Mercaptoalkylamine Coordination Compounds of Platinum(II) and Palladium(II) and Their Anticancer Activity

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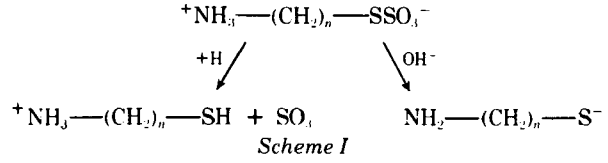
Abstract □ A series of coordination compounds of platinum(II) and palladium(II) with several amino- and heterocyclic aminoalkyl mercaptans was synthesized, and their structures were determined by IR absorption and elemental analyses. Because of the tendency of the mercapto group to undergo oxidation on reaction with metals, as observed with copper(II), the complexes were obtained by use of the aminoalkylthiosulfates, which decomposed to the thiol in either acid or alkaline solution. Furthermore, palladium–sulfide complex formation by reaction with an aminoalkyltrithiocarbonate made it possible to distinguish between metal–sulfur and metal–nitrogen bonds in the 650–400-cm^{-1} region. Anticancer screening against L-1210 lymphoid leukemia in mice did not reveal positive activity among the compounds tested.

Keyphrases □ Platinum—mercaptoalkylamine coordination compounds, antineoplastic activity, structure–activity relationships □ Palladium—mercaptoalkylamine coordination compounds, antineoplastic activity, structure–activity relationships □ Antineoplastic agents, potential—platinum, palladium, mercaptoalkylamine coordination compounds, structure–activity relationships

cis-Dichlorodiammineplatinum(II) and a number of closely related diaminodichloro platinum(II) complexes have shown appreciable anticancer activity in several tumor systems (1, 2). This discovery resulted from the observation (3) that certain coordination compounds of platinum(II) inhibited bacterial cell division without inhibiting growth. It is now known that for anticancer activity with the platinum(II) complexes, two *cis*-monodentate (or one bidentate) leaving groups are required; the most active complexes have contained chloride, bromide, oxalate, or malonate ligands (4). In addition, the complexes should be neutral, their geometries should be either square planar or octahedral, and the ligands *trans* to the leaving groups should be strongly bonded and relatively inert amines.

Little work has been reported on platinum complexes having ligands with phosphorus, oxygen, or sulfur donor atoms. Lindoy *et al.* (5) reported the formation of some sulfur–nitrogen complexes containing ligands with platinum(II), palladium(II), nickel(II), copper(II), copper(I), silver(I), and mercury(II), but these complexes were not tested for anticancer activities.

With the assumptions that palladium(II) complexes are generally more reactive than platinum(II) complexes (6) and that sulfur-containing ligands should be bound more strongly than nitrogen-containing ligands, a series of complexes was prepared with sulfur–nitrogen ligands (mercaptoalkylamines) coordinated with both platinum(II) and palladium(II). Following a postulation of anticancer activity of the platinum(II) complexes that depends on dissociation of the complexes (7), such compounds could be expected to possess at least the same order anticancer activity as that of the known platinum(II) compounds. Attempts also were made to prepare corresponding nickel(II) and copper(II) complexes.



Scheme I

DISCUSSION

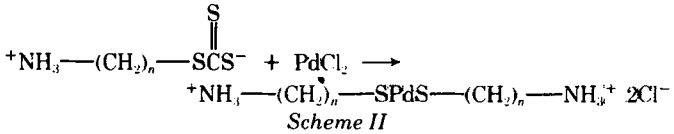
Palladium(II) and platinum(II) are sufficiently large that four ligands may fit on these metals with less repulsion in a square planar complex, regardless of whether the ligands are weak or strong field ligands. Ligands used in this study are considered to be strong field ligands: primary and secondary aliphatic amines, the sulfide ion, and the chloride ion. In the first transition series, only very strong field ligands can effect the spin pairing necessary for stabilization of the square planar arrangement. With heavier metals, however, low-spin square planar complexes can result even with weak field ligands. In the present series, with both large metals and strong field ligands, it can be assumed that square planar complexes exist.

The reaction of mercaptoethylamine with copper(II) resulted in an oxidation–reduction reaction, so a derivative of the thiol group was employed to avoid this reaction and to give mercaptoalkylamine complexes. Use of the aminoalkylthiosulfates provided a method of obtaining the desired ligands since the thiosulfates hydrolyze in either acidic or alkaline solution to give the thiol or thiol anion (8) (Scheme I). A cyclic or chelate complex should result, with chloride, water, or both filling the metal-ion coordination capacity. Complete loss of the S=O stretching frequency of the uncomplexed ligands at 1220–1190 cm^{-1} also confirmed that the thiosulfate group was not present in the metal complexes.

Since the sulfur ion is a class b (soft) base, it should coordinate with palladium(II) and platinum(II) (class b soft acids) prior to the amine group (class a hard base). A reaction that illustrates this situation occurs with the aminoalkyltrithiocarbonates. In this case, however, carbon disulfide is eliminated, and a metal–mercaptide complex may be isolated in acidic solution (9) (Scheme II). Here, there is no possibility that metal–nitrogen bonds may be formed since the amine groups are protonated. This reaction made it possible to distinguish Pd–S from Pd–N IR absorption bands, both of which occur in the 650–400-cm^{-1} region. Metal–sulfur stretching modes are also found in the 400–250-cm^{-1} region (10). Again, there is no possibility of confusion with metal–chloride stretching frequencies in the 350–300-cm^{-1} region since, in the palladium sulfide compound formation, no metal–chloride bond results.

The structures of the palladium(II) and platinum(II) complexes were determined by IR absorption spectra and elemental analyses. Where NH_2 groups were present, stretching frequencies of the coordinated amines were lowered by 100 cm^{-1} or more from those of the free NH_2 groups in the 3550–3330- and 3400–3250-cm^{-1} ranges. Observed frequencies for the NH_2 groups in the complexes were in the same range as those of Pd(II) complexes of methionine (3360–3090 cm^{-1}) (11). Frequencies for the Pd–N and Pt–N bonds were found in the 560–420-cm^{-1} range and could be distinguished from the Pd–S bonds, which were revealed from the reaction with the aminoalkyltrithiocarbonate.

Metal–sulfur stretching frequencies were located in the 390–355-cm^{-1} range (10). Also, one or two bands in the region between 650 and 600 cm^{-1} could be assigned to metal–sulfur coordination. Metal chloride bands were observed at 350–300 cm^{-1} (10), in the same region as for Pt(II)



Scheme II

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Table I—IR Absorption Frequencies

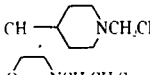
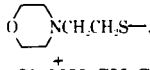
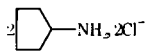
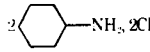
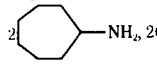
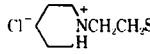
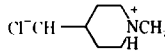
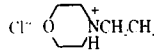
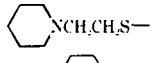
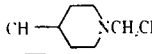
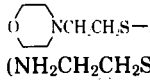
Compound	Ligands	Frequencies (KBr), cm^{-1} O–H	N–H	Pd–N or Pt–N	Pd–S or Pt–S	Pd–Cl or Pt–Cl
		Palladium Complexes				
I	$NH_2CH_2CH_2S—, Cl^-, H_2O$	3500–3400	3190, 3100	510	650, 615, 380	335, 320
II	$NH_2CH_2CH_2CH_2S—, Cl^-, H_2O$	3500–3400	3200, 3150	485, 465	620, 390	330, 300
III		3550–3450		490, 465	625, 375	345, 320
IV		3550–3450		490, 470	650, 620, 370	300 (br)
V		3550–3450		510, 480	650, 615, 360	300
VI	$2Cl^-\overset{+}{N}H_3CH_2CH_2S—$	3500–3400			650, 610, 355	
VII		3480–3360	3200, 3120	435, 420		315, 300
VIII		3480–3360	3200, 3100	450, 425		330, 315
IX		3460–3360	3200, 3110	460, 435		335, 320
X	$(NH_2CH_2CH_2S—)_2, Cl^-$	3480–3360	3220, 3170, 3080	505	650, 380	350
		Platinum Complexes				
XI	$Cl^-\overset{+}{N}H_3CH_2CH_2S—, Cl^-, 2H_2O$	3560–3400			620, 390	320
XII		3600–3400			625, 420	320
XIII		3560–3400			620, 590, 390	310 (br)
XIV		3600–3400			650, 610, 370	310 (br)
XV	$NH_2CH_2CH_2S—, Cl^-, H_2O$	3580–3400	3200, 3120	535	620, 590, 390	315 (br)
XVI		3540–3380		500	620, 590, 390	310 (br)
XVII		3560–3360		505	620, 590, 380	310 (br)
XVIII		3560–3360		560	615, 590, 370	310 (br)
XIX	$(NH_2CH_2CH_2S—)_2, Cl^-$	3520–3340	3230, 3160, 3090	510	650, 390	355

Table II—Physical Constants

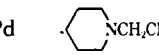
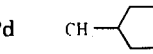
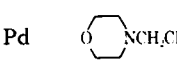
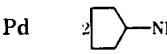
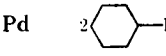
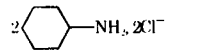
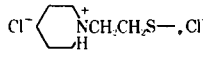
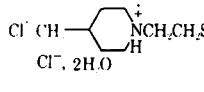
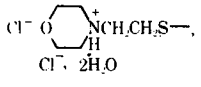
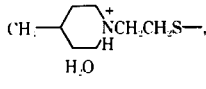
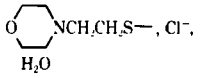
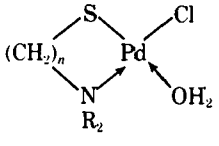
Compound	M	Ligands	Formula	Decomposition Point	Yield, %	Analysis, %	Calc.	Found
I	Pd	$NH_2CH_2CH_2S—, Cl^-, H_2O$	$C_2H_8ClNOPdS$	323°	34	C	10.18	10.52
						H	3.42	3.47
						Cl	15.13	15.13
						N	5.94	6.01
						S	13.59	13.47
II	Pd	$NH_2CH_2CH_2CH_2S—, Cl^-, H_2O$	$C_3H_{10}ClNOPdS$	285°	68	C	14.41	14.78
						H	4.03	3.73
						Cl	14.18	14.08
						N	5.60	5.97
						S	12.82	12.59
III	Pd		$C_7H_{16}ClNOPdS$	210°	78	C	27.64	27.57
						H	5.30	5.17
						Cl	11.66	11.42
						N	4.61	4.60
						S	11.54	11.20
IV	Pd		$C_8H_{18}ClNOPdS·H_2O$	213°	65	C	28.58	28.58
						H	5.98	5.80
						Cl	10.54	10.55
						N	4.17	4.20
						S	9.53	9.46
V	Pd		$C_6H_{14}ClNOPdS$	236°	74	C	23.54	23.78
						H	4.60	4.19
						Cl	11.58	11.51
						N	4.58	4.62
						S	10.45	9.95
VI	Pd	$2Cl^-\overset{+}{N}H_3CH_2CH_2S—$	$C_4H_{12}N_2PdS_2·2HCl·H_2O$	220°	63	C	13.90	13.73
						H	3.50	3.31
						N	8.10	7.89
						S	18.55	18.10
VII	Pd		$C_{10}H_{22}Cl_2N_2Pd·6H_2O$	180°	30	C	26.36	26.50
						H	6.50	6.16
						Cl	15.56	15.19
						N	6.14	5.89
VIII	Pd		$C_{12}H_{26}Cl_2N_2Pd·6H_2O$	187°	77	C	29.79	29.46
						H	6.90	6.68
						Cl	14.66	14.21
						N	5.79	5.56

Table II—*Continued*

Compound	M	Ligands	Formula	Decomposition Point	Yield, %		Analysis, % Calc.	Found
IX	Pd		$C_{14}H_{30}Cl_2N_2Pd{\cdot}6H_2O$	180°	78	C	32.86	33.15
						H	7.26	6.90
						Cl	13.86	13.51
						N	5.47	5.52
X	Pd	$(NH_2CH_2CH_2S—)_2$, Cl^-	$C_4H_{12}Cl_2N_2PdS_2{\cdot}H_2O$	313°	27	C	13.82	13.70
						H	4.06	4.24
						Cl	20.39	19.90
						N	8.06	7.94
						S	18.44	17.98
XI	Pt	$Cl^-\overset{+}{N}H_3CH_2CH_2S—$, Cl^-, $2H_2O$	$C_2H_{10}ClNO_2PtS{\cdot}HCl$	330°	66	C	6.40	6.60
						H	2.90	2.72
						N	3.70	3.73
						S	8.46	8.50
XII	Pt		$C_7H_{18}ClNO_2PtS{\cdot}HCl$	232°	83	C	18.79	18.10
						H	4.27	3.90
						Cl	15.85	15.53
						N	3.13	2.97
						S	7.16	7.14
XIII	Pt		$C_8H_{20}ClNO_2PtS{\cdot}HCl{\cdot}H_2O$	240°	87	C	20.04	20.43
						H	4.83	4.53
						Cl	14.79	14.50
						N	2.92	2.81
						S	6.69	7.20
XIV	Pt		$C_6H_{16}ClNO_3PtS{\cdot}HCl$	265°	70	C	16.04	16.48
						H	3.80	3.12
						Cl	15.78	15.76
						N	3.11	3.07
						S	7.14	7.22
XV	Pt	$NH_2CH_2CH_2S—$, Cl^-, H_2O	$C_2H_8ClNOPtS{\cdot}H_2O$	340°	66	C	6.99	6.76
						H	2.93	2.46
						Cl	10.34	9.89
						N	4.07	3.80
						S	9.35	9.02
XVI	Pt		$C_7H_{16}ClNOPtS$	258°	67	C	21.41	21.42
						H	4.11	3.87
						Cl	9.03	8.86
						N	3.57	3.58
						S	8.16	8.33
XVII	Pt		$C_8H_{18}ClNOPtS$	239°	49	C	23.57	23.16
						H	4.69	4.63
						N	3.44	3.82
						S	7.86	7.53
XVIII	Pt		$C_6H_{14}ClNO_2PtS{\cdot}2H_2O$	280°	48	C	16.73	16.73
						H	4.17	3,80
						Cl	8.23	8.18
						N	3.25	3.25
						S	7.45	7.50
XIX	Pt	$(NH_2CH_2CH_2S—)_2$, Cl^-	$C_4H_{12}Cl_2N_2PtS_2{\cdot}8H_2O$	245°	24	C	8.54	8.70
						H	4.98	4.65
						N	4.97	4.73
						S	11.41	10.97



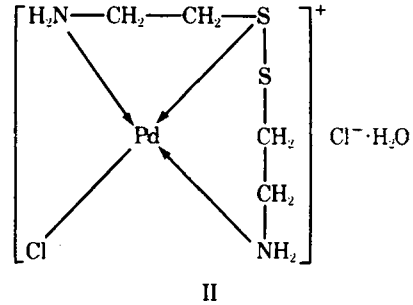
I

complexes of ethionine and *S*-methyl-L-cysteine with chloride ligands (10). Broad bands for water were shown in the 3600–3400-cm^{-1} region for many complexes. IR absorption frequencies for the various bonds observed are listed in Table I. Other physical constants for the complexes are listed in Table II.

Palladium(II) Complexes—The IR absorption spectra indicated clearly that the mercaptoamines derived from the thiosulfates acted as bidentate ligands, being coordinated to palladium(II) *via* the sulfur and nitrogen. Both chloride ion and water also were coordinated to give type I structures. Elemental analyses agreed with this structure.

For the palladium(II) complex of bis(2-aminoethyl) disulfide, however, IR absorption and elemental analyses indicated a type II structure. Polymeric complexes are not commonly found with palladium(II) and platinum(II) but are possible with halogen and sulfur ligands. Three strong bands for NH_2 stretching of the palladium–cystamine complex were exhibited at 3300–3090 cm^{-1}, and Pd–N stretching at 500 cm^{-1} showed coordination of both nitrogens. Strong C–S stretching frequencies at 1270–1220 cm^{-1} indicated that the disulfide linkage was intact, and Pd–S bands at 650 and 380 cm^{-1} showed coordination to sulfur. Pd–Cl bands appeared at 350 cm^{-1}, and a positive test for ionic chloride was given by the disulfide complex but not for the mercaptoamine complexes.

Cycloalkylamine complexes of palladium(II) were also prepared since *cis*-dichloro-bis(cycloalkylamine) platinum(II) complexes have shown promising anticancer activities (12). Elemental analyses and IR ab-

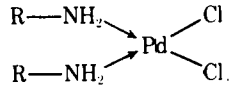


II

Table III—Antileukemic Activities in Mice [a]

Compound	Dose, mg/kg	Animal Weight Difference (T − C), g [b]	Survival (T − C), % [c]
I	200	−3.6	111
II	100	−2.4	103
III	100	−1.1	105
IV	25	−0.7	106
X	12.5	−0.6	101
XIII	12.5	−0.9	107
XV	200	−1.4	107
XVI	50	−1.5	98
XVIII	50	−0.6	102
XIX	100	−2.1	103

[a] Mice were infected with L-1210 lymphoid leukemia. Compounds were administered intraperitoneally every 4th day, for a total of three injections, beginning on the 1st day after tumor implantation. The vehicle was either saline or saline with polysorbate (Tween) 80. Six mice were used at each dosage level. [b] Average weight change of test group minus average weight change of control animals on Day 5. [c] Ratio of mean survival time of treated animals to that of control animals. Observations were made for 20 days.



III

sorption for the cycloalkylamine complexes indicated type III structure, analogous to the previously determined cycloalkylamine complexes of Pt(II). Actually, there were two Pd–N bands at 495 and 476 cm^{-1} and two Pd–Cl bands at 327 and 306 cm^{-1} for the dichlorodiamminepalladium(II) *cis* structure but only one band of each type for the *trans* structure (13). The IR spectra showed, in general, two bands of each type and agreed closely with those for the *cis* structures. The *cis*-isomer of dichlorodiamminepalladium(II) isomerizes to the *trans* structure on standing, however (13).

Platinum(II) Complexes—Platinum(II) complexes were formed in both acidic and slightly alkaline media. In acidic solution, the thiosulfates were cleaved to the mercaptans and the amino groups remained protonated, so only Pt–S coordination took place. Pt–S bands around 650–590 and 420–370 cm^{-1} appeared, along with Pt–Cl bands at 320–310 cm^{-1}. The IR absorption spectra, combined with elemental analyses, indicated structures of type IV.

In slightly alkaline solution, both Pt–S and Pt–N coordination could take place and cyclic type I complexes were formed, as indicated by IR absorption. The NH_2 stretching frequencies at 3500–3300 cm^{-1} were lowered by about 100 cm^{-1} in the mercaptoethylamine complex. The Pt–N frequencies were at 560–500 cm^{-1}, and Pt–S bands appeared at 620–590 and 390–370 cm^{-1}. A broad Pt–Cl band was observed at 315–310 cm^{-1}, and water was recognized by absorption at 3600–3400 cm^{-1}. Elemental analyses were in agreement with this structure (I).

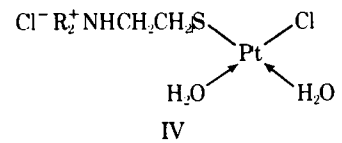
The platinum complex of cystamine was found to have a type II structure analogous to the palladium complex. Absorption bands for Pt–N, Pt–S, and Pt–Cl, as well as N–H stretching frequencies, were very similar for the platinum(II) and palladium(II) cystamine complexes.

Nickel(II) and Copper(II) Complexes—Attempts to prepare nickel (II) complexes by the procedures described here, in acidic and slightly alkaline solution, did not result in isolatable products. Jicha and Busch (14) reported the formation of two types of nickel(II) complexes of 2-mercaptoethylamine in alkaline solution, one the 2:1 chelate and the other having a structure of type $M(ML_2)_2Cl_2$.

Attempts to prepare copper(II) complexes by these methods also were unsuccessful.

Anticancer Tests—Anticancer screening was carried out[1] using mice infected with L-1210 lymphoid leukemia. Table III lists the most favorable dosage level of compound giving a measurable response in comparison to survival times and toxicities of control animals. None of the compounds tested produced survival times great enough in comparison to those of controls (T/C, %) to be listed as active.

Since the most active known platinum coordination compounds have a *cis*-dichloro function, the results presented here indicate that such a function is necessary for activity. Although a coordinated water molecule should be replaced equally as readily as a chloride ion (16), the biological replacing group may not replace a water molecule as readily or at all if it is ionic. If the anticancer mechanism of *cis*-dichlorodiammineplatinum depends upon binding to DNA (17, 18), then binding to ionic groups would appear to be favored.



IV

EXPERIMENTAL[2]

The following procedures are representative.

***N,S*-(2-Aminoethanethio)chloroaquopalladium(II)**—2-Aminoethanethiosulfuric acid (0.1572 g, 0.001 mole) was dissolved in 35 ml of water, and the pH was adjusted to 8.0 with 0.04 *N* NaOH. A solution (10 ml) containing 0.1773 g (0.001 mole) of palladium(II) chloride in hot 0.04 *N* HCl was added dropwise with stirring. The solution became yellow, and the pH was maintained at 6.5–6.8 by the alternate dropwise addition of 0.04 *N* NaOH and the palladium chloride solution. Stirring was continued for 1 hr after addition was complete, and the yellow product was filtered, washed with water and ethanol, and dried at 60° for 2 days. The yield was 0.0611 g (34.5%) of product, which decomposed above 323°.

Anal.—Calc. for $C_2H_8ClNOPdS$: C, 10.18; H, 3.42; Cl, 15.13; N, 5.94; S, 13.59. Found: C, 10.52; H, 3.47; Cl, 15.13; N, 6.01; S, 13.47.

Bis-(*S*-2-aminoethanethio)palladium(II) Dihydrochloride—2-Aminoethanetrithiocarbonic acid (0.6132 g, 0.004 mole) was dissolved in 35 ml of *N*,*N*-dimethylformamide. A solution of palladium(II) chloride (0.3546 g, 0.002 mole) in 12 ml of hot 0.04 *N* HCl was added dropwise with stirring. A yellow precipitate appeared immediately, and the solution became red-yellow. After the addition was complete, the pH had decreased to 2.5, and the solution was stirred for 30 min. The precipitate was filtered, washed with water and ethanol, and dried in a desiccator. The dried product was brown and weighed 0.2238 g (63% yield); it decomposed above 220°.

Anal.—Calc. for $C_4H_{12}N_2PdS_2 \cdot 2HCl \cdot H_2O$: C, 13.90; H, 3.50; N, 8.10; S, 18.15. Found: C, 13.73; H, 3.31; N, 7.89; S, 18.10.

***cis*-Dichlorodi(cyclohexylamine)palladium(II)**—Solutions of potassium tetrachloropalladate(II) (0.3264 g, 0.001 mole) in 15 ml of water and cyclohexylamine (0.1984 g, 0.002 mole) in 5 ml of water were cooled to 1° and mixed, and light-brown crystals appeared immediately. The mixture was stored at 1° for 24 hr, and the product was filtered, washed with cold water, and dried. The yield was 0.2538 g (77.8%) of product, which decomposed above 187°.

Anal.—Calc. for $C_{12}H_{26}Cl_2N_2Pd \cdot 6H_2O$: C, 29.79; H, 6.90; Cl, 14.66; N, 5.79. Found: C, 29.46; H, 6.68; Cl, 14.21; N, 5.56.

Chloro-*N,N',S*-(cystamine)palladium(II) Chloride—Cystamine dihydrochloride (1.125 g, 0.005 mole) was dissolved in 70 ml of water, and the pH was adjusted to 8.0 using 0.04 *N* NaOH. A solution (50 ml) containing 0.8865 g (0.005 mole) of palladium(II) chloride in hot 0.04 *N* HCl was added dropwise with stirring along with sufficient alkali to maintain the pH at 6.5–7.0. A yellow precipitate appeared but dissolved on further addition and reappeared when the addition neared completion. Stirring was continued for 1 hr after the addition; the yellow product was filtered, washed with ethanol, and dried at 70° for 2 days. The yield was 0.2383 g (26.9%) of material, decomposing above 313°.

Anal.—Calc. for $C_4H_{12}Cl_2N_2PdS_2 \cdot H_2O$: C, 13.82; H, 4.06; Cl, 20.39; N, 8.06; S, 18.44. Found: C, 13.70; H, 4.24; Cl, 19.90; N, 7.94; S, 17.98.

***S*-(2-Aminoethanethio)chlorodiaquoplatinum(II) Hydrochloride**—To a solution of 2-aminoethanethiosulfuric acid (0.1572 g, 0.001 mole) in 25 ml of water was added dropwise with stirring a solution of 0.4151 g (0.001 mole) of potassium tetrachloroplatinate(II) in 10 ml of water. Stirring was continued for 1 hr after the addition; the yellow precipitate was filtered, washed with water, and dried at 70° overnight. The product weighed 0.2728 g (65.7%) and decomposed above 330°.

Anal.—Calc. for $C_2H_{11}Cl_2NO_2PtS$: C, 6.40; H, 2.90; N, 3.70; S, 8.46. Found: C, 6.60; H, 2.72; N, 3.73; S, 8.50.

[1] By the Division of Cancer Treatment, National Cancer Institute, in accordance with their protocol (15).

[2] Melting points were determined with a Mel-Temp capillary melting-point block and are uncorrected. IR spectra were obtained using a Perkin-Elmer model 457 A grating spectrophotometer and were corrected against polystyrene bands. Elemental analyses were done by Strauss Microanalytical Laboratory, Oxford, England.

Potassium tetrachloroplatinate(II) was a gift of Engelhard Minerals and Chemicals Co., supplied through the courtesy of Dr. Carl D. Keith. Palladium(II) chloride and potassium tetrachloropalladate(II) were obtained from Ventron Corp. The organic ligands were prepared by Dr. J. J. Lanzillo (19) and were recrystallized before use.

***N,S*-(2-Aminoethanethio)chloroaquoplatinum(II)** — 2-Aminoethanethiosulfuric acid (0.1572 g, 0.001 mole) was dissolved in 25 ml of water, and the pH was adjusted to 7.4 with 0.01 *N* NaOH. An aqueous solution (10 ml) of potassium tetrachloroplatinate(II) (0.4151 g, 0.001 mole) was added dropwise with stirring along with sufficient alkali to maintain a pH of 7.0–7.4. Stirring was continued for 1 hr after the addition; the yellow product was filtered, washed with water, and dried at 70° overnight, yielding 0.2742 g (66%), mp 340° dec.

Anal.—Calc. for $C_2H_8ClNOPtS \cdot H_2O$: C, 6.99; H, 2.93; Cl, 10.34; N, 4.07; S, 9.35. Found: C, 6.76; H, 2.46; Cl, 9.89; N, 3.80; S, 9.02.

Chloro-*N,N',S*-(cystamine)platinum(II) Chloride—Cystamine dihydrochloride (0.225 g, 0.001 mole) was dissolved in 35 ml of water, and the pH was adjusted to 7.4 with 0.01 *N* NaOH. A solution of 0.4151 g (0.001 mole) of potassium tetrachloroplatinate(II) in 10 ml of water was added dropwise with stirring, and stirring was continued for 2 hr after the addition. The yellow product was filtered, washed with water, and dried at 70° overnight. The yield was 0.42 g (52.6%) of material, which decomposed above 183°.

Anal.—Calc. for $C_4H_{12}Cl_2N_2PtS_2 \cdot 8H_2O$: C, 8.54; H, 4.98; N, 4.97; S, 11.41. Found: C, 8.70; H, 4.65; N, 4.73; S, 10.97.

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Ion-Pair Liquid Chromatographic Assay of Decongestants and Antihistamines

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Abstract □ The quantitative determinations of combinations of antihistamine and decongestant drugs including phenylephrine, *dl*-ephedrine, ψ-ephedrine, phenylpropanolamine, pyrilamine, pheniramine, *l*-ephedrine, chlorpheniramine, brompheniramine, oxymetazoline, naphazoline, and antazoline contained in solid and liquid dosage forms are described. All active ingredients except the ephedrine optical isomers were separated from other ingredients with ion-paired high-pressure liquid chromatography. Manipulation of the mobile phase either by changing the hydroalcoholic ratio or by changing the alkyl chain length of the counterion (sulfonic acid) for achieving optimum separations is discussed. The method is simple, short, accurate, and precise.

Keyphrases □ Decongestants—analysis, ion-pair liquid chromatography, various cough and cold preparations, structure–activity relationships □ Antihistaminics—analysis, ion-pair liquid chromatography, various cough and cold preparations, structure–activity relationships □ Liquid chromatography, ion-pair—analysis, decongestants and antihistaminics in various cough and cold preparations, structure–activity relationships □ Structure–activity relationships—decongestants and antihistaminics, various cough and cold preparations

Combinations of decongestant and antihistamine pharmaceutical preparations are widely used for cough and cold treatment. Generally, such preparations contain one decongestant and one antihistamine, but several contain more than one decongestant. These combination preparations are made in various forms, *e.g.*, syrup, elixir, tablet, capsule, and timed-release tablet or capsule. Some liquid formulations may also contain preservative(s), dye(s), or flavor(s).

High-performance liquid chromatography (HPLC) has become useful for pharmaceutical preparation analysis. Decongestant and antihistamine compounds were analyzed using a strong cation-exchange column (1), and the separation of two decongestants and one antihistamine was demonstrated using a nonpolar reversed-phase column and heptanesulfonic acid as an ion-pairing agent (2, 3). This report describes a comprehensive analytical procedure applicable to numerous decongestants and antihistamines and discusses ways to achieve a desired separation by changing the alkyl chain length of sulfonic acid or by altering the hydroalcoholic composition of the mobile phase.

EXPERIMENTAL

Chemicals and Reagents—The following drugs and preservatives were used: phenylephrine (I), *dl*-ephedrine (II), ψ-ephedrine (III), phenylpropanolamine (IV), pyrilamine (V), pheniramine (VI), *l*-ephedrine (VII), chlorpheniramine (VIII), brompheniramine (IX), diphenhydra-

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