

Note

Two new abnormal by-products of attempted Fischer-type bis-indolisation of cyclohexane-1,3-dione and dimedone

Manas Chakrabarty* & Archana Batabyal

Department of Chemistry, Bose Institute,
93/1, A.P.C. Road, Calcutta 700 009, India.

and

Amarendra Patra

Department of Chemistry, University of Calcutta,
92, A.P.C. Road, Calcutta 700 009, India.

Received 9 December 1997; accepted (revised) 8 June 1998

An attempt to bring about the bis-indolisation of cyclohexane-1,3-dione and dimedone separately by treatment with phenylhydrazine (two equiv.) in dry benzene in the presence of stoichiometric amounts (two equiv.) of phosphorous trichloride furnishes, besides the corresponding bis-(phenylhydrazones), the respective 2-oxo-bis(phenylhydrazones) as new by-products which have been identified by spectral analyses. A mechanism for the formation of the latter has been proposed.

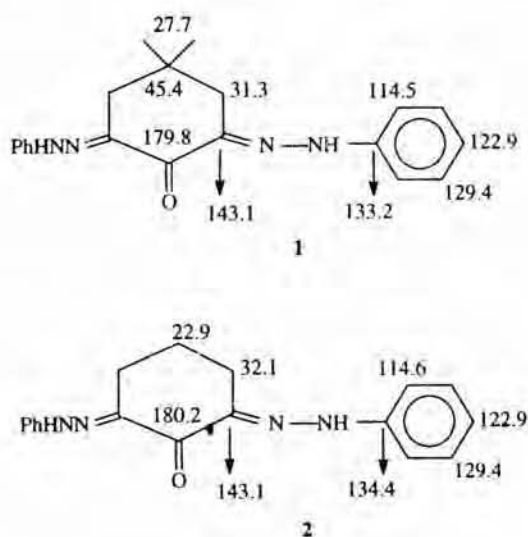
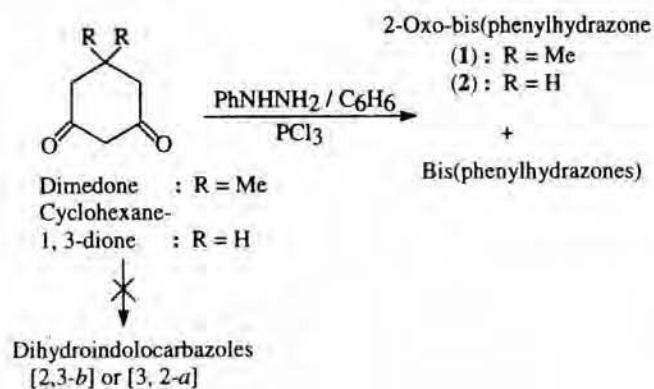
As a part of our ongoing programme on the synthesis of indolocarbazoles¹, the Fischer-type bis-indolisation reactions of cyclohexane-1,3-dione and dimedone were attempted by phosphorous trichloride — a reagent which had earlier been demonstrated by us to be effective for the indolisation of cyclohexanones to tetrahydrocarbazoles, hence carbazoles².

Accordingly, each of the substrates was treated in dry benzene with two equivalents each of phenylhydrazine and phosphorous trichloride. Usual work-up, followed by column chromatography (CC), furnished two products in each case. The more polar products were identified as the corresponding bis(phenylhydrazones) on the basis of their spectral data and by direct comparison with synthetic samples. The less polar product from dimedone, C₂₀H₂₂N₄O (HR EI-MS : M⁺ 334.1788), appeared to be different from the corresponding bis(phenylhydrazone) (FW 320), the two mono-indolisation products, phenylhydrazonocarbazoles (FW 303) and the two bis-indolisation products, dihydroindolocarbazoles (FW 286). Diagnostically, the appearance of two equivalent methylenes (δ_{H} 2.54, 4H, s) and a carbonyl

group (δ_{C} 179.8, s) besides the signal for the methyl (δ_{H} 1.09, 6H, s) in the NMR spectra of this product identified it as the 2-oxo derivative **1** of dimedone bis(phenyl-hydrazone). The derived structure was corroborated by mass spectral data.

Similarly, the less polar product from cyclohexane-1,3-dione, analysing for C₁₈H₁₈N₄O, was identified as the corresponding 2-oxo-bis(phenylhydrazone) **2** due to the absence of a methyl signal and the conspicuous appearance of an A₂X₄ spin system (δ 1.96, 2H, quintet and 2.72, 4H, t, $J = 6$ Hz, CH₂CH₂CH₂) and a carbonyl group (δ_{C} 180.2, s) in its ¹H and ¹³C NMR spectra, respectively. The mass spectral data of **2** were also in conformity with the assigned structure. The most likely ¹³C NMR assignments of both the 2-oxo components, derived by comparison with standard compounds, have been depicted in **Scheme I**.

Interestingly, both **1** and **2** lacked the carbonyl absorption bands in their IR spectra probably because the two phenylhydrazono NH protons are intramolecularly hydrogen-bonded to the carbonyl oxygen, which significantly lowers the carbonyl band. During monitoring of the reactions (TLC), one major and one minor products were observed to be formed in each case. These were later identified as the corresponding bis(phenylhydrazones) and their 2-oxo derivatives, respectively. But the isolated yields of the former were indeed slightly more than those of the latter. We presumed that the bis(phenylhydrazones) were the actual products which underwent autoxidation³ catalysed by silica gel of both TLC and CC grades used for chromatography. This assumption proved to be at least partially correct when the bis(phenyl-hydrazone) of each of the substrates was kept adsorbed on a silica gel column separately for a day and then eluted out. In each case, the 2-oxo derivative was isolated in significantly better yield (not further discussed in the Experimental). However, in the absence of quantitative studies, which was precluded by the instability of the bis(phenylhydrazones) in solutions, the formation of the 2-oxo derivatives additionally through other mechanisms can not be ruled out. For example, at least in one previous case of Fischer indolisation, phenylhydrazinium cation, formed *in situ*, reportedly acted as an oxidising agent, leading to altogether



Scheme I

different products, pyrazolocarbazoles⁴.

Both 2-oxo derivatives as well as their formation as by-products in attempted Fischer-type indolisation reactions have not been documented earlier. The observed failure to bring about the targeted bis-indolisations is not, however, entirely unexpected, since double-Fischer indolisations have been sometimes reported to be problematic⁵.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. NMR spectra (CDCl₃) were recorded on Bruker AM 300L (¹H : 300 MHz; ¹³C : 75 MHz; APT) and JEOL GSL-500 (¹H : 500 MHz; ¹³C : 125 MHz; DEPT 135) spectrometers, and LR and HREI-MS and CI-MS (NH₃) on Kratos AEI MS9, VG Tribid and JEOL DX 303 mass

spectrometers, respectively. CC was performed on silica gel (60-120 mesh, Qualigens, India) and TLC over silica gel G (E. Merck, India) plates. Elemental analyses were carried out at the Microanalytical Laboratory of the University of Calcutta, Calcutta. Petrol refers to pet. ether of bp 60-80 °C. Phosphorous trichloride, purchased from M/s Wilson Laboratories, Bombay was used as procured.

Attempted bis-indolisation: General procedure. PCl₃ (1 mL; 11 mmoles) was added dropwise with stirring to a solution of cyclohexanedione (5 mmoles) and PhNHNH₂ (1 mL; 10 mmoles) in dry benzene (60 mL) at room temperature. After stirring for 30 min, the mixture was poured into an excess of cold saturated aq. NaHCO₃, and the resulting solution extracted with benzene (3 x 100 mL). The benzene extract was washed free of alkali, dried (Na₂SO₄) and the solvent distilled off. The residue, a mixture of two products (TLC) in each case, was separated into its components by CC.

2-Oxo-dimedone bis(phenylhydrazone) 1: Eluted in petrol-EtOAc (99:1), red crystals (yield 0.31g, 18%), mp 162-164 °C (MeOH). Anal. Calcd for C₂₀H₂₂N₄O: C, 71.85; H, 6.58; N, 16.76%. Found: C, 71.79; H, 6.61; N, 16.82%; UV (EtOH): 213, 250, 290, 471 nm; IR (KBr): 3400 (br, NH) cm⁻¹; ¹H NMR (500 MHz) (additional data): δ 6.98-7.04 (4H, m) and 7.26-7.36 (6H, m, all Ar-H), 14.09 (2H, s, 2 x PhNH-N=); ¹³C NMR (125 MHz): see structure 1 in Scheme I; HR EI-MS: m/z 334.1788 (M⁺; 100%), 242 (8), 94 (13), 93 (97), 92 (66), 91 (87), 77 (33).

2-Oxo-cyclohexane-1,3-dione bis(phenylhydrazone) 2. Eluted in petrol-EtOAc (99:1), red crystals (yield 0.21g, 14%), mp 129-130 °C (MeOH). Anal. Calcd for C₁₈H₁₈N₄O: C, 70.58; H, 5.88; N, 18.3%. Found: C, 70.47; H, 5.90; N, 18.23%; UV (MeOH): 213, 250, 289 (sh), 475 nm; ¹H NMR (300 MHz) (additional data): δ 7.03 (4H, t, J = 6.5 Hz, 4x *o*-Ar-H), 7.2-7.6 (6H, m, 4 x *m*- and 2 x *p*-Ar-H), 14.0 (2H, s, 2 x NH); ¹³C NMR (75 MHz): see structure 2 in Scheme I; CI-MS (NH₃): m/z 307 (M+H; 100%), 216 (33), 94 (62), 93 (22).

The bis(phenylhydrazones) of dimedone (0.32 g, 20%) and cyclohexane-1,3-dione (0.235 g, 16%), both eluting out in petrol-EtOAc (19:1) as orange semi-solids, were identified by direct comparison (co-TLC and superimposable IR spectra) with authentic samples prepared following the literature procedure (EtOH / gl. AcOH)⁶. Both the compounds were also

identified on the basis of their UV, IR, ^1H NMR and EI-MS data.

Acknowledgement

The authors are thankful to Dr W Amrein, ETH, Zurich, Switzerland and Dr P Bladon, University of Strathclyde, Glasgow, UK for recording HR EI-MS, Dr T Pathak, Uppsala University, Uppsala, Sweden for CI-MS, Dr T Miyase, University of Shizuoka, Shizuoka, Japan for 500/125 MHz $^1\text{H}/^{13}\text{C}$ NMR spectra, and to the CSIR, New Delhi for the award of a research grant to MC and a fellowship to A B. They are also grateful to the authorities of Bose Institute, Calcutta for providing laboratory facilities.

References

- 1 Chakrabarty M & Batabyal A, *Synth Commun*, 26, **1996**, 3015.
- 2 Chakrabarty M, Batabyal A & Patra A, *Indian J Chem*, 31B, **1992**, 199.
- 3 Norman R O C & Coxon J M, *Principles of Organic Synthesis*, 3rd edn. (Blackie Academic & Professional, London), 1993, p.556.
- 4 Teuber H-J & Vogel L, *Chem Ber*, 103, **1970**, 3319.
- 5 Bergman J & Pelcman B, *J Org Chem*, 54, **1989**, 824.
- 6 Gardner P D, Haynes G R & Brandon R L, *J Org Chem*, 22, **1957**, 1206.