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An Efficient Route for the Preparation of Highly Soluble Platinum(II) Antitumour Agents

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Following the demonstration in 1969 of the potent anti-cancer activity of *cis*-$Pt(NH_3)_2Cl_2$, this complex has become a useful addition to the range of clinical chemotherapeutic agents [1, 2]. In the search for improved effectiveness a large number of analogous compounds of general formula *cis*-PtA_2X_2 (where A_2 is either two monodentate and one bidentate amine ligand, and X_2 is either two monodentate or one bidentate anionic ligand) have subsequently been prepared [3].

The currently accepted synthesis of these potential antitumour agents is:

$$K_2PtCl_4 + 4\,KI \rightarrow K_2PtI_4 + 4\,KCl \quad (1)$$

$$K_2PtI_4 + 2A \rightarrow \textit{cis}\text{-}PtA_2I_2 + 2\,KI \quad (2)$$

$$\textit{cis}\text{-}PtA_2I_2 + 2AgNO_3 \rightarrow \textit{cis}\text{-}[PtA_2(OH_2)_2](NO_3)_2 + 2\,AgI \quad (3)$$

$$\textit{cis}\text{-}[PtA_2(OH_2)_2](NO_3)_2 + 2\,MX \rightarrow \textit{cis}\text{-}[PtA_2X_2] + 2\,MNO_3 \quad (4)$$

(M = alkali metal or H)

The high *trans* effect of coordinated iodide ensures that the *cis* configuration is attained in step (2). This stereochemistry is retained during subsequent reaction. If the anion to be added in the final step is a base derived from a carboxylic acid, pH adjustment is needed to ensure its deprotonation.

While investigating methods for the rapid and efficient synthesis of radiolabelled agents we became aware of the limitations of this procedure: after step (4) highly soluble *cis*-PtA_2X_2 are difficult to separate from MNO_3 without loss of yield. Here we report a method, of general applicability, used to prepare *cis*-$Pt(NH_3)_2$(CBDCA) (where CBDCA is the dianion derived from 1,1-cyclobutanedicarboxylic acid) in good yield and high purity, *viz.*:

$$\textit{cis}\text{-}Pt(NH_3)_2I_2 + Ag_2SO_4 \rightarrow \textit{cis}\text{-}[Pt(NH_3)_2(OH_2)_2]SO_4 + 2\,AgI$$

$$\textit{cis}\text{-}[Pt(NH_3)_2(OH_2)_2]SO_4 + Ba(CBDCA) \rightarrow \textit{cis}\text{-}Pt(NH_3)_2(CBDCA) + BaSO_4$$

Cis-$Pt(NH_3)_2I_2$ [4] (2.98 g, 6.17 mmol) was added to a solution containing slightly less than the stoichiometric amount of silver sulphate (1.88 g; 6.03 mmol) in distilled water (250 cm^3). The mixture was stirred for 4 h in a dim light, filtered and concentrated to 150 cm^3.

The barium salt of CBDCA was prepared *in situ* by the addition of $Ba(OH)_2 \cdot 8H_2O$ (1.91 g, 6.05 mmol) to a solution (100 cm^3) of 1,1-cyclobutanedicarboxylic acid (1.00 g, 6.94 mmol). [In fact we have isolated a pure sample of BaCBDCA (% Ba: Calc. 49.1, Found 48.9), the infrared spectrum of which indicates the complete disappearance of the carboxylic acid band of the free acid at 1720 cm^{-1} and the appearance of carboxylate band at 1575 cm^{-1}].

On mixing the two solutions barium sulphate is immediately precipitated. After filtration and concentration of the filtrate a white crystalline residue was recovered. This was washed with ethanol and dry diethyl ether (100 cm^3) and dried *in vacuo* to give *cis*-$Pt(NH_3)$(CBDCA) in 88% yield. *Anal.*: % Calc., C 19.4, H 3.2, N 7.5, Pt 52.6; % Found, C 19.5, H 3.4, N 7.7, Pt 52.7.

This procedure has worked successfully for a large number of potential anti-cancer agents. For example *cis*-$Pt(NH_3)$(EMA) (EMA is the dianion of ethylmalonic acid) is prepared in similar high yield. *Anal.*: % Calc., C 16.7, H 3.3, N 7.8, Pt 54.3; % Found, C 16.4, H 3.7, N 7.6, Pt 54.6.

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