Inorganica Chimica Acta, 46 (1980) 45–49
©Elsevier Sequoia S.A., Lausanne – Printed in Switzerland

Complexes of 9-Methyl-6-mercaptopurine with some Divalent Metal Ions

NORAH BARBA BEHRENS and DAVID M. L. GOODGAME

Chemistry Department, Imperial College of Science and Technology, London, SW7 2AY, U.K.

Received May 19, 1979

The preparations and spectral properties are reported of some complexes formed by 9-methyl-6-mercaptopurine (9 MeMP) and divalent Co, Ni, Cu, Cd and Hg. The involvement of the exocyclic sulphur atom of the purine ligand is much greater than that of O6 in 9-methylhypoxanthine and examples of 9MeMP chelating via N7 and S are reported, as well as compounds in which the ligand binds by N7 or S alone.

Introduction

As part of our work on the coordination of pyrimidine and purine derivatives to metal ions we recently reported some complexes formed by 9-methyladenine (9Mead) [1] and 9-methylhypoxanthine (9Mehyp) [2]. We have now carried out a similar study with 9-methyl-6-mercaptopurine (9MeMP) to compare the coordinating ability of the sulphur atom on C6 with the rather feeble donor properties of the exocyclic O atom on C6 of 9Mehyp.

Purines with a sulphur atom on C6 are of interest because 6-mercaptopurine (6MP) has anti-cancer activity. The precise basis of its chemotherapeutic action is not known, but it has been shown to inhibit the synthesis of purine nucleotides and to be incorporated into nucleic acids [3, 4].

6-Mercaptopurine and its derivatives can exist in thiol or thione forms, but spectroscopic and X-ray

TABLE I. Analytical Data of Some Complexes of 9-Methyl-6-mercaptopurine (L).

Complex		Colour	Analytical Results					
			Found %			Calculated %		
			C	H	N	C	H	N
$CoLCl_2$	1	dark green	25.00	2.52	19.65	24.34	2.04	18.92
$CoLBr_2$	2	dark green	18.95	1.73	14.32	18.72	1.57	14.55
CoL_2Cl_2	3	green	31.12	2.64	24.41	31.18	2.61	24.24
CoL_2Br_2	4	pink	26.02	2.19	20.66	26.15	2.19	20.33
$CoL_2(BF_4)_2 \cdot 3H_2O$	5	pink	24.11	2.54	17.79	23.29	2.93	18.09
$NiLCl_2$	6	yellow	25.05	2.46	19.33	24.36	2.04	18.93
$NiLCl_2 \cdot 2H_2O$	7	yellow	21.43	3.06	16.42	21.71	3.03	16.88
NiL_2Cl_2	8	yellow	31.16	2.68	24.10	31.19	2.61	24.25
$NiL_2Cl_2 \cdot 2H_2O$	9	green	29.38	2.61	22.41	28.98	2.83	22.49
$NiL_2Br_2 \cdot 2H_2O$	10	green	24.95	2.74	18.65	24.55	2.72	19.09
$NiL_2Br_2 \cdot 4H_2O$	11	green	23.51	2.59	17.72	23.11	3.23	17.98
$NiL_2(BF_4)_2 \cdot 3H_2O$	12	green	24.37	2.67	17.83	23.66	2.71	17.14
$CuLCl_2$	13	yellow	23.80	2.12	18.63	23.97	2.01	18.63
$CuLBr_2$	14	yellow	19.42	1.59	14.82	18.49	1.55	14.36
$HgLCl_2$	15	white	16.70	1.36	12.84	16.46	1.38	12.80
$HgLBr_2$	16	white	14.01	1.12	10.46	13.98	1.15	10.63
$CdLCl_2$	17	white	20.85	1.72	15.91	20.61	1.73	16.02
$CdLBr_2$	18	white	16.92	1.40	12.59	16.43	1.38	12.77

TABLE II. Reflectance Spectral band Energies (cm^{-1}) of Some Complexes of 9-Methyl-6-mercaptopurine (L).

CoLCl$_2$	22,600vs^a	15,750	6300	5200		
CoLBr$_2$	22,300vs^a	14,800	5750br^b			
CoL$_2$Cl$_2$	20,400sh^c	18,180	16.950	14,300wsh	9200	6060
CoL$_2$Br$_2$	19,000sh	17,950	15.150	8850	5650	
CoL$_2$(BF$_4$)$_2$·3H$_2$O	19,000br	9700sh	7900			
NiLCl$_2$	22,600	12,350	7350			
NiLCl$_2$·2H$_2$O	22,600	12,350	7350			
NiL$_2$Cl$_2$	d	14,600	8700^e			
NiL$_2$Cl$_2$·2H$_2$O	d	14,600	8700^e			
NiL$_2$Br$_2$·2H$_2$O	d	16,000	9800	~7000^f		
NiL$_2$Br$_2$·4H$_2$O	d	16,000	9800	~7000^f		
NiL$_2$(BF$_4$)$_2$·3H$_2$O	d	16,000	9800	~7000^f		
CuLCl$_2$	14,800sh^c					
CuLBr$_2$	13,000sh^c					

[a] CT band. [b] Centre of broad, multicomponent band. [c] On edge of strong U.V. band. [d] ν_3 transition obscured by strong U.V. absorption. [e] Asymmetric to lower energy. [f] Energy approximate because of vibrational bands in same region.

TABLE III. Infrared (IR; 200–400 cm^{-1}) and Raman (R; 150–400 cm^{-1}) Spectra (cm^{-1}) of 9-Methyl-6-mercaptopurine (L) and Some of Its Complexes.

	Ligand Bands		ν(M–X)	ν(M–OH$_2$)	ν(M–N)	Unassigned
L	IR	291mw, 276ms, 212m, 205m				
	R	292m, 278w, 216mbr, 168m				
CoLCl$_2$	IR	303m	325vs, 316vs			290m, 280m, 252mw, 213ms
CoLBr$_2$	IR	300ms	250vsbr			215s
CoL$_2$Cl$_2$	IR	290s				252s, 215s
CoL$_2$Br$_2$	IR	302s				258mbr, 215mbr
CoL$_2$(BF$_4$)$_2$·3H$_2$O	IR	300s		335mbr		250mw
NiLCl$_2$	IR	277m			230sbr	250mssh
NiLCl$_2$·2H$_2$O	IR	277m			230s	250ms
NiL$_2$Cl$_2$	IR	292s	266ms			251mw, 214vs
NiL$_2$Cl$_2$·2H$_2$O	IR	291s	265ms			246wsh, 212vs
NiL$_2$Br$_2$·2H$_2$O	IR	300m		330brsh^a		278w, 245m, 222s
NiL$_2$Br$_2$·4H$_2$O	IR	303s		330brsh^a		270m, 230w
NiL$_2$(BF$_4$)$_2$·3H$_2$O	IR	305s		330brsh^a		278w, 245w, 222m
HgLCl$_2$	IR	355m^b	316s			276w, 253w, 218ms
	R	355m^b	315s			345w, 262mw, 175m
HgLBr$_2$	IR	332m^b	216vs			270mw
	R	334m^b	215vs			158vs
CdLCl$_2$	IR	310m				264wsh, 219s
CdLBr$_2$	IR	308m				264w, 213s

[a] Overlapping ligand band. [b] Tentative assignment.

evidence suggests that the thione form, with the proton on N1, predominates [5, 6].

A few metal complexes of 6-mercaptopurine have been described [7–10] and the anti-cancer activity of some palladium and platinum complexes of 6MP has been explored [11]. X-ray structural studies have shown that 6MP coordinates only by the sulphur atom in [Cu^I(6MPH)Cl$_2$]$_2$ · 2H$_2$O [12] and in Hg(6MP)$_2$Cl$_2$ [13]. However, in bis(6-mercapto-9-benzylpurinato)palladium(II)–dimethylacetamide [14] and in [Cu(9MeMP)Cl$_2$] · H$_2$O [15] the purine ligands chelate via S and N7.

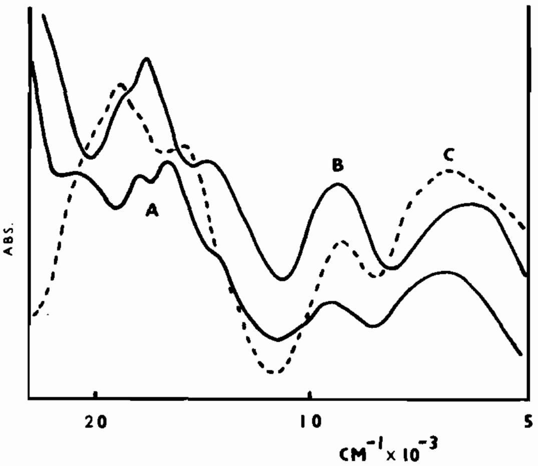


Fig. 1. Reflectance spectra of: (a) Co(9MeMP)$_2$Cl$_2$; (b) Co(9MeMP)$_2$Br$_2$; (c) polymeric Copy$_2$Cl$_2$.

Results and Discussion

The complexes we have prepared with 9-methyl-6-mercaptopurine are listed in Table I. The X-ray powder photographs of complex numbers 1–4 and 13–18 of Table I were obtained, but no isomorphous pairs were identified.

Cobalt and Nickel Complexes

By refluxing 9MeMP with hydrated cobalt chloride or bromide in ethanol the complexes Co(9MeMP)$_2$X$_2$ (X = Cl or Br) were formed irrespective of variations in the ligand to metal ratio employed. With the corresponding nickel halides, use of ethanol as solvent also gave 2:1 complexes, but these were usually hydrated (Table I). On changing the solvent to ethyl acetate or nitromethane 1:1 complexes were isolated for both metal ions.

The dark green complexes Co(9MeMP)X$_2$ were hygroscopic. Their electronic spectra (Table II) are typical of distorted tetrahedral geometry, as are the energies of the ν(Co–X) bands in their low frequency spectra (Table III). The electronic band energies are lower than those found for the tetrahedral CoN$_2$X$_2$ chromophores in Co(9Mead)X$_2$ [1, 16] or Co(9Mehyp)$_2$X$_2$ [2]. This suggests the presence of either an NSX$_2$ donor set, by chelation of 9MeMP through S and N7 or by the formation of 9MeMP bridges involving these same donor atoms, or an S$_2$X$_2$ donor set involving bridging via S alone. Although NS chelation seems the most probable, the spectral evidence is insufficient to distinguish between these possibilities. However, further evidence for the presence of a Co–S bond in these complexes is provided by an intense electron transfer band at relatively low frequency (*ca.* 22.500 cm^{-1}) in their electronic spectra.

For these complexes, and for those to be discussed subsequently and thought to contain bidentate 9MeMP ligands, no attempt has been made to assign the other low frequency vibrational bands listed in Table III to particular 'ν(M–S)' or 'ν(M–N)' modes. The extensive coupling expected for N–S chelation or bridging renders such designations so approximate as to be of very little value.

The electronic spectra of Co(9MeMP)$_2$X$_2$ (X = Cl or Br) and of all the nickel complexes have band energies and the relatively low intensities characteristic of these metal ions in distorted octahedral coordination geometries (Table II).

The spectra of Co(9MeMP)$_2$X$_2$ are quite unlike those of the compounds Co(pyrimidine-2-thione)$_2$X$_2$ (X = Cl or Br) which contain very distorted octahedral CoN$_2$S$_2$X$_2$ chromophore [17]. As may be seen from Fig. 1, they are, however, very similar to the spectrum of the halide-bridged polymeric form of Copy$_2$Cl$_2$. It appears, therefore, that in Co(9MeMP)$_2$X$_2$ the purine ligands coordinate via N7 and the metal ion achieves six-coordination by halide bridges rather than by binding to the exocyclic sulphur atom.

Further support for this comes from the fact that their low frequency spectra have no bands above 200 cm^{-1} assignable to ν(Co–X). For a halide bridged polymeric structure involving a divalent metal ion such bands are generally <200 cm^{-1} (*e.g.*, 167 and 188 cm^{-1} for polymeric Copy$_2$Cl$_2$ [18]).

Both the electronic and the low frequency i.r. spectra of Ni(9MeMP)$_2$Cl$_2$ and Ni(9MeMP)$_2$Cl$_2$·2H$_2$O are virtually identical. This similarity and the absence of a ν(Ni–OH$_2$) band in the far i.r. implies that the water molecules in the dihydrate are not coordinated. Each complex has a medium–strong intensity band near 265 cm^{-1} assignable to ν(Ni–Cl). These observations and the fact that the electronic band energies are intermediate between those formed for NiN$_4$Cl$_2$ and NiS$_4$Cl$_2$ environments [19, 20] point to 9MeMP functioning as an N–S chelate in these complexes with the formation of an NiN$_2$S$_2$Cl$_2$ chromophore.

Chelating 9MeMP ligands also appear to be present in the compounds Ni(9MeMP)$_2$Br$_2$nH$_2$O (n = 2 or 4) and Ni(9MeMP)$_2$(BF$_4$)$_2$·3H$_2$O but with water molecules and not anions completing the coordination sphere. The low frequency i.r. spectra show a broad ν(Ni–OH$_2$) band at 330 cm^{-1} and their electronic spectra are virtually identical, with the electronic band energies somewhat higher than for the chlorides discussed above, as expected.

As in the case of the 2:1 nickel chloride complexes, the far i.r. and the electronic spectra of Ni(9MeMP)Cl$_2$ and Ni(9MeMP)Cl$_2$·2H$_2$O were virtually identical and the water molecules in the hydrate are not coordinated. From their electronic band energies both compounds belong to the class of complexes containing an NiNCl$_5$ chromophore,

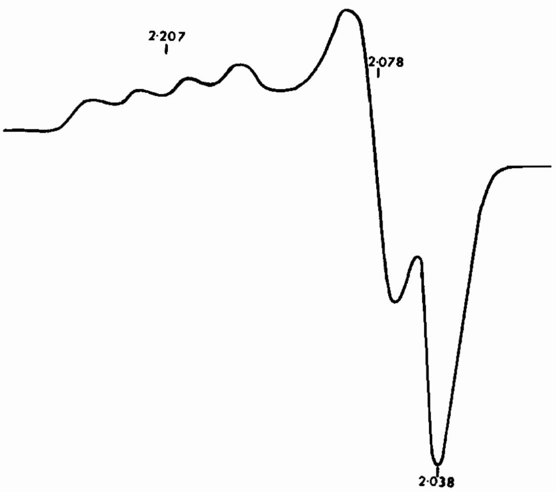


Fig. 2. Q-band (35.92 GHz) e.p.r. spectrum of polycrystalline Cu(9MeMP)Br_2.

achieved by chloride bridges [16, 21]. As the 9MeMP ligands are unidentate in these complexes the strong bands at 230 cm^{-1} in their low frequency spectra have been assigned as 'ν(Ni–N)' in Table III, in the sense that the mode concerned probably has appreciable ν(Ni–N) character.

In view of the presence of chelating 9MeMP in the nickel tetrafluoroborate complex it was thought worthwhile to prepare a cobalt(II) analogue so as to attempt to dehydrate it to a complex containing the $[Co(9MeMP)_2]^{2+}$ ion. With ethyl acetate as solvent a six-coordinate complex $Co(9MeMP)_2(BF_4)_2 \cdot 3H_2O$ was obtained.

On heating this compound in a thermogravimetric balance, it lost one molecule of water between 120 and 145 °C (wt. loss found 2.89; calc. 2.91%). The resulting, octahedral dihydrate lost no further weight up to 190 °C, but at that temperature it decomposed. These results suggest that the original trihydrate should be formulated as $[Co(9MeMP)_2(OH_2)_2] \cdot (BF_4)_2 \cdot H_2O$ containing bidentate, probably chelating, 9MeMP ligands, but that $[Co(9MeMP)_2](BF_4)_2$ is thermally unstable at the temperature required for complete dehydration.

The corresponding nickel tetrafluoroborate complex behaved in a similar fashion, losing initially one molecule of water and then decomposing as the coordinated water molecules were removed.

Copper Complexes

With ethanol as solvent the yellow complexes Cu(9MeMP)X_2 (X = Cl or Br) were obtained. Sletten and Apeland [15] obtained the related compound $[Cu(9MeMP)Cl_2] \cdot H_2O$ from acidified 1:1 water/dioxane, and showed by X-ray studies that the 9MeMP chelates via S and N7 and that the molecular geometry about the copper ion consists of planar $CuNSCl_2$ units connected by long (2.737 Å) Cu–Cl bonds to form centrosymmetric dimers. The electronic spectrum of the anhydrous chloride we have prepared is typical of such a coordination geometry.

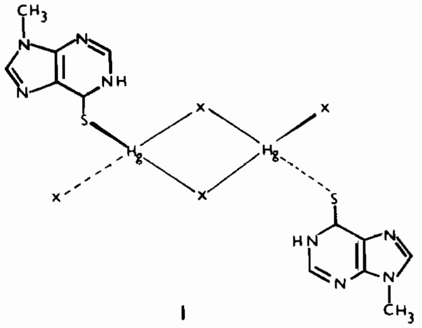
The Q-band e.p.r. spectrum of the bromide (Fig. 2) consists of a three g-value spectrum (g = 2.207, 2.078, and 2.038) with clear resolution of the lowest field band into four Cu hyperfine components (A = 0.015 cm^{-1}). The corresponding spectrum of the chloride merely shows a broad band centred on $g_{eff} \sim 2.09$ with asymmetry to low field but with no clearly resolved components. This lack of resolution observed for the chloride is a common feature of halogen-bridged copper species and the clear resolution found for the bromide implies that the latter has rhombic, planar geometry with no, or little, intermolecular association.

Mercury and Cadmium Complexes

Despite the similarity of the stoichiometry of the compounds Hg(9MeMP)X_2 (X = Cl or Br) to those of their 9Mead [1] and 9Mehyp [2] analogues their vibrational spectra (Table III) are not consistent with either the polymeric, tetrahedral HgL_2X_2 structure of Hg(9Mead)X_2 or the trigonal $HgLX_2$ structure found for Hg(9Mehyp)Cl_2 [22]. Both of these structural types would lead to antisymmetric and symmetric ν(Hg–X) bands in the vibrational spectra and such pairs of bands are not observed.

The Raman spectrum of Hg(9MeMP)Br_2 has a very intense band at 215 cm^{-1}, with a corresponding, strong i.r. band at 216 cm^{-1}, whereas the Raman spectrum of the chloride is quite clear in this region. This band is reasonably assigned to terminal ν(Hg–Br) and there is an analogous ν(Hg–Cl) band for the chloride at 315 cm^{-1} (Raman) and 316 cm^{-1} (i.r.).

A likely geometry is a halogen bridged dimer as in I. The ν(Hg–X) modes associated with the halide bridges in such a structure would be expected to be below 200 cm^{-1} [23], the limit of our i.r. measurements. The Raman spectra had a band at 175 cm^{-1} for the chloride and at 158 cm^{-1} for the bromide, but the free ligand has a Raman band in this region (168 cm^{-1}) and the shift of only 17 cm^{-1} on replacing Cl by Br seems far too small for both, or either, of these bands to be ν(Hg–X) bridge modes.



I

Although in I we have depicted the 9MeMP as coordinating through S this has been done by analogy with the known structure of $Hg(6MP)_2Cl_2$, as we have been unable reliably to assign any ν(Hg–S) or ν(Hg–N) bands in the vibrational spectra. Some evidence for coordination of 9MeMP via sulphur is, however, provided by the shifts to lower energy observed for the so-called 'thioamide bands III and IV' [24] in the mid i.r. region. Band III which occurs at 998 cm^{-1} in 9MeMP shifts to 950 cm^{-1} in both mercury complexes, and band IV moves from 875 cm^{-1} in the free ligand to 868 cm^{-1} in $Hg(9MeMP)Cl_2$ and to 840 cm^{-1} in the bromide analogue.

The low frequency i.r. spectra of the cadmium compounds showed no bands above 200 cm^{-1} assignable to ν(Cd–X) so it appears likely that they have polymeric, halide-bridged structures.

In conclusion, the results of this work show that the exocyclic sulphur atom in 9-methyl-6-mercaptopurine has a much greater tendency to coordinate to the metal ions studied here than does the O6 atom of 9-methylhypoxanthine. This leads to a more diverse coordination behaviour in which chelates involving S and N7 may be formed as well as unidentate coordination by N7 or S alone.

Experimental

Preparations

9-Methyl-6-mercaptopurine was prepared by the method of Beaman and Robins [25].

Most of the complexes were prepared by refluxing for 24 hr equimolar proportions of 9-MeMP and the appropriate metal salt in ethanol [for $M(9MeMP)X_2$ (M = Cu, Cd, Hg; X = Cl, Br), $Co(9MeMP)_2X_2$ (X = Cl, Br), $Ni(9MeMP)_2X_2 \cdot 2H_2O$ (X = Cl, Br)], ethyl acetate [for $Ni(9MeMP)Cl_2 \cdot 2H_2O$], or nitromethane [for $Co(9MeMP)X_2$ (X = Cl, Br)]. The solid complex either formed directly during this process or was obtained by concentration of the clear solution. The solids were thoroughly washed with the solvent employed and dried *in vacuo.*

$M(9MeMP)_2(BF_4)_2 \cdot 3H_2O$ (M = Co or Ni): The general method outlined above was used, with ethyl acetate as solvent, but with a 2:1 mole ratio of metal tetrafluoroborate to 9MeMP.

$Ni(9MeMP)_xCl_2$ (x = 1 or 2): these were obtained by heating the corresponding dihydrates to 130 °C *in vacuo.*

Physical Measurements

These were carried out as described previously [1,2].

Acknowledgements

We thank the CONACYT (National Council of Science and Technology of Mexico) for the award of a postgraduate scholarship to N.B.B., and Dr. R. Osborne for the X-ray powder photographs.

References

1 N. Barba Behrens, D. M. L. Goodgame, and Z. Warnke, *Inorg. Chim. Acta, 31,* 257 (1978).
2 N. Barba Behrens and D. M. L. Goodgame, *Inorg. Chim. Acta,* Submitted. Paper 257(B).
3 G. A. Le Page, *Cancer Res., 23,* 1202 (1963).
4 G. M. Brown, *Ann. N.Y. Acad. Sci., 60,* 315 (1954).
5 E. Sletten, J. Sletten, and L. H. Jensen, *Acta Cryst., B25,* 1330 (1969).
6 G. M. Brown, *Acta Cryst., B25,* 1338 (1969).
7 A. K. Ghosh and S. Chatterjee, *J. Inorg. Nucl. Chem., 26,* 1459 (1964).
8 R. Weiss and H. Venner, *Z. physiol. Chem., 345,* 122 (1966).
9 C. D. Brigando and D. Colaitis, *Bull. Soc. Chim. Fr.,* 3440 (1969).
10 A. A. Grinberg, Y. S. Varshavskii, M. I. Gelfman, N. V. Kiseleva, and D. B. Smolenskaya, *Russ. J. Inorg. Chem., 13,* 422 (1968).
11 S. Kirschner, Y-K. Wei, D. Francis, and J. G. Bergman, *J. Med. Chem., 9,* 369 (1966).
12 M. R. Caira and L. R. Nassimbeni, *Acta Cryst., B31,* 1339 (1975); A. L. Shoemaker, P. Singh, and D. J. Hodgson, *ibid., B32,* 979 (1976).
13 P. Lavertue, J. Hubert, and A. L. Beauchamp, *Inorg. Chem., 15,* 322 (1976).
14 H. I. Heitner and S. J. Lippard, *Inorg. Chem., 13,* 815 (1974).
15 E. Sletten and A. Apeland, *Acta Cryst., B31,* 2019 (1975).
16 M. A. Guichelaar and J. Reedijk, *Rec. Trav. Chim. Pays-Bas, 97,* 295 (1978).
17 J. Abbot, D. M. L. Goodgame, and I. Jeeves, *J. Chem. Soc. Dalton,* 880 (1978).
18 M. Goldstein and W. D. Unsworth, *Inorg. Chim. Acta, 4,* 342 (1970).
19 D. M. L. Goodgame, M. Goodgame, M. A. Hitchman, and M. J. Weeks, *J. Chem. Soc. A,* 1769 (1966).
20 S. L. Holt and R. L. Carlin, *J. Am. Chem. Soc., 86,* 3017 (1964).
21 D. M. L. Goodgame, M. Goodgame, and G. W. Rayner Canham, *Inorg. Chim. Acta, 3,* 406 (1969), and refs. therein.
22 N. Barba Behrens, B. A. Cartwright, D. M. L. Goodgame, and A. C. Skapski, *Inorg. Chim. Acta, 31,* 1471 (1978).
23 G. B. Deacon, J. H. S. Green, and D. J. Harrison, *Spectrochim. Acta, 24A,* 1921 (1968).
24 B. Singh and K. P. Thakur, *J. Inorg. Nucl. Chem., 36, 1735 (1974).*
25 A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc., 83,* 4038 (1961).