THE PREPARATION AND SOME REACTION OF 2,2-DIPHENYL-1-(3,6-DINITRO-4-COUMARINYL) HYDRAZYL FREE RADICAL.

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ABSTRACT

The new persistent 2,2-diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazyl free radical **4** was obtained by potassium permanganate or lead dioxide oxidation of the corresponding 2,2-diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazine **3**; hydrazine **3** reacts with nitrous acid to give successively the 2-(p-nitrophenyl)-2-phenyl-1-(3,6-dinitro-4-coumarinyl) hydrazine **6** and 2,2-(p-nitrophenyl)-1-(3,6-dinitro-4-coumarinyl) hydrazine **7**. Compound **6** results also from free radical **4** and sodium nitrite in the presence of 15-C-5 crown ether. The structure of new compounds was confirmed by means of TLC,UV-Vis,¹H-NMR, IR and for the free radicals by the EPR spectra.

RESUMO

O novo radical livre estável 2,2-difenil-1-(3,6-dinitro-4-cumarinil)hidrazila **4** foi obtido pela oxidação da 2,2-difenil-1-(3,6-dinitro-4-cumarinil) hidrazina correspondente **3** com permanganato de potássio ou dióxido de chumbo. A hidrazina **3** reage sucessivamente com ácido nítrico para formar a 2-(p-nitrofenil)-2-fenil-1-(3,6-dinitro-4-cumarinil) hidrazina **6** e a 2,2-(p-nitrofenil)-1-(3,6-dinitro-4-cumarinil) hidrazina **7**. O composto **6** também é formado pelo radical livre **4** e nitrito de sódio na presença do éter de coroa 15-C-5. A estrutura dos novos compostos foi confirmada por meio de cromatografia em camada delgada, ultravioleta, infravermelho, RMN de ¹H e de espectra de ressonância paramagnética de elétrons.

KEYWORDS : Free Radicals, Nitro-Coumarins, Diphenylhydrazines, Crown ethers.

INTRODUCTION

The first persistent free radical of hydrazyl type 2,2-diphenyl-1-picrylhydrazyl (DPPH) was synthesized by Goldschmidt and Renn¹ in 1922.

The interest of scientists for this substance and its analogues continues to receive attention due to their implications in diverse acid-base or redox processes (the generation or scavenger the short life radical species), applications in analytical chemistry, etc.²⁻⁸

In this paper we report the synthesis of a new hydrazyl-type free radical where the picryl moiety from DPPH was substituted with a heterocyclic ring, the 3,6-dinitrocoumarinyl respectively in order to investigate its chemical reactivity. It involves the reaction of 3,6-dinitro-4-chloro-2H-1-benzopyran-2-one⁹ **1** with 1,1-diphenylhydrazin hydrochloride¹⁰ **2** in the presence of an excess of NaHCO₃, in DMF or ethanol, to give 2,2-diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazin **3** (DPCH). This compound in the presence of PbO₂ or KMnO₄ suspended in dichloromethane or anhydrous acetone respectively, is transformed in 2,2-diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazyl **4** free radical (DPCH[•]).

EXPERIMENTAL

Melting points (uncorrected) were determined in open capillary. IR spectra were recorded in KBr pellet with an UR-20 apparatus. Thin-layer chromatography (TLC) was realized on silica gel Merck plates. Unidimensional technique and visualisation was done with iodine. The EPR spectra were recorded at room temperature on a JES-3B (JEOL) spectrometer with 100 kHz field modulation using the X-band frequency. The parameter of the EPR spectra were measured and compared with those of Fremy's salt ($a_N = 13.0$ G). UV-Vis spectral determination were performed with a Specord UV-Vis spectrophotometer. ¹H-NMR spectra were recorded on a Varian Gemini-300 MHz instrument in DMSO-d₆.

2,2-Diphenyl-1-(3,6-dinitro-4-coumarinyl) hydrazine 3

To 0.81 g (3 mmol) 3,6-dinitro-4-chloro-2H-1-benzopyran-2-one **1** in 8 mL DMF, 0.78 g (3.5 mmol) 1,1-diphenylhydrazine hydrochloride **2** and 0.63 g (7 mmol) NaHCO₃ were added and the reaction mixture was stirred at room temperature for two hours. The mixture was poured into 150 mL water. The precipitate was filtered off, washed with water and dried. The crude product (1.03 g 82.4 %) was recrystallized from ethanol or methanol to give yellow crystals with m.p. 170-171°. TLC R_f 0.63 (toluene-ethyl acetate 7:3 v/v). The substitution in this reaction, the DMF with ethanol or isopropanol, lowered yield and a more impure product was obtained. UV-Vis.(CH₂Cl₂) λ_{max} 344 nm (log ε = 3.94); in basic medium (treatment of CH₂Cl₂ solution with 0.01 M NaOH in methanol) the corresponding salt **5** has λ_{max} 444 nm (log ε = 4.00). IR (KBr cm⁻¹) 3255 (NH) 1730, 1690 (CO) 1610 (C=C) 1545, 1350 (NO₂); ¹H-NMR (δ ppm): 11.56(s, 1H, N-H); 9.48(d, 1H; J_{5,7}=2.39) 8.56(dd, 1H; H-7; J_{7,5}=2.33); 7.71(d, 1H; H-8; J_{8,7}=9.21); 7.38(t, 4H; H-11, H-13, H-17, H-19); 7.17(m, 6H; H-10, H-12, H-14, H-16, H-18, H-20). ¹³C-NMR(DMSO, δ ppm): 155.27(C=O); 112.86(C-3); 143.92(C-4); 116.60(C-4a); 121.04(C-5); 144.04(C-6); 128.33(C-7); 119.10(C-8); 154.85(C-8a); 145.52(2C, C-9, C-15); 119.99(4C, C-10, C-14, C-16, C-20); 129.01(4C, C-11, C-13, C-17, C-19); 124.51(2C, C-12, C-8). Anal. Calcd. for C₂₁H₁₄O₆N₄(418.37) found: N, 13.2(calcd. N, 13.38)

2,2-Diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazyl free radical 4

Ten milligrams (0.024 mmol) of compound **3** were oxidized by stirring in 20 mL anhydrous dichloromethane or anhydrous acetone solution with an excess of KMnO₄ (0.1 g 0.63 mmol) or PbO₂. The color of the reaction mixture changed from yellow to violet. Inorganic compounds were then filtered off. The filtrate is adequately stable for physical measurements or some chemical reactions. EPR spectra (Fig.1) UV-Vis (CH₂Cl₂) λ_{max} 515 nm. The violet solution of free radical **4** passes easily to hydrazine **3** (evinced by TLC) by stirring it for five minutes with 5 % aqueous ascorbic acid.

2-(p-Nitrophenyl)-2-phenyl -1-(3,6-dinitro-4-coumarinyl) hydrazine 6

Method A. To 0.2 g (0.48 mmol) **3** in 75 mL dichloromethane were added 1 g (14.5 mmol) of sodium nitrite. Then were added with stirring during five minutes at room temperature 75 mL HCl 1 M. The organic layer was washed with water and dried over anhydrous sodium sulphate. The solvent was removed and 0.16 g (72.7 %) **6** crude product results. After preparative TLC or recrystallization from 7:3 toluene / ethyl acetate the yellow-brown product has m.p. 165-166°. TLC R_f 0.18 (CH₂Cl₂ - ethanol 9.5 : 0.5). UV-Vis (CH₂Cl₂) λ_{max} 308 nm (log ε = 4.03). In basic medium the corresponding salt, λ_{max} 435 nm (log ε = 4.20). IR (KBr cm⁻¹) : 3240 (NH) 1710 (CO) 1615 (C=C) 1540, 1350 (NO₂). ¹H-NMR (δ ppm) 11.42(s, 1H, N-H); 7.75-9.52(m, 3H, H-5, H-7, H-8); 7.2-7.56(m, 9H, H-10, H-11, H-13, H-14, H-16, H-17, H-18, H-19, H-20). Anal. Calcd. for C₂₁H₁₃O₈N₅(463.37) found: N, 14.9(calcd. N, 15.10)

Method B. To a solution of 4 free radical in dichloromethane, obtained from 20 mg (0.048 mmol) compound 3, 100 mg (0.45 mmol) 15-C-5 crown ether and 80 mg (1.16 mmol) sodium nitrite were added. After two hours of stirring at room temperature (the colour changed to redish-brown) the reaction mixture was filtered. The filtrate was washed with water and with HCl 1 M and then dried over anhydrous sodium sulphate. The TLC and UV-Vis analysis proved the presence of compound 6.

2,2- (p-Nitrophenyl)- 1 - (3,6-dinitro-4-coumarinyl) hydrazine 7

To 0.2 g (0.48 mmol) compound 3 in 75 mL dichloromethane were added 75 mL HCl 1 M. Then were added in portions, with stirring, during a period of two hours 1.5 g (21.74 mmol) of sodium nitrite. The stirring was continued at room temperature for 24 hours. The dichloromethane layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was removed and 0.2 g (83.3 %) 7 were obtained. After crystallization from ethanol, the yellow product had m.p. 204-205°. TLC R_f 0.09 (CH_2Cl_2 - ethanol 9.5 : 0.5).

UV-Vis (CH_2Cl_2) $\lambda_{\max}$ 356 nm ($\log \epsilon = 3.57$). In basic medium the corresponding salt, $\lambda_{\max}$ 459 nm ($\log \epsilon = 3.70$). IR (KBr cm^{-1}) : 3260 (NH) 1695 (CO) 1620 (C=C) 1530, 1345 (NO_2). $^1\text{H-NMR}$ (δ ppm): 11.39(s, 1H; N-H); 9.29(d, 1H; H-5; $J_{5,7}=1.8$); 8.54(dd, 1H; H-7; $J_{7,8}=9$; $J_{7,5}=1.9$); 7.84(d, 1H; H-8; $J_{8,7}=8.90$); 7.18(d, 4H; H-10, H-14, H-16, H-20; $J=7.92$); 8.5(d, 4H; H-11, H-13, H-17, H-19; $J=7.92$).

Anal. Calcd. for $\text{C}_{21}\text{H}_{12}\text{O}_{10}\text{N}_6$ (508.37) found: N, 16.21 (calcd. N, 16.52).

Oxidation of compounds 6 and 7 to the corresponding free radicals 8 and 9.

The 2- (p-nitrophenyl) - 2 - phenyl -1 - (3,6 -dinitro -4 -coumarinyl) hydrazyl free radical 8 and 2,2 - (p - nitrophenyl) - 1 - (3,6 - dinitrocoumarinyl) hydrazyl free radical 9, was synthesised from corresponding hydrazines 6 and 7 with KMnO_4 or PbO_2 as described for the preparation of free radical 4. EPR spectra (Fig.1) UV-Vis (CH_2Cl_2) $\lambda_{\max}$ 507 nm for 8 and $\lambda_{\max}$ 502 for the free radical 9 .

Fig.1 The EPR spectra of the 4,8 and 9 free radicals

RESULTS AND DISCUSSION

2,2-Diphenyl-1-(3,6-dinitro-4-coumarinyl)hydrazyl free radical is stable in solution for 24 hours ; it was not obtained in solid state and the characteristic violet colour for the radical solution in dichloromethane ($\lambda_{\max}$ 515 nm) slowly became yellow-brown, losing its EPR signal. The EPR spectrum is similar with DPPH $\cdot$ (5 lines $a_{N(2)} = 9.0$ G). DPCH $\cdot$ passes easily to hydrazine 3 ($\lambda_{\max}$ 344 nm) by stirring it with an aqueous ascorbic acid solution. The hydrazinic hydrogen in 3 shows an acid character (especially influenced by -NO $_2$ group from position 3 in the coumarinic ring) confirmed by reaction with alkaline hydroxide in ethanol (the same behaviour like DPPH)^{11,12}

The reaction is accompanied by the colour change of the reaction mixture from yellow ($\lambda_{\max}$ in dichloromethane, 344 nm) to red ($\lambda_{\max}$ 444 nm), corresponding to salt 5. Similarly to DPPH $\cdot$ ^{8,13}, the $\cdot$ NO $_2$ radical reacts with 3 or 4 to give a tri and tetranitro hydrazines mixture 6 and 7, which were separated by TLC and identified :

Their oxidation with PbO $_2$ or KMnO $_4$ leads to the corresponding free radicals confirmed "in situ" by EPR.(Fig.1)

The substances 6 and 7 were also obtained from dichloromethane solution of salt 5, by NO $_2$ bubbling that leads first to compound 4, which traps NO $_2$ in excess giving the corresponding substituted nitrohydrazines :

Some Reactions of Nitrocoumarins

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DPCH[•] is a good radical scavenger. The reaction of DPCH[•] or the corresponding hydrazine DPCH with sodium nitrite in the presence of 15-C-5 crown ether affords the selective formation of 2-phenyl-2-(p-nitrophenyl)-1-(3,6-dinitro-4-coumarinyl)hydrazine **6**. The mechanism may be represented as follows:

i) The electron transfer reaction:

Due to DPCH[•] 4 high hydrophobicity, it is necessary to transport the nitrite anion from the solid phase to organic phase (CH₂Cl₂) as a supramolecular complex (15-C-5...Na)⁺NO₂⁻ consequently:

ii) The persistent free radical **4** reacts with the supramolecular complex yielding the nitro free radical NO₂[•]:

iii) The nitro free radical generated in this way, is trapped by the excess of radical **4** forming compound **6**:

2-(p-Nitrophenyl)-2-phenyl-1-(3,6-dinitrocoumarinyl)hydrazine **6** was confirmed by TLC, and after the separation and oxidation, the presence of the corresponding free

radical **8** was proved by EPR "in situ". A similar behaviour was also observed for DPPH¹⁴.

The compounds **6** and **7** can be prepared also from **3** with nitrous acid at the room temperature. The reaction proceeds if sodium nitrite is added to the biphasic system containing **3** dissolved in dichloromethane and dilute hydrochloric acid (aqueous phase). After shaking well for 5 min. compound **6** is formed (yield 70 %). A larger contact time (24 h stirring) yields substance **7** (yield about 70 %). This method is simple and efficient for the selective synthesis of the compounds **6** and **7** respectively. Nitrous acid generated in this reaction probably comes from nitrogen oxides. Nitrogen dioxide will be generated *via* oxidation of the hydrazyl radicals which finally will go to compounds **6** and **7** respectively. In conclusion, DPCH can participate both in proton and electron transfer reactions depending on the reaction partners. Compounds **3**, **6** and **7** have acid character and show different distributions in the biphasic system water - organic solvent, depending on aqueous state pH. The extraction yields of compounds **3**, **6** and **7** in buffered aqueous solution / dichloromethane 1:1 (v/v)- obtained in the dichloromethane phase are given as mass percent :

Compounds	pH 7	pH 9	pH 11 (Titrisol Merck)
3	0	8	44
6	0	53	81
7	63	87	95

It can be observed that the extractions are more efficient at high pH and the yields increase with increasing acidity of the hydrazine derivative, (due to additional nitro groups) the order being **3** < **6** < **7**

CONCLUSIONS

The hydrazines **3**, **6** and **7** were synthesised and characterised by TLC, UV-Vis, IR, ¹H-NMR and EPR (after oxidation to the corresponding hydrazyl-free radicals).

The substitution of the picryl-moiety by 3,6-dinitrocoumarinyl one affords hydrazines with same chemical behaviour but the corresponding free radicals are less stable, having shorter life-times comparing to DPPH.

Of the set of hydrazyl free radicals described here, the unsubstituted one DPCH, appears to be the most stable.

The syntheses of mono and dinitro derivatives of DPCH involved interphase processes with NO₂ as homolytical reagent.

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