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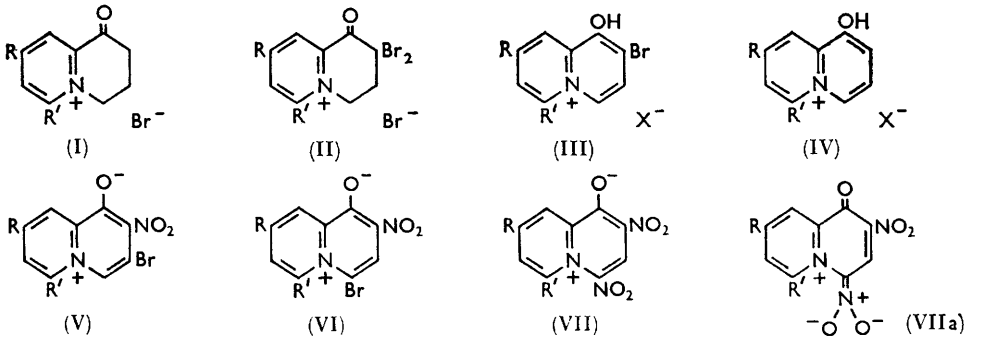
583. *Quinolizines. Part VIII.*[1] *The Nitration of 1-Hydroxyquinolizinium Salts.*

By A. Fozard and Gurnos Jones.

The nitration of 1-hydroxyquinolizinium salts has been shown to give three nitro-compounds, formulated as (VI), (VII), and (VIII). The synthesis of 6-methyl- and 8-methyl-1-hydroxyquinolizinium salts is described.

We have reported[2] the ready bromination of 1-hydroxyquinolizinium salts (IV; R = R′ = H) to give 2-bromo-1-hydroxyquinolizinium bromide (III; R = R′ = H, X = Br). Such ready electrophilic substitution was unexpected in a compound which carries a formal positive charge, and so nitration of the hydroxy-compound (IV; R = R′ = H) was attempted. When the hydroxyquinolizinium bromide (IV; R = R′ = H, X = Br) was heated for 15 seconds in a boiling solution of dilute nitric acid a good yield of an orange-red product (VI; R = R′ = H) was obtained. Longer heating led to production of a second nitration product (VII; R = R′ = H) and this was the major product when 1-hydroxyquinolizinium bromide (IV; R = R′ = H, X = Br) was nitrated with acetic anhydride–nitric acid at 0°. Since the evidence reported below indicates that the initial nitration is followed by substitution by the bromide ions present in the solution, the nitration was also performed on 1-hydroxyquinolizinium nitrate (IV; R = R′ = H, X = NO_3), and a third nitration product thereby obtained (VIII). To facilitate interpretation of the n.m.r. spectra and to indicate the generality of the nitration, 1-hydroxy-6-methylquinolizinium salts (IV; R = H, R′ = Me) and 1-hydroxy-8-methylquinolizinium salts (IV; R = Me, R′ = H) were synthesised by the route (I ⟶ IV). The 1-hydroxy-8-methylquinolizinium salts were successfully nitrated to give compounds of type (VI; R = Me, R′ = H) and (VII; R = Me, R′ = H), but no nitration product of either type could be obtained from 1-hydroxy-6-methylquinolizinium bromide. The evidence for the structures advanced for the nitration products is given below.



The third nitration product, obtained by nitration of 1-hydroxyquinolizinium nitrate (IV; R = R′ = H, X = NO_3) has the simplest structure (VIII) and will be considered in detail first. The micro-analytical results agreed best with $C_9H_6N_2O_3$, and the i.r. spectrum showed absorption at 1580 and 1330 cm.$^{-1}$, assigned to a nitro-group. No strong absorption was found in the 3700—3100 cm.$^{-1}$ region, indicating the absence of a phenolic hydroxyl group, but a very strong absorption band at 1260 cm.$^{-1}$ is in the region associated with C–O stretching in phenoxides.[3] Catalytic reduction proceeded smoothly, with an uptake of three molecules of hydrogen, to give an amino-phenol (IX; X = Br), with all

[1] Part VII, *J.*, 1964, 2763.
[2] Fozard and Jones, *J.*, 1963, 2203.
[3] Parker and Kershenbaum, *J. Phys. Chem.*, 1959, **63**, 1342.

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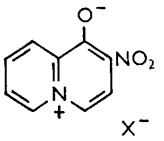
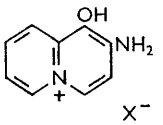
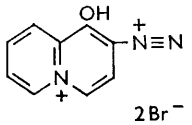
the characteristics of a simple quinolizinium salt. The i.r. spectrum showed the presence of hydroxy- and amino-groups, and the reduction product (IX; X = Br) gave a green colour with neutral ferric chloride and formed a complex with cupric acetate. Treatment of the amino-compound (IX; X = Br) with pentyl nitrite in ethanolic hydrochloric acid gave a diazonium salt (X), coupling with alkaline 2-naphthol. As with 1-amino-2-hydroxyquinolizinium bromide,[1] diazotisation in aqueous acid gave an insoluble diazonium bromide (X) which could be isolated and kept at room temperature for some time without decomposition. When the diazonium salt (X) was heated in dry dimethylformamide evolution of nitrogen occurred and the product was a 2-bromo-1-hydroxyquinolizinium salt, isolated as the picrate (III; R = R′ = H, X = picrate) identical with specimens obtained by other routes.[2] This confirms the structure (IX) assigned to the reduction product and implies that the oxygen function and the nitro-group in the nitration product (VIII) are adjacent. Since the nitration product (VIII) does not occur as a salt with an associated anion it is most probably zwitterionic, as shown in structure (VIII), and this is confirmed by the protonation which occurs in concentrated acid, resulting in a considerable change in the u.v. and visible spectrum.



(VIII)



(IX)



(X)

The first nitration product obtained from 1-hydroxyquinolizinium bromide (IV; R = R′ = H, X = Br) was shown by microanalysis to possess the empirical formula $C_9H_5BrN_2O_3$. The i.r. and u.v. absorption of this nitration product were very similar to those of compound (VIII), and catalytic reduction gave the same 2-amino-1-hydroxyquinolizinium salt (IX), although four molecules of hydrogen were required to complete the reduction. As the bromine atom in the nitration product was not ionic, two formulæ, (V) or (VI), appeared most likely, and the evidence available leads us to prefer formula (VI; R = R′ = H). The substituted 1-hydroxyquinolizinium bromides (IV; R = Me, R′ = H, X = Br) and (IV; R = H, R′ = Me, X = Br) were submitted to brief treatment with hot dilute nitric acid, and a product (VI; R = Me, R′ = H) was obtained from the former, very similar in properties to the compound (VI; R = R′ = H) obtained from 1-hydroxyquinolizinium bromide. However, 1-hydroxy-6-methylquinolizinium bromide (IV; R = H, R′ = Me, X = Br) gave no isolatable nitration product under these conditions, and in view of the extreme insolubility of the two compounds of general formula (VI) it is most unlikely that the product (VI; R = H, R′ = Me) can have been formed. This we assume to be due to steric hindrance at position 4 exercised by the 6-methyl group and seems to provide the strongest evidence for preferring formula (VI) to (V). Attempts to perform nucleophilic replacement of the bromine atom in the bromo-nitro-compound (VI; R = R′ = H) were unsuccessful. No replacement was observed after prolonged treatment with silver acetate in hot acetic acid, and phenylhydrazine converted the bromo-nitro-compound (VI; R = R′ = H) into 2-amino-1-hydroxyquinolizinium salts (IX).

The third nitration product, isolated after treatment of 1-hydroxyquinolizinium salt with hot dilute nitric acid for periods greater than 15 seconds, or by nitration with acetic anhydride–nitric acid, is formulated as a dinitro-derivative (VII; R = R′ = H). Since the dinitro-derivative is obtained when the bromo-nitro-compound (VI; R = R′ = H) is heated with dilute nitric acid, the previous placing of the bromine atom at position 4 in (VI) implies that the second nitro-group in the dinitro-derivative is also at position 4. Reduction of the dinitro-derivative (VII) proceeded readily with uptake of 6 molecules of

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hydrogen, but no crystalline products could be obtained from the reduction mixture. A noteworthy feature of the i.r. spectrum of the dinitro-derivative (VII; R = R′ = H) and of its homologue (VII; R = Me, R′ = H) was a band at 1655 cm.$^{-1}$ in the region associated with carbonyl stretching, and this may indicate stronger contributions from canonical forms of type (VIIa) than are found in the mononitro-derivatives (VI) and (VIII).

The n.m.r. spectrum of the bromonitro-compound (VI; R = R′ = H) in liquid sulphur dioxide showed a collection of protons in the region τ 0·2—2·5, all of which must be attached to the aromatic system. Unfortunately the total number of protons could not be calculated, as the low solubility of the nitration product led to a high background noise with correspondingly low accuracy in integration. The n.m.r. spectrum of the 8-methyl homologue (VI; R = Me, R′ = H) in trifluoroacetic acid (in which the protonated form is present) showed an aromatic methyl group at τ 7·2 and a total of five protons between τ 0·2 and 2·0, in accord with the formula given.

Experimental

2,2-Dibromo-6-methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide (II; R = H, R′ = Me).—The 6-methyl ketone bromide (I; R = H, R′ = Me) [4] (3·5 g.) was dissolved in 50% aqueous hydrobromic acid (75 ml.) and bromine (6·0 g.) in hydrobromic acid (25 ml.) was added with stirring, which was continued for 15 min. after addition. The mixture was heated on a water-bath for 15 min. and then evaporated under reduced pressure. Water was added to the residue and re-evaporated giving a pale yellow solid which was suspended in acetone and the mixture filtered. This substantially pure *dibromo-ketone bromide* (II; R = H, R′ = Me) (4·96 g., 85%) was crystallised from ethanol as small yellow needles, m. p. 228—229·5° (Found: C, 30·2; H, 3·05. $C_{10}H_{10}Br_3NO$ requires C, 30·0; H, 2·5%); $\lambda_{max.}$ 2760 Å ($\log_{10}$ ε 3·83) in water.

2,2-Dibromo-8-methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide (II; R = Me, R′ = H).—Prepared from the 8-methyl ketone bromide (I; R = Me, R′ = H) [4] as described above, in 90% yield, the *dibromo-8-methyl ketone bromide* crystallised from ethanol as blunt yellow needles, m. p. 221—223° (Found: C, 30·05; H, 2·75. $C_{10}H_{10}Br_3NO$ requires C, 30·0; H, 2·5%); $\lambda_{max.}$ 2600 Å ($\log_{10}$ ε 3·74) in water.

2-Bromo-1-hydroxy-6-methylquinolizinium Bromide (III; R = H, R′ = Me, X = Br).—The dibromo-6-methyl ketone (II; R = H, R′ = Me) (4 g.) was heated at 160° (oil-bath) until evolution of hydrogen bromide ceased. The residue was pure *2-bromo-1-hydroxy-6-methylquinolizinium bromide* (3·16 g., 100%) recrystallised from ethanol as needles, m. p. 228—229° (Found: C, 36·15; H, 3·0. $C_{10}H_9Br_2NO,H_2O$ requires C, 35·65; H, 3·3%); $\lambda_{max.}$ 2160 and 3680 Å ($\log_{10}$ ε 4·45 and 4·12) in water. The bromide gave a violet colour with aqueous ferric chloride.

2-Bromo-1-hydroxy-8-methylquinolizinium Bromide (III; R = Me, R′ = H, X = Br).—Prepared as described above from the dibromo-8-methyl ketone (II; R = Me, R′ = H) the *2-bromo-1-hydroxy-8-methylquinolizinium bromide* was an amorphous solid, m. p. 225—226° (decomp.) (Found: C, 37·95; H, 3·2. $C_{10}H_9Br_2NO$ requires C, 37·65; H, 2·85%); $\lambda_{max.}$ 2160 and 3650 Å ($\log_{10}$ ε 4·61 and 4·18) in water.

1-Hydroxy-6-methylquinolizinium Salts (IV; R = H, R′ = Me).—A solution of the bromohydroxyquinolizinium bromide (III; R = H, R′ = Me, X = Br) (2·75 g.) in 95% ethanol was hydrogenated at atmospheric temperature and pressure, 10% palladium on carbon (0·75 g.) being used. One molar equivalent of hydrogen was absorbed. Filtration and evaporation of the filtrate gave an oily residue, which crystallised on cooling (1·98 g., 92%). *1-Hydroxy-6-methylquinolizinium bromide* (IV; R = H, R′ = Me, X = Br) crystallised from ethanol as platelets, m. p. 281—283° (decomp.) (Found: C, 47·95; H, 4·5; N, 5·7. $2C_{10}H_{10}BrNO,H_2O$ requires C, 48·2; H, 4·4; N, 5·6%); $\lambda_{max.}$ 2050, 2400, and 3410 Å ($\log_{10}$ ε 4·52, 4·07, and 4·14) in water. The *picrate* (IV; R = H, R′ = Me, X = picrate) crystallised from ethanol as yellow rhombs, m. p. 232—234° (Found: C, 49·5; H, 3·2. $C_{16}H_{12}N_4O_8$ requires C, 49·5; H, 3·1%).

[4] Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.

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1-*Hydroxy*-8-*methylquinolizinium Salts* (IV; R = Me, R′ = H).—Prepared as described for the 6-methyl isomer the 1-hydroxy-8-methylquinolizinium bromide (IV; R = Me, R′ = H, X = Br) (85%) crystallised from ethanol as rhombs, m. p. 210—211·5° (Found: C, 47·0; H, 4·65; N, 5·8. $C_{10}H_{10}BrNO,H_2O$ requires C, 46·55; H, 4·7; N, 5·4%); $\lambda_{max.}$ 2070, 2330, and 3370 Å ($\log_{10}\varepsilon$ 4·65, 4·18, and 4·19) in H_2O. The *picrate* (IV; R = Me, R′ = H, X = picrate) crystallised from ethanol as blunt yellow needles, m. p. 228—232° (Found: C, 49·5; H, 3·3. $C_{16}H_{12}N_4O_8$ requires C, 49·5; H, 3·1%).

Nitration of 1-*Hydroxyquinolizinium Bromide*.—(*a*) The bromide (IV; R = R′ = H, X = Br) (1·0 g.) was dissolved in 7% aqueous nitric acid (20 ml.), and the solution was boiled for 15 sec. When the solution was cooled in ice a red precipitate formed and was washed with water; it had m. p. 232° (decomp.) (0·625 g., 57%). Crystallisation from 80% aqueous ethanol gave small red needles of 4-*bromo*-1-*hydroxy*-2-*nitroquinolizinium betaine* (VI; R = R′ = H), m. p. 234° (decomp.) (Found: C, 40·25; H, 2·2; N, 10·3. $C_9H_5BrN_2O_3$ requires C, 40·15; H, 1·9; N, 10·4%); $\lambda_{max.}$ 2070, 2680, 3230, and 4570 Å ($\log_{10}\varepsilon$ 4·55, 4·33, 3·86, and 4·48) in water; $\lambda_{max.}$ 2590 and 3970 Å in concentrated sulphuric acid; $\nu_{max.}$ 1580, 1330 (NO_2), and 1260 cm.$^{-1}$ ($C{-}O^-$) in Nujol mull.

(*b*) The bromide (IV; R = R′ = H, X = Br) (0·50 g.) was dissolved in 10% aqueous nitric acid (10 ml.), and the solution was boiled under reflux for 5 min. When the solution was cooled in ice a yellow crystalline solid was obtained (0·086 g., 18%). Recrystallisation from acetone gave pale orange rhombs of 1-*hydroxy*-2,4-*dinitroquinolizinium betaine* (VII; R = R′ = H), m. p. 292° (decomp.) (Found: C, 45·95; H, 2·15; N, 17·85. $C_9H_5N_3O_5$ requires C, 45·95; H, 2·1; N, 17·85%); $\lambda_{max.}$ 2080, 2470sh, 2540, and 4200 Å ($\log_{10}\varepsilon$ 4·25, 4·12, 3·98, and 4·33) in water; $\nu_{max.}$ 1655 (C=O), 1570, 1320 (NO_2), and 1255 cm.$^{-1}$ (CO^-) in Nujol mull or KBr disc.

(*c*) The bromide (IV; R = R′ = H, X = Br) (0·45 g.) was suspended in acetic anhydride (10 ml.) at 0°, and a mixture of concentrated nitric acid (1·5 ml.), glacial acetic acid (3·5 ml.), and acetic anhydride (5 ml.) was added dropwise over 20 min. During the addition the suspended solid dissolved to give an orange solution and towards the end of the addition a yellow solid precipitated. Filtration, followed by washing of the precipitate with ether, gave the dinitro-derivative (VII; R = R′ = H), m. p. 292° (0·045 g., 9%), identical with that obtained as in (*b*) above.

1-*Hydroxyquinolizinium Nitrate* (IV; R = R′ = H, X = NO_3).—1-Hydroxyquinolizinium bromide (IV; R = R′ = H, X = Br) (0·5 g.) in water (5 ml.) was treated with silver nitrate (0·36 g.) in water (5 ml.). The mixture was filtered, and the filtrate evaporated under reduced pressure. The residue was suspended in ethanol–ethyl acetate, and the mixture filtered. 1-*Hydroxyquinolizinium nitrate* (IV; R = R′ = H, X = NO_3) was purified from ethanol–ethyl acetate as an amorphous solid, m. p. 170—171° (Found: C, 52·05; H, 3·9. $C_9H_8N_2O_4$ requires C, 51·9; H, 3·85%). The nirate gave a red colour with neutral ferric chloride and showed a broad absorption band at 1400—1260 cm.$^{-1}$ (NO_3^-) in Nujol mull.

Nitration of 1-*Hydroxyquinolizinium Nitrate*.—A solution of the nitrate (IV; R = R′ = H, X = NO_3) (0·25 g.) in 7% aqueous nitric acid (5 ml.) was boiled for 15 sec., then cooled in ice, giving deep orange crystals (0·07 g., 31%). Recrystallisation from 80% aqueous ethanol gave orange rhombs of 1-*hydroxy*-2-*nitroquinolizinium betaine* (VIII), m. p. >340° (Found: C, 56·15; H, 2·85; N, 14·8. $C_9H_6N_2O_3$ requires C, 56·85; H, 3·2; N, 14·7%); $\lambda_{max.}$ 2120, 2290sh, 2570, and 4290 Å ($\log_{10}\varepsilon$ 4·21, 4·10, 4·03, and 4·24) in water; $\lambda_{max.}$ 2530 and 3880 Å in concentrated sulphuric acid; $\nu_{max.}$ 1580, 1330 (NO_2) and 1260 cm.$^{-1}$ (CO^-) in Nujol mull.

Nitration of 1-*Hydroxy*-8-*methylquinolizinium Bromide*.—The hydroxyquinolizinium bromide (IV; R = Me, R′ = H, X = Br) (0·5 g.) was dissolved in 7% aqueous nitric acid (10 ml.), and the solution was boiled. After 5 sec. at the b. p. a precipitate was observed, and on cooling the solution in ice a red solid was obtained (0·305 g., 55%). Recrystallisation from 80% aqueous ethanol gave 4-*bromo*-1-*hydroxy*-8-*methyl*-2-*nitroquinolizinium betaine* (VI; R = Me, R′ = H), as feathery red crystals, m. p. >340° (Found: C, 43·0; H, 2·45; N, 10·1. $C_{10}H_7BrN_2O_3$ requires C, 42·45; H, 2·4; N, 9·9%); $\lambda_{max.}$ 2100, 2410, 3250, 3790sh, and 4440 Å ($\log_{10}\varepsilon$ 4·45, 4·19, 3·66, 3·94, and 4·31) in water; $\lambda_{max.}$ 2600, 3440, and 3980 Å in concentrated sulphuric acid.

The filtrate, after removal of the nitration product (VI; R = Me, R′ = H), was boiled for a further 5 min. and cooled, giving 1-*hydroxy*-8-*methyl*-2,4-*dinitroquinolizinium betaine* (VII, R = Me, R′ = H), (0·05 g.), recrystallised from acetone as microcrystalline yellow needles, m. p. >340° (Found: C, 48·2; H, 2·9; N, 17·1. $C_{10}H_7N_3O_5$ requires C, 48·2; H, 2·85; N, 16·85%); $\lambda_{max.}$ 2150, 2570, and 4320 Å ($\log_{10}\varepsilon$ 4·33, 3·99, and 4·42) in 75% ethanol; $\lambda_{max.}$ 2580

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and 3790 Å in concentrated sulphuric acid; $\nu_{max.}$ 1655 cm.$^{-1}$ (CO), 1560, 1330 cm.$^{-1}$ (NO_2), and 1250 (CO^-) in Nujol mull.

2-Amino-1-hydroxyquinolizinium Salts (IX).—(*a*) The nitration product (VI; R = R′ = H) (0·75 g.) in 80% aqueous ethanol (200 ml.) was hydrogenated at atmospheric temperature and pressure, 10% palladium on carbon catalyst being used (0·75 g.). Three molar equivalents of hydrogen were quickly absorbed, and a fourth more slowly. The filtered solution was evaporated, and the residue triturated with acetone, giving a solid (0·515 g., 77%). Recrystallisation from ethanol–ethyl acetate gave *2-amino-1-hydroxyquinolizinium bromide* (IX; X = Br) as blunt yellow needles, m. p. 180—181° (Found: C, 44·45; H, 3·9; N, 11·1. $C_9H_9BrN_2O$ requires C, 44·8; H, 3·75; N, 11·6); $\lambda_{max.}$ 2160, 2345, 3230, and 3570 Å ($\log_{10}\varepsilon$ 4·30, 4·25, 3·88, and 3·89) in water; $\nu_{max.}$ 3420, 3330 (NH_2) and 3160 cm.$^{-1}$ (OH) in Nujol mull. The aminohydroxy-bromide gave a green colour with neutral ferric chloride and a deep red-brown colour with cupric acetate. The *picrate* (IX; X = picrate) crystallised from ethanol as yellow needles, m. p. 211—213° (Found: C, 46·3; H, 3·4; N, 18·3. $C_{15}H_{11}N_5O_8$ requires C, 46·3; H, 2·85; N, 18·0%).

(*b*) The mononitro-derivative (VIII) was hydrogenated as described in (*a*). Three molar equivalents of hydrogen were absorbed. After filtration the solution was passed through an Amberlite IRA 400 (Br) column. Working up as in (*a*) gave the aminohydroxy-bromide (IX; X = Br) in 45% yield.

1-Hydroxyquinolizinium-2-diazonium Dibromide (X).—The aminohydroxyquinolizinium bromide (IX; X = Br) (0·5 g.) in 15% aqueous hydrobromic acid (12 ml.) was cooled to −8° and treated dropwise with aqueous sodium nitrite until an excess of nitrite was present. An orange solid precipitated, and was dried in a vacuum desiccator at room temperature (0·38 g., 55%); $\nu_{max.}$ 2130 and 2095 cm.$^{-1}$ ($\overset{+}{N}\equiv N$) in Nujol mull. The dibromide (X) darkened slowly in sunlight, and gave a violet insoluble precipitate when added to alkaline 2-naphthol.

2-Bromo-1-hydroxyquinolinium Picrate (III; R = R′ = H, X = picrate).—The diazonium dibromide (X) (0·345 g.) was suspended in dry dimethylformamide (5 ml.), the mixture heated in an oil-bath until nitrogen evolution was observed (about 120°), and this temperature maintained until nitrogen evolution ceased. The solution was evaporated under reduced pressure, and the residue dissolved in ethanol (charcoal) and re-evaporated. The semi-solid residue was dissolved in water and treated with aqueous sodium picrate, giving 2-bromo-1-hydroxyquinolizinium picrate (III; R = R′ = H, X = picrate), m. p. 170·5—173·5°, identical with a sample prepared by another route [2] (Found: C, 40·2; H, 2·2. Calc. for $C_{15}H_9BrN_4O_8$: C, 39·75; H, 2·0%).

Attempted Reduction of the Dinitro-derivative (VII; R = R′ = H).—The dinitro-derivative (VII; R = R′ = H) (0·35 g.) was suspended in 75% aqueous ethanol (130 ml.) and hydrogenated at atmospheric temperature and pressure, 10% palladium on carbon catalyst (0·3 g.) being used. An uptake of 6 molar equivalents was observed, after which absorption ceased. After filtration and evaporation of the filtrate an oily solid was obtained, but this could not be purified.

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Department of Chemistry, University of Keele,
Keele, Staffs.

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