

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

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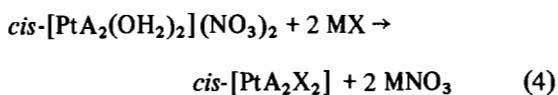
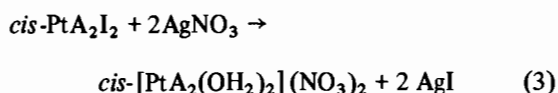
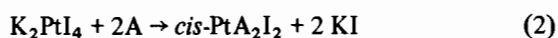
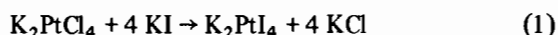
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Following the demonstration in 1969 of the potent anti-cancer activity of *cis*-Pt(NH₃)₂Cl₂, this complex has become a useful addition to the range of clinical chemotherapeutic agents [1, 2]. In the search for improved effectiveness a large number of analogous compounds of general formula *cis*-PtA₂X₂ (where A₂ is either two monodentate and one bidentate amine ligand, and X₂ is either two monodentate or one bidentate anionic ligand) have subsequently been prepared [3].

The currently accepted synthesis of these potential antitumour agents is:

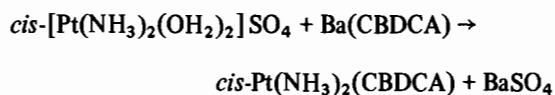
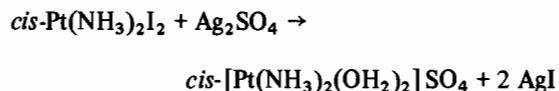


(M = alkali metal or H)

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*-PtA₂X₂ are difficult to separate

from MNO₃ without loss of yield. Here we report a method, of general applicability, used to prepare *cis*-Pt(NH₃)₂(CBDCA) (where CBDCA is the dianion derived from 1,1-cyclobutanedicarboxylic acid) in good yield and high purity, *viz.*:



Cis-Pt(NH₃)₂I₂ [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 cm³). The mixture was stirred for 4 h in a dim light, filtered and concentrated to 150 cm³.

The barium salt of CBDCA was prepared *in situ* by the addition of Ba(OH)₂·8H₂O (1.91 g, 6.05 mmol) to a solution (100 cm³) 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 cm³) and dried *in vacuo* to give *cis*-Pt(NH₃)₂(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(NH₃)₂(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.

Acknowledgments

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