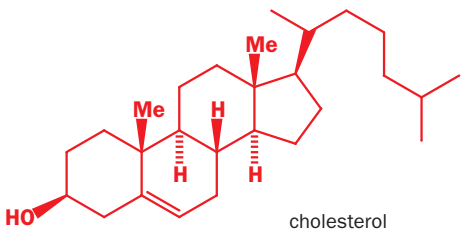
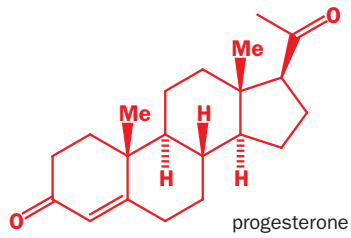
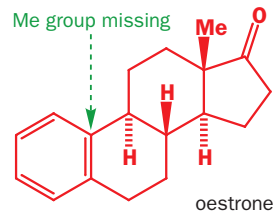


cholesterol



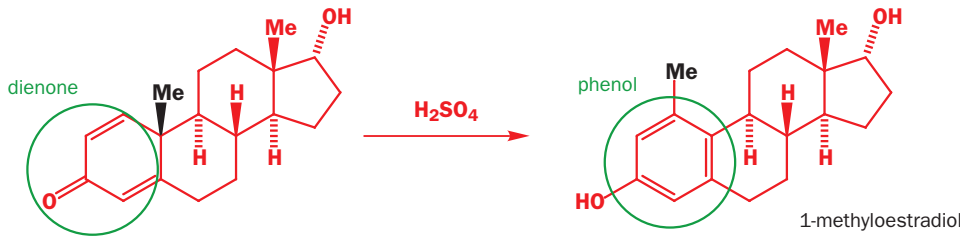
progesterone



oestrone

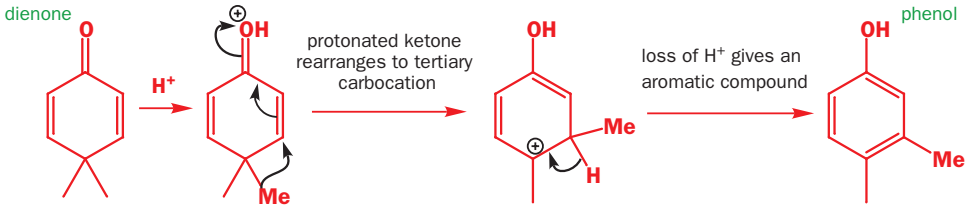
Oestrone lacks one of progesterone's methyl groups, probably removed in the body as CO_2 after oxidation. In 1946, Carl Djerassi, a man whose work led directly to the invention of the contraceptive pill, showed that another derivative of cholesterol could be rearranged to the oestrone analogue 1-methyloestradiol—notice how the methyl group has this time migrated to an adjacent carbon atom. At the same time, the dienone has become a phenol.

■ Carl Djerassi, an American born in Vienna in 1923, worked chiefly at CIBA, Syntex in Mexico, and at Stanford. He developed syntheses of human steroids from compounds in plants, was a pioneer of mass spectrometry, and is a colourful campaigner for peace and disarmament.



1-methyloestradiol

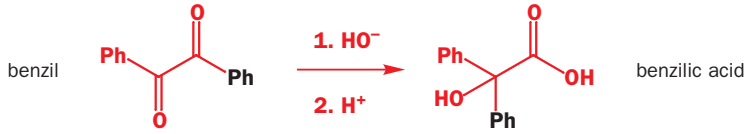
This type of rearrangement is known helpfully as a **dienone–phenol rearrangement**, and we can consider it quite simply as a type of *reverse* pinacol rearrangement. Pinacol and semipinacol rearrangements are driven by the formation of a carbonyl group. The rearranged cation is stabilized by being next to oxygen, and it can rapidly lose H^+ to give a carbonyl compound. In the key step of a dienone–phenol rearrangement, a protonated carbonyl compound rearranges to a tertiary carbocation.



The reaction is driven from dienone to phenol because the product cation can rapidly undergo elimination of H^+ to become aromatic.

The benzilic acid rearrangement

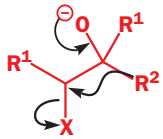
You have seen rearrangements in which carbonyl groups form at the migration origin: the migrating group in the pinacol and semipinacol rearrangements is 'pushed' by the oxygen's lone pair as it forms the new carbonyl group. You have also seen carbonyl groups being destroyed at the migration terminus: the migrating group in the dienone–phenol rearrangement is 'pulled' towards the protonated carbonyl group. The first rearrangement reaction ever to be described has both of these at once.



benzilic acid

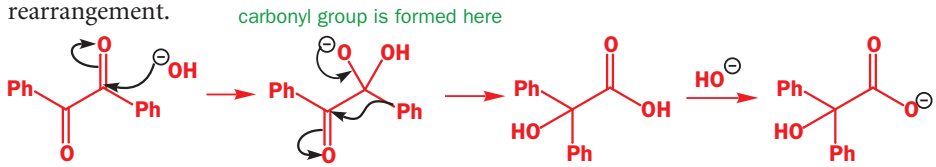
In 1838, Justus von Liebig found that treating 'benzil' (1,2-diphenylethan-1,2-dione) with hydroxide gave, after acid quench, 2-hydroxy-2,2-diphenylacetic acid, which he called 'benzilic acid'.

▶ You may find it helpful to think of the benzilic acid rearrangement as a semipinacol rearrangement in which we have a breaking C=O π bond instead of a leaving group.



compare the migration step with this semipinacol rearrangement

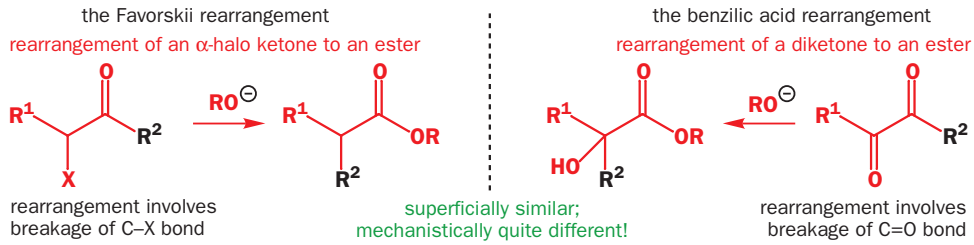
The mechanism of this **benzilic acid rearrangement** starts with attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.



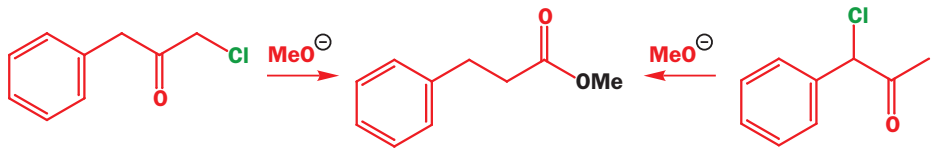
With alkoxides, the benzilic acid rearrangement can lead directly to esters by the same sort of mechanism.

The Favorskii rearrangement

We hope you have appreciated the smooth mechanistic progression so far in this chapter, from Wagner–Meerwein to pinacol and semipinacol through dienone–phenol to benzilic acid. Our aim is to help you gain an overall view of the types of rearrangements that take place (and why) and not to present you with lots of disconnected facts. It is at this point, however, that our mechanistic journey takes a hairpin bend. A surprising one, too, because, when we show you the Favorskii rearrangement, you would be forgiven for wondering what the fuss is about: surely it's rather like a variant of the benzilic acid rearrangement?



Well, this is what chemists thought until 1944, when some Americans found that two isomeric α-chloro ketones gave exactly the same product on treatment with methoxide. They suggested that both reactions went through the same intermediate.



■ A full discussion of this point requires Baldwin's rules, which appear in Chapter 41.

That intermediate is a three-membered cyclic ketone, a cyclopropanone: the alkoxide acts not as a nucleophile (its role in the benzilic acid rearrangement) but as a base, enolizing the ketone. The enolate can alkylate itself intramolecularly in a reaction that looks bizarre but that many chemists think is not unreasonable. The product is the same cyclopropanone in each case.