	2.00	1.03	51.5	52.3	2.17	2.18	1.14	52.3	52.5
		3.18	2.00	1.59	79.5	50.0	2.75	2.18	1.41	64.7	51.3
		3.96	2.00	1.94	97.0	49.0	3.27	2.18	1.65	75.7	50.5
X4	0.215	1.43	2.00	0.77	38.5	53.9	1.54	2.18	0.84	38.5	54.5
		2.21	2.00	1.14	57.0	51.6	2.11	2.18	1.12	51.4	53.1
		2.83	2.00	1.43	71.5	50.5	2.71	2.18	1.40	64.0	51.6
		4.27	2.00	1.96	98.0	45.8	3.26	2.18	1.65	75.7	50.6
X8	0.215	1.42	2.00	0.62	31.0	43.7	1.49	2.18	0.67	30.7	45.0
		2.22	2.00	1.00	50.0	45.0	2.06	2.18	0.93	42.7	45.1
		2.83	2.00	1.27	63.5	44.9	2.61	2.18	1.19	54.6	45.6
		3.72	2.00	1.66	83.0	44.6	3.16	2.18	1.42	65.1	44.9
X12	0.215	3.00	2.00	0.81	40.5	27.0	3.00	2.18	0.86	39.5	28.7
		4.31	2.00	1.18	59.0	27.4	4.49	2.18	1.31	60.1	29.2
		7.54	2.00	1.97	98.5	26.1	5.98	2.18	1.77	81.2	29.6
X16	0.215	4.27	2.00	0.91	45.5	21.3	4.46	2.18	0.99	45.4	22.2
		6.37	2.00	1.39	69.5	21.8	5.33	2.18	1.19	54.6	22.3
		...	...	...	...	...	7.10	2.18	1.60	73.4	22.5
X20	0.215	5.53	2.00	0.36	18.0	6.5	11.10	2.18	0.78	35.8	7.0
		8.14	2.00	0.62	31.0	7.6	13.70	2.18	1.03	47.2	7.5
		11.06	2.00	1.00	50.0	9.0	16.66	2.18	1.34	61.5	8.0
IR-120	0.37	1.89	1.91	0.83	43.5	43.9	1.96	2.18	0.83	38.1	42.3
		2.76	1.91	1.27	66.5	46.0	2.81	2.18	1.22	56.0	43.4
		3.62	1.91	1.69	88.5	46.7	3.68	2.18	1.58	72.5	42.9
IR-200	0.37	2.06	2.00	0.70	35.0	34.0	2.73	2.18	0.93	42.7	34.1
		2.75	2.00	0.92	46.0	33.5	3.62	2.18	1.21	55.6	33.5
		4.14	2.00	1.35	67.5	32.6	4.52	2.18	1.50	68.8	33.2
		5.49	2.00	1.74	87.0	32.4	5.42	2.18	1.77	81.2	32.7
Am-15	0.37	2.64	1.91	0.93	48.7	35.2	...	...	...	...	...
		3.52	1.91	1.21	63.4	34.4	3.52	2.15	1.24	57.7	35.3
		4.42	1.91	1.50	78.5	33.9	4.39	2.15	1.53	70.9	34.7
		...	...	...	...	...	5.28	2.15	1.81	84.2	34.4

if the further expansion and/or segment separation is too small to accommodate more organic cations by exchange, P_R should remain practically constant with increase in $(A)_e$ or decrease in P_A; this is so for higher cross-linked resins in hydrogen form.

For the resins X1 and X2 (Tables I and II), the value of P_R increases to a small extent with increase in $(A)_e$ or decrease in P_A. For the resin X4, the variation in the values of P_R is to a lesser extent than that for resin X2, for cinchonine sulfate and cinchonidine sulfate; for quinine sulfate and quinidine sulfate, the value of P_R is practically independent of P_A. For the resin X8 the values of P_R for all the four cinchona alkaloid sulfates are practically independent of P_A and for higher values of P_A are less than those for the resin X4. The decrease is more for quinine sulfate and quinidine sulfate than that for cinchonine sulfate and cinchonidine sulfate. This decrease may be attributed to the reduced pore size because of higher X; the higher value of P_R for cinchonine sulfate and cinchonidine sulfate than that for quinine sulfate and quinidine sulfate should be due to the smaller size of cinchonine and cinchonidine than that of quinine and quinidine. For resins of higher degree of cross-linking, X12, X16, and X20, the behavior is similar and the value of P_R decreases with increase in X.

Similar studies were carried out with resins IR-120, IR-200, and Am-15 of different particle size (IR-120: a = 0.58, 0.37; IR-200: a = 0.84, 0.58, 0.37, 0.23; Am-15: a = 1.13, 0.84, 0.58, 0.37). It was observed that the values of P_R were practically independent of a. Tables I and II give some representative data. The macromolecular resins IR-200 and Am-15 presumably have the value of X as approximately 20 but have expanded structure and hence are more porous than the gel-type resin X20; the values of P_R for IR-200 and Am-15 are therefore higher than those for the resin X20.

Nomenclature—

$(A)_i$ = the initial concentration of alkaloid sulfate solution in meq./L.,

$(A)_e$ = the equilibrium concentration of alkaloid sulfate in external solution in meq./L.,

$(\bar{A})_e$ = the meq. of alkaloid in the resin phase per liter of solution, at equilibrium,

$(\bar{H})_i$ = the meq. of resin per liter of the solution in the hydrogen form, initially,

$P_A = 100 \cdot (\bar{A})_e/(A)_i$ = the percent exchange of alkaloid sulfate at equilibrium,

$P_R = 100 \cdot (\bar{A})_e/(\bar{H})_i$ = the percent resin capacity exchanged at equilibrium.

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Keyphrases

Cinchona alkaloids
Ion-exchange resins—alkaloids, exchange equilibria
Sulfate, total—equilibrium mixture
Alkaloid sulfate concentration

Antiradiation Compounds IX. Dithiocarbamates of Strongly Basic Pyridines and Pyrimidines

By WILLIAM O. FOYE and DOUGLAS H. KAY

Dithiocarbamates of exceptionally strong bases in the pyridine and pyrimidine series, *e.g.*, the 1-alkyl-2- and 4-imino derivatives, have been obtained. Significant protection in mice against ionizing radiation was provided by a dithiocarbamate of one of the strong bases, whereas the dithiocarbamates of weaker bases have generally shown a lower level of protection.

BROWN (1) reported that the introduction of an alkyl group on one of the ring nitrogens of aminopyrimidines greatly increases the basicity of the molecule, the amino group being converted to the imino form. For example, 2-aminopyrimidine has a pKa of 3.54 and 1,2-dihydro-2-imino-1-methylpyrimidine has a pKa of 10.75. Likewise, in the aminopyridine series Albert (2) reported that 2-aminopyridine and 4-aminopyridine have pKa values of 6.9 and 9.2, respectively, whereas the alkylated derivatives, 1,2-dihydro-2-imino-1-methylpyridine and 1,4-dihydro-4-imino-1-methylpyridine have pKa values of 12.2 and 12.5, respectively.

Dithiocarbamates of these exceptionally strong bases were desired as potential antiradiation agents. Such compounds could be considered cyclic dithio acid analogs of mercaptoethylguanidine, which is also strongly basic. Of the compounds mentioned above, only 1,2-dihydro-2-imino-1-methylpyridine has previously been treated with carbon disulfide (3), giving a compound described as 1,2-dihydro-1-methyl-2-pyridinylimmonium 1,2-dihydro-1-methyl-2-pyridinyldithiocarbamate (I). The reactions of amino and imino pyrimidines and pyridines with carbon disulfide described here also gave dithiocarbamate salts rather than zwitterions. The latter might be expected since dithiocarbamate formation takes place preferentially on the weaker of two competing bases and cation formation on the stronger (4). Infrared absorption spectra of the dithiocarbamates of the strongly basic imines showed stretching frequencies for both C=S (~1000 cm.$^{-1}$) and C=N (1650–1675 cm.$^{-1}$), which supports the structures proposed (I). Dithiocarbamates of the corresponding weak (nonalkylated) bases were also prepared for comparison of radiation-protective activity.

Antiradiation testing results show that the dithiocarbamate of one of the imines protects mice at a higher level of radiation (1,000 r) than has generally

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