Synthesis of 2-Aminotropone Oximes and 2-Alkoxytropone Imines†

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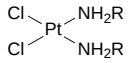
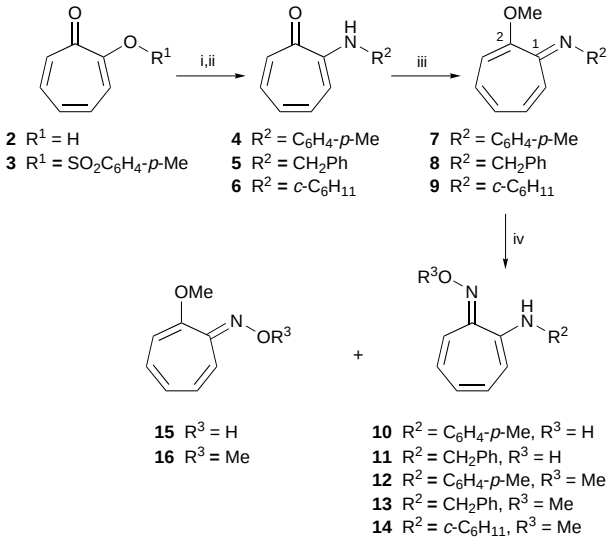
A synthetic route was developed for preparation of 2-aminotropone oximes **10–14**, a new class of compounds, from tropolone **2**; 2-methoxytropone imines **7–9** and tropylium salts **17** were generated as the key intermediates.

cis-Diamminedichloroplatinum analogues **1** are used as drugs for clinical cancer chemotherapy.[2,3] In order for **1** to exhibit significant biological activity, the two amino groups must be in a *cis* configuration in **1**.[4,5] Here we report the preparation of 2-aminotropone oximes (*e.g.*, **10–14**), in which the two adjacent nitrogen atoms are attached to a planar nucleus and could coordinate to Pt to form *cis*-platinum complexes.



1 R = alkyl, aryl

Reaction of tropone with $NH_2OH·HCl$ and pyridine in methanol generates tropone oxime and 2-aminotropone.[6] Under the same conditions, 2-alkyltropones can also be converted to 2-alkyltropone oximes and 2-alkyl-7-aminotropones,[7] yet tropolone **2** remains intact.[8] By replacement of pyridine with various bases, including NaOH, NaOMe, NaOAc, Na_2CO_3 and Et_3N, we were also unable to convert tropolone to the corresponding oximes by using $NH_2OH·HCl$. The unusual resonance phenomenon associated with tropolone and an inherent intramolecular hydrogen bonding between the OH and the C=O groups[9] may decrease its reactivity towards oxime formation. Furthermore, our attempts to oximate 2-(*p*-tolylsulfonyl)tropone and 2-aminotropone were also unsuccessful. Herein we report an indirect way to convert tropolone **2** to the desired 2-aminotropone oximes **10–14**. To the best of our knowledge, this provides the only available up-to-date route for the preparation of 2-aminotropone oximes, an unprecedented class of compounds.



2 R^1 = H
3 R^1 = $SO_2C_6H_4$-*p*-Me

4 R^2 = C_6H_4-*p*-Me
5 R^2 = CH_2Ph
6 R^2 = *c*-C_6H_{11}

7 R^2 = C_6H_4-*p*-Me
8 R^2 = CH_2Ph
9 R^2 = *c*-C_6H_{11}

15 R^3 = H
16 R^3 = Me

10 R^2 = C_6H_4-*p*-Me, R^3 = H
11 R^2 = CH_2Ph, R^3 = H
12 R^2 = C_6H_4-*p*-Me, R^3 = Me
13 R^2 = CH_2Ph, R^3 = Me
14 R^2 = *c*-C_6H_{11}, R^3 = Me

Scheme 1 *Reagents and conditions:* i, for **2**→**3**: *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C (96%); ii, for **3**→**4**: *p*-$MeC_6H_4NH_2$, BuOH, reflux (72%); for **3**→**5**: $PhCH_2NH_2$, BuOH, reflux (76%); for **3**→**6**: cyclohexylamine, BuOH, reflux (65%); iii, for **4–6**→**7–9**: Me_2SO_4, toluene, reflux, $NaHCO_3$ (aq) (60–65%); iv, for **7**→**10**+**15** and **8**→**11**+**15**: $NH_2OH·HCl$, NaOMe, MeOH; for **7–9**→**12–14**+**16**: $NH_2OMe·HCl$, NaOMe, MeOH

After tosylation of **2**,[10] the resultant toluene-*p*-sulfonate **3** was treated with various amines,[11] including *p*-toluidine, benzylamine and cyclohexylamine, in BuOH under reflux to give the corresponding 2-aminotropones **4–6** in 65–76% yields (Scheme 1). Methylation[11] of **4–6** with dimethyl sulfate in toluene under reflux followed by treatment with $NaHCO_3$ afforded the 2-methoxytropone imines **7–9** in 60–65% overall yields. Upon reaction with $NH_2OR·HCl$ (R = H or Me) and NaOMe in MeOH, **7–9** were converted to the desired oximes **10–14** in 24–54% yields. The spectroscopic data are summarized in Table 1. In these reactions, an unexpected by-product (*i.e.*, 2-methoxytropone oxime **15** or **16**) was generated and its structure was determined with the aid of single-crystal X-ray diffraction analysis.§ Formation of oximes **10–14** came from a nucleophilic attack of **7–9** by NH_2OR (R = H or Me) at the C-2 position and formation of oximes **15** and **16** came from an attack at the C-1 position.

Furthermore, we found that reactions of 2-aminotropones **4–6** with methyl fluorosulfonate gave the corresponding isolable tropylium salts **17** (Scheme 2).[12] The desired oximes **10–14** can be obtained by treatment of **17** with $NH_2OH·HCl$ or $NH_2OMe·HCl$. Moreover, we were able to synthesize 2-aminotropone imines **18–20** in high yields (>80%) by treating tropylium salts **17** with primary amines, including *p*-toluidine and benzylamine.[13] These 2-aminotropone imines were also obtained in excellent yields (91–98%) by the reactions of 2-methoxytropone imines **7** and **8** with amines (Scheme 2 and Table 1).[11]

In conclusion, 2-methoxytropone imines **7–9** and tropylium salts **17** were prepared readily from tropolone **2** *via* toluene-*p*-sulfonate **3** and 2-aminotropones **4–6**. These key intermediates (*i.e.*, **7–9** and **17**) were successfully converted to the 2-aminotropone oximes (**10** and **11**) and oxime methyl ethers (**12–14**) upon treatment with $NH_2OR·HCl$ (R = H or Me), and to 2-aminotropone imines **18–20** with primary amines. Use of the resultant new nitrogen-containing planar compounds to form *cis*-diamminedichloroplatinum analogues and to test their biological activity are under investigation in our laboratory.

Experimental

General Procedure for the Conversion of 2-*Methoxytropone Imines* (**7–9**) *to* 2-*Aminotropone Oximes* **10–14**.—To a clear solution of $NH_2OH·HCl$ or $NH_2OMe·HCl$ (2.30 mmol) and NaOMe (2.30 mmol) in MeOH (20 mL) was added a 2-methoxytropone imine (**7–9**, 2.22 mmol). The reaction mixture was stirred at room temperature for 4.0 h. After the solvent was removed under reduced

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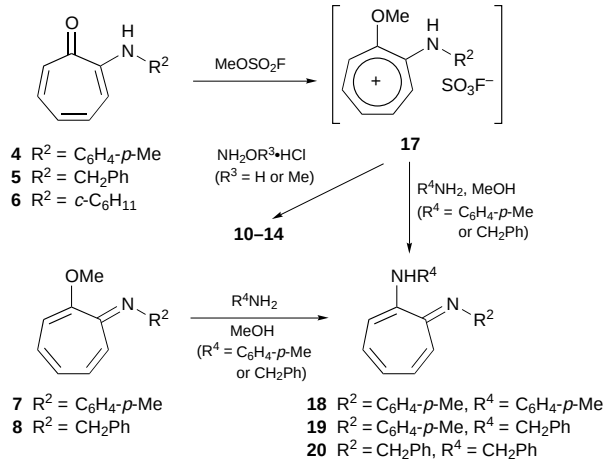
‡Deceased April 4, 1996.

§Details of the X-ray crystal-structure determination will be reported elsewhere.

Table 1 Conversion of 2-methoxytropone imines **7–9** to a mixture of oximes **10–16** or to 2-aminotropone imines **18–20** by the use of various nitrogen-containing reagents

Imine	Reagent	Products (% in yield)[a]	δ_H ($CDCl_3$)	δ_C ($CDCl_3$)	ν_{max}/cm^{-1}	Mp (*T*/°C)	Found (calcd) (%) C	H	N
7	$NH_2OH·HCl$	**10** (28) + **15** (50)	**10**: 2.31 (s, 3 H), 6.12–7.20 (m, 10 H), 7.46 (br s, 1 H); **15**: 3.72 (s, 3 H), 5.80–7.11 (m, 5 H), 9.83 (br s, 1 H)	**10**: 21.9, 106.3, 117.6, 121.6, 125.8, 130.9, 132.9, 133.1, 135.8, 137.6, 145.8, 151.0; **15**: 55.6, 104.9, 120.7, 124.2, 129.0, 131.1, 149.9, 157.0	**10**: 3315 (OH, NH), 1583 (C═N); **15**: 3298 (OH), 1599 (C═N)	**10**: liq.; **15**: 132–133	**10**: 74.26 (74.31)	6.55 (6.24)	12.26 (12.38)
							15: 63.48 (63.57)	5.99 (6.00)	9.38 (9.27)
8	$NH_2OH·HCl$	**11** (24) + **15** (50)	**11**: 4.43 (d, 2 H), 5.82–7.33 (m, 12 H)	**11**: 47.4, 103.4, 115.6, 119.1, 127.2, 127.4, 128.7, 132.0, 132.4, 137.4, 146.2, 150.1	**11**: 3352 (OH, NH), 1584 (C═N)	**11**: liq.	**11**: 74.18 (74.31)	6.31 (6.24)	12.49 (12.38)
7	$NH_2OMe·HCl$	**12** (54) + **16** (30)	**12**: 2.33 (s, 3 H), 4.00 (s, 3 H), 6.11–7.28 (m, 9 H), 7.62 (br s, 1 H); **16**: 3.84 (s, 3 H), 4.01 (s, 3 H), 5.82–6.94 (m, 5 H)	**12**: 20.9, 62.1, 105.3, 117.3, 120.7, 124.9, 129.9, 132.0, 132.2, 134.8, 136.6, 144.8, 148.4; **16**: 560, 62.0, 105.2, 120.9, 124.3, 129.0, 131.0, 151.0, 151.2	**12**: 3152 (NH), 1583 (C═N); **16**: 1590 (C═N)	**12**: liq.; **16**: liq.	**12**: 74.88 (74.97)	6.73 (6.71)	11.57 (11.66)
							16: 65.45 (65.44)	6.84 (6.71)	8.40 (8.48)
8	$NH_2OMe·HCl$	**13** (47) + **16** (25)	**13**: 4.02 (s, 3 H), 4.49 (d, 2 H), 5.82–7.43 (m, 10 H), 7.87 (br s, 1 H)	**13**: 47.2, 62.0, 103.3, 116.5, 119.2, 127.2, 127.4, 128.8, 132.0, 132.5, 134.9, 137.8, 146.3, 148.6	**13**: 3360 (NH), 1584 (C═N)	**13**: liq.	**13**: 75.09 (74.97)	6.63 (6.71)	11.77 (11.66)
9	$NH_2OMe·HCl$	**14** (51) + **16** (31)	**14**: 0.92–2.00 (m, 11 H), 3.43 (br s, 1 H), 3.96 (s, 3 H), 5.81–7.06 (m, 5 H)	**14**: 24.7, 25.7, 32.4, 50.8, 61.9, 115.4, 118.0, 131.8, 132.5, 145.4, 148.5	**14**: 3338 (NH), 1583 (C═N)	**14**: liq.	**14**: 72.44 (72.38)	8.63 (8.68)	12.15 (12.06)
7	*p*-$MeC_6H_4NH_2$	**18** (98)	**18**: 2.41 (s, 3 H), 2.49 (s, 3 H), 6.19–7.32 (m, 14 H)	**18**: 20.9, 114.5, 121.5, 122.6, 130.0, 133.2, 133.4, 142.5, 152.1	**18**: 3059 (NH), 1587 (C═N)	**18**: 143–144	**18**: 83.83 (83.96)	6.71 (6.71)	9.25 (9.33)
7	$PhCH_2NH_2$	**19** (91)	**19**: 2.32 (s, 3 H), 4.54 (s, 2 H), 6.10–7.32 (m, 15 H)	**19**: 20.8, 47.2, 105.4, 119.9, 120.7, 120.9, 127.2, 127.4, 130.0, 131.9, 133.0, 133.7, 137.4, 148.4, 150.8, 155.1	**19**: 3265 (NH), 1582 (C═N)	**19**: 113–114	**19**: 84.09 (83.96)	6.80 (6.71)	9.24 (9.33)
8	$PhCH_2NH_2$	**20** (95)	**20**: 4.62 (br s, 4 H), 6.27–7.33 (m, 16 H)	**20**: 50.0, 111.6, 119.1, 126.8, 127.2, 128.4, 133.8, 139.3, 153.2	**20**: 3055 (NH), 1591 (C═N)	**20**: 81–82	**20**: 84.03 (83.96)	6.56 (6.71)	9.38 (9.33)

[a]All data are satisfactory for the high- and low-resolution mass spectroscopy.



Scheme 2

pressure, the residue was purified by use of column chromatography (EtOAc/hexanes = 1:5 as eluent) to give a 2-aminotropone oxime (**10–14**) and a 2-methoxytropone oxime (**15** or **16**) in a pure form. The yields and spectroscopic data are listed in Table 1.

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