117. *Photochemical Transformations. Part XII.* The Photolysis of Azides.*

By D. H. R. Barton and L. R. Morgan, jun.

The photolysis of non-aromatic azides affords " activated " nitrenes which, in general, react further by three different routes: (A) isomerisation to imine, (B) hydrogen abstraction from the solvent to give amine, and (C) 1,5-hydrogen abstraction followed by cyclisation to pyrrolidines. The latter route has been shown to provide convenient and simple syntheses of proline and conessine. The general scope of the reaction by route (C) has been examined and the reactivity of nitrenes and carbenes has been compared. The mechanism of the cyclisation of " activated " nitrenes to pyrrolidines has been studied and evidence for a diradical intermediate secured. A preliminary account of this work has already appeared.[1]

The main objective of the work described in the present paper was the synthesis of the steroidal alkaloid conessine (XII).[2] Before this could be accomplished it was necessary to design a new reaction for the construction of the pyrrolidine ring. It is true that this structural feature has been synthesised before, by the Hofmann–Freytag–Loeffler reaction,[3] but only the preparation of saturated derivatives of conessine was reported. This is presumably because the exacting conditions of the reaction, and also its mechanism,[3] preclude work with unsaturated precursors such as would be required for a true conessine synthesis.

We felt that the photolysis of azides (as I) would furnish " activated " nitrenes (as II)[4] which would be transformed into stable molecular products in various ways.[5] First, nitrenes can be stabilised by 1,2-hydrogen migration to furnish imines (as III) (route A). The second possibility, especially if the nitrene is " activated," is hydrogen abstraction, for example from solvent, to furnish amines (as IV) (route B). The third, and desired, path (route C) would be by internal 1,5-hydrogen shift, suitably through a diradical (as V), to give pyrrolidines (as VI). We have, in fact, been able to observe all these reactions. First, however, it is convenient to describe several exploratory experiments designed to examine the chemical behaviour of " activated " nitrenes.

The photolysis of hydrazoic acid in benzene affords aniline, although the yield is poor.[6] In comparable reactions the photolysis of n-butyl and n-octyl azide in benzene was studied. The expected *N*-n-butyl- (22%) and *N*-n-octyl-aniline (31%) were obtained. The procedure is convenient for preparing such monosubstituted anilines. We have also confirmed that the photolysis of phenethyl azide in cyclohexane,[7] followed by reduction with lithium aluminium hydride to convert the imine into an amine, affords only phenethylamine and no significant amount of indoline. In contrast, we find that the photolysis of 3-phenylpropyl azide gives tetrahydroquinoline (21%).

The photolysis of n-propyl azide in cyclohexane afforded propionaldehyde imine, isolated as propionaldehyde 2,4-dinitrophenylhydrazone (59%). The corresponding reaction on n-butyl azide (I; R = H) gave (in ethanol, 22%; in ether, 14%) pyrrolidine

* Part XI, *J.*, 1961, 3313.

[1] Barton and Morgan, *Proc.*, 1961, 206.

[2] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115, and other papers by Haworth, McKenna, and their collaborators; see also Fieser and Fieser, " Steroids," Reinhold Publishing Corpn., New York, 1959, pp. 857 *et seq.*

[3] Buchschacher, Kalvoda, Arigoni, and Jeger, *J. Amer. Chem. Soc.*, 1958, **80**, 2905; Buzzetti, Wicki, Kalvoda, and Jeger, *Helv. Chim. Acta*, 1959, **42**, 388; Corey and Hertler, *J. Amer. Chem. Soc.*, 1958, **80**, 2903; 1959, **81**, 5209.

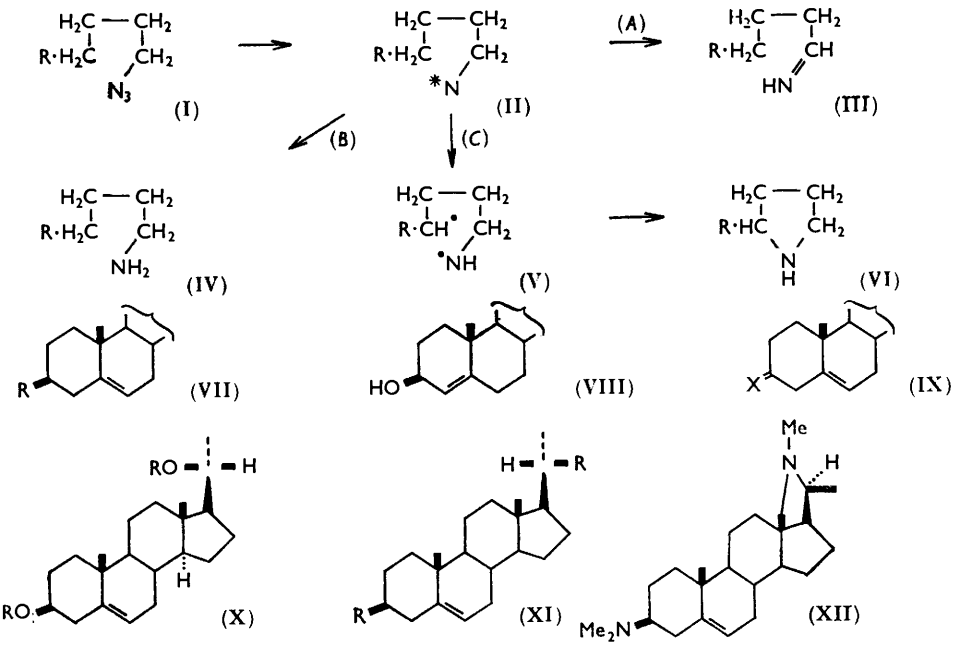
[4] Cf. Smolinsky, *J. Amer. Chem. Soc.*, 1960, **82**, 4717; 1961, **83**, 2489.

[5] Boyer and Canter, *Chem. Rev.*, 1954, **54**, 1.

[6] Cf. Keller and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 1122.

[7] Smith and Brown, *J. Amer. Chem. Soc.*, 1951, **73**, 2435.

(VI; R = H) (route C above). In addition some imine was formed (12% and 16%, respectively). In this and subsequent cases imines were characterised and determined as the corresponding 2,4-dinitrophenylhydrazones. n-Heptyl azide (I; R = Pr^n) furnished 2-propylpyrrolidine (VI; R = Pr^n) (15%) when cyclohexane was used as solvent, as well as heptanal imine (45%). With these preliminary experiments (in which no attempt was made to find optimum conditions) completed, a more systematic study was made of the conversion of n-octyl azide (I; R = Bu^n) into 2-butylpyrrolidine (VI; R = Bu^n) by route C. The results are summarised in the Table. The best solvent appears to be cyclohexane and this was indeed used in most of the sequential investigations.



We have, of course, checked that all the photolyses reported in this paper owe nothing to thermal reactions. It was, however, possible that the thermal decomposition of azides would furnish nitrenes which could react by route C instead of by route A. Indeed, one

Transformation of n-octyl azide into 2-butylpyrrolidine.

Solvent *	Yield (%)	Solvent *	Yield (%)
Ethanol	34	Cyclohexane	35
Ether	25	Glacial acetic acid	5
Dimethylformamide	17	Ethanolic hydrogen chloride	0[a]
Tetrahydrofuran	31	Ethanolic sodium hydroxide	0[b]

* 1% solutions. [a] Imine 45%. [b] Imine 37%.

or two examples of this kind are already known [4,7] in the thermal decomposition of aromatic azides where the competition with route A is, of course, not available. However, in a test case, the thermal decomposition of n-octyl azide in n-hexadecane [4] at 230° gave n-octanal imine (32%), but no detectable amount of the pyrrolidine (VI; R = Bu^n).

We were now in a position to test the utility of the reaction in the synthesis of natural products. First, we report a simple synthesis of proline (VI; R = CO_2H). Cyclopentanone was converted into the corresponding lactone and thence into ethyl δ-bromovalerate. Displacement with azide ion furnished ethyl δ-azidovalerate (I; R = CO_2Et). On photolysis this gave a basic fraction affording ethyl 1-toluene-*p*-sulphonylproline

on treatment with toluene-*p*-sulphonyl chloride. Hydrolysis of the latter gave proline (VI; R = CO_2H) in an overall yield (from the azide) of 15%.

Secondly, we describe the synthesis of conessine. Some preliminary experiments were required here in order to control the functionality of rings A and B. Treatment of cholesterol toluene-*p*-sulphonate (VII; R = *p*-$C_6H_4Me{\cdot}SO_3$) with azide ion gave 3β-azidocholest-5-ene (VII; R = N_3), the constitution of which was proved by reduction with lithium aluminium hydride to the known 3β-aminocholest-5-ene [8] (VII; R = NH_2). Substitution without inversion is thus demonstrated, no doubt because of the cyclosteroid phenomenon.[9] Irradiation of 3β-azidocholest-5-ene (VII; R = N_3) in ethanol, followed by removal of the ethanol and reduction with lithium aluminium hydride in ether, gave 3β-aminocholest-5-ene (VII; R = NH_2) (33%) and cholest-4-en-3β-ol (VIII) (20%). Photolysis in cyclohexane and similar further processing afforded the amine (VII; R = NH_2) (22%) and the alcohol (VIII) (13%). We consider that the 3β-" activated " nitrene either removes hydrogen from the solvent (route B) or rearranges to the imine (IX; X = NH) (route A). Route C is not available to it for conformational reasons. Traces of water present must permit the hydrolysis of the imine to the corresponding ketone (IX; X = O), which, in these particular experiments, rearranged to the conjugated isomer and thus ended, after reduction, as the alcohol (VIII).

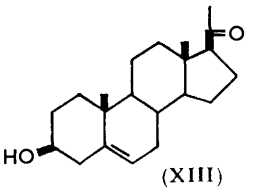
The above results show that it is possible to convert a 3β-hydroxy-5-ene system in a steroid into a 3β-amino-5-ene system through an intermediate azide in a not unreasonable overall yield. We therefore next took the known pregn-5-ene-3β,20β-diol [10] (X; R = R′ = H), made therefrom the ditoluene-*p*-sulphonate (X; R = *p*-$C_6H_4Me{\cdot}SO_2$), and treated this with azide ion, to give 3β,20α-bisazidopregn-5-ene (XI; R = N_3). The constitution and stereochemistry of this compound were proved by reduction with lithium aluminium hydride, followed by *N*-methylation with formic acid and formaldehyde to the known 3β,20α-bisdimethylaminopregn-5-ene [11] (XI; R = NMe_2).

Photolysis of 3β-20α-bisazidopregn-5-ene (XI; R = N_3) in cyclohexane, removal of the solvent, reduction with lithium aluminium hydride in tetrahydrofuran, *N*-methylation of the product with formic acid–formaldehyde, and chromatography gave two well-defined compounds. Elution with chloroform–benzene gave conessine (XII), the identity of which was established by comparison with an authentic specimen kindly provided by Professor R. D. Haworth, F.R.S. Before conessine was eluted from the column there came 3β-hydroxypregn-5-en-20-one (XIII). Remethylation of the non-crystalline fractions, and further chromatography gave a little more conessine (total yield, 4·5%) as well as additional hydroxypregnenone (XIII). The origin of the latter has not been established but it may well be derived from the imine-ketone (XIV): if this resists reduction at the 20-imino-group for steric reasons, then the hydroxypregnenone (XIII) could well be formed on reduction and *N*-methylation (hydrolysis of $\rangle C{=}NMe$, or equivalent process). An example of the hydrolysis of a 3-imino-group has already been discussed (see above). We may add that the conessine synthesis was repeated several times with the same results.

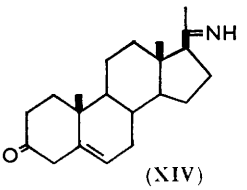
Having established that the photolysis of azides can give useful results, we extended the range of examples. All the reactions were carried out in cyclohexane, unless specified to the contrary. Photolysis of cyclopentyl azide gave cyclopentanone imine (55%) (route A) as well as the trimer (XV) (5%). Photolysis of cyclohexyl azide gave cyclohexanone imine (51%) (route A) and cyclohexylamine (33%) (route B); in ethanol the respective yields were 21% and 45%. Cycloheptyl azide on photolysis followed by reduction with lithium aluminium hydride afforded cycloheptanol (15%), derived from adventitious hydrolysis of cycloheptanone imine and then reduction, as well as cycloheptylamine (53%)

[8] See Julian, Magnani, Meyer, and Cole, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.
[9] Fieser and Fieser, ref. 2, pp. 314 *et seq.*
[10] Klyne and Miller, *J.*, 1950, 1972; Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 2283.
[11] Cerny, Habler, and Šorm, *Chem. Listy*, 1957, **51**, 2344.

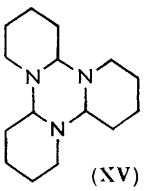
(routes A and B). In spite of a careful search, no evidence for the formation of nortropane (XVI) could be secured. (+)-Neomenthyl azide (XVII), readily prepared from (−)-menthyl toluene-*p*-sulphonate by azide ion displacement, gave on photolysis a trace of (−)-menthone (route A) and mainly (+)-neomenthylamine (50%) (route B). Irradiation of allyl azide afforded acraldehyde imine (52%) (route A).



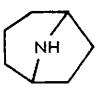
(XIII)



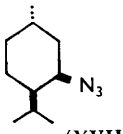
(XIV)



(XV)

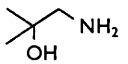


(XVI)



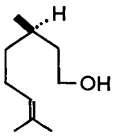
(XVII)

(XVIII)

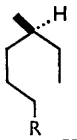


(XIX)

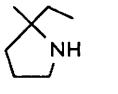
(XX)



(XXI)



(XXII)



(XXIII)

We also examined the irradiation of ethyl (±)-α-azidopropionate. It will be recalled that photolysis of the corresponding optically active amides with circularly polarised light was one of the classical experiments by W. Kuhn [12] on possible modes of formation of optically active compounds *de novo*. Although the selective destruction of the azide grouping was effected in Kuhn's experiments, we are not aware that the photochemical reaction involved was ever defined. In fact, we find that ethyl α-azidopropionate gives ethyl pyruvate imine (34%) by route A. Presumably the same reaction was under investigation by Kuhn *et al.*[12] when they examined the corresponding amide.

If one accepts that photolysis of azides affords " activated " nitrenes, then it is instructive to see how far the chemistry of these intermediates parallels that of the analogous carbenes. The attack of the nitrenes upon aromatic rings, already exemplified, is one such parallel with carbene chemistry. Another parallel would be addition to olefinic linkages to furnish ethyleneimines. In preliminary experiments, we have looked for this reaction but so far it has not been found. A further parallel with carbene chemistry has, however, been discovered in the photolysis of t-butyl azide. We were able to isolate 1,1-dimethylethylenimine (XVIII) (as the picrate, 12%) as well as the ring-opened derivative (XIX) (as the picrate, 5%). The classical experiments of Whitmore *et al.*[13] on the formation of 1,1-dimethylcyclopropane by the action of base on neopentyl chloride are known [14] to involve cyclisation of the carbene (XX; X = CH). The formation of the ethylenimine (XVIII) represents a corresponding cyclisation of the nitrene (XX; X = N).

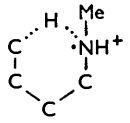
This nitrene cyclisation is probably best regarded as a bond insertion, in contrast to the proposed course of the reaction of nitrenes by route C above, where a diradical intermediate (as V) is postulated. Bond insertion, by definition, implies retention of stereochemistry whereas a diradical intermediate (as V) would be expected to lead to an equilibrated or racemic product. We have secured information on the stereochemical course of route C reactions in the following way.* Naturally occurring (+)-citronellol (XXI) was converted into its toluene-*p*-sulphonate. Ozonolysis of the latter and reduction of the ozonide gave (+)-4-methylhexanol [15] (XXII; R = OH). Conversion into the

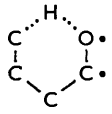
* We thank Dr. P. Kabasakalian (Schering Corpn., Bloomfield, New Jersey) for pointing out in discussion that (+)-citronellol is a convenient starting material for investigations of the kind reported herein.

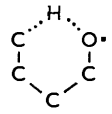
[12] W. Kuhn and Knopf, *Z. physiol. Chem.*, 1930, **7**, *B*, 292; *Naturwiss.*, 1930, **18**, 183.
[13] Whitmore and Zook, *J. Amer. Chem. Soc.*, 1942, **64**, 1783, and earlier papers.
[14] Friedman and Berger, *J. Amer. Chem. Soc.*, 1961, **83**, 501.
[15] Cason, Brewer, and Pepper, *J. Org. Chem.*, 1948, **13**, 239.

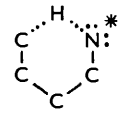
toluene-*p*-sulphonate and displacement with azide ion afforded the corresponding azide [16] (XXII; R = N_3). Photolysis of this azide in cyclohexane gave (+)-4-methylhexylamine, isolated as the hydrochloride [17] (35%), and 2-ethyl-2-methylpyrrolidine (XXIII), likewise isolated as its hydrochloride (16%) and further characterised as its 3,5-dinitrobenzoyl derivative. The hydrochloride and 3,5-dinitrobenzoyl derivative were devoid of optical activity and therefore racemic. These experiments exclude a bond-insertion mechanism, according to our definition of bond insertion, and support the existence of the diradical intermediate (as V) already discussed.

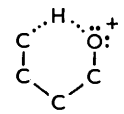
The " activated " nitrene reactions reported in the present paper have something in common with a number of other reactions useful for attacking " unactivated " C–H bonds. The classical Hofmann–Freytag–Loeffler reaction [18] involves the preferred transition state (XXIV). The photochemically induced cyclisation of ketones [18] to cyclobutanols requires the transition state (XXV). The activated alkoxyl radicals derived from nitrite photolysis [19] demand the transition state (XXVI). Photolysis of hypochlorites [20] requires the same arrangement of atomic nuclei. The rearrangement of activated nitrenes described in the present paper demands transition state (XXVII). The formation of tetrahydrofurans from the oxidation of alcohols by lead tetra-acetate [18] is, formally, comparable with the route C reactions reported above. We consider that such oxidations are best regarded as reactions of 6-electron positive oxygen as in transition state (XXVIII). In all these reactions a transition state containing six atomic nuclei is either preferred or


(XXIV)


(XXV)


(XXVI)


(XXVII)


(XXVIII)

mandatory. We believe that an important conformational requirement is involved which must be satisfied if reactions of the kind herein under discussion are to proceed smoothly. The " six " conformational factor must either be provided by the preferred conformation of the starting material or by a conformation which is easily populated as a result of thermal equilibration. For example, aliphatic compounds, where opposed conformations are relatively easily available, undergo the reactions of types (XXIV) through (XXVIII) without difficulty, whereas simple cyclohexyl derivatives, in general, do not. This is because the required " six " conformation, here the boat form, is not available in sufficient concentration.*

Experimental

Ultraviolet absorption spectra were obtained for ethanol solutions on the Unicam S.P. 500 spectrophotometer. Unless specified to the contrary, the light petroleum used was of b. p. 40—60°. M. p.s were determined on the Kofler block. Unless stated otherwise, alumina (grade 3), standardised according to Brockmann and Schodder,[21] was used for chromatography. $[\alpha]_D$ are for $CHCl_3$ solutions.

* The theme developed in this last paragraph was part of a lecture delivered by one of us (D. H. R. B.) at the Annual General Meeting of the Chemical Society, at Liverpool in April, 1961 (see *Proc. Chem. Soc.*, 1961, 197).

[16] Levene and Rothen, *J. Biol. Chem.*, 1936, **115**, 415.
[17] Levene and Marker, *ibid.*, 1936, **115**, 267.
[18] For references see Schaffner, Arigoni, and Jeger, *Experientia*, 1960, **16**, 169.
[19] For references see Nussbaum and Robinson, *Tetrahedron*, 1961, in the press.
[20] Greene, Savitz, Lan, Osterholtz, and Smith, *J. Amer. Chem. Soc.*, 1961, **83**, 2196; Walling and Padura, *ibid.*, p. 2207; Akhtar and Barton, *ibid.*, p. 2213; Mills and Petrow, *Chem. and Ind.*, 1961, 946; Jenner, *J. Org. Chem.*, in the press.
[21] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

Preparation of Azides.—Ethyl α-azidopropionate,[22] n-propyl,[23] n-butyl,[23] n-heptyl,[24] n-octyl,[24] cyclopentyl,[23] cyclohexyl,[23] cycloheptyl,[23] allyl,[25] phenethyl,[7] and 3-phenylpropyl [26] azide were prepared according to the literature cited. The procedure used for the preparation of *t-butyl azide*, b. p. 68—71°, n_D^{23} 1·3865 (Found: C, 48·3; H, 9·1; N, 42·6. $C_4H_9N_3$ requires C, 48·45; H, 9·15; N, 42·4%), was essentially that of Henkel and Weygand.[27]

A solution of cholesteryl toluene-*p*-sulphonate (7 g.) in 0·92M-methanolic lithium azide [28] (200 ml.) was refluxed for 24 hr., filtered, evaporated to ~100 ml., diluted with water (200 ml.), and extracted with ether. Evaporation of the combined dried ethereal extracts resulted in an oil which was chromatographed over alumina. Elution with light petroleum and crystallisation from acetone gave 3β-*azidocholest-5-ene* (3 g., 57%), m. p. 61—63°, $[\alpha]_D^{25}$ −19° (*c* 1·71), $\lambda_{max.}$ 270 mμ (log ε 1·75), $\nu_{max.}$ (in Nujol) 2110 (azide) cm.$^{-1}$ (Found: C, 78·9; H, 11·1; N, 10·0. $C_{27}H_{45}N_3$ requires C, 78·75; H, 11·0; N, 10·2%). Reduction of 3β-azidocholest-5-ene with lithium aluminium hydride in ether [29] gave 3β-aminocholest-5-ene,[8] m. p. 89—93°, $[\alpha]_D^{25}$ −24·6° (*c* 1·15).

A solution of (−)-menthyl toluene-*p*-sulphonate [30] (15 g.) in 0·92M-methanolic lithium azide [28] (200 ml.) was refluxed for 18 hr., filtered, evaporated to half volume, diluted with water (200 ml.), and extracted with ether. Removal of the ether gave (+)-*neomenthyl azide* (6 g., 72%) as a colourless oil, $[\alpha]_D^{26}$ +10·1° (*c* 1·10), $\lambda_{max.}$ 270 mμ (log ε 1·70), $\nu_{max.}$ (liquid) 2110 (azide) cm.$^{-1}$ (Found: C, 66·2; H, 10·6; N, 23·2. $C_{10}H_{19}N_3$ requires C, 66·25; H, 10·5; N, 23·2%). Reduction of (+)-neomenthyl azide with lithium aluminium hydride [29] in ether gave (+)-neomenthylamine,[31] b. p. 84—87° (15 mm.), $[\alpha]_D^{25}$ +15·7° (*c* 1·15) {hydrochloride, m. p. 187—188°, $[\alpha]_D^{26}$ +21·5° (*c* 1·32)}.

General Procedure for Photochemical Reactions.—Except where stated otherwise, the irradiations were carried out under oxygen-free nitrogen in a quartz flask with a 125 w mercury lamp, at the b. p. of the solvent. The flask was placed at 12 cm. from the light source. The solutions contained 0·1—1·0% of azide. Aliquot portions were removed at 30-minute intervals for measurement of ultraviolet or infrared absorption. When there was no further change the mixture was irradiated for a further 30 min. and then worked up. In each case a control experiment was carried out without irradiation. It was shown by measurements of the ultraviolet absorption as well as by the appropriate isolation of starting material that in no case was there a thermal chemical reaction.

Irradiation of Hydrazoic Acid in Benzene.—Solid sodium azide (1 g.) was dissolved in warm water (2 ml.) and to it was added benzene (40 ml.). After the mixture had cooled to 0°, concentrated sulphuric acid (0·68 g.) was added, the temperature being kept at ⩾10°. After the addition the mixture was cooled to 0° and the organic layer decanted and dried. After drying, the benzene solution was irradiated for 2 hr. at ~15°. The evolution of nitrogen bubbles began in a few minutes and continued for an hour; irradiation was continued for an additional 15 min. and then stopped. The benzene was evaporated and the remaining yellow oil distilled; it had b. p. 75—77°/20 mm., n_D^{20} 1·5889 (125 mg.). Comparison of the infrared spectra with authentic aniline proved the identity. Treatment of the oil with acetyl chloride yielded acetanilide (m. p. and mixed m. p.).

Irradiation of n-Butyl Azide.—(a) *In benzene.* The azide (3 g.) in dry redistilled benzene (300 ml.) was irradiated for 4 hr. Removal of the benzene and distillation gave *N*-n-butylaniline [32] (1·1 g., 22%), b. p. 123—125°/2 mm., n_D^{23} 1·5395 [hydrochloride, m. p. 113—115° (decomp.)].

(b) *In ethanol.* The azide (5 g.) in anhydrous absolute ethanol (350 ml.) was irradiated for 2 hr. The ethanolic solution was treated with a stream of dry hydrogen chloride, and the solvent removed. The remaining oil was steam-distilled and the distillate extracted with

[22] Forster and Fierz, *J.*, 1908, **93**, 669.
[23] Boyer, Canter, Hamer, and Putney, *J. Amer. Chem. Soc.*, 1956, **78**, 325.
[24] Lieber and Chao, *J. Org. Chem.*, 1957, **22**, 238.
[25] Forster and Fierz, *J.*, 1908, **93**, 1174.
[26] Boyer and Morgan, *J. Amer. Chem. Soc.*, 1959, **81**, 3369.
[27] Henkel and Weygand, *Ber.*, 1943, **76**, 812.
[28] Huisgen and Ugi, *Ber.*, 1957, **90**, 2914.
[29] Boyer, *J. Amer. Chem. Soc.*, 1951, **73**, 5865.
[30] Phillips, *J.*, 1925, **127**, 2584.
[31] McNiven and Read, *J.*, 1952, 153.
[32] Reilly and Hickinbottom, *J.*, 1918, **113**, 99; Hickinbottom, *J.*, 1937, 1119.

ether. Removal of the ether from the combined ethereal extracts yielded n-butyraldehyde, isolated as the 2,4-dinitrophenylhydrazone (12%) (m. p. and mixed m. p.). Neutralisation of the residue and extraction with ether yielded pyrrolidine, isolated as its picrate (22%) (m. p. and mixed m. p.).

(c) *In ether.* The azide (4 g.) in anhydrous ether was irradiated for 3 hr. The ethereal solution was treated with a stream of dry hydrogen chloride and the white precipitate collected and identified as pyrrolidine hydrochloride (700 mg., 14%), m. p. 117—119° (decomp.). Neutralisation of the hydrochloride afforded pyrrolidine (picrate, m. p. and mixed m. p.). Removal of the ether and treatment of the resulting oil with 2,4-dinitrophenylhydrazine reagent furnished the 2,4-dinitrophenylhydrazone (1·5 g., 16%) (m. p. and mixed m. p.) of butyraldehyde.

Irradiation of n-Octyl Azide.—(a) *In benzene.* The azide (3 g.) in dry redistilled benzene (100 ml.) was irradiated for 3 hr. The yellow solution was extracted with 6N-sulphuric acid (2 × 25 ml.), and the acid washings were neutralised and extracted with ether (2 × 50 ml.), yielding *N*-n-octylaniline [32] (1·2 g., 31%), b. p. 177—178°/23 mm., n_D^{25} 1·6391, identified as the toluene-*p*-sulphonyl derivative (m. p. and mixed m. p.).

(b) *In cyclohexane.* The azide (3 g.) in dry cyclohexane (400 ml.) was irradiated for 3 hr. Removal of the solvent afforded an oil, from which 2-n-butylpyrrolidine [33] (700 mg., 35%) was isolated, having b. p. 169—171°, n_D^{21} 1·4431 (Found: C, 75·45; H, 13·65; N, 10·95. Calc. for $C_8H_{17}N$: C, 75·5; H, 13·45; N, 11·0%). The compound was characterised as its chloroplatinate which, recrystallised from ethanol, had m. p. 177—178° (decomp.).[34]

(c) *In other solvents.* The results are given in the theoretical section of this paper.

Irradiation of n-Propyl Azide.—The azide (4 g.) in cyclohexane (400 ml.) was irradiated until nitrogen ceased to be evolved and the solvent then removed *in vacuo*. The resulting oil was digested on a steam-bath with 2,4-dinitrophenylhydrazine reagent. Crystallisation of the product from ethanol gave the 2,4-dinitrophenylhydrazone (6·2 g., 59%), m. p. and mixed m. p. 155—156°, of propionaldehyde.

Irradiation of n-Heptyl Azide.—The azide (5 g.) in dry cyclohexane (400 ml.) was irradiated for 6 hr. The solvent was removed *in vacuo* and the resulting liquid (2·1 g.) was fractionally distilled, yielding 2-n-propylpyrrolidine [33] (600 mg., 15%), b. p. 144—145°, n_D^{25} 1·4478. Treatment with benzenesulphonyl chloride in pyridine afforded colourless needles (recrystallised from ethanol) of the acyl derivative,[33] m. p. 67—68° (Found: C, 58·15; H, 7·2; N, 5·1. Calc. for $C_{13}H_{19}NO_2S$: C, 58·0; H, 7·1; N, 5·2%). In addition, there was isolated from the residue of the distillation n-heptaldehyde imine, characterised as the 2,4-dinitrophenylhydrazone [35] (1·8 g., 45%; m. p. and mixed m. p.).

Irradiation of Cyclopentyl Azide.—The azide (4·1 g.) in cyclohexane (350 ml.) was irradiated under reflux for 8 hr. After nitrogen evolution had ceased the semisolid which was slowly precipitated was collected. Polymerisation commenced immediately and after a day the precipitate had become a viscous oil. Dissolution in ethanol–acetone (1 : 1; 20 ml.) and slow evaporation at room temperature gave a solid residue. This solid (142 mg., 5%) was washed with cold acetone and identified as isotripiperideine [23] (m. p. and mixed m. p.).

Removal of the excess of cyclohexane *in vacuo* afforded a viscous oil which was digested with 2,4-dinitrophenylhydrazine (7 g.) in 95% ethanol (140 ml.) and concentrated hydrochloric acid (10 ml.) on the steam-bath for 2 hr. Chromatography of the product over bentonite–Celite (3 : 1), elution with benzene, and crystallisation from ethanol yielded cyclopentanone 2,4-dinitrophenylhydrazone (5·06 g., 55%) (m. p. and mixed m. p.).

Irradiation of Cyclohexyl Azide.—(a) *In cyclohexane.* The azide (5 g.) in cyclohexane (350 ml.) was irradiated for 2 hr. with 500 w lamp at room temperature. Removal of the cyclohexane *in vacuo*, chromatography of the resulting oil over alumina, and elution with light petroleum, gave cyclohexanone (2 g., 51%), b. p. 70—73°/12 mm., identified as the 2,4-dinitrophenylhydrazone (m. p. and mixed m. p.). Further elution with chloroform–benzene (2 : 3) afforded cyclohexylamine, isolated as the hydrochloride (1·5 g., 33%) (m. p. and mixed m. p. and infrared spectrum).

(b) *In ethanol.* The azide (3 g.) in anhydrous ethanol (250 ml.) was irradiated for 4 hr. The excess of ethanol was removed *in vacuo* and the resulting oil chromatographed over alumina.

[33] Cantor and Vanderwerf, *J. Amer. Chem. Soc.*, 1958, **80**, 970.
[34] Hess, *Ber.*, 1919, **52**, 1636.
[35] Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2953.

Elution with light petroleum afforded cyclohexanone (500 mg., 21%), b. p. 70—75°/12 mm., identified as the 2,4-dinitrophenylhydrazone (m. p. and mixed m. p.). Further elution with chloroform–benzene (2 : 3) afforded cyclohexylamine, isolated as the hydrochloride (1·5 g., 45%) (m. p. and mixed m. p.).

Irradiation of Cycloheptyl Azide.—The azide (3 g.) in cyclohexane (300 ml.) was irradiated for 6 hr. under reflux. Immediately after the evolution of nitrogen ceased the solution was added to a three-fold excess of lithium aluminium hydride in anhydrous ether (150 ml.) and gently refluxed for 2 hr. The mixture was worked up in the usual manner [29] and the resulting yellow oil (2·1 g.) was treated in pyridine (30 ml.) and benzene (20 ml.) with 3,5-dinitrobenzoyl chloride (6 g.) in benzene (30 ml.). The mixture was shaken and then set aside overnight at room temperature. Working up in the usual manner afforded a dark residue which was chromatographed over alumina. Elution with light petroleum yielded cycloheptyl 3,5-dinitrobenzoate [36] (1·1 g., 15%) (m. p. and mixed m. p.). Further elution with benzene gave N-*cycloheptyl*-3,5-*dinitrobenzamide* (3·5 g., 53%) (m. p. and mixed m. p.). (Found: C, 55·0; H, 5·6; N, 13·5. $C_{14}H_{17}N_3O_5$ requires C, 54·7; H, 5·6; N, 13·7%).

The total irradiation product was treated with 3,5-dinitrobenzoyl chloride as above and the product investigated by paper chromatography, ultraviolet light being used for detection. In 43 : 12 butanol–acetic acid saturated with water, cycloheptyl 3,5-dinitrobenzoate and cycloheptyl-3,5-dinitrobenzamide (most intense spot) were detected, but no other spots were visible.

Irradiation of (+)-Neomenthyl Azide.—The azide (4 g.) in cyclohexane (300 ml.) was irradiated for 4 hr. Removal of the excess of solvent and chromatography over alumina gave, on elution with chloroform–light petroleum (1 : 9), a trace of menthone, isolated as the semicarbazone (50 mg.) (m. p. and mixed m. p.). Further elution with chloroform–benzene (2 : 8) afforded (+)-neomenthylamine [31] (2 g., 50%), $[\alpha]_D^{25}$ +14° (*c* 1·20), b. p. 84—87°/15 mm. {hydrochloride, m. p. and mixed m. p. 187—188·5°/ $[\alpha]_D^{25}$ +20° (*c* 1·20)}. Infrared comparison confirmed the identity.

Irradiation of t-Butyl Azide.—The azide (5 g.) in cyclohexane (200 ml.) was irradiated for 2 hr. The resulting yellow basic solution was fractionally distilled, yielding 2,2-dimethylethylenimine [37] (500 mg., 12%), b. p. 69—70°, n_D^{25} 1·4049 (Found: C, 67·6; H, 12·7; N, 19·7. Calc. for C_4H_9N: C, 67·55; H, 12·75; N, 19·7%). 2,2-Dimethylethyleniminium picrate [37] was prepared by adding picric acid in dry toluene at 0—5° to 2,2-dimethylethylenimine in toluene. The yellow precipitate was collected, washed with toluene and carbon tetrachloride, and dried in a desiccator, then having m. p. 124—126° (Found: C, 40·65; H, 4·2; N, 18·9. Calc. for $C_{10}H_{12}NO_7$: C, 40·0; H, 4·05; N, 18·65%). Treatment of the residue from the above distillation with toluene (20 ml.) saturated with picric acid resulted in yellow crystals of 1-amino-2-methylpropan-2-ol picrate [37] (210 mg., 5%). Recrystallised from acetonitrile this formed yellow plates, m. p. 139—141° (Found: C, 38·05; H, 4·55; N, 17·4. Calc. for $C_{10}H_{14}N_4O_8$: C, 37·75; H, 4·45; N, 17·6%).

Irradiation of Ethyl α-Azidopropionate.—Ethyl α-azidopropionate [22] (5 g.) in cyclohexane (400 ml.) was irradiated for 6 hr. When gas ceased to be evolved, the solvent was removed *in vacuo*. The remaining oil was extracted four times with ether. The combined ethereal extracts were evaporated in an air-stream and the remaining oil (2·8 g.) treated with 2,4-dinitrophenylhydrazine reagent in ethanol at 80° for 5 hr. Upon cooling, ethyl pyruvate 2,4-dinitrophenylhydrazone separated as yellow needles (3·5 g., 34%) (m. p. and mixed m. p., after crystallisation from dioxan–ethanol).

Irradiation of Allyl Azide.—Allyl azide (4 g.) in cyclohexane (450 ml.) was irradiated at 60° until nitrogen ceased to be evolved (4·5 hr.). The solvent was removed *in vacuo* and the remaining viscous oil was treated with ethanolic (10% HCl) 2,4-dinitrophenylhydrazine reagent on a steam-bath for several hours. Acraldehyde 2,4-dinitrophenylhydrazone separated and crystallised from 95% ethanol as red needles (5·9 g., 52%) (m. p. and mixed m. p.).

Irradiation of Phenethyl Azide.—The azide (2 g.) in cyclohexane (200 ml.) was irradiated for 4 hr. with a 500 w lamp. The solvent was removed *in vacuo* and the resulting dark oil dissolved in anhydrous ether (50 ml.). The ethereal solution was added dropwise to a suspension of lithium aluminium hydride (200 mg.) in anhydrous ether (50 ml.) and refluxed for 2 hr. The mixture was worked up in the usual manner. Passing a stream of dry hydrogen chloride into the ethereal solution afforded a colourless flocculent precipitate, which was collected.

[36] Reichstein, *Helv. Chim. Acta*, 1926, **9**, 799.
[37] Schatz and Clapp, *J. Amer. Chem. Soc.*, 1955, **77**, 5113.

After recrystallisation from ethanol this formed colourless plates of phenethylamine hydrochloride [38] (0·7 g., 42%), m. p. 215—216° (decomp.), identified by infrared comparison and mixed m. p.

Irradiation of 3-Phenylpropyl Azide.—The azide (3 g.) in cyclohexane (300 ml.) was irradiated for 5 hr. with a 500 w lamp. A stream of dry hydrogen chloride was passed in at room temperature. The cream-coloured precipitate that was formed was collected and recrystallised from ethanol as colourless prisms of tetrahydroquinoline hydrochloride [39] (0·5 g., 21%) (m. p., mixed m. p., and infrared spectrum).

Pyrolysis of n-Octyl Azide.—A solution of the azide (5 g.) in n-hexadecane (30 ml.) was added dropwise to stirred hexadecane (350 ml.) maintained at 230° in a nitrogen atmosphere. The decomposition was practically instantaneous; however, heating was continued for an additional 10—15 min. to ensure completion. The cooled solution was chromatographed over alumina, and the hexadecane removed with light petroleum. Further elution with benzene–ether (3 : 1) removed trimeric octanal, isolated and characterised as its 2,4-dinitrophenylhydrazone (3·1 g., 32%) (m. p. and mixed m. p.). Chloroform–methanol (7 : 1) afforded a red oil (1·2 g.) which resisted purification and contained <2% of nitrogen.

Preparation and Irradiation of 4-Methylhexyl Azide.—(+)-Citronellol {25 g., $[\alpha]_D$ +4·57° (*c* 2·21)} was converted into *citronellyl toluene*-p-*sulphonate* in the usual manner with pyridine and toluene-*p*-sulphonyl chloride. The yellow oil (42 g.) was chromatographed over alumina (grade 5) in light petroleum, to give the toluene-*p*-sulphonate as a colourless oil (35 g., 74%), $[\alpha]_D$ +1·6° (*c* 1·12) (Found: C, 65·65; H, 8·5; S, 10·1. $C_{17}H_{26}O_3S$ requires C, 65·8; H, 8·45; S, 10·3%).

The toluene-*p*-sulphonate (30 g.) in methylene chloride (150 ml.) was cooled in ice, and ozonised oxygen passed through it for 8 hr. When the production of fog ceased (negative tetranitromethane test) the solution was added dropwise with stirring to a three-fold excess of lithium aluminium hydride in ether (125 ml.) and refluxed for 8 hr. Working up in the usual manner afforded 4-methylhexan-1-ol [15] (2·3 g., 21%), b. p. 83—84°/23 mm., $[\alpha]_D$ +2·41° (*c* 1·21).

4-Methylhexan-1-ol (2·3 g.) was converted into the toluene-*p*-sulphonate with pyridine and toluene-*p*-sulphonyl chloride. The isolated oil (5·1 g.) in acetone (30 ml.) was added to sodium azide (3 g.) in water (10 ml.). The heterogeneous mixture was refluxed for 24 hr. and worked up in the usual manner. 4-Methylhexyl azide [16] (1·9 g., 67%) was isolated, having b. p. 50—54°/10 mm., $[\alpha]_D$ +3·83° (*c* 1·41).

This azide (613 mg.) in cyclohexane (50 ml.) was irradiated at 67—70° for 6½ hr. The yellow solution was diluted with anhydrous ether (50 ml.) and added to a slurry of ether (50 ml.) and a three-fold excess of lithium aluminium hydride. The product, worked up in the usual manner, was a yellow oil which formed a hydrochloride. This salt was fractionally recrystallised in ether–ethanol, affording two hydrochlorides, 4-methylheptylamine hydrochloride [17] (229 mg., 35%), m. p. and mixed m. p. 125—127 (decomp.), $[\alpha]_D$ +3·21 (*c* 0·83 in H_2O) (infrared spectrum identical with that of an authentic sample), and *2-ethyl-2-methylpyrrolidine hydrochloride* (108 mg., 16%), α 0°, m. p. 128—134° (decomp.) (Found: C, 55·25; H, 11·75; N, 9·25. $C_7H_{18}ClN$ requires C, 55·4; H, 11·95; N, 9·25%). The latter salt (50 mg.) in benzene (15 ml.) and pyridine (10 ml.) was treated with 3,5-dinitrobenzoyl chloride (2 g.) in benzene (7 ml.). Next morning the mixture was worked up in the usual manner. The resulting dark oil was chromatographed over alumina. Elution with light petroleum gave 1-(3,5-*dinitrobenzoyl*)-2-*ethyl*-2-*methylpyrrolidine*. Crystallised from ethanol, this had m. p. 110—112°, α 0 (Found: C, 54·9; H, 5·7; N, 13·55. $C_{14}H_{17}N_3O_5$ requires C, 54·7; H, 5·6; N, 13·7%).

Irradiation of 3β-Azidocholest-5-ene.—(a) *In ethanol.* The azide (400 mg.) in anhydrous ethanol (125 ml.) was irradiated for 8 hr. The solvent was removed and the remaining oil dried *in vacuo*. The oil (310 mg.) was added in anhydrous ether (25 ml.) to a suspension of lithium aluminium hydride (500 mg.) in anhydrous ether (25 ml.). Following Boyer's procedure [29] yielded a semisolid (262 mg.) which was chromatographed over alumina; elution was with (*A*) light petroleum (200 ml.), (*B*) benzene–light petroleum (1 : 4; 300 ml.), (*C*) benzene–light petroleum (1 : 1; 250 ml.), and (*D*) benzene–chloroform (1 : 4; 200 ml.). Fractions (*B*) yielded cholest-4-en-3β-ol [40] (75 mg., 20%) (m. p. and mixed m. p.); fractions (*D*) yielded 3β-aminocholest-5-ene (125 mg., 33%) (m. p. and mixed m. p.), $[\alpha]_D^{24}$ −23° (*c* 1·10).

[38] Wohl and Berthold, *Ber.*, 1910, **43**, 2183.
[39] Skita and Meyer, *Ber.*, 1912, **45**, 3594.
[40] McKennis and Gaffney, *J. Biol. Chem.*, 1948, **175**, 217.

(b) *In cyclohexane.* Irradiation of the azide (400 mg.) under similar conditions to those employed above and working up in the same way yielded cholest-4-en-3β-ol (55 mg., 13%) and 3β-aminocholest-5-ene (85 mg., 22%).

Synthesis of Conessine.—Pregn-5-ene-3β,20β-diol [10] was converted into the *ditoluene-p-sulphonate* in the usual manner with pyridine and toluene-*p*-sulphonyl chloride. Recrystallised from ether–light petroleum this had m. p. 140—142° (decomp.), $[\alpha]_D^{25}$ −46·7° (*c* 0·45) (Found: C, 67·1; H, 7·4; S, 10·15. $C_{35}H_{46}O_6S_2$ requires C, 67·05; H, 7·4; S, 10·2%).

A solution of the diester (1·93 g.) in 0·92M-methanolic lithium azide [28] (200 ml.) was refluxed for 24 hr., diluted with water (300 ml.), and extracted with chloroform. The chloroform extracts yielded an oil (1·19 g.) which was chromatographed over alumina. Elution with light petroleum afforded 3β,20α-*bisazidopregn-5-ene* as an oil, $[\alpha]_D^{25}$ −27° (*c* 1·25), $\lambda_{max.}$ 270 mμ (log ε 1·75), $\nu_{max.}$ (in Nujol) 2110 (azide) cm.$^{-1}$ (Found: C, 68·3; H, 8·8; N, 22·9. $C_{21}H_{32}N_6$ requires C, 68·45; H, 8·75; N, 22·8%).

Identification was based upon reduction of 3β,20α-bisazidopregn-5-ene to 3β,20α-diaminopregn-5-ene which was methylated with formic acid–formaldehyde,[41] yielding 3β,20α-bisdimethylaminopregn-5-ene,[11] m. p. 140—142°, $[\alpha]_D^{16}$ −40° (*c* 1·51).

The azide (3·15 g.) in cyclohexane (300 ml.) was irradiated for 4 hr. The solution was added to a suspension of lithium aluminium hydride (3 g.) in anhydrous tetrahydrofuran (250 ml.), and the reduction carried out in the usual manner. The resulting yellow oil (2·6 g.) was methylated with formic acid–formaldehyde, an amber semisolid (2·1 g.) being isolated. Careful chromatography over alumina (grade 3) and elution with light petroleum–benzene (1 : 5) gave 3β-hydroxypregn-5-en-20-one [30] (500 mg.) (m. p. and mixed m. p.). Elution with chloroform yielded an unidentified semisolid (250 mg.) (Found: C, 84·1; H, 13·2; N, 2·1%). Further elution with chloroform–benzene (1 : 9) afforded conessine [2] (105 mg.), recrystallising from aqueous acetone as flat needles, m. p. and mixed m. p. 124—125°, $[\alpha]_D^{23}$ −2° (*c* 7·3), $[\alpha]_D^{20}$ +24° (*c* 0·65 in absolute ethanol). Comparison of the infrared spectrum with that of an authentic sample confirmed identity. Chloroform–methanol (9 : 1) eluted the remainder of the material (oil) from the column. The isolated oil was remethylated with formic acid–formaldehyde and rechromatographed over alumina. Elution with light petroleum–benzene (1 : 5) yielded the hydroxypregnenone (750 mg.) whilst chloroform–benzene (1 : 9) gave additional conessine (10 mg.). The total yield of conessine was 115 mg. (4·5%).

Synthesis of Proline.—δ-Bromovaleric acid [42] was prepared from δ-valerolactone [43] and esterified with sulphuric acid and ethanol.[44] *Ethyl δ-azidovalerate*, b. p. 105—107°/13 mm. n_D^{29} 1·4463 (Found: C, 49·3; H, 7·7; N, 24·3. $C_7H_{13}N_3O_2$ requires C, 49·1; H, 7·65; N, 24·55%), was prepared from the bromo-ester and sodium azide in the usual manner.

The azide (3 g.) in cyclohexane (300 ml.) was irradiated for 6 hr. and the resulting solution extracted with dilute hydrochloric acid. The acid washings were neutralised with aqueous sodium hydrogen carbonate and extracted with ether. Treatment of the residue from the combined ethereal extracts with pyridine and toluene-*p*-sulphonyl chloride resulted in the formation of the 1-toluene-*p*-sulphonylproline ethyl ester as colourless plates, m. p. 130—133° (from aqueous ethanol) (Found: C, 56·7; H, 6·6; N, 4·6. Calc. for $C_{14}H_{19}NO_4S$: C, 56·55; H, 6·45; N, 4·7%). Alkaline hydrolysis with 10% aqueous sodium hydroxide gave proline (overall yield, 265 mg., 15%) (m. p., mixed m. p., and infrared spectrum).

We thank the Government Grants Committee of the Royal Society, the Department of Scientific and Industrial Research, and British Petroleum Ltd. for financial assistance. One of us (L. R. M.) acknowledges the award of a Postdoctorate Fellowship from the U.S. Public Health Service. We thank the Research Institute for Medicine and Chemistry, Cambridge, Mass., for a gift of pregn-5-ene-3β,20β-diol.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7. [*Received, September 25th*, 1961.]

[41] See, *e.g.*, Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 887.
[42] Boorman, Linstead, and Rydon, *J.*, 1933, 585.
[43] Robertson and Smith, *J.*, 1937, 373.
[44] Merchant, Wickert, and Marvel, *J. Amer. Chem. Soc.*, 1927, **49**, 1830.