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Formation of 3,3,5,7-Tetranitrooxindole and 3,5,7-Trinitroindazole by Nitration of Oxindole

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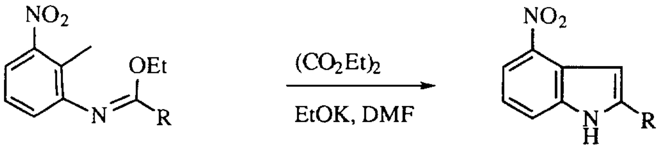
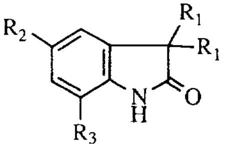
Abstract: Nitration (HNO_3/H_2SO_4) of oxindole gave 3,3,5,7-tetranitrooxindole (**1c**), which readily underwent ring-opening and decarboxylation to 4,6-dinitro-2-(dinitromethyl)aniline (**4b**), which in turn could be cyclized to 3,5,7-trinitroindazole (**5**). Copyright © 1996 Elsevier Science Ltd

We have recently developed a useful route to 4- and 6-nitroindoles based on a base induced cyclization.[1]

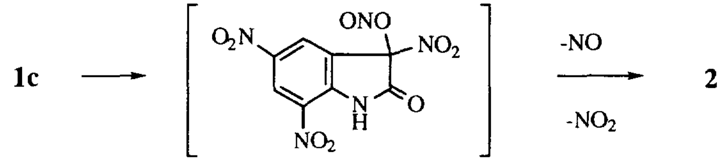


With appropriate modification of the starting materials this approach could be extended to the synthesis of e.g. 6-nitrooxindole as well as 7-nitro-3-hydroxy-2-quinolone. In this connection we have studied the nitration (HNO_3/H_2SO_4) of oxindole (**1d**), which under the appropriate literature conditions[2, 3] gave the expected products 5-nitrooxindole (**1a**) and 5,7-dinitrooxindole (**1b**). However, TLC analysis revealed the coformation (in small amounts) of at least two products, A and B, with the compositions $C_8H_3N_5O_9$ and $C_7H_3N_5O_6$, respectively. By increasing of the amount of HNO_3 one of the compounds (A) crystallized (now as the major product) directly from the reaction mixture. The spectral data (e.g. the absence of a signal for a CH_2 group and the appearance of a distinct signal for a quaternary carbon atom in the ^{13}C NMR spectrum at 106.5 ppm)[4] suggested structure **1c**,[5] which is not unexpected since several examples of dinitration at various types of active methylene groups are recorded in the literature.[6]

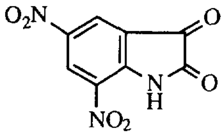


1a $R_1=R_3=H$; $R_2=NO_2$
1b $R_1=H$; $R_2=R_3=NO_2$
1c $R_1=R_2=R_3=NO_2$
1d $R_1=R_2=R_3=H$

The *gem*-dinitro compound **1c** slowly decomposes at 35 °C to NO$_x$ and the known[7] compound 5,7-dinitroisatin (**2**) but can be stored for at least 3 years at -25 °C. The mass spectrum of **1c** and that of 5,7-dinitro-isatin are consequently in principle identical. Upon heating (ca 160 °C at the Kofler bench) it explodes with a flash. The ^{15}N NMR spectrum of **1c** (now prepared using ^{15}N enriched HNO$_3$) featured 3 signals in the ratio 1:1:2 at -16.13, -18.76 and -23.12 ppm respectively (relative to CH$_3$ ^{15}NO$_2$ with DMSO-d6 as solvent). Heating of this solution indicated that a nitro-nitrite rearrangement[8] preceded the formation of 5,7-dinitroisatin (**2a**).



Treatment of **1c** with dilute aqueous sodium hydroxide resulted, *via* nucleophilic ring opening and decarboxylation,[9] in formation of the zwitter-ionic *gem*-dinitro compound **3**. The high acidity of the aliphatic proton in the neutral version of **3**, *i.e.* **4b**, is in harmony with data (pK$_A$=0.03) previously reported[10] for the parent tetranitro compound (**4a**). Like **4a**, compound **3/4b**[11] formed a stable potassium salt which could be recrystalized from water.[12]



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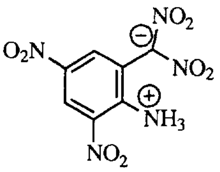

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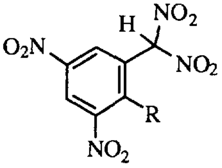
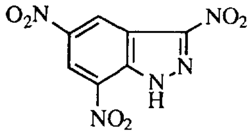


4a R=H
b R=NH$_2$
c R=OH
d R=NHCH$_3$



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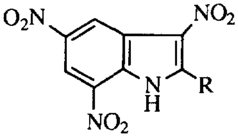


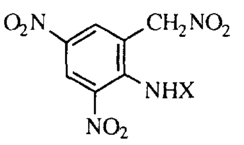
6a R=H
b R=CH$_3$

The NMR spectra of **3/4b** indicate the presence of more than one species in solution. The same is true for the hydroxy analogue **4c**, which has recently been synthesized by Honey[6] *via* treatment of the oxime of salicylaldehyde with N$_2$O$_4$. This phenomenon is explained in terms of intramolecular hydrogen bonding.

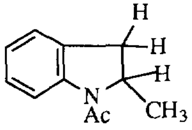
In harmony the *N*-methyl analogue **4d** (prepared by tetranitration of *N*-methyloxindole followed by ring rupture or by treatment of **1c** with CH_2N_2) only showed the presence of one species in solution.

The ring-opened *gem*-dinitro compound **3/4b** could be cyclized with HNO_2, which yielded 3,5,7-trinitroindazole (**5**), which proved to be identical with product B from the nitration of oxindole. Formaldehyde and **4b** yielded 3,5,7-trinitroindole (**6a**) when heated in acetic acid, whereas acetaldehyde reacted considerably slower (to **6b**). No useful procedure could be devised for higher aldehydes due to the instability of **3/4b** under acidic conditions.

2-Methyl-3,5,7-trinitroindole (**6b**) has previously been synthesized by Bendz and Robinson[13] who prepared the precursors 4,6-dinitro-2-nitromethylaniline (**7a**) and its *N*-acetyl derivative (**7b**) *via* a multi-step procedure. In the final step[13] a Madelung cyclization under mild conditions of **7b** gave **6b**. This procedure has later been used by Noland.[14,15] During the present study it was found that nitration of *N*-acetyl-2-methylindoline (**8**) readily afforded **6b** using a procedure already applied[16] on *N*-acetylindoline, (in this case yielding 3,5,7-trinitroindole).



7a X=H
b X=$COCH_3$



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At this point we returned to the nitration originally studied and it was established that isolation of the tetranitro compound **1c** in a high yield (an experiment starting with 13.3 g of oxindole gave directly 24.0 g of **1c**) required temperatures between 10-15 °C and the utilization of pure HNO_3. Temperatures around 25-35 °C and HNO_3 containing NO_x gave 3,5,7-trinitroindazole (**5**), identical with compound B discussed above, as the main product isolated in 80% yield. In the last mentioned experiment oxindole could be replaced by 3,3,5,7-tetranitrooxindole (**1c**) as well as by the ring opened compound **3/4b**.

The details of the mechanism for the ring transformation leading to 3,5,7-trinitroindazole (**5**), which can readily be independently synthesized[17,18] by nitration of 5-nitroindazole, is not clear but it seems likely that **1c** is ring-opened and decarboxylated, cyclized, and reduced finally yielding **5**.

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References and Notes

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4. A similar nitration of 3-methyloxindole gave 3,5,7-trinitro-3-methyloxindole which exhibited a distinct signal from the aliphatic quaternary carbon atom at 87.83 ppm.
5. **1c** IR(KBr): 3326, 3093, 1774, 1616, 1591, 1550, 1466, 1341, 1189, 1091, 934, 806 cm^{-1}; ^1H NMR: 9.01 (d, 1H), 9.02 (d, 1H), J=1.7 Hz, 12.5 (br s, 1H) ppm; ^{13}C NMR: 106.5(s), 120.3(s), 126.0(d), 128.8(d), 131.8(s), 142.0(s), 146.3(s), 159.9(s) ppm.
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9. Easy decarboxylation of *gem*-dinitro compounds, particularly 2,2-dinitroacetic acids, has previously been observed.[9a,9b]

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11. **3/4b** IR(KBr): 3483, 3370, 3093, 1613, 1582, 1527, 1481, 1320, 1225, 1210, 1125, 930, 743, 718, 696 cm^{-1}.
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18. **5**, mp 227-228° (lit.[17] 227-228°C). IR(KBr): 3287, 3101(w), 1644(w), 1561(s), 1538(s), 1496, 1392, 1357(s), 1301(s), 1168, 1134, 976, 799 cm^{-1} (lit.[17] 1570, 1540, 1360 cm^{-1}).

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