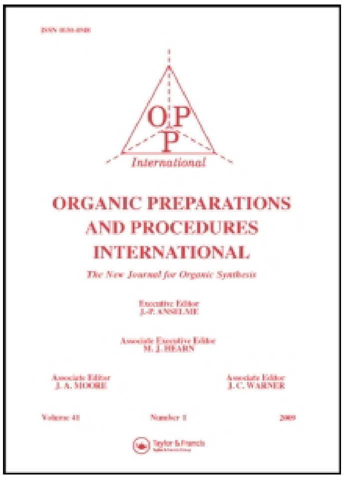

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SYNTHESIS OF NITROXYL DERIVATIVES OF BENZO[a]PYRENE

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SYNTHESIS OF NITROXYL DERIVATIVES OF BENZO[a]PYRENE

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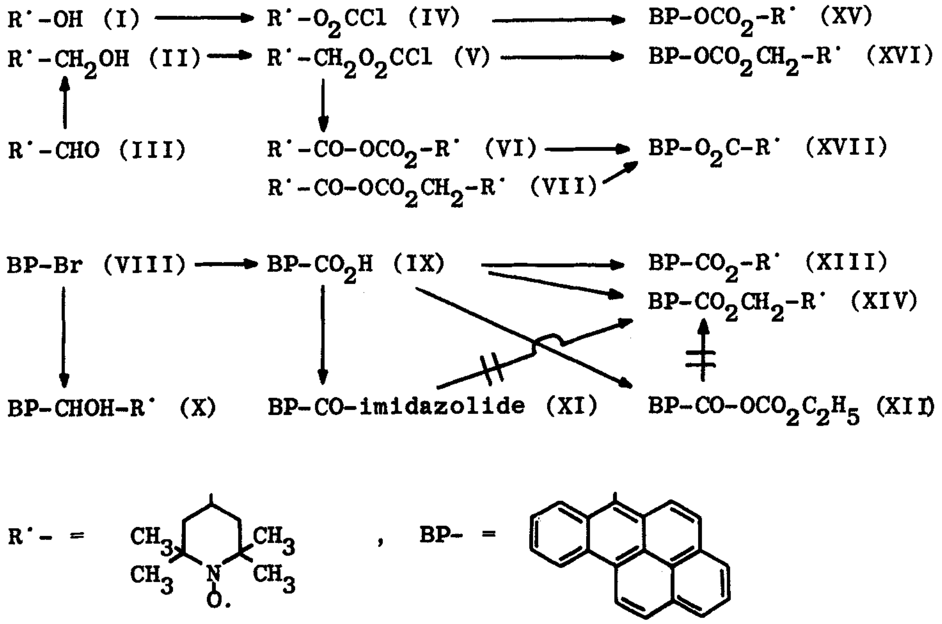
Benzo[a]pyrene (BP) derivatives with different functional groups at the 6-position have been used to influence the reactivity of this carcinogenic hydrocarbon.[1] Since the interaction of BP derivatives with deoxyribonucleic acid[2] has not yet been demonstrated by the spin labeling method, the synthesis of suitable compounds (X, XIII-XVII) has been developed and is reported now in this work.



The new chloroformate (IV, V) and anhydride (VI, VII) nitroxyl radicals might be of interest for other examples of spin labeling. All compounds synthesized gave the m/e signals for M^+ in the mass spectra. The non-radical derivatives IX, XI, and XII gave the expected NMR spectra (in d_6-DMSO or in $CDCl_3$). The new radicals showed the nitroxyl three-line spectra in ESR (in $CHCl_3$) with a_N= 16 Gauss. Only diradical VII gave weak spin-spin interaction.

EXPERIMENTAL

All mps. are uncorrected. The elemental analyses were obtained from Alfred Bernhardt, D-5251 Elbach and from Ilse Beetz, D-8640 Kronach.

4-Hydroxymethyl-2,2,6,6-tetramethylpiperidine-1-oxyl (II).-To a mixture of the aldehyde III[3] (1.84g, 10 mmol), ether (40 ml) and 0.5 M aqueous dipotassium phosphate (40 ml) was added sodium borohydride (380mg, 10 mmol). The mixture was stirred for 2 hrs, the aqueous phase extracted with ether (2x15 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give 1.65g (89%) orange product, mp. 117-119° (after resublimation at 65°/0.001 Torr).

Anal. Calcd for $C_{10}H_{20}NO_2$: C, 64.48; H, 10.82; N, 7.52.
Found: C, 64.29; H, 10.78; N, 7.50.

4-Chlorocarboxy-2,2,6,6-tetramethylpiperidine-1-oxyl (IV) and 4-Chlorocarboxymethyl-2,2,6,6-tetramethylpiperidine-1-oxyl (V). - To a mixture of the alcohol I[4] (1.72g, 10 mmol) or II (1.86 g, 10 mmol) and pyridine (0.79ml, 10 mmol) in benzene (50 ml) was added a 0.4 M solution of phosgene in benzene (75 ml, 30 mmol). The solution was stirred for 3 hrs, then filtered and evaporated at 30°, the residues were sublimed, giving 1.62g

(69%) IV as red crystals, mp. 60-61° (after resublimation at 45°/0.01 Torr).

Anal. Calcd for $C_{10}H_{17}ClNO_3$: C, 51.17; H, 7.30; Cl, 15.11; N, 5.97. Found : C, 50.96; H, 7.10; Cl, 14.92; N, 5.83.

Equally obtained were 1.32g (53%) V as red crystals, mp. 49° (after resublimation at 35°/0.001 Torr).

Anal. Calcd for $C_{11}H_{19}ClNO_3$: C, 53.11; H, 7.70; Cl, 14.26; N, 5.63. Found : C, 53.02; H, 7.80; Cl, 14.51; N, 5.65.

4-Carboxy(2,2,6,6-tetramethyl-1-oxo-piperidyl)-4'(2',2',6',6'-tetramethyl-1'-oxo-piperidyl)-carbonate (VI) and 4-Carboxy(2,2,6,6-tetramethyl-1-oxo-piperidyl)-4'-methyl(2',2',6',6'-tetramethyl-1'-oxo-piperidyl)-carbonate (VII).- A mixture of 2,2,6,6-tetramethyl-1-oxo-piperidine-4-carboxylic acid[3] (200 mg, 1 mmol), chloroformate IV (234mg, 1 mmol) or V (248mg, 1 mmol), benzene (13 ml), and triethylamine (140 µl, 1 mmol) was stirred for 20 hrs. The solvent was evaporated, the residue was extracted and washed on filtration with benzene (13 ml). Hexane (60-100 ml) was added to the filtrate to give after 3 days at 4° 255mg (64%) red crystals VI, mp. 140-141° (after recrystallisation from benzene/hexane).

Anal. Calcd for $C_{20}H_{34}N_2O_6$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.48; H, 8.51; N, 6.99.

Equally obtained were 297mg (72%) carbonate VII as red crystals, mp. 130-132° (after recrystallisation from benzene/hexane.

Anal. Calcd for $C_{21}H_{36}N_2O_6$: C, 61.14; H, 8.80; N, 6.79. Found: C, 61.34; H, 8.72; N, 6.74.

Metalation of 6-bromo-benzo[a]pyrene (VIII).- The bromo compound VIII[5] (3.31g, 10 mmol) was dissolved in benzene (200ml) by heating, the clear solution was cooled to 45°, 1.2 M phenyllithium in ether (10 ml, 12 mmol) was added and the mixture was stirred under nitrogen at 40° for 3 hrs.

6-Benzo[a]pyrenyl-carboxylic-acid (IX).- The solution of metalated VIII was poured into a mixture of solid carbon dioxide and ether (100 ml). After 16 hrs at room temperature, the solvents were evaporated and the residue was suspended in xylene (600 ml). Hydrogen chloride was passed through the suspension on heating to reflux temperature. After 30 min refluxing, the solution was filtered through a preheated glass filter and cooled, giving 1.54g (52%) of the acid IX as a yellow powder, mp. 243° (dec.)(after recrystallisation from xylene).

Anal. Calcd for $C_{21}H_{12}O_2$: C, 85.12; H, 4.08.
Calcd for $C_{21}H_{12}O_2 \cdot 1/4\ H_2O$: C, 83.84; H, 4.19.
Found: C, 83.94; H, 4.32.

A sample of the acid IX (296mg, 1 mmol) decarboxylated to BP on heating for 5 min at 255°. Chromatography with chloroform on alumina (10g, basic, activity III) yielded on evaporation of the solvent 227mg (90%) BP, identical with an authentical sample (in mixed mp. and IR spectrum). This acid IX had not been accessible by hydrolysis of its amide.[6]

6-Benzo[a]pyrenyl-4'(hydroxymethyl-2',2',6',6'-tetramethylpiperidine-1'-oxyl)(X).- The solution of metalated VIII was added in 5 min at 30° to a solution of the aldehyde III (1.84g, 10 mmol) in benzene (100 ml). After 16 hrs at 25°, the solution was extracted with water (2x100 ml), dried with $MgSO_4$ and evaporated. Chromatography with chloroform on alumina (500g, basic, activity IV) yielded as the first fraction 0.7g (28%) BP and as a second fraction 2.15g (49%) of product X. Recrystallisation (by heating with chloroform/ethanol (1/1) and addition of hexane to the clear solution) gave a yellow powder, mp. 243° (dec.).

Anal. Calcd for $C_{30}H_{30}NO_2$: C, 82.54; H, 6.93; N, 3.21.
Found: C, 82.17; H, 6.86; N, 3.22.

6-Benzo[a]pyrenyl-carboximidazolide (XI).- A mixture of the acid IX (888mg, 3 mmol), benzene (30 ml), and thionyl chloride (1 ml, 14 mmol) was refluxed for 45 min. The solvent was evaporated, imidazole (1g, 13 mmol) and tetrahydrofuran (30 ml) were added. The solution was refluxed for 16 hrs, then chloroform (60 ml) was added. The solution was extracted with N hydrochloric acid (3x25 ml), dried (Na_2CO_3), and the solvents were evaporated. The residue was dissolved in chloroform (30 ml), and methanol (250 ml) was added. A non-crystalline precipitate was immideately removed by filtration. After 3 days at 4°, 659mg (63%) brown crystals (XI) were obtained, mp. 230° (after recrystallisation from tetrahydrofuran/methanol).

Anal. Calcd for $C_{24}H_{14}N_2O$: C, 83.22; H, 4.07; N, 8.09.
Found: C, 83.35; H, 4.01; N, 8.15.

Heating of this imidazolide XI with the alcohols I or II for 24 hrs in tetrahydrofuran left all compounds unchanged.

6-Benzo[a]pyrenyl-carboxy-ethyl-carbonate (XII).- To a mixture of the acid IX (1.0g, 3.4 mmol), benzene (50 ml), and ethyl chloroformate (0.5 ml, 5.3 mmol) was added triethylamine (0.7 ml, 50 mmol) in 20 min with stirring. The solution was stirred for 1 hr, then filtered, the solvent was evaporated, the residue was extracted and washed on filtration with benzene (10 ml). Hexane (60 ml) was added, giving after 24 hrs at 4° 822mg (65%) XII as brown crystals, mp. 107° (after recrystallisation from benzene/hexane).

Anal. Calcd for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38.
Found: C, 78.22; H, 4.22.

Heating of this carbonate XII with the alcohols I or II for 24 hrs in tetrahydrofuran gave decomposition products of XII only.

6-Benzo[a]pyrenyl-carboxylic-acid-4'(2',2',6',6'-tetramethyl-1'-oxo-piperidyl-)ester (XIII) and 6-Benzo[a]pyrenyl-carboxylic-acid-4'-methyl(2',2',6',6'-tetramethyl-1'-oxo-piperidyl-) ester (XIV).- A mixture of the acid IX (300mg, 1 mmol), benzene (70 ml), and thionyl chloride (3.6 ml, 50 mmol) was refluxed for 90 min. The solvent was evaporated, the residue was dissolved in benzene (50 ml), pyridine (7.9 ml, 100 mmol) and the alcohol I (206mg, 1.2 mmol) or II (223mg, 1.2 mmol) were added. The solution was stirred for 60 min at 75°, then the solvents were evaporated at 40°. Chromatography of the residue with chloroform on alumina (30g, basic, activity III) and crystallisation from benzene (10 ml)/hexane (80 ml) gave after 16 hrs at 4° 280mg (62%) brown crystals XIII, mp. 177° (after recrystallisation from ethanol and subsequent recrystallisation from chloroform/hexane).

Anal. Calcd for $C_{30}H_{28}NO_3$: C, 79.97; H, 6.26; N, 3.11.
Found: C, 79.29; H, 6.08; N, 2.84.

Equally obtained were 250mg (54%) XIV as brown crystals, mp. 151-152° (after recrystallisation from n-propanol and subsequent recrystallisation from benzene/hexane).

Anal. Calcd for $C_{31}H_{30}NO_3$: C, 80.14; H, 6.51; N, 3.02.
Found: C, 80.32; H, 6.60; N, 2.84.

6-Benzo[a]pyrenyl-4'(2',2',6',6'-tetramethyl-1'-oxo-piperidyl-) carbonate (XV), 6-Benzo[a]pyrenyl-4'-methyl(2',2',6',6'-tetramethyl-1'-oxo-piperidyl-)carbonate (XVI), and 2,2,6,6-Tetramethyl-1-oxo-piperidyl-4-carboxylic-acid-6'-benzo[a]pyrenyl-ester (XVII).- 6-Acetoxy-benzo[a]pyrene[7] (310mg, 1 mmol) was dissolved in tetrahydrofuran (15 ml), 1.2 M phenyllithium in ether (1 ml, 1.2 mmol) was added, and the mixture was stirred under nitrogen for 1 hr at room temperature. The chloroformate IV (352mg, 1.5 mmol) or V (373mg, 1.5 mmol) or the anhydride VI (598mg, 1.5 mmol) or VII (619mg, 1.5 mmol) was added and the suspension was stirred for 16 hrs. The solvent was evaporated and the residue chromatographed with benzene on alumina (80g, acid, activity III) and crystallized from methanol with the use of carboraffin to give 360mg (77%) XV as brown crystals, mp. 208° (dec.)(after recrystallisation from methanol.

Anal. Calcd for $C_{30}H_{28}NO_4$: C, 77.23; H, 6.05; N, 3.00.
Found: C, 76.76; H, 6.05; N, 2.98.

The yield of XVI was 334mg (69%) brown crystals, mp. 166-167° (dec.)(after recrystallisation from methanol).

Anal. Calcd for $C_{31}H_{30}NO_4$: C, 77.47; H, 6.29; N, 2.91.
Found: C, 77.08; H, 6.28; N, 2.84.

From VI were obtained 270mg (60%) of product XVII, from VII were obtained 338mg (75%) XVII, as a yellow powder, mp. 228^{o} (dec.)(after recrystallisation from methanol).

Anal. Calcd for $C_{30}H_{28}NO_3$: C, 79.97; H, 6.26; N, 3.11.
Found: C, 79.75; H, 6.26; N, 3.04.

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