# Reaction of Nitrosyl Chloride Gas with Unsaturated Steroids

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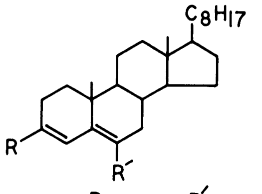
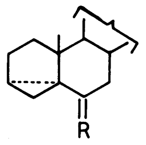
Reaction of nitrosyl chloride gas at 0 °C with 3,5-cholestadiene (**1**) provided 3,6*β*-dinitro-5-chloro-5*α*-cholest-3-ene (**4**) and with 3*α*,5-cyclo-5*α*-cholestan-6-one (**2**) afforded 3*β*-chloro-5-nitro-5*α*-cholestan-6-one (**7**) and 3*β*-chloro-6-nitrato-5-cholestene (**8**). Similar reaction with 6-hydroxylimino 3*α*,5-cyclo-5*α*-cholestane (**3**) gave 3*β*,6-dichloro-5-cholestene (**10**), 3*β*-chloro-6-nitratoimino-5*α*-cholestane (**11**) and 3*β*,5-dichloro-6-nitroimino-5*β*-cholestane (**12**). Compound **12** upon hydrolysis furnished 3*β*,5-dichloro-5*β*-cholestan-6-one (**14**). The structures of these compounds were established on the basis of their spectral properties, and some pertinent chemical transformations. Mechanisms for the formation of some unusual products are discussed.

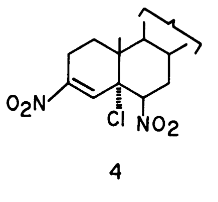
One of the remarkable features of nitrosyl chloride gas is that with the help of it nitro and chloro groups can simultaneously be introduced with ease at unsaturated regions of an organic molecule. Taking advantage of this ability of nitrosyl chloride, nitro and chloro groups were successfully incorporated on adjacent carbon atoms in steroidal olefins.[1–4] For this purpose we have selected, 3,5-cholestadiene (**1**), 3*α*,5-cyclo-5*α*-cholestan-6-one (**2**) and its oxime (**3**) to study the chemical behavior of nitrosyl chloride on the unsaturated functionalities in steroids. Interesting results were envisaged because nitrosyl chloride has been used, exiguously in the advancements of steroid chemistry.



| | R | R′ |
|---|---|---|
| 1, | H | H |
| 5, | $NO_2$ | $NO_2$ |



| | R |
|---|---|
| 2, | O |
| 3, | N–OH |



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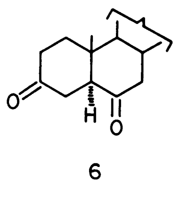

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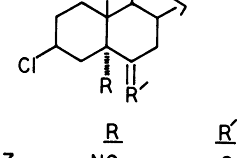
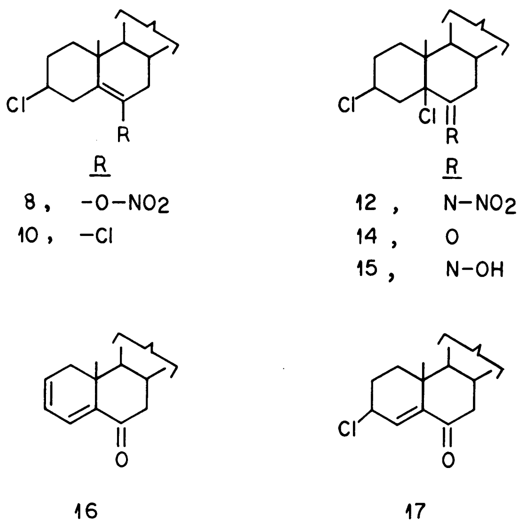


| | R | R′ |
|---|---|---|
| 7, | $NO_2$ | O |
| 9, | H | O |
| 11, | H | $N-ONO_2$ |
| 13, | H | N–OH |



| | R |
|---|---|
| 8, | $-O-NO_2$ |
| 10, | –Cl |

| | R |
|---|---|
| 12, | $N-NO_2$ |
| 14, | O |
| 15, | N–OH |

Chart 1.

## Results and Discussion

Reaction of nitrosyl chloride with **1** in $CCl_4$ at 0 °C afforded a crystalline product **4** which in its IR spectrum showed an absorption band at 1640 for (C=C), two sets of strong bands at 1570, 1385 and at 1530, 1355 $cm^{-1}$, clearly indicated the presence of two nitro groups, former being a saturated and latter the unsaturated one.[5] Its proton NMR spectrum displayed a singlet at $\delta$ 6.35 for C-4 vinylic proton and a triplet at $\delta$ 4.80 ($J$=3 Hz) for C6-$\alpha$H (equatorial).[6] Compound (**4**) gave 3,6-dinitro-3,5-cholestadiene (**5**) on heating in pyridine and on reducing with Zn–acetic acid, it gave 5*α*-cholestane-3,6-dione (**6**). These observations helped in concluding that the compound **4** is 5-chloro-3,6*β*-dinitro-5*α*-cholest-3-ene: The formation of which follows the same mechanism as given earlier.[4]

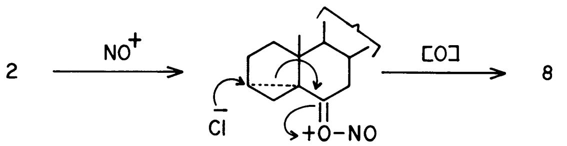
Compound **2** when treated with nitrosyl chloride in the similar fashion afforded 3*β*-chloro-5-nitro-5*α*-cholestan-6-one (**7**) and 3*β*-chloro-6-nitrato-5-cholestene (**8**). The position of nitro group at C-5 in **7** was established by the fact that the signal of the methine proton ($>C\underline{H}-NO_2$) was absent in its proton NMR spectrum and the presence of the absorption bands at 1578 and 1380 $cm^{-1}$ in its IR spectrum supported the saturated and tertiary nature of the nitro group.[5]

The IR spectrum of **8** exhibited characteristic absorption bands for nitrato group[5,7] at 1645, 1285, 875, and 770 $cm^{-1}$ and a weak band at 1630 $cm^{-1}$ for (C=C). Moreover, Zn–acetic acid reduction is known to convert the nitrato group into hydroxyl group.[8] When **8** was subjected to this reduction it gave 3*β*-chloro-5*α*-cholestan-6-one (**9**): Presumably the enol formed in the reaction tautomerized to **9** owing to the acidic conditions of the reaction medium. Mechanism for the formation of **8** is given in Scheme 1.

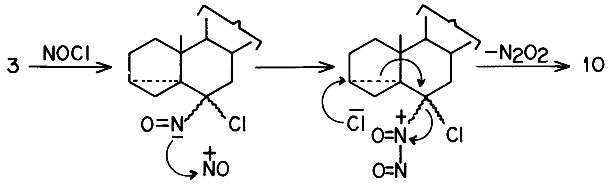
Treatment of **3** with nitrosyl chloride as described earlier provided 3*β*,6-dichloro-5-cholestene (**10**), 3*β*-chloro-6-nitratoimino-5*α*-cholestane (**11**) and 3*β*,5-dichloro-6-nitroimino-5*β*-cholestane (**12**).

Formation of *gem*-chloronitroso derivatives from the reaction of nitrosyl chloride and oximes is known.[9] Further nitrosation of *gem*-chloronitro derivative may lead to the elimination of $N_2O_2$ from the molecule. In view of this aspect the mechanism for the formation of **10** is proposed as in Scheme 2.

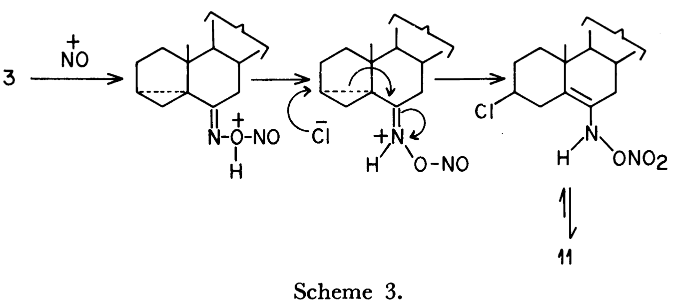
The compound **11** showed four intense bands at 1630, 1275, 875, and 770 $cm^{-1}$ for nitrate function besides a medium band at 1650 $cm^{-1}$ for (C=N) in its IR spectrum. The notching observed in the band at 875 was perhaps due to the N–O–N bonding, hence accounts for the presence of *N*-nitrate grouping. Zn–acetic acid reduction of **11** provided the ketone **9** and its oxime **13**. The formation of **11** involves enamine–imine tautomerism which is depicted in Scheme 3.



Scheme 1.



Scheme 2.



Scheme 3.

As far as the formation of **12** is concerned, it is assumed that the cyclopropane ring is opened by the attack of chlorine generated as a result of the dissociation of nitrosyl chloride gas. The conversion of hydroxylimino group into nitroimino group by nitrosyl chloride[10,11] involves the formation of *N*-nitrosonitrone species as intermediate which spontaneously rearranges to nitroimine.[12]

In the proton NMR spectrum of **12** the C-3 proton resonated at relatively downfield and showed half band width (≈6.5 Hz) indicating its equatorial nature and cis geometry of A/B ring junction.[6] Chemical justification for this fact was obtained by the hydrolysis of nitroimine **12** to obtain 3*β*,5-dichloro-5*β*-cholestan-6-one (**14**) which was found different from its 5*α*-epimer.[13] The ketone **14** was converted into its oxime **15** which in turn gave the parent nitroimine **12** when treated with nitrosyl chloride. Dehydrochlorination of **14** provided 2,4-cholestadien-6-one (**16**) and 3*β*-chloro-4-cholesten-6-one (**17**).

## Experimental

Melting points were determined on a Koffler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer. Proton nuclear magnetic resonance spectra were taken on a Varian A 60 instrument with $(CH_3)_4Si$ as internal reference, and mass spectra were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were performed by Instrumentation Centre at our University. Compounds **1**,[14] **2**,[15] and **3**[16] were prepared according to the literature. Nitrosyl chloride gas was prepared according to Morton and Wilcox's method.[17]

**Reaction of 1 with NOCl.** The solution of **1** (2 g) in $CCl_4$ (100 mL) was cooled to 0 °C and dried NOCl was bubbled into it for 2 h. The reaction mixture was kept overnight at 0 °C and the solvent was evaporated under reduced pressure and the residue was taken in ether, washed with water, and dried ($Na_2SO_4$). After removal of the solvent, the oily residue was subjected to the column chromatography over silica gel (40 g). Elution with light petroleum (bp 60—80 °C):ether (25:1) gave **4**, recrystallized from methanol (1.4 g, 70%); mp 156 °C (positive Beilstein test); IR (KBr) 1640, 1570, 1530, 1385, 1355, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.72 (3H, s, 18-$CH_3$), 1.05 (3H, s, 19-$CH_3$), 4.80 (1H, t, *J*=3 Hz, 6*α*-H), 6.35 (1H, s, 4-H); MS, *m/z* (relative intensity) 496/494 (0.20/0.60, $M^{+}$), 413 (5), 396 (12), 383 (6), 382 (14), 107 (25), 105 (25). Found: C, 65.56; H, 8.67; N, 5.60%. Calcd for $C_{27}H_{43}N_2O_4Cl$: C, 65.52; H, 8.69; N, 5.66%.

**Dehydrochlorination of 4.** In pyridine (200 mL), **4** (500 mg) was refluxed for 2 h. The reaction mixture was diluted with water and organic mass was extracted with ether and ethereal layer was washed with dil HCl (5%), $NaHCO_3$ solution (5%) and water and dried ($Na_2SO_4$). Removal of the solvent gave **5** as an oil, crystallized from methanol (400 mg, 80%); mp 113 °C (lit,[4] 113 °C) (negative Beilstein test); IR (KBr) 1651, 1515, 1380 $cm^{-1}$; $^1H$ NMR

($CDCl_3$) $\delta$=0.71 (3H, s, 18-$CH_3$), 1.10 (3H, s, 19-$CH_3$), 7.7 (1H, s, 4-H).

**Zinc-Acetic Acid Reduction of 4.** In 50 mL of warm acetic acid, **4** (500 mg) was dissolved and zinc dust (2 g) was added gradually over a period of 10 min. The mixture was heated under reflux for 4 h, water (5 mL) was added with regular intervals. It was diluted with water and organic mass was extracted with ether. The ethereal layer was worked up, dried ($Na_2SO_4$) and the solvent was evaporated to get **6** as an oil, crystallized from acetone (300 mg, 60%); mp 167 °C (lit,[18] mp 169 °C) (negative Beilstein test); IR (nujol) 1710 $cm^{-1}$.

**Reaction of 2 with NOCl.** The reaction of **2** (5 g) in $CCl_4$ (250 mL) with NOCl was performed as earlier. After usual work up an oily mass was obtained which was chromatographed over a column of silica gel (80 g). Elution with light petroleum (bp 60—80 °C) afforded **7**, recrystallized from methanol (1.8 g, 36%): mp 92 °C (positive Beilstein test), IR (nujol) 1718, 1578, 1390, 740 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$=0.75 (3H, s, 18-$CH_3$), 1.18 (3H, s, 19-$CH_3$), 1.7 (2H, d, 4-$H_2$), 3.4 (1H, m, $W_{1/2}$=16 Hz, 3$\alpha$-H, A/B ring junction trans;[6] MS, *m/z* (relative intensity) 421/419 (2/6, M-$NO_2$), 418 (20), 416 (61), 318 (45), 306 (3), 304 (9), 270 (35). Found: C, 69.61; H, 9.49; H, 3.02%. Calcd for $C_{27}H_{44}NO_3Cl$; C, 69.60; H, 9.45; N, 3.01%. Further elution with light petroleum (bp 60—80 °C):ether (25:1) afforded **8**, recrystallized from methanol (2.5 g, 50%); mp 124 °C (positive Beilstein test); IR (KBr) 1645, 1630, 1285, 875, 770, 725 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$=0.77 (3H, s, 18-$CH_3$), 1.20 (3H, s, 19-$CH_3$), 3.80 (1H, m, $W_{1/2}$=17 Hz, 3$\alpha$-H); MS, *m/z* (relative intensity) 467/465 (0.50/1.50 $M^{\dagger}$), 416 (1), 414 (2), 398 (45), 370 (15).

**Zinc-Acetic Acid Reduction of 8.** In warm acetic acid (100 mL), **8** (1 g) was dissolved and zinc dust (5 g) was added portionwise during 15 min. The mixture was stirred for 1 h at 30 °C. It was concentrated to half volume and diluted with saturated brine (300 mL) and filtered, and then worked up as usual to obtaine crude **9**, crystallized from methanol (600 mg, 60%); mp 127 °C (lit,[19] 128—129 °C); IR (nujol) 1705, 740 $cm^{-1}$.

**Reaction of 3 with NOCl.** Reaction of NOCl with **3** (5 g) in $CCl_4$ (250 mL) was carried out worked up in the similar fashion. An orange-colored oily mass thus obtained was chromatographed over a column of silica gel (80 g). Elution with light petroleum (bp 60—80 °C) furnished **10**, recrystallized from light petroleum (bp 40—60 °C) (1.1 g, 22%); mp 95 °C (positive Beilstein test); IR (nujol) 1650, 770, 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.65 (3H, s, 18-$CH_3$), 1.28 (3H, s, 19-$CH_3$), 3.68 (1H, m, $W_{1/2}$=17 Hz, 3$\alpha$-H); MS, *m/z* (rel intensity) 440/438 (2/6, $M^{\dagger}$), 437 (3), 435 (9), 424 (6), 422 (17), 405 (16), 403 (47). Found: C, 73.88; H, 10.00%. Calcd for $C_{27}H_{44}Cl_2$: C, 73.80; H, 10.02%. Further elution with light petroleum (bp 60—80 °C):ether (85:1) afforded **11**, recrystallized from acetone (2.3 g, 46%); mp 114 °C (positive Beilstein test); IR (KBr) 1650, 1630, 1275, 865, 770, 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.72 (3H, s, 18-$CH_3$), 1.19 (3H, s, 19-$CH_3$), 4.7 (1H, m, $W_{1/2}$=18 Hz, 3$\alpha$-H, A/B ring junction trans);[6] MS, *m/z* (rel intensity) 467/465 (1/3, M-$CH_3$), 440 (12), 438 (35), 405 (4), 403 (3), 403 (7). Found: C, 67.47; H, 9.31; N, 5.85%. Calcd for $C_{27}H_{45}N_2O_3Cl$: C, 67.43; H, 9.37; N, 5.83%. Continued elution with light petroleum (bp 60—80 °C):ether (80:1) provided **12**, recrystallized from methanol (1.3 g, 26%); mp 124—126 °C (positive Beilstein test); IR (KBr) 1638, 1557, 1362, 760, 680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.72 (3H, s, 18-$CH_3$), 1.12 (3H, s, 19-$CH_3$), 2.8 (2H, d, *J*=4.5 Hz, 4-Hz), 4.82 (1H, m, $W_{1/2}$=6.5 Hz, 3$\beta$-H, A/B ring junction cis);[6] MS, *m/z* (rel intensity) 464/462 (3/9, M-HCl), 431 (5), 404 (13), 402 (40), 386 (4), 384 (12). Found: C, 65.00; H, 8.86; N, 5.58%. Calcd for $C_{27}H_{44}N_2O_2Cl_2$: C, 64.93; H, 8.82; N, 5.61%.

**Zinc-Acetic Acid Reduction of 11.** In warm acetic acid (100 ml), **11** (1 g) was dissolved and zinc dust (10 g) was added portionwise in 15 min. The mixture was stirred for 30 min at 30 °C. Acetic acid was evaporated to its half volume and saturated brine (300 mL) was added. After working up in usual fashion and oil was obtained which was chromatographed over silica gel (40 g) column. Elution with light petroleum (bp 60—80 °C): ether (40:1) gave **9** (500 mg, 50%). Further elution with light petroleum (bp 60—80 °C): ether (10:1) furnished **13**, recrystallized from methanol (100 mg, 10%); mp 172 °C (lit,[20] mp 175 °C); IR (nujol) 1653, 730 $cm^{-1}$.

**Hydrolysis of 12.** A mixture of **12** (2 g), methanol (250 mL) and HCl (10 mL) was heated under reflux for 1 h and was diluted with excess of water, and worked up in usual fashion which fetched **14** as yellowish sticky semisolid (1.7 g, 85%), (positive Beilstein test); IR (nujol) 1720, 760, 675 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.80 (3H, s, 18-$CH_3$), 1.15 (3H, s, 19-$CH_3$), 1.9 (2H, d, *J*=4 Hz, 4-Hz), 4.0 (1H, m, $W_{1/2}$= 8 Hz, 3$\beta$-H, A/B ring junction cis);[6] MS *m/z* (rel intensity) 456/454 (5/15, $M^{\dagger}$), 452 (26), 418 (20), 416 (62), 398 (4), 382 (10), 353 (13). Found: C, 71.29; H, 9.62%. Calcd for $C_{27}H_{44}OCl_2$: C, 71.21; H, 9.67%.

**Oximation of 14.** A mixture of **14** (500 mg), hydroxylamine hydrochloride (1 g) and sodium acetate trihydrate (1.5 g) in ethanol (60 mL) was heated under reflux for 1.5 h. The excess of ethanol was evaporated and cold water was poured in. The crude oxime was filtered, washed with water and air dried. Recrystallization from ethanol yielded **15** (350 mg, 70%); mp 153 ° (lit,[21] mp 155 °C): IR (KBr) 3450, 1668, 750, 695 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$=0.65 (3H, s, 18-$CH_3$), 1.18 (3H, s, 19-$CH_3$), 4.50 (1H, m, $W_{1/2}$=8 Hz, 3$\beta$-H, A/B ring junction cis),[6] 7.90 (1H, s, 6=N-OH).

**Reaction of 15 with NOCl.** In $CCl_4$ (20 mL), 15 (250 mg) was dissolved and cooled to 0 °C. NOCl gas was passed through the solution for 1 h. The solvent was evaporated and taken in ether and worked as usual. Removal of the solvent gave crude **12**, crystallized from methanol (150 mg, 60%); mp 123—126 °C.

**Dehydrochlorination of 14.** **14** (1 g) was refluxed in pyridine (20 mL) for 2 h. The reaction mixture after work up provided an oil which was chromatographed over silica gel (25 g). Elution with light petroleum (bp 60—80 °C): ether (20:1) afforded **16**, recrystallized from acetone (200 mg, 20%); mp 127—128 °C (lit,[22] mp 128 °C) (negative Beilstein test); IR (KBr) 1673, 1625 $cm^{-1}$ continued elution with light petroleum (bp 60—80 °C):ether (15:1) furnished **17**, recrystallized from light petroleum (bp 40—60 °C) (350 mg, 35%); mp 165 °C (lit,[21] mp 165 °C) (positive Beilstein test); IR (KBr) 1685, 1620, 740 $cm^{-1}$.

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## References

1) K. Tanabe and R. Hayashi, *Chem. Pharm. Bull. (Tokyo)*, **10**, 1177 (1962).

2) A. Terada and A. Hassner, *Bull. Chem. Soc. Jpn.*, **40**, 1937 (1967).

3) Shafiullah and M. R. Ansari, *J. Indian. Chem. Soc.*, in press.

4) Shafiullah and S. Husain, *J. Chem. Res. (S)*, **1983**, 255.

5) R. M. Silverstein, G. C. Basster, and T. C. Morill, "Spectrometric Identification of Organic Compounds," Wiley, San-Fransisco (1981).

6) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San-Fransisco (1964).

7) N. B. Colthup, L. H. Daly, and S. S. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York (1975).

8) F. Hodoson, I. Jude, N. Serben, and A. Balogh, *Chem. Ber.*, **95**, 1094 (1962).

9) H. Rheinboldt and M. Dewald, *Liebigs. Ann. Chem.*, **451**; 273 (1927); **455**; 300 (1927); **460**: 305 (1928).

10) M. J. Hair and G. A. Boswell, Jr., *J. Org. Chem.*, **42**, 4251 (1977).

11) Y. Komeichi, S. Tomioka, T. Iwasaki, and K. Watanabe, *Tetrahedron Lett.*, **1970**, 4677.

12) J. A. Boswell, *J. Org. Chem.*, **33**, 3699 (1968).

13) B. Rezabora, J. Hora, V. Landa, Cerny, and F. Sorm, *Steroids*, **11**, 475 (1968).

14) F. Jarreau, M. B. Tchouber, and R. Gouteral, *Bull. Soc. Chim. Fr.*, **1962**, 887.

15) I. M. Heilbron, J. Hodges, and F. S. Spring, *J. Chem. Soc.*, **1938**, 759.

16) M. S. Ahmad, Shafiullah, and M. Mushfiq, *Tetrahedron Lett.*, **1970**, 2739.

17) J. R. Morton and H. W. Wilcox, *Inorg. Synth.*, **4**, 48 (1953).

18) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, **1937**, 801.

19) A. Windans and O. Dalmer, *Chem. Ber.*, **52**, 162 (1919).

20) E. G. Ford, P. Chakravorty, and E. S. Wallis, *J. Am. Chem. Soc.*, **60**, 413 (1938).

21) M. Hussain and N. H. Khan, *Synth. Commun.*, **11**, 185 (1981).

22) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951); M. S. Ahmad and N. K. Pillai, *Aust. J. Chem.*, **26**, 603 (1973).