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Reactions of Diapocarotenals with *N*-Bromosuccinimide and Synthetic Applications

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The allylic alcohols 8,8′-diapo-20-hydroxycarotene-8,8′-dial (*4*), 8,8′-diapo-20,20′-dihydroxycarotene-8,8′-dial (*5*), and 12,12′-diapo-20-hydroxycaroten-12,12′-dial (*12*) are described for the first time. Their preparation from the corresponding diapocarotenals crocetindial (*1*) and 12,12′-diapo-12,12′-dial (*10*) by *N*-bromosuccinimide (NBS) treatment *via* the corresponding bromides 8,8′-diapo-20-bromocarotene-8,8′-dial (*2*), 8,8′-diapo-20,20′-dibromocarotene-8,8′-dial (*3*), and 12,12′-diapo-20-bromocarotene-12,12′-dial (*11*) has been investigated.

The acetates 8,8′-diapo-20-acetoxycarotene-8,8′-dial (*6*), 8,8′-diapo-20,20′-diacetoxycarotene-8,8′-dial (*7*), and 12,12′-diapo-20-acetoxycaroten-12,12′-dial (*13*) represent useful intermediates for the synthesis of cross-conjugated carotenals.

On the basis of previous experience with NBS-treatment of carotenoids, the reaction of NBS with crocetindial was expected to give either the acetylenic analogue or to result in allylic subsitution.[1–3] Preliminary studies revealed that such treatment resulted in allylic substitution in the 20-position, providing a useful intermediate in the synthesis of the cross-conjugated carotenals of the rhodopinal series.[4,5]

The aim of the present project was to study in more detail the reaction of NBS with diapocarotenals, and to characterize further the primary products and derivatives thereof, suitable as intermediates in the synthesis of more stable C_{40} cross-conjugated carotenals.

RESULTS AND DISCUSSION

Treatment of crocetindial (*1*) with NBS in ethanol-free chloroform gave the rather unstable bromide *2*, judged by chromatographic data, electronic and mass spectra. As a minor product was obtained the unstable dibromide *3*, directly transferred to and identified as the diol *5*. Proof of dominant (if not exclusive) bromine substitution in 20,20′-position rather than in the 19,19′-methyl groups comes from the ^1H NMR spectra of the diol *5* and the diacetate *7*. One signal only at δ 1.85 (d_5-pyridine) and δ 1.93 ($CDCl_3$), respectively, was observed for the methyl groups, integrating for 6 protons.

In mixture with the dibromide *3* was presumably some 8,8′-diapo-20,20′-dibromocarotene 8,8′-dial (*3b*), judged by the loss of Br_2 from the molecular ion on electron impact. On subsequent derivatization was isolated an additional unreactive product (*3c*) of the same polarity as *3*, but with more hypsochromically displaced electronic spectrum, and for which no mass spectrum could be obtained.

Hydrolysis of the bromides *2* and *3* was accomplished by treatment with silver acetate or deactivated alumina. In small scale test reactions the silver acetate catalyzed hydrolysis afforded some of the acetates *6* and *7*, but the main batch gave the alcohols *4* and *5* and practically no acetates. Alkaline hydrolysis of the monobromide *2* gave unsatisfactory results. Thus treatment of *2* with 10 % KOH in methanol and ether (1:1) gave the methyl ether *8* as the only product. Moist ether or dioxane, or a two-face system with THF-ether (1:1) and 10 % aqueous K_2CO_3 did not seem to attack the bromide *2*, *cf.* Ref. 2, whereas treatment with dioxane – 10 % aqueous KOH (1:1) and dioxane – 10 % aqueous K_2CO_3 (4:1) gave con-

version to the alcohol *4*, albeit with low pigment recovery.

In preparative work conversion of the relatively unstable bromide to the alcohol was generally effected without isolation of the bromide, also because the alcohol was more readily separated from the starting material *1*.

Presence of acetic acid during the NBS-reaction [2] gave predominantly bromide and only trace amounts of the acetate *6*. Acetylation of the alcohols *4* and *5* with acetic anhydride in pyridine provided the acetates *6* and *7* in quantitative yield. Oxidation of the mono-ol *4* to the trial *9* was quantitatively effected with activated MnO_2,[6] while oxidation with NiO_2 [7,8] and DDQ [9,10] gave less satisfactory results.

On the basis of the reaction between crocetindial (*1*) and NBS which almost exclusively gave bromination in the central methyl group, one might expect that the carbonyl groups have some directive influence. If the C_{10}-dial *10* exhibits the same influence from the carbonyl groups, this compound should not be brominated. However, it suffered bromination, but much slower than crocetindial (*1*). Allylic bromination by NBS is considered to be a radical reaction.[11,12] It has been shown that addition of a radical initiator like benzoyl peroxyde [13] or azodiisobutyronitrile [14] promotes the reaction in cases where the normal conditions give unsatisfactory results. Addition of small amounts of benzoyl peroxide gave slightly higher yield of the bromide *11* (from 6 to 11 % at 50 °C and with four times excess of NBS), while addition of azodiisobutyronitrile did not increase the yield of *11*.

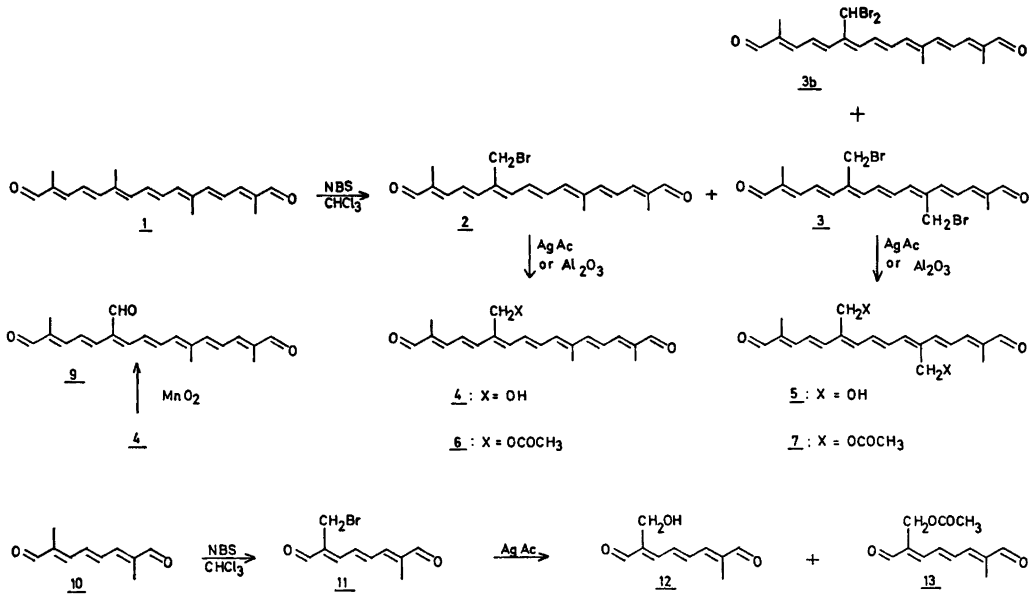
The bromide obtained (*11*) seemed to be much more resistent towards hydrolysis, than *2* and *3*, but hydrolysis to *12* could be effected with silver acetate in a mixture of ether-THF-water.

The acetates *6*, *7*, and *13* are considered useful intermediates for the preparation of apocarotenals by Wittig condensation of the aldehydes with appropriate phosphoranes, followed by hydrolysis of the acetate and allylic oxidation, in principle as for the oxidation of *4* to *9*. Thus the preparation of stable cross-conjugated C_{40}-carotenals like renierapurpurin-20-al from the acetate *6* has been carried out.[15]

The stereochemistry of the new compounds described (*4* – *9*) will be discussed separately.[16] For convenience only *trans*-configuration of the polyene chain is given in Scheme 1.

EXPERIMENTAL

Materials and methods. These were as described elsewhere.[17] Relative R_F-values on TLC



Scheme 1.

(silica gel G) were as follows: *1* > *2* = *8* > *3* = *6* > *7* > *4* > *5* and *10* > *11* > *13* > *12*.

Yields were calculated on the basis of extinction coefficients: *E* (1 %, 1 cm = 3 200 for C_{10}-dial (*10*) and derivatives, *E* (1 %, 1 cm) = 3 300 for crocetindial (*1*), *E* (1 %, 1 cm = 3 000 for derivatives of *1* in cases where crystallization was not effected and individual determination of extinction coefficients not determined. Due to the ready *trans-cis* isomerization extinction coefficient for crystalline and dissolved materials differ and calculation of yields are approximate.

NBS-reaction with crocetindial (*1*). Introductory experiments: Crocetindial (*1*, 1 equiv. in ethanol-free chloroform was added to a suspension of NBS (1 equiv.) in ethanol-free chloroform and the mixture stirred at 50 °C for 4 h. Chromatography on silica gel G (25 % acetone in petroleum ether = 25 % APE) gave in order of decreasing R_F-values recovered crocetindial (*1*, 15 – 25 %), 8,8′-diapo-20-bromocarotene-8,8′-dial (*2*, 70 – 80 %), 8,8′-diapo-20,20′-dibromocarotene-8,8′-dial (*3*) in mixture with tentatively other dibromo products (5 – 10 %) and 8,8′-diapo-20-hydroxycarotene-8,8′-dial (*4*, 4 – 6 %). Impure *3* had λ_{max} (acetone) *441* and 465 nm (most intense maximum is italicized), *m/e* (210 °C) 456, 454, and 452 (M, 1.5, 3.2, and 1.7 %, respectively), 375 and 373 (M – Br, both 3.5 %), 294 (M_{3b} – Br_2, 2.4 %) and 83 (100 %).

The reaction was tested with addition from very little to large excess of acetic acid. Judged by TLC and mass spectra, some, but very little, of the monoacetate *6* was obtained in mixture with the tentatively dibrominated material, in addition to the monobromo derivative *2*, the hydrolysed product *4*, and unreacted *1*.

Uncoloured reaction products were not searched for.

Substitution of bromides 2 and 3. The monobromide (*2*) was treated with ether – 10 % KOH in methanol (1:1) at room temperature for 2½ h. This gave 8,8′-diapo-20-methoxy-8,8′-dial (*8*); 43 % after purification by TLC.

The following reactions were carried out without isolation of the bromides *2* and *3* from the NBS product mixture above: The product mixture in THF – ether – 10 % aqueous K_2CO_3 (1:1:1), stirred at room temperature for 24 h, did not give any conversion of *2* to *4*. The pigment recovery was 91 % before chromatography. Treatment with 5 % KOH in dioxane – water (1:1) gave after 4 min 13 % pigment recovery. TLC showed low yield of the alcohol *4*. The NBS product mixture in dioxane-10 % aqueous K_2CO_3 (4:1) kept at room temperature for 24 h gave 27 % pigment recovery before chromatography. TLC on kieselgel G gave the bromide *2* (2.1 % of starting crocetindial) and the alcohol *4* (6.8 %) in addition to recovered crocetindial (*1*) and minor products not further investigated.

The NBS product mixture in benzene stirred with neutral or basic alumina (grade III) for 5 min gave satisfactory conversion of *2* to the alcohol *4* (see below).

The NBS product mixture in THF-ether (1:1), treated with an aqueous suspension of silver acetate gave conversion of the bromides *2* and *3* to the corresponding alcohols *4* and *5* in mixture with their acetates *5*-monoacetate, *6*, and *7* (see below).

The fraction containing the dibromide *3* treated as above with silver acetate for 15 h gave after TLC on silica gel G (35 % APE) mixed alcohols and acetates in addition to tentatively unreacted material. The tentatively unreacted material (*3c*) exhibited λ_{max} (acetone) 357, *434*, and 459 nm. The mass spectrum could not be obtained (temperatures from 140 to 210 °C).

NBS-reaction of crocetindial (1) followed by hydrolysis. From the above experiments the following two procedures were developed:

(*a*) Crocetindial (*1*, 400 mg) in ethanol-free chloroform (70 ml) was added to a suspension of NBS (240 mg) in ethanol-free chloroform (20 ml) and the mixture stirred at 50 °C. The reaction, which was repeated several times and monitored by TLC, gave after 4 h 70 – 80 % conversion to bromides and 95 – 100 % pigment recovery. The mixture was diluted with benzene (500 ml), neutral Al_2O_3 grade III [18] (100 g) added and the mixture stirred for 5 min. The Al_2O_3 was removed by filtration and washed with benzene and methanol. The solvents were evaporated, and the pigments chromatographed on a silica gel column, eluted with APE. This gave recovered crocetindial (*1*, 87.8 mg, *E* (1 %, 1 cm) = 3 360 in acetone) and 8,8′diapo-20-hydroxycarotene-8,8′-dial (*4*, 85.0 mg, 20 %).

(*b*) Crocetindial (*1*, 2.40 g) was treated as above with NBS (1.44 g). The reaction mixture was filtered, the chloroform removed, and the residue dissolved in THF-ether (1:1, 1 l). Due to solubility problems, the pigment was first partly dissolved in hot THF, and then diluted with ether. Some undissolved pigment remained. By addition of water (200 ml) a two-face system was obtained. Silver acetate (420 mg) was added, and the suspension stirred until all bromide was transferred to alcohol (*ca.* 6 h). Co-chromatography test showed that only the alcohols *4* and *5* were formed, and practically none of the corresponding acetates *6* and *7*. The suspension was filtered, washed with water and dried (Na_2SO_4). Column chromatography on silica gel eluted with benzene/chloroform/acetone gave recovered crocetindial (*2*, 483 mg, 20 %); 8,8′-diapo-20-hydroxycarotene-8,8′-dial (*4*, 1.116 g, 44 %) and 8,8′-diapo-20,20′-dihydroxycarotene-8,8′-dial (*5*, 71.2 mg, 2.7 %).

8,8′-Diapo-20-bromocarotene-8,8′-dial (*2*) had λ_{max} (acetone) *440* and 465.5, *m/e* (190 °C) 376 and 374 (M, 32 and 34 %), 295 (M – Br, 55 %) and 80 (100 %).

8,8′-Diapo-20,20′-dibromocarotene-8,8′-dial (*3*)

was tentatively obtained in mixture with other products and could not be further investigated (see above under Substitution of bromides *2* and *3*).

8,8'-Diapo-20-hydroxycarotene-8,8'-dial (*4*). *4* from procedure (a) above was crystallized from acetone/hexane as a *cis-trans* mixture (14.3 mg); m.p. 178.5–179 °C; λ_{max} (acetone) *434.5* (*E* (1 %, 1 cm) = 2980) and 460 nm; λ_{max} (KBr) 3410 (–OH), 1069, 1010 (prim. OH) cm^{-1}; δ ($CDCl_3$) 1.91 s (6 H, H-19,19'), 2.22 s (3 H, H-20'), 4.43 and 4.53 (2 H, $-CH_2OH$), 6.3–7.2 (10 olefinic H), 9.50 and 9.53 (2 aldehyde H); *m/e* (140 °C), 312 (M, 100 %), 296 (M–16, 1.8 %), 294 (M–18, 1.1 %) and 281 (M–31, 2.2 %).

8,8'-Diapo-20,20'-dihydroxycarotene-8,8'-dial (*5*) from procedure (b) above was rechromatographed on a silica gel column (10 % acetone in chloroform), and showed δ (d_5-pyridine) 1.85 s (6 H, H-19, 19'), no signals due to CH_3–20,20', 4.80 and 4.86 (4 H, H-20,20'), 9.76, 9.80 and 9.82 (2 H, H-8,8'). *5* was crystallized from methanol; yield 8.5 mg; m.p. 190.5–192.5 °C; λ_{max} (acetone) *432.5* (*E* (1 %, 1 cm) = 2410) and 457 nm, λ_{max} (methanol) 265.5, 328 and *433.5* nm; ν_{max} (KBr) 3437 and 3395 (OH), 1021 and 1010 (prim. OH); *m/e* (200 °C) 328 (M, 100 %), 312 (M–16, 4.5 %), 310 (M–18, 3.2 %), and 299 (M–31, 3.1 %).

8,8'-Diapo-20-acetoxycarotene-8,8'-dial (*6*). 8,8'-Diapo-20-hydroxycarotene-8,8'-dial (*4*, 42.5 mg) treated at room temperature with acetic anhydride (1.0 ml) in dry pyridine (10 ml) for 12 h gave *6*. The product was purified on a silica gel column eluted with APE; yield 41.3 mg (88 %). Crystallization from APE gave 13-*cis*-*6* (13.6 mg); m.p. 166–167 °C; λ_{max} (acetone *432.5* (*E* (1 %, 1 cm) = 2840) and 458 nm; λ_{max} (hexane) 261, 312, 324, 401, *423.5* and 449.5 nm, % D_B/D_{II} = 0.40;[6] ν_{max} (KBr) 1732 cm^{-1} (–CO–O–); δ ($CDCl_3$) 1.92 s (6 H, H-19,19'), 2.06 s (3 H, H-20'), 2.22 s (3 H, $-OCOCH_3$), 4.91 s (2 H, $-CH_2OAc$), 6.4–7.15 (10 olefinic H), 9.52 and 9.54 (2 aldehydic H); *m/e* (140 °C) 354 (M, 100 %) and 295 (M–59, 7.9 %).

8,8'-Diapo-20,20'-diacetoxycarotene-8,8'-dial (*7*). 8,8'-Diapo-20,20'-dihydroxycarotene-8,8'-dial (*5*, 30.6 mg) treated at room temperature with acetic anhydride (0.5 ml) in dry pyridine (5 ml) for 17 h gave *7*. The product was purified on a silica gel column eluted with benzene/chloroform; yield 22.1 mg (72 %). ^1H NMR ($CDCl_3$) before crystallization showed two peaks for the acetate $-CH_3$; δ($CDCl_3$) 2.09 and 2.13. Crystallization from chloroform/acetone gave *trans*-*7*, yield 10.2 mg; m.p. 208–208.5 °C; λ_{max} (acetone) *434* (*E* (1 %, 1 cm) = 2780) and 459 nm, λ_{max} (hexane) 260, 308, 319, *427* and 452 nm; ν_{max} (KBr) 1729 cm^{-1} (CO–O); δ ($CDCl_3$) 1.93 s (6 H, H-19,19'), 2.09 s (6 H, $-OCOCH_3$), 5.04 s (4 H, H-20,20'), 6.5–7.1 (10 olefinic H) and 9.60 s (2 H, H-8,8'); *m/e* (210 °C) 412 (M, 77 %), 353 (M–59, 6.8 %), 292 (M–120, 14 %), and 95 (100 %).

8,8'-Diapo-20-methoxycarotene-8,8'-dial (*8*) had λ_{max} (acetone) *436* and 461 nm, *m/e* 326 (M, 100 %), 295 (M–31, 3.5 %) and 381 (M–45, 3.0 %).

8,8'-Diapo-carotene-8,8'-20-trial (*9*). 8,8'-Diapo-20-hydroxycarotene-8,8'-dial (*2*, 44.8 mg) in acetone (20 ml) was added activated MnO_2 (1 g) and stirred for 1½ h. The mixture was filtered and the solvent removed. TLC on silica gel G (25 % APE) gave *12* yield 38.5 mg (87 %). Crystallization from chloroform/acetone yielded *cis*-*12* (7.9 mg); m.p. 179–183 °; λ_{max} (acetone) *443.5* (*E* (1 %, 1 cm) = 2390) and 462 nm, λ_{max} (hexane) 260, 269, 311.5, 322, *431.5*, and 455.5 nm; ν_{max} (KBr) 1666 and 1608 (conj. C=O) and 909 cm^{-1}; δ ($CDCl_3$) 1.93 s (6 H, H-19,19'), 2.11 s (3 H, H-20'), 6.5–7.7 (10 olefinic H), 9.52 s (2 H, H-8,8'), 9.82 (1 H, H-20); *m/e* (180 °C) 310 (M, 100 %), and 281 (M–29, 5.7 %).

NBS-reaction with 12,12'-diapo-12,12'-dial (*10*). *10* was treated with NBS as crocetindial (*1*) above. Optimal yield of the monobromide *11* was obtained after 11 h at 50 °C with 4 times excess of NBS. The reaction was tested with and without addition of benzoylperoxide (a spatula tip), and gave slightly higher yield with this admixture (8 % against 13 % under the conditions above). Thus from *10* (50.5 mg) treated under the optimum conditions was isolated after chromatography on silica gel 60 PF (22 % APE) the following five zones, ranged in order of decreasing R_F-values: product A (traces); λ_{max} (ether) 278, *m/e* (95 °C) 326, 324 and 322 (M, 0.4, 0.7, and 0.3 %, respectively), 299, 297, and 295 (M–29, 0.7, 1.1, and 0.7 %), 245 and 243 (M–Br, 52 and 54 %), and 91 (100 %), *10* (26.7 mg, 53 % of starting material), 12,12'-diapo-20-bromocarotene-12,12'-dial (*11*, 5.3 mg, 11 % of starting material), product B (traces); λ_{max} ($CHCl_3$) *331.5* and 347.5 nm, *m/e* (95 °C) 245 and 243 (9.6 and 10.0 %), 164 (245, 243–Br, 100 %), and product C (1.8 mg, 4 % of starting material); λ_{max} ($CHCl_3$) *342* and (353) nm, *m/e* (145 °C) 242 and 240 (8.8 and 8.1 %), 162 (100 %), no evident molecular ion.

12,12'-Diapo-20-bromocaroten-12,12'-dial (*11*) exhibited λ_{max} (ether) *328* and 341; λ_{max} ($CHCl_3$) *335* and 347.5; δ ($CDCl_3$) 1.19 s ($-CH_3$, 3 H), 4.29 s ($-CH_2Br$, 2 H), 7.0–7.2 (4 olefinic H), 9.57 and 9.60 ($-CHO$, 2 H); *m/e* (95 °C) 244 and 242 (M, 19 %) and 163 (M–Br, 100 %).

12,12'-Diapo-20-hydroxycaroten-12,12'-dial (*12*) and *12,12'-diapo-20-acetoxycaroten-12,12'-dial* (*13*). *11* (5.1 mg) was dissolved in THF-ether (1:1, 10 ml). Water (3 ml) and silver acetate (130 mg) were added and the suspension stirred for 22 h at room temperature. This gave after chromatography on silica gel 60 PF (22 % APE) recovered *11* (0.5 mg, 10 %), *13* (0.8 mg, 16 %); λ_{max} ($CHCl_3$) *329* and 344, *m/e* (95 °C) 222 (M, 30 %), 193 (M–29, 3.2 %), 162 (M–60, 100 %), 133 (M–60–29, 78 %), and *12* (1.3 mg, 25 %), λ_{max} ($CHCl_3$) *329.5* and 344, *m/e* (95 °C) 180

(M, 100 %), 162 (M−18, 35 %), 151 (M−29, 40 %), and 133 (M−18−29, 57 %).

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