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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 (HNO3/H2SO4) 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 <u>e.g.</u> 6-nitrooxindole as well as 7-nitro-3-hydroxy-2-quinolone. In this connection we have studied the nitration (HNO₃/H₂SO₄) 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 CgH₃N₅O₉ and C₇H₃N₅O₆, respectively. By increasing of the amount of HNO₃ 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 CH₂ group and the appearance of a distinct signal for a quaternary carbon atom in the ¹³C 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



The gem-dinitro compound 1c slowly decomposes at 35 °C to NO_x and the known⁷ 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 ¹⁵N NMR spectrum of 1c (now prepared using ¹⁵N enriched HNO₃) featured 3 signals in the ratio 1:1:2 at -16.13, -18.76 and -23.12 ppm respectively (relative to CH₃ ¹⁵NO₂ with DMSO-d6 as solvent). Heating of this solution indicated that a nitro-nitrite rearrangement⁸ 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 reported¹⁰ for the parent tetranitro compound (4a). Like 4a, compound 3/4b¹¹ formed a stable potassium salt which could be recrystalized from water.¹²



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 Honey⁶ via treatment of the oxime of salicylaldehyde with N₂O₄. 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 HNO₂, 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 Robinson¹³ who prepared the precursors 4,6-dinitro-2-nitromethylaniline (**7a**) and its *N*-acetyl derivative (**7b**) via a multi-step procedure. In the final step¹³ 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 applied¹⁶ on *N*-acetylindoline, (in this case yielding 3,5,7-trinitroindole).



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 HNO₃. Temperatures around 25-35 °C and HNO₃ 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. Ic 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; ¹³C 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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- 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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- 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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