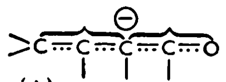
254. *Reduction by Dissolving Metals. Part XIV.* Some Stereochemical Aspects of the Reduction of αβ-Unsaturated Ketones.*

By A. J. BIRCH, HERCHEL SMITH, and R. E. THORNTON.

Theoretical aspects of the addition of cations to mesomeric anions are briefly reviewed. The stereochemistry of the process in relation to the reversible or irreversible addition of protons is discussed and extended to an examination of the expected course of reduction of certain αβ-unsaturated ketones by means of metal–ammonia reagents. The reduction of 1 : 2 : 3 : 4 : 9 : 10-hexahydro-7-methoxy-1-oxophenanthrene by lithium and ethanol in ammonia leads initially to *cis*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-methoxy-1-oxophenanthrene, which is convertible into the more stable *trans*-isomer.

EARLY in our investigations of the processes whereby unsaturated compounds are reduced by metal–ammonia reagents,[1] it became clear that the products are formed by the addition of protons to mesomeric anions which contain at least two possible reactive positions. Hence it was necessary to consider the factors influencing the choice of position in reactions of this type. Theoretical ideas were advanced [2] in 1947 on this subject, which is fundamental also for other reactions. It was pointed out that the constitution of the product depends in whether the addition is reversible or irreversible. Under reversible conditions the product is the thermodynamically stable one; under irreversible conditions it is determined by the relative rates of addition to the possible positions in which a free anionic charge can appear. In general this position appears to be that in which the charge is most stable, provided the cation requires very little energy to detach it from the molecule of which it forms a part. Essentially the same views have more recently been put forward by other workers.[3,4] The theory proved to be of great utility in indicating methods by which isomers of other than the lowest energy state can be produced, and in explaining the products obtained in the reduction of benzene rings by means of metal–alcohol–liquid ammonia reagents.[1] It proved possible to prepare an unconjugated *cyclo*hexadiene from the conjugated one,[4] and for heteroenoid systems to predict that a cation should be added irreversibly to the carbon atom β to the oxygen in an anion such as (A). This prediction was verified by conversion of 3-acetoxycholesta-3 : 5-diene into cholest-5-en-3-one [5] through the mesomeric anion of 3-hydroxycholesta-3 : 5-diene (an essential step in the Oxford synthesis of cholesterol [6]). In more recent work on the alkylation of unsaturated ketones, *e.g.*, in the Harvard synthesis of steroids [7] and the synthesis of lanosterol,[6] the same factors are undoubtedly involved.



(A)

In connection with our programme of work on the synthesis of analogues of steroid hormones we have turned our attention to the problem of obtaining stereoisomers of other than the lowest energy-level by the irreversible addition of protons to the mesomeric anions formed by the reduction of polycyclic αβ-unsaturated ketones. In view of Zimmerman's recent elegant work [9] based on the same kind of ideas, but with somewhat more favourable substances, we present a preliminary account of some of our work.

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* Part XIII, *Austral. J. Chem.*, 1955, **8**, 512.

[1] Birch, Part I, *J.*, 1944, 430, and subsequent papers; cf. *Quart. Rev.*, 1950, **4**, 69.

[2] Birch, *Discuss Faraday Soc.*, 1947, **2**, 246.

[3] De la Mare, Hughes, and Ingold, *J.*, 1948, 17; Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, p. 700; Kornblum, Smiley, Blackwood, and Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.

[4] Birch, *J.*, 1950, 1551.

[5] Birch, *J.*, 1950, 2325.

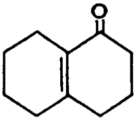
[6] Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.

[7] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

[8] Woodward, Patchett, Barton, Ives, and Kelly, *ibid.*, 1954, **76**, 2853.

[9] Zimmerman, *ibid.*, 1956, **78**, 1168.

For discussion the simplest example is the reduction of 1 : 2 : 3 : 4 : 5 : 6 : 7 ; 8-octahydro-1-oxonaphthalene (I). The intermediate dianion (II) will initially add a proton to the β-anionic carbon atom, which will be highly basic. In general, when this position is capable of giving rise to stereoisomers the more stable configuration would be expected since the proton-donor normally present (ammonia, an alcohol, ammonium chloride) has pK_a far lower than that of the resulting hydrocarbon. The deciding factor will therefore be the most stable conformation of the anion, not the path of approach of the proton donor (cf. ref. 10). For the α-position other considerations apply. The enolate anion is stable under the reduction conditions unless a large excess of an " acid " is present; the pK of the enol-form should be 10—12. This stability protects the group from further reduction and permits eventual isolation of the ketone. The keto-form is produced during the isolation and its configuration will be determined by the choice between the canonical forms (III) and (IV) in the attack by the proton-donor. It is clearly seen that although the form (III) is the more stable anion, the path of approach is hindered, being axial to both rings, while in the form (IV) it is axial to one ring and equatorial to the other. Conceivably, therefore, the *cis*-ketone could initially be formed.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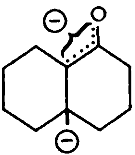
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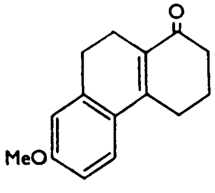

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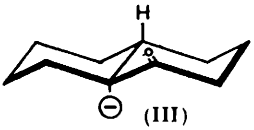

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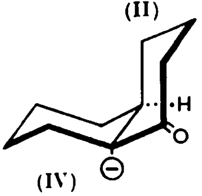

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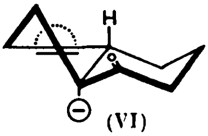

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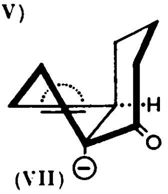

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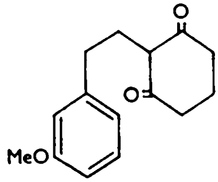

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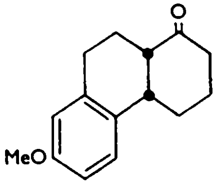

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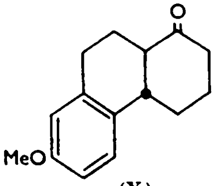

(X)

We have tested this hypothesis on more complex compounds *e.g.*, the phenanthrene (V), more closely related to our synthetic programme. In this case the principles involved are the same, except that the fused aromatic ring will tend to flatten the attached ring (VI; *trans*-form; VII, *cis*-form). This would be expected to reduce the difference in energy-level between the ketones * themselves without greatly affecting the relative rates of addition to the anionic charges in the enolate anions (VI) and (VII).

The ketone (V) was synthesised by a type of route already well established.[12] 3-Methoxyphenethyl bromide condensed with the potassium salt of 1 : 5-dimethoxy*cyclo*hexa-1 : 4-diene in liquid ammonia to a product hydrolysed by acid to the *cyclo*hexane-1 : 3-dione (VIII). Cyclisation of this with polyphosphoric acid gave the phenanthrene ketone (V).

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* Klyne [11] has reviewed current ideas on the factors governing the relative stabilities of various stereoisomeric decalones.

[10] Barton and Robinson, *J.*, 1954, 3045.
[11] Klyne, *Experientia*, 1956, **12**, 119.
[12] Birch and Smith, *J.*, 1951, 1882.

Reduction of the ketone (V) with lithium and ethanol in ammonia under defined conditions gave an octahydro-oxomethoxyphenanthrene (IX), m. p. 68—71°, which on treatment with mineral acid or passage in light petroleum through alkaline alumina was converted into an isomer. This isomer from its m. p. (111°) is the known *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-oxo-7-methoxyphenanthrene (X) whose stereochemistry is established through its relation to œstrone.[13] Neither of the two compounds can be an enol, since no hydroxyl band, but the expected carbonyl band, is present in the infrared spectra. These spectra, although similar, differ significantly in the region 8—15 μ. Equilibration of the *trans*-isomer with methanolic potassium hydroxide gave a mixture whose infrared spectrum showed bands characteristic of both *cis*- and *trans*-isomers in an estimated ratio of 1 : 4. The free-energy difference is therefore, as expected, rather small (about 0·8 kcal. mole^{-1}). It is of interest that the *cis*-ketone can be purified by chromatography on the earth, " Florex," without equilibration.*

The generally accepted rule that the stable isomer predominates in the products of reduction by dissolving metal [10, 11] undoubtedly holds under usual experimental conditions for carbon–carbon systems and for the β-position in αβ-unsaturated ketones. The fact that stable isomers are usually isolated from the latter must depend on the ready establishment of equilibria during isolation, for example, by chromatography on alumina.[14] It is noteworthy that the *trans*-junction was produced by reduction of an α-octalone derivative to the corresponding decalol with a large excess of lithium and ethanol in liquid ammonia.[15] In this case equilibration of the initial *cis*-decalone derivative, if formed, must have occurred before reduction of the carbonyl group.

The theoretical treatment above may need to be modified for reactions in non-polar media where effects due to proximity of the metal cation may need to be considered.

EXPERIMENTAL

Evaporations were carried out under reduced pressure. Light petroleum means the fraction, b. p. 60—80°. Florex is a grade of Florida fuller's earth prepared by the Floridin Co., Warren, Pennsylvania.

1 : 2 : 3 : 4 : 9 : 10-*Hexahydro-7-methoxy-1-oxophenanthrene* (V).—1 : 5-Dimethoxy*cyclo*hexadiene (60 g.) was added to a solution of potassium amide (from the metal, 8·8 g.) in liquid ammonia (500 c.c.). After 10 min. 3-methoxyphenethyl bromide (25·3 g.) in ether was added with stirring during 20 min. Water was added and the mixture extracted with ether–ethyl acetate (1 : 1; 3 × 200 c.c.). The oily product was isolated in the usual manner and treated under nitrogen with 2N-sulphuric acid on the steam-bath for 25 min. The product was dissolved in ethyl acetate, and the solution extracted portion-wise with 2N-sodium hydroxide until acidification failed to give an oil. The oil soon crystallised; it was filtered off, washed with water, and dried *in vacuo*, to give the crude 2-3′-methoxyphenethyl*cyclo*hexane-1 : 3-dione as a pale buff solid (26 g.). A portion recrystallised from ethyl acetate–light petroleum had m. p. 150°. Robinson and Schittler [16] give m. p. *ca.* 150°. The finely powdered crude dione was added to a solution of phosphoric oxide (80 g.) in phosphoric acid (*d* 1·75; 60 c.c.) and kept at 110° for 45 min. The mixture was cooled, added to water (1 l.), and extracted with ether (4 × 250 c.c.). The product was dissolved in benzene (100 c.c.) and adsorbed on alumina (200 g.). Elution with benzene (2 l.) gave the 1 : 2 : 3 : 4 : 9 : 10-hexahydro-7-methoxy-1-oxophenanthrene (12 g.), m. p. 77—78° after recrystallisation from light petroleum

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* [*Added, January 29th,* 1957].—Johnson, Ackerman, Eastham, and DeWalt (*J. Amer. Chem. Soc.*, 1956, **78**, 6302) have observed that the less stable isomer is produced in the reduction of a substituted 1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-octahydro-8-methoxyphenanthrene by a metal–ammonia reagent. From an examination of models it is apparent that this result would follow from a similar kinetic control of the reduction process.

[13] Robinson and Walker, *J.*, 1936, 747; 1938, 183; Anner and Miescher, *Helv. Chim. Acta*, 1948, **31**, 2173.

[14] Cf. Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905; Bladon, Henbest, Jones, Lovell, Wood, Woods, and Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

[15] Birch and Smith, *J.*, 1956, 4909.

(Found: C, 78·7; H, 7·15. Calc. for $C_{15}H_{16}O_2$: C, 78·9; H, 7·1%). Robinson and Schittler [16] give m. p. 75—76°. Light absorption in EtOH: $\lambda_{max.}$ 240·5 and 332 mμ (ε 24,000 and 12,600).

cis-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro-7-methoxy-1-oxophenanthrene* (IX).—The above hexahydromethoxyoxophenanthrene (10 g.) in tetrahydrofuran (250 c.c.) was added to a solution of lithium (1·4 g.) in liquid ammonia (1500 c.c.). After 10 min. ethanol was run in until the blue colour was discharged. Water was immediately added and the mixture was extracted with ether (4 × 500 c.c.). The product was an oil which was adsorbed from light petroleum–benzene (4 : 1; 100 c.c.) on Florex. Elution with light petroleum (1 l.) and recrystallisation from the same solvent gave cis-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro-7-methoxy-1-oxophenanthrene* (5·9 g.), m. p. 68—71° (Found: C, 78·2; H, 7·9. $C_{14}H_{18}O_2$ requires C, 78·3; H, 7·9%). The infrared spectrum had bands at 1709, 989, and 864 cm.$^{-1}$. Crystallisation of the product without chromatography gave a less pure product, m. p. 65—68°.

trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro-7-methoxy-1-oxophenanthrene* (X).—(*a*) The above *cis*-ketone (5·8 g.) in benzene (25 c.c.) was adsorbed on basic alumina (150 g.). Elution with benzene and recrystallisation of the product from light petroleum gave the *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-methoxy-1-oxophenanthrene (5 g.), m. p. 111° (Found: C, 78·4; H, 7·7. Calc. for $C_{15}H_{18}O_2$: C, 78·3; H, 7·9%). Robinson and Walker [13] give m. p. 109°. The infrared spectrum had bands at 1706 and 776 cm.$^{-1}$.

(*b*) The *cis*-isomer (IX) (0·57 g.) was refluxed in ethanol (75 c.c.) containing 6N-hydrochloric acid (18 c.c.) for 45 min. Brine (100 c.c.) was added and the product collected in ether. It was dissolved in light petroleum–benzene (1 : 1; 50 c.c.) and adsorbed on Florex (30 g.). Elution with light petroleum gave the *trans*-isomer (IX) (0·46 g.), m. p. 109° (Found: C, 78·4; H, 7·7%).

The *trans*-ketone (0·62 g.) was refluxed under nitrogen in methanol (80 c.c.) containing potassium hydroxide (0·8 g.) for 1 hr. The solution was cooled rapidly and poured into 0·2N-hydrochloric acid (220 c.c.) and extracted with ether. The product was purified by percolating its solution in light petroleum through Florex (9 g.). Its infrared spectrum had bands at 989, 864, and 776 cm.$^{-1}$, from the relative intensity of which it was estimated that the ketonic mixture contained approximately 80% of the *trans*- and 20% of the *cis*-isomer.

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[16] Robinson and Schlittler, *J.*, 1935, 1288.