Heterocyclic Quinones with Bridgehead Nitrogen Atoms. Part I. Pyrrolo[1,2-*a*]quinoxaline-6,9-dione and Pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione

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Received May 23, 1978
Revised August 29, 1980

The synthesis and some reactions of pyrrolo[1,2-*a*]quinoxaline-6,9-dione and pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione are described.

J. Heterocyclic Chem., **17**, 1705 (1980).

Heterocyclic quinones with bridgehead nitrogen atoms are relatively few in number. In the last decade renewed interest in the use of heterocyclic quinones as drugs has been stimulated by the discovery of a number of antibiotics containing the indoloquinone system, *e.g.*, the mitomycins (I)(2). These have marked antibiotic and antitumor activity.

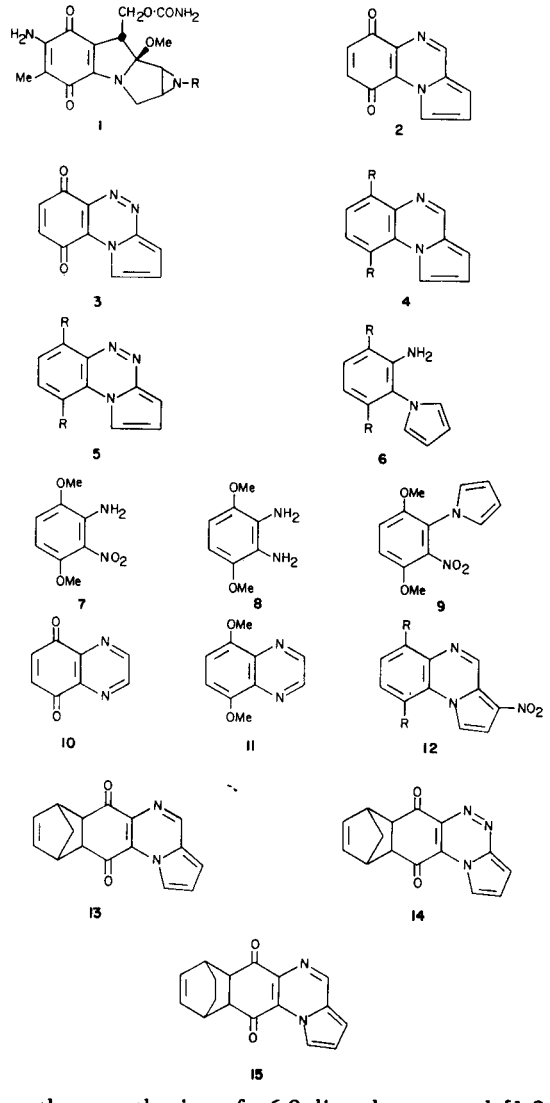
This paper describes the synthesis of pyrrolo[1,2-*a*]-quinoxaline-6,9-dione (II) and pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione (III), the routes employed being a combination of the methods available for obtaining ring systems with shared nitrogens and those used for preparing quinones.

Thus, the method of approach to both II and III was to synthesize the 6,9-dimethoxy-derivatives (IV and V, respectively) (R = OMe) of the parent fused heterocycles and to convert these into the corresponding quinones by demethylation, followed by oxidation.

Pyrrolo[1,2-*a*]quinoxaline derivatives were first obtained by Taylor and Hand (3) as by-products from the Diels-Alder reactions of quinoxaline derivatives with maleic anhydride. Cheeseman (4) has reported an alternative and more convenient synthesis of the ring system, which involves the cyclisation of an acyl derivative of *N*-(2-amino)phenylpyrrole (VI, R = H). Thus pyrrolo-[1,2-*a*]quinoxaline (IV, R = H) was prepared in excellent yield by heating (VI, R = H) with 90% formic acid under reflux.

Gross and Gloede (5) had previously described the preparation of (VI, R = H) from *ortho*-phenylenediamine and 2,5-diethoxytetrahydrofuran and also the conversion of (VI, R = H) into pyrrolo[2,1-*c*]benzotriazine (V, R = H) by treatment with aqueous nitrous acid. This facile intramolecular cyclisation is a reflection of the general ease with which pyrroles undergo electrophilic substitution.

Gross (6) has in fact reported the synthesis of many substituted pyrroles by treatment of primary amines with a suitably substituted tetrahydrofuran, *e.g.*, 2,5-dichloro-, 2,5-diethoxy- or 2,5-dimethoxytetrahydrofuran. However, it is usually most convenient to use the 2,5-diethoxy-derivative, since it is commercially available.



For the synthesis of 6,9-dimethoxypyrrolo[1,2-*a*]-quinoxaline, the method of Cheeseman (4) was employed. We found it more convenient to use 3,6-dimethoxy-2-nitroaniline (VII) (whose synthesis (7) we have previously reported) as a precursor rather than 2,3-diamino-1,4-dimethoxybenzene (VIII), since the *ortho*-diamine is somewhat unstable to air. Also with the *o*-nitroaniline (in

0022-152X/80/081705-04$02.25

contrast to the *o*-diamine), there is no possibility of cyclisation to yield a benzimidazole when the first stage of the synthesis is carried out in the presence of acetic acid.

Heating 3,6-dimethoxy-2-nitroaniline (VII) with 2,5-diethoxytetrahydrofuran in acetic acid under reflux for 3 hours gave *N*-(3,6-dimethoxy-2-nitro)phenylpyrrole (IX) in 63% yield. Catalytic hydrogenation of (IX) gave 69% yield of the corresponding amino compound (VI, R = OMe) as an off-white solid which proved to be somewhat unstable in light and air and was consequently used directly in the next stage.

When *N*-(2-amino-3,6-dimethoxy)phenylpyrrole (VI, R = OMe) was treated with 90% formic acid under reflux, the expected 6,9-dimethoxypyrrolo[1,2-*a*]quinoxaline (IV, R = OMe) was obtained in 77% yield, whilst reaction of (VI, R = OMe) with aqueous nitrous acid gave 83% yield of the required 6,9-dimethoxypyrrolo[2,1-*c*][1,2,4]benzotriazine (V, R = OMe).

The ^{1}H nmr spectrum of (IV, R = OMe) in deuteriochloroform shows a low field singlet (δ = 8.73) and a multiplet (δ = 8.65) which are attributed to the protons in positions 4 and 1 respectively and arise from the deshielding effect of the quinoxalinic and pyrrolic nitrogens. The spectrum of (V, R = OMe) in deuteriochloroform shows a low-field multiplet at δ = 8.55, which is due to the proton in position 1. It might be expected that, in both cases, the proton in the 1-position would give rise to a doublet, but because of long-range coupling with the proton in position 3, a multiplet is observed.

Oxidative demethylation of dimethoxy compounds, using 6*M* nitric acid, has been employed in the preparation of certain heterocyclic compounds, thus, *e.g.*, the dione (X) may be obtained by treatment of 5,8-dimethoxyquinoxaline (XI) using nitric acid (8). However, reaction of 6,9-dimethoxypyrrolo[1,2-*a*]quinoxaline (IV, R = OMe) with 6*M* nitric acid gave, not unexpectedly in view of the susceptibility of the pyrrole ring towards electrophilic substitution, the mononitro derivative (XII, R = OMe).

Cheeseman (9) has reported the formation of the 3-nitro derivative on treatment of the parent system, pyrrolo-[1,2-*a*]quinoxaline (IV, R = H) with potassium nitrate and concentrated sulphuric acid. The position of the nitro group in compound (XII, R = OMe) follows from a comparison of its ^{1}H nmr spectrum with that of the starting material (IV, R = OMe). The spectrum of each compound shows a low-field signal centered at δ = 8.65 for compound (IV, R = OMe) and at δ 8.82 for compound (XII, R = OMe), which may be attributed to the proton in position 1, but, whereas with compound (IV, R = OMe) this signal appears as a multiplet (see earlier discussion), in the case of the 3-nitro derivative a doublet is observed, since there is no proton in position 3 to give rise to long-range coupling with the proton in position 1.

Alkyl aryl ethers may be cleaved, often very efficiently, by means of boron tribromide in a suitable solvent under mild conditions (10). The choice of solvent depends upon the solubility and the degree of reactivity of the alkyl aryl ether used. Refluxing dichloromethane is often used as the reaction medium, but if a higher reaction temperature is required, dry benzene is frequently employed as the solvent.

Treatment of 6,9-dimethoxypyrrolo[1,2-*a*]quinoxaline (IV, R = OMe) and 6,9-dimethoxypyrrolo[2,1-*c*][1,2,4]-benzotriazine (V, R = OMe) with boron tribromide in dry benzene under prolonged reflux gave, after work-up, the corresponding dihydroxy compounds (IV and V, R = OH) in 61% and 50% yields respectively. These dihydroxy compounds, whose infra-red spectra show a broad band at 3300 cm^{-1} arising from the O-H stetching vibrations, proved to be rather unstable in air and were directly oxidised to the corresponding quinones without further purification; they were, however, characterised by conversion into their diacetoxy derivatives by reaction with acetic anhydride in the presence of anhydrous sodium acetate.

Oxidation of compounds (IV and V, R = OH) with silver oxide in acetone afforded the corresponding quinones, *viz.*, pyrrolo[1,2-*a*]quinoxaline-6,9-dione (II) and pyrrolo-[2,1-*c*][1,2,4]benzotriazine-6,9-dione (III) respectively in about 40% yields. Silver oxide was chosen as the oxidising agent since it has proved to be useful for the preparation of sensitive quinones of high oxidation potential (11).

March and Jouillé (12) demonstrated that benzimidazole-4,7-dione could form Diels-Alder adducts with a range of conjugated dienes. In the present work the heterocyclic quinones (II and III) gave stable Diels-Alder adducts (XIII) and (XIV) respectively with cyclopentadiene and whilst pyrrolo[1,2-*a*]quinoxaline-6,9-dione (II) gave a single adduct (XV) with cyclohexa-1,3-diene, pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione (III) on treatment with this diene in benzene under reflux gave rise to a mixture of compounds which proved impossible to separate even by chromatography.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. Ir spectra were reported with either a Perkin-Elmer 337 or a Beckmann-Acculab I spectrophotometer for potassium bromide discs. ^{1}H Nmr spectra were recorded with a JEOL C-60HL High Resolution instrument for solutions in deuteriochloroform unless otherwise stated (TMS as internal standard). The microanalyses were carried out by the analytical department of May and Baker, Ltd., Dagenham, England, and by C.H.N. Analysis, Ltd., Leicester, England.

N-(3,6-Dimethoxy-2-nitro)phenylpyrrole (IX).

A mixture of 3,6-dimethoxy-2-nitroaniline (3.96 g., 0.02 mole), 2,5-diethoxytetrahydrofuran (3.2 g., 0.02 mole) and acetic acid (1.5 cm^3) was heated under reflux for 3 hours. The reaction mixture was then cooled and poured into ice-water (100 cm^3). The crude product which precipitated out was filtered off, washed well with water and dried. On crystallization from petroleum ether (b.p. 60-80°)-benzene, compound IX (3.1 g., 63%) was obtained as orange needles, m.p. 165°; ir: 1550 s, 1280

s, 1100 s, 820 s, 800 s and 740 s cm^{-1}; nmr (carbon tetrachloride): δ 3.65 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.12 (m, 2H, pyrrole Ha), 6.55 (t, *J* 3.5 Hz, 2H, pyrrole Hb) and 6.88 (s, 2H, ArH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.8; N, 11.3. Found: C, 57.6; H, 4.9; N, 10.9.

N-(2-Amino-3,6-dimethoxy)phenylpyrrole (VI, R = OMe).

A suspension of *N*-(3,6-dimethoxy-2-nitro)phenylpyrrole (3.0 g., 0.012 mole) in ethanol (250 cm^3) was hydrogenated over 10% palladium-charcoal (0.3 g.) at 20° and 4 atmospheres until no more hydrogen was consumed. The reaction solution was filtered and the filtrate was evaporated to dryness under reduced pressure to leave compound VI (R = OMe) (1.8 g., 69%) as an off-white solid; ir: 3500 m, 3390 s, 1625 m, 1505 s, 1268 s, 1250 m, 1093 s, 790 m and 730 s cm^{-1}. The product deteriorated in quality on exposure to light and air and was therefore used directly in the next stage.

6,9-Dimethoxypyrrolo[1,2-*a*]quinoxaline (IV, R = OMe).

A mixture of *N*-(2-amino-3,6-dimethoxy)phenylpyrrole (1.50 g., 0.0068 mole) and formic acid (90%; 5 cm^3) was heated under reflux for 10 minutes. The reaction mixture was then cooled and poured into ice-water (50 cm^3). On basification of the resulting aqueous solution with sodium hydroxide (5.0 g.) in water (20 cm^3), a product precipitated out which was filtered off, washed well with water and dried. Compound IV (R = OMe) (1.29 g., 77%) was purified by vacuum sublimation to give white needles, m.p. 110-111°; ir: 1510 s, 1340 m, 1280 s, 1100 m, 1075 s, 810 m and 735 s cm^{-1}; nmr: δ 3.97 (s, 6H, OCH_3), 6.8 (m, 4H pyrrole H and ArH), 8.65 (m, 1H, pyrrole H) and 8.73 (s, 1H, quinoxaline H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.3; N, 12.3. Found: C, 68.6; H, 5.2; N, 12.3.

6,9-Dimethoxypyrrolo[2,1-*c*][1,2,4]benzotriazine (V, R = OMe).

A solution of *N*-(2-amino-3,6-dimethoxy)phenylpyrrole (1.00 g., 0.0045 mole) in concentrated hydrochloric acid (3.0 cm^3) and water (5.0 cm^3) was cooled in an ice-bath and the temperature maintained between 0-5°. Sodium nitrite (0.62 g., 0.009 mole) in water (5.0 cm^3) was added dropwise, the temperature of the reaction solution being maintained below 5°. The mixture was then allowed to stand at room temperature for 30 minutes, when aqueous sodium hydroxide (2*M*) was added until neutrality was achieved. The aqueous solution was then extracted with chloroform (2 × 50 cm^3); the combined extracts were dried (magnesium sulfate) filtered and the filtrate evaporated to dryness under reduced pressure to leave a yellow solid. On crystallization from methanol, compound V (R = OMe) (0.87 g., 83%) was obtained as yellow needles, m.p. 159-160°; ir: 1605 w, 1280 s, 1225 s, 1068 m and 730 s cm^{-1}; nmr: δ 4.03 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 7.0 (m, 3H, pyrrole H and ArH), 7.45 (m, 1H, pyrrole H) and 8.55 (m, 1H, pyrrole H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.9; H, 4.8; N, 18.4. Found: C, 62.6; H, 5.0; N, 18.3.

6,9-Dihydroxypyrrolo[1,2-*a*]quinoxaline (IV, R = OH) and 6,9-Dihydroxypyrrolo[2,1-*c*][1,2,4]benzotriazine (V, R = OH).

Excess boron tribromide (5.0 g.) in dry benzene (20 cm^3) was added to the dimethoxy compound (IV, R = OMe and V, R = OMe) (0.50 g., 0.0022 mole) dissolved in dry, refluxing benzene (20 cm^3). The reaction mixture was then heated under reflux for x hours, while protected with a calcium chloride tube. The cooled mixture was hydrolysed carefully with water. The aqueous layer was separated from the organic layer and then adjusted to *p*H 7 with powdered sodium bicarbonate. The resultant precipitate was filtered off, washed well with water and dried. The dihydroxy compound obtained in this way proved to be somewhat unstable and was used directly in the next stage.

Compound IV (R = OH) (0.27 g., 61%) was obtained after 3 hours of heating as an off-white solid; ir: 3260 br, m, 1445 m, 1265 m, 990 m and 735 s cm^{-1}.

Compound V (R = OH) (0.22 g., 50%) was obtained after 5 hours of heating as a brown solid; ir: 3480 br, m, 3100 br, s, 1620 s, 1328 s, 1280 s, 1225 s, 1005 m, 824 m and 723 s cm^{-1}.

6,9-Diacetoxypyrrolo[1,2-*a*]quinoxaline (IV, R = OAc) and 6,9-Diacetoxypyrrolo[1,2-*c*][1,2,4]benzotriazine (V, R = OAc).

The dihydroxy compound (IV, R = OH and V, R = OH) (x g.) in acetic anhydride (5.0 cm^3) was heated under reflux with anhydrous sodium acetate (0.1 g.) for y hours. After treatment with water (15 cm^3), the solid which separated out was filtered off, washed well with water and dried.

For 6,9-dihydroxypyrrolo[1,2-*a*]quinoxaline (0.15 g., 0.00075 mole), the reaction mixture was heated for 1 hour. The crude off-white product was crystallised from ethanol to give compound IV (R = OAc) (0.11 g., 51%) as white needles, m.p. 152-153°; ir: 1765s, 1755 sh, s, 1360 m, 1320 m, 1200 m, 1170 s, 1005 w and 710 w cm^{-1}; nmr: δ 2.44 (s, 3H, $COCH_3$), 2.49 (s, 3H, $COCH_3$), 6.9 (m, 3H, pyrrole H and ArH), 7.17 (m, 1H, pyrrole H), 8.23 (m, 1H, pyrrole H) and 8.76 (s, 1H, quinoxaline H).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 62.1; H, 4.4; N, 9.65. Found: C, 62.5; H, 4.2; N, 9.7.

For 6,9-dihydroxypyrrolo[2,1-*c*][1,2,4]benzotriazine (0.10 g., 0.0005 mole), the reaction mixture was heated for 2 hours. The crude yellow product was crystallised from petroleum ether (b.p. 60-80°)-benzene to give compound V (R = OAc) (0.11 g., 78%) as yellow needles, m.p. 207-209°; ir: 1770 s, 1755 sh, s, 1375 m, 1350 m, 1207 s, 1182 s, 875 m and 725 m cm^{-1}; nmr: δ 2.52 (s, 6H, $COCH_3$), 7.0-7.6 (m, 4H, pyrrole H and ArH) and 8.12 (q, 1H, pyrrole H).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.9; H, 3.85; N, 14.7. Found: C, 58.7; H, 4.0; N, 14.6.

Pyrrolo[1,2-*a*]quinoxaline-6,9-dione (II) and Pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione (III).

Anhydrous sodium sulphate (0.1 g.) and excess silver oxide (0.5 g.) were added to a solution of the dihydroxy compound (IV, R = OH and V, R = OH) (0.25 g., 0.0012 mole) in acetone (25 cm^3). The mixture was stirred at room temperature until thin layer chromatography indicated that no starting material was present. The reaction solution was filtered and the filtrate evaporated to dryness under reduced pressure to leave a dark-coloured residue. Crystallisation from petroleum (b.p. 60-80°)-benzene gave the pure quinone.

Compound II (0.10 g., 40%) was obtained as violet needles, m.p. 180-182°; ir: 1655 s, 1280 m, 1090 m, 1065 m, 852 w and 760 m cm^{-1}; nmr (acetone-d_6): δ 7.14 (s, 2H, CH=CH), 7.40 (d, 2H, pyrrole H) and 9.32 (m, 2H, pyrrole H and quinoxaline H).

Anal. Calcd. for $C_{11}H_6N_2O_2$: C, 66.7; H, 3.0; N, 14.1. Found: C, 66.5; H, 3.2; N, 13.5.

Repeated purifications did not lead to better analytical data.

Compound III (0.10 g., 40%) was obtained as violet needles, m.p. 230° dec.; ir: 1670 s, 1650 s, 1400 w, 1320 s, 1075 m, 1063 m, 990 m, 857 m and 773 m cm^{-1}; nmr: δ 7.02 (s, 2H, CH=CH), 7.64 (m, 2H, pyrrole H) and 9.05 (q, 1H, pyrrole H).

Anal. Calcd. for $C_{10}H_5N_3O_2$: C, 60.3; H, 2.5; N, 21.1. Found: C, 60.5; H, 2.65; N, 20.6.

6,9-Dimethoxy-3-nitropyrrolo[1,2-*a*]quinoxaline (XII, R = OMe).

6,9-Dimethoxypyrrolo[1,2-*a*]quinoxaline (0.25 g., 0.0011 mole) was treated with nitric acid (6*M*; 10 cm^3) and stirred at room temperature for 1 hour. The mixture was then filtered and the filtrate neutralised with powdered sodium bicarbonate. The resultant yellow precipitate was filtered off, washed well with water and dried. On crystallisation from ethanol, compound XII (R = OMe) (0.24 g., 80%) was obtained as yellow needles, m.p. 179-182°; ir: 1530 m, 1515 s, 1480 m, 1325 s, 1210 m, 1055 m and 745 s cm^{-1}; nmr: δ 3.97 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.03 (m, 2H, pyrrole H and ArH), 7.41 (s, 1H, ArH), 8.7 (d, 1H, pyrrole H) and 8.92 (s, 1H, quinoxaline H).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.1; H, 4.0; N, 15.4. Found: C, 56.9; H, 4.15; N, 14.7.

Repeated purifications did not lead to better analytical data.

Diels-Alder Reactions on Pyrrolo[1,2-*a*]quinoxaline-6,9-dione (II) and Pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione (III).

General method.

The diene (0.001 mole) was added to a solution of the dione (II or III) (0.0005 mole) in benzene (20 cm^3) and the mixture heated under reflux for 3 hours. The hot solution was then filtered and the filtrate evaporated to dryness under reduced pressure to leave the solid adduct which was recrystallised from ethanol.

The adduct XIII (0.09 g., 68%) was obtained as yellow needles, m.p. 150-3°; ir: 1650 m, 1420 m, 1095 s and 725 m cm^{-1}; nmr: δ 1.63 (d, 2H, CH_2), 3.7 (m, 4H, CH-CH), 6.10 (q, 2H, CH=CH), 7.5 (m, 2H, pyrrole H), 8.77 (s, 1H, quinoxaline H) and 9.2 (q, 1H, pyrrole H).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.7; H, 4.5; N, 10.6. Found: C, 72.6; H, 4.6; N, 10.4.

The adduct XIV (0.09 g., 70%) was obtained as orange-yellow needles, m.p. 240° dec.; ir.: 3000 w, 1680 s, 1660 s, 1330 s, 1253 s, 1048 s, 760 s and 685 m cm^{-1}; nmr: δ 1.64 (s, 2H, CH_2), 3.7 (m, 4H, CH-CH), 6.05 (q, 2H, CH=CH), 7.45 (m, 2H, pyrrole H) and 9.2 (q, 1H, pyrrole H).

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.9; H, 4.15; N, 15.8. Found: C, 67.4; H, 4.2; N, 15.6.

The adduct XV (0.10 g., 75%) was obtained as red flakes, m.p. 220° dec.; ir: 2960 br, s, 2950 w, 2925 w, 1660 s, 1645 s, 1390 m, 1320 m, 1300 m, 1235 s, 1030 m and 740 m cm^{-1}; nmr: δ 1.2 (m, 4H, CH_2-CH_2), 6.15 (q, 2H, CH=CH), 7.55 (m, 2H, pyrrole H), 8.75 (s, 1H, quinoxaline H) and 9.15 (q, 1H, pyrrole H).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.3; H, 5.1; N, 10.1. Found: C, 72.9; H, 5.2; N, 9.9.

Acknowledgement.

We thank Dr. G. C. J. Martin for helpful discussions.

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