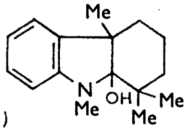
92. *The Autoxidation of 2-Hydroxy-1,3,3-trimethyl-2-t-butylindoline and 1,3,3-Trimethyl-2-methyleneindoline.**

By B. Robinson.

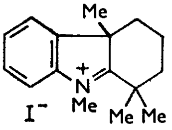
1,2,3,4,10,11-Hexahydro-10-hydroxy-1,1,9,11-tetramethylcarbazole (I), 2-hydroxy-1,3,3-trimethyl-2-t-butylindoline (III; R = Bu^{t}), and 1,3,3-trimethyl-2-methyleneindoline (XII) are autoxidised to oxindole derivatives which in the last two cases are shown to be 1,3,3-trimethyloxindole (V). 2-Hydroxy-1,3,3-trimethyl-2-phenylindoline (III; R = Ph) and 2-hydroxy-1,3,3-trimethylindoline (III; R = H) are not autoxidised.

It has been observed[1] that 1,2,3,4,10,11-hexahydro-10-hydroxy-1,1,9,11-tetramethylcarbazole (I), obtained by treatment of 2,3,4,11-tetrahydro-1,1,9,11-tetramethyl-1*H*-carbazolium iodide[2] (II) with alkali, is quantitatively converted into an oxindole derivative on exposure to air and light for 4 hr. This transformation was shown[1] to be dependent on oxygen, but attempts to purify the product as a preliminary step in the structural investigation failed. Formation of formaldehyde during the autoxidation was, however, detected by odour, and the possibility that the product contained a hydroperoxide group was shown to be unlikely since treatment with 2-ethoxy-1,2-dihydro-1-methyl-6,8-dinitroquinoline[3] gave only unchanged reagent. A simple analogue of (I), 2-hydroxy-1,3,3-trimethyl-2-t-butylindoline (III; R = Bu^{t}), has therefore now been synthesised in order to investigate this autoxidation.

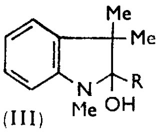
Fischer cyclisation of ethyl t-butyl ketone[4] phenylhydrazone under non-catalytic thermal conditions[5] gave 3-methyl-2-t-butylindole which was converted into the Grignard derivative with methylmagnesium iodide and methylated with methyl iodide in refluxing benzene, to give 3,3-dimethyl-2-t-butyl-3*H*-indole. Quaternisation of this base with methyl iodide in a sealed tube at 100° gave 1,3,3-trimethyl-2-t-butyl-3*H*-indolium iodide (IV) which on basification gave compound (III; R = Bu^{t}) as colourless rosettes.



(I)



(II)



(III)

On exposure to air and sunlight this compound soon became pink and was, after 24 hr., completely converted into a red oil whose infrared spectrum was superimposable on that of authentic 1,3,3-trimethyloxindole (V);[6] this transformation was both oxygen-dependent and photocatalytic. Decoloration of the oil by partition between 4N-hydrochloric acid and ether afforded the oxindole (V) in 62% yield [from (IV)]. The formation of the oxindole (V) from the base (III; R = Bu^{t}) involves rupture of the 2,10-bond, and investigation of the gaseous products formed during the autoxidation showed that the liberated t-butyl group gave rise to a mixture of methane with ethylene or ethane, three unidentified C_2, C_3, or C_4 hydrocarbons, isobutene, and formaldehyde.

Possible mechanisms for the autoxidation of compound (III; R = Bu^{t}) [and by analogy for the autoxidation of (I)] are: (*a*) Removal of the hydrogen atom from the hydroxyl group by the oxygen diradical to give a radical (VI), which by homolysis of the

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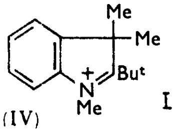
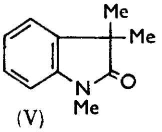
* A preliminary communication of this work has appeared: Robinson, *Chem. and Ind.*, 1962, 1291.

[1] Robinson, Ph.D. Thesis, Manchester, 1960.
[2] Robinson and Smith, *J.*, 1960, 4574.
[3] Rieche, Schmitz, and Dietrich, *Chem. Ber.*, 1959, **92**, 2239.
[4] Whitmore, Noll, and Meunier, *J. Amer. Chem. Soc.*, 1939, **61**, 683.
[5] Fitzpatrick and Hiser, *J. Org. Chem.*, 1957, **22**, 1703.
[6] Julian, Pikl, and Boggess, *J. Amer. Chem. Soc.*, 1934, **56**, 1797.

2,10-bond as shown yields the oxindole (V) and a t-butyl radical which further reacts under the autoxidation conditions giving the mixture of gases detected (either this radical or one formed by its degradation could also lead to a chain mechanism). (*b*) Intrusion of the oxygen diradical between the 2,10-bond to afford a peroxide (VII) which, on subsequent homolysis of the O–O bond as shown, followed by loss of hydroxyl radical, gives the oxindole (V) and a t-butoxy-radical which would be expected to give rise to acetone amongst other products. The failure to detect acetone during the autoxidation casts doubt on the second postulate.

The complexity of the gases liberated probably accounts for the failure[1] to purify the oxindole product of autoxidation of the carbazole (I) which, if a similar autoxidation mechanism operates, is probably a mixture of 1,3-dimethyloxindoles with 3-substituents arising from the intermediate isohexyl radical 3-substituent.


(IV)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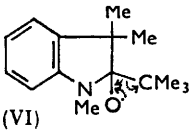
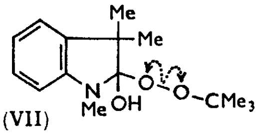
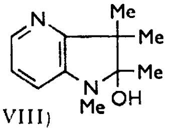
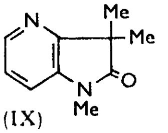

(VI)

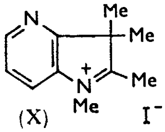

(VII)

The report[7] that 2,3-dihydro-2-hydroxy-1,2,3,3-tetramethyl-1,4-diazaindene (VIII), m. p. 91°, becomes pink and liquefies on exposure to air is probably a further instance of this type of autoxidation, leading here to the formation of the oxindole analogue (IX).

Both 2-hydroxy-1,3,3-trimethyl-2-phenylindoline[8] (III; R = Ph), the synthesis of which paralleled that of (III; R = Bu^t) starting from propiophenone phenylhydrazone through a series of known intermediates, and 2-hydroxy-1,3,3-trimethylindoline[9,10] (III; R = H) were recovered unchanged after exposure to air and sunlight. This failure to autoxidise could be due to the greater bond energies of the Ph–C and H–C bonds in these compounds with respect to the corresponding C–C bonds in (I) and (III; R = Bu^t).[11] Alternatively, the steric effect of the t-butyl group in (III; R = Bu^t) or its equivalent in (I) may be a decisive factor in the autoxidation of these compounds, although this is unlikely in view of the suggested analogous autoxidation of (VIII) to (IX).


(VIII)


(IX)


(X)

Although the iodide (X) on treatment with N-sodium hydroxide gives the hydroxy-amine (VIII),[7] ultraviolet and infrared spectral examination showed that, on similar treatment of 1,2,3,3-tetramethyl-3*H*-indolium iodide (XI) with base, 1,3,3-trimethyl-2-methyleneindoline (XII) was produced exclusively, either by proton extraction from C-10 rather than addition of hydroxyl anion to C-2 of (XI), or by spontaneous dehydration of the corresponding 2-hydroxyindoline initially produced. On exposure to air and sunlight the colourless base (XII) rapidly began to redden, as observed previously[12-14] with this compound, and was, over a period of 10 days, completely converted into a deep red oil whose infrared spectrum was almost identical with that of authentic compound (V).[6] This oil afforded the oxindole (V) in 41% yield [from (XI)] and a small quantity of an

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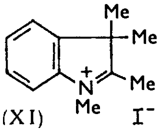
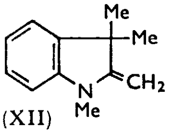
[7] Ficken and Kendall, *J.*, 1961, 584.
[8] Leuchs, Heller, and Hoffmann, *Ber.*, 1929, **62**, 871.
[9] Ciamician and Piccinini, *Ber.*, 1896, **29**, 2465.
[10] Brunner, *Monatsh.*, 1896, **17**, 255.
[11] Walling, " Free Radicals in Solution," Wiley, New York, 1957, p. 50.
[12] Brunner, *Ber.*, 1898, **31**, 612.
[13] Brunner, *Monatsh.*, 1900, **21**, 156.
[14] Plancher, *Ber.*, 1898, **31**, 1488.

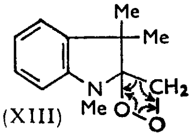
acid- and ether-insoluble red-purple solid. As expected, this reaction was oxygen-dependent, but unlike the autoxidation of (III; R = Bu^t) it was not photocatalytic.



(XI)



(XII)



(XIII)

A possible mechanism for this autoxidation would involve addition of the oxygen diradical across the exocyclic methylene group of (XII) to give (XIII) which could dissociate as shown to give the oxindole (V) and formaldehyde, the formation of which during the autoxidation was detected. It is likely that similar autoxidation of related enamines, which have previously been observed to redden on aerial exposure, (cf., *e.g.*, refs. 1, 7, 14—16) occurs.

EXPERIMENTAL

1,2,3,4,10,11-*Hexahydro*-10-*hydroxy*-1,1,9,11-*tetramethylcarbazole* (I) *and its Autoxidation*.—2,3,4,11-Tetrahydro-1,1,9,11-tetramethyl-1*H*-carbazolium iodide[2] (II) (145 mg.) in water (15 c.c.) was treated with an excess of 3N-sodium hydroxide, the liberated pseudo-base then being extracted with ether (2 × 15 c.c.). After drying and removal of the ether, the *base* (I) was obtained as a colourless oil (in quantitative yield) which was immediately distilled [b. p. 80—90° (bath-temp.)/0·01 mm.] (Found: C, 77·9; H, 9·45. $C_{16}H_{23}NO$ requires C, 78·35; H, 9·45%) and had $\lambda_{max.}$ 259, 307—308 mμ (ε 9320, 2160, respectively, in ethanol). On storage in air and sunlight the viscosity of the oil increased and after 4 hr., when conversion into an oxindole derivative was quantitative (ultraviolet and infrared spectra), a gum remained. Attempts to crystallise or distil this failed.

The base (I) was unchanged after storage in an evacuated sealed tube for 3 weeks, but on subsequent exposure to air and sunlight autoxidation occurred as above.

3-*Methyl*-2-*t-butylindole*.—Ethyl t-butyl ketone[4] (34 g.) and redistilled phenylhydrazine (35 g.) were mixed and added to redistilled monoethylene glycol (500 c.c.). The solution was then refluxed until the evolution of ammonia had ceased (9 days).[5] After cooling, water (2·5 l.) was added and the liberated oil extracted with ether (3 × 250 c.c.). The combined ether extracts were washed with 2N-hydrochloric acid (3 × 200 c.c.), water (2 × 250 c.c.) and dried, and the solvent was removed to leave a dark-brown oil (51 g.). Addition of picric acid (50 g.) to this oil in benzene afforded deep red needles (39·2 g., 31%), m. p. 148—150° (sublimation from 98°). A second crop (7·8 g., 6%), m. p. 147—150° (sublimation from 101°), was obtained by concentration of the mother-liquors. A further recrystallisation from benzene gave deep red needles, m. p. 151° (sublimation from 102°) (Found: C, 54·4; H, 4·8; N, 14·2. $C_{19}H_{20}N_4O_7$ requires C, 54·8; H, 4·8; N, 13·5%). Decomposition of the *picrate* by partition between dilute aqueous ammonia and ether followed by passage of the ethereal solution through an alumina (grade H) column, drying, and removal of the solvent gave the *indole* as a pale yellow oil, b. p. 152—154°/12 mm. (Found: C, 83·6; H, 9·2. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%), $\lambda_{max.}$ 228—229, 286 mμ, $\lambda_{infl.}$ 292 mμ (ε 36,000, 7600, 6800, respectively, in ethanol).

3,3-*Dimethyl*-2-*t-butyl*-3H-*indole*.—A solution of 3-methyl-2-t-butylindole (6·6 g.) in dry ether (25 c.c.) was added to an ether solution of methylmagnesium iodide (from 1·5 g. of magnesium and 9·0 g. of methyl iodide in 30 c.c. of ether). After the vigorous evolution of methane had subsided, the solution was refluxed for ¾ hr. and the ether then allowed to distil off. Dry benzene (24 c.c.) was added and the solution was refluxed whilst methyl iodide (30 c.c.) was added dropwise during 1 hr. After a further 3 hours' refluxing, ether (50 c.c.) was added, followed by ice and dilute acetic acid. The ether–benzene layer was extracted with 3N-hydrochloric acid (3 × 75 c.c.), the combined acid extracts were basified by careful addition of sodium hydroxide pellets, and the liberated base was extracted with ether (2 × 100 c.c.). The dried ether extract yielded a pale-yellow oil (6·0 g., 85%) which was dissolved in ethanol (30 c.c.) containing picric acid (6·5 g.). The crystalline picrate formed had m. p. 168—171°

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[15] Brunner, *Ber.*, 1898, **31**, 1943.

[16] Boyd-Barrett, *J.*, 1932, 321.

(sublimation from 135°) (9·8 g., 64%). A further crop, m. p. 167—171° (sublimation from 137°) (1·6 g., 10%), was obtained by concentration of the mother-liquors. The pure *picrate* crystallised from ethanol as yellow needles, m. p. 169—171° (sublimation from 134°) (Found: C, 55·6; H, 4·85; N, 13·2. $C_{20}H_{22}N_4O_7$ requires C, 55·8; H, 5·15; N, 13·0%).

The *base*, liberated from the pure picrate, was obtained as a colourless oil, b. p. 142—144°/12 mm. (Found: C, 83·7; H, 9·3. $C_{14}H_{18}N$ requires C, 83·6; H, 9·5%), $\lambda_{max.}$ 259 mμ (ε 6300 in ethanol), $\lambda_{max.}$ 234, 286, $\lambda_{infl.}$ 239 mμ (ε 5900, 5500, 6000, respectively, in ethanol–hydrochloric acid).

The *methiodide* (IV) was prepared by heating the base (1·1 g.) in methyl iodide (6 c.c.) in a sealed tube at 100° for 4 hr. (longer heating led to extensive decomposition). The product (0·72 g., 38%) was crystallised once from methanol–ether, to give colourless needles, m. p. 189—190° (Found: C, 51·9; H, 6·0; N, 3·95. $C_{15}H_{19}NI$ requires C, 52·4; H, 6·4; N, 4·1%).

*2-Hydroxy-*1,3,3-*trimethyl-*2-*t-butylindoline* (III; R = Bu^t) *and its Auoxidation.*—The above methiodide (470 mg.) was dissolved in water (10 c.c.), and the solution basified by the addition of an excess of 3N-sodium hydroxide. The liberated pseudo-base was extracted with ether (2 × 10 c.c.), the combined ether extracts, after drying and removal of the solvent, yielding compound (III; R = Bu^t) as a colourless oil which soon completely crystallised in rosettes, m. p. 58—61°, $\lambda_{max.}$ 250, 298 (ε 8500, 3400 respectively in ethanol), $\lambda_{max.}$ 234, 241, 284 mμ (ε 5300, 5100, 6100, respectively, in ethanol–hydrochloric acid), $\nu_{max.}$ (in Nujol) 3520 ± 10m (OH) cm.$^{-1}$. On exposure to air and sunlight the rosettes soon became pink [an elemental analysis was therefore not performed] and were, after 24 hr., converted into a red oil whose infrared spectrum (liquid film) was superimposable upon that of the oxindole (V). This oil was dissolved in ether (10 c.c.), the ethereal solution being washed with 3N-hydrochloric acid (2 × 10 c.c.) and water (10 c.c.), dried, and evaporated, to give compound (V) as a pale yellow oil [155 mg., 62% from (IV)] which crystallised on being seeded and was proved identical by m. p., mixed m. p., ultraviolet and infrared spectra with an authentic specimen.[6] When compound (III; R = Bu^t) was kept in an evacuated sealed tube or exposed to air in the dark for 4 days, no oxindole formation was detected spectroscopically, the only change being a pink coloration. On subsequent exposure to air and sunlight both samples readily underwent autoxidation as described above. By passage of oxygen over the compound in sunlight and collection of the gaseous products at −78° [solid carbon dioxide–light petroleum (b. p. 60—80°)] gas analysis of the condensate by infrared spectroscopy and vapour-phase chromatography with a 17% squalene–Celite column detected methane, ethylene or ethane, isobutene, and 3 unidentified C_2, C_3, or C_4 hydrocarbons. By passage of the gaseous products into a solution of chromotropic acid in 12N-sulphuric acid, formaldehyde was detected.[17]

3-*Methyl-*2-*phenylindole.*—This was prepared by the method used for 3-methyl-2-t-butylindole. Refluxing propiophenone (53·6 g.) and redistilled phenylhydrazine (43·2 g.) in redistilled monoethylene glycol (600 c.c.) for 48 hr. gave the indole (41·7 g., 50%) as prisms, m. p. 92—93° (lit.,[18] 93—95°) [from light petroleum (b. p. 60—80°) with charcoal].

3,3-*Dimethyl-*2-*phenyl-*3H-*indole.*—By the method used for 3,3-dimethyl-2-t-butyl-3*H*-indole, 3-methyl-2-phenylindole (14·6 g.) yielded the 3*H*-indole (13·4 g., 86%), an oil, b. p. 160—170° (bath temperature)/10 mm. (lit.,[19] 141—145°/1·5 mm.). The picrate crystallised from methanol as yellow prisms, m. p. 152—154° (sintering from 135°) (lit., 158—160°,[8] 153—155° [19]). The methiodide was obtained by quaternisation with methyl iodide in a sealed tube at 100° [8] and crystallised from methanol–ether as yellow needles, m. p. 206—208° (lit.,[8] 203°).

2-*Hydroxy-*1,3,3-*trimethyl-*2-*phenylindoline* (III; R = Ph).—By the method described for the preparation of (III; R = Bu^t), the above methiodide (3·32 g.) gave the pseudo-base (III; R = Ph) (1·60 g., 69%), which crystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 108—109° (lit.,[8] 107—108°), unchanged on exposure to air and sunlight.

2-*Hydroxy-*1,3,3-*trimethylindoline* (III; R = H).—Reduction of compound (V) with sodium in ethanol [9] afforded the pseudo-base (III; R = H) as prisms [from light petroleum (b. p. 60—80°)], m. p. 80—92°, unchanged by further recrystallisation (lit., 97—98°,[9] 95° [10]) (Found: C, 74·7; H, 8·5. Calc. for $C_{11}H_{15}NO$: C, 74·55; H, 8·55%), which remained unchanged on exposure to air and sunlight.

1,3,3-*Trimethyl-*2-*methyleneindoline* (XII) *and its Autoxidation.*—Treatment of the iodide [12]

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[17] Feigl, " Spot Tests in Organic Analysis," Elsevier Publ. Co., Amsterdam, 1960, p. 349.

[18] Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, **67**, 1203.

[19] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.

(XI) (497 mg.) with an excess of 3N-sodium hydroxide afforded the oily base[13] (XII), $\nu_{max.}$ (film) 1650 ± 5s (exocyclic C=C), that soon became red in air. After 10 days' exposure, a deep red oil resulted having $\nu_{max.}$ (film) 1710 ± 5s (oxindole C=O) but no band at 1650 ± 5 cm.$^{-1}$. This spectrum was almost identical with that of the oxindole (V). Partition of the red oil between 3N-hydrochloric acid (10 c.c.) and ether (10 c.c.) left a trace of insoluble red-purple solid. The ethereal layer was washed with 3N-hydrochloric acid (10 c.c.) and water (10 c.c.) and dried. Removal of the solvent gave the oxindole (V) (119 mg., 41% from the methiodide) which crystallised and was fully identified as usual. Formaldehyde was detected as above during the autoxidation. The base was unchanged (spectra) after 3 days *in vacuo* although it had become pink and autoxidised later in air. It also autoxidised in air in the dark.

This work was carried out during the tenure of an I.C.I. Research Fellowship. The gas analysis was performed by Dr. R. B. Cundall and Mr. P. A. Griffiths.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 2nd,* 1962.]