[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Stereochemical Course of Hydrogenation of Ring D-Unsaturated Equilenane Derivatives

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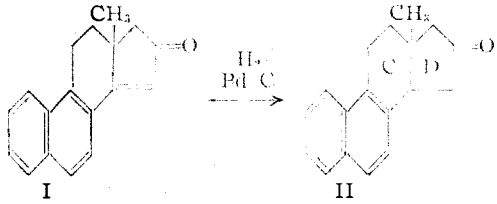
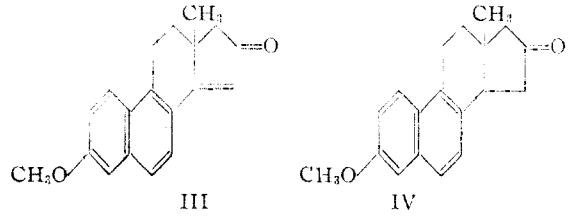
In several communications from this Laboratory, we have reported on a method for synthesizing the steroid ring system by way of Δ^{14-15}-unsaturated 16-keto derivatives such as I.[3] The final step of these syntheses has involved a selective hydrogenation to ketones such as 16-equilenone (II), in which the C:D ring configuration may become *cis* or *trans*. Since most of the natural steroids have these rings in the *trans* configuration, it has been of considerable interest to study the stereochemical course of this reduction and possible methods for its control. Significant progress has now been made in this direction.

Hydrogenation of I with palladium-on-carbon catalyst in dioxane was reported[3b] to give predominately one stereoisomer of II, m. p. 168.5–169°. By reduction of the ketone group this isomer was converted into a hydrocarbon (β-equilenane) identical with that obtained from β-17-equilenone; this isomer of II is therefore presumed to be *trans* by analogy to equilenin.[4,5]



Since it is well-known that alkali or acid frequently will alter the stereochemical course of a reduction,[6] the effect was tested in the present case. Potassium hydroxide accelerated the palladium-catalyzed hydrogenation of I and led to a different isomer of II, m. p. 94.5–95°. Since Clemmensen reduction gave α-equilenane, identical with the hydrocarbon from α-17-equilenone, the new isomer is considered to be the *cis* form.

Neutral hydrogenation of the methoxyl substituted ketone III was found to give 3-methoxy-16-equilenone (IV) as a difficultly separable mixture of isomers from which one, m. p. 169.5–171°, could be isolated in 24–29% yield.[3c] Alkaline hydrogenation has now afforded in excellent yield material melting at 171–172°. This, however, proved to be the stereoisomer of the above ketone, since a mixture of the two showed a large melting point depression. Similarly, alkaline reduction of the phenolic ketone corresponding to III gave a different isomer from that obtained under neutral conditions, but identical with that prepared by demethylation of this new isomer of IV.



In order to establish the configuration of these isomers, the 16-carbonyl group was reduced using the technique of Huang-Minlon.[7] The 169.5–171° isomer of IV gave *trans*-3-methoxyequilenane (VIII) identical with a sample prepared by reducing the 17-keto group of *dl*-equilenin methyl ether. The 171–172° isomer of IV gave *cis*-3-methoxyequilenane identical with that from *dl*-isoequilenin methyl ether. Thus, the alkaline hydrogenation of III had led to the *cis* isomer of IV in excellent yield, while both isomers were formed under neutral conditions with the *trans* isomer apparently predominating. When the hydrogenation was carried out in dioxane solution containing a trace of acetic acid, the proportion of *trans*-isomer was increased, so that 38% could readily be isolated.[7a] In acetic acid alone as the solvent, the hydrogenation with palladium became less selective, leading to considerable reduction of the ketone group as well as the double bond.

The similar behavior of ketones I and III on alkaline hydrogenation, leading to the C:D configurations of α-equilenone and isoequilenin, respectively, provides another excellent analogy in support of the similar *cis* configuration for each.

It could be demonstrated that the alkaline effect, in promoting *cis* hydrogenation, involved the ketone group rather than the catalyst. Wolff–Kishner reduction of the desoxy ketone I gave 14,15-dehydroequilenane (V) in excellent yield. That the double bond remained in conjugation with the ring was shown by the ultraviolet ab-

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(3) (a) Wilds, THIS JOURNAL, **64**, 1421 (1942); (b) Wilds and Beck, *ibid.*, **66**, 1688 (1944); (c) Wilds and Close, *ibid.*, **69**, 3079 (1947); (d) Wilds and T. L. Johnson, *ibid.*, **70**, 1166 (1948).

(4) Wilds, Beck and T. L. Johnson, *ibid.*, **68**, 2161 (1946).

(5) The recent work of Bachmann and Dreiding, *ibid.*, **72**, 1323, 1329 (1950), and Bachmann and Ramirez, *ibid.*, **71**, 2273 (1949), provides new evidence in support of the *trans* configuration for equilenin and β-17-equilenone.

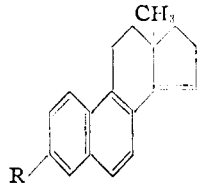
(6) Weidlich, *Die Chemie*, **58**, 30 (1945), has reviewed this for α,β-unsaturated ketones.

(7) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

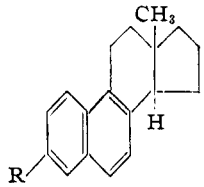
(7a) We are inclined to attribute this effect to ensuring that the catalyst surface is not alkaline, since we prepared the catalyst under alkaline conditions. Indeed, it seems possible that variations in the ratio of stereoisomers obtained by different investigators in reducing α,β-unsaturated ketones including cholestenone might be due to variations in the alkalinity or acidity of the catalyst surface.

sorption spectrum. Hydrogenation of this hydrocarbon gave *trans*-equilenane (VII) regardless of whether acidic or alkaline conditions were used.[8] The alkaline effect with I and III must, then, involve an activation of the α,β-unsaturated ketone system by the alkali. This will be considered further in a later section.

The practical effect of these results is to point out the route to *trans* C:D rings. In the methoxy series palladium hydrogenation of 3-methoxy-14,15-dehydroequilenane (VI), prepared by Wolff–Kishner reduction of III, led to *trans*-3-methoxyequilenane (VIII) as the only product isolated.

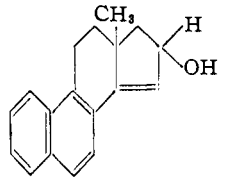


V, R = H
VI, R = CH_3O

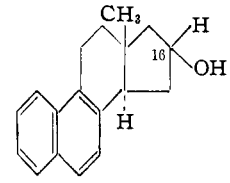


VII, R = H
VIII, R = CH_3O

The importance of extending these experiments to related compounds with substituents in ring D is obvious, and such work is in progress.[9] Reduction of the ketone group in I with lithium aluminum hydride gave in excellent yield a single isomer corresponding to formula IX.[10] Hydrogen-



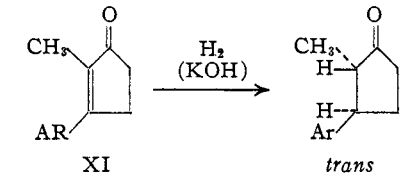
IX



X

ation of this unsaturated alcohol gave one isomer of the saturated alcohol X in good yield. This compound m. p. 123.5–124°, was shown to have the *trans* C:D ring fusion by oxidation to *trans*-16-equilenone.[11] In contrast, the epimer of this alcohol, m. p. 183.5–184.5°, was produced by lithium aluminum hydride reduction of *trans*-16-equilenone. It is quite interesting that these 16-keto derivatives, like 17-keto steroids,[12] give essentially a single stereoisomeric alcohol with lithium aluminum hydride, but with the favored configuration reversed by the presence of a 14,15-double bond. It is not possible at this time to assign definite configurations to these 16-hydroxy epimers.

Turning now to the question of how alkali might influence the palladium-catalyzed hydrogenation of α,β-unsaturated ketones, a satisfactory mechanism must take into account several observations: (1) the carbonyl group seems to be necessary for the alkaline effect, (2) alkali favors a *cis* configuration with Δ^4-3-ketosteroids as well as with ketones such as I and III containing an aromatic nucleus, (3) with ketones such as XI alkaline hydrogenation favors the *trans* configuration.[13]

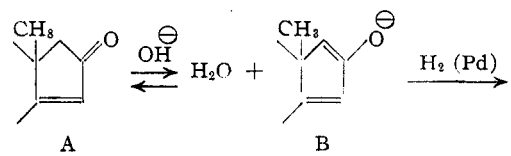


XI *trans*

Weidlich,[6] in connection with compounds of type XI, has suggested that hydrogenation in acidic medium proceeds by 1,2-addition to the double bonds (C=O as well as C=C) and in alkaline medium by 1,4-addition followed by ketonization. While this view can account for the *trans* isomer resulting from ketones such as XI, it does not seem applicable to those such as I, cholestenone, etc. In the latter type direct 1,4-addition might be expected to give the *trans* isomer because of the steric effect of the angular methyl group in determining direction of absorption on the catalyst (see below).

Two *a priori* ways in which the alkali might be acting on these unsaturated ketones are (a) enolization of the carbonyl group or (b) attack by the anionoid reagent at the β-carbon of the double bond. In the hope of throwing light on this point, I was hydrogenated in the presence of potassium *t*-butoxide. This reagent likewise favored the *cis* ketone II. On the assumption that approach of the bulky *t*-butoxide anion to the β-position (C_{14}) would be hindered, it seems probable that the enolization effect is operative.

The following suggested mechanism appears to be in agreement with the facts currently available.



A B

(8) The finding of Peak, [*Nature*, **140**, 280 (1937)], that the configuration of the reduction product of β-ergostenol (Δ^{14-15}) was not altered by acid or alkali parallels our results.

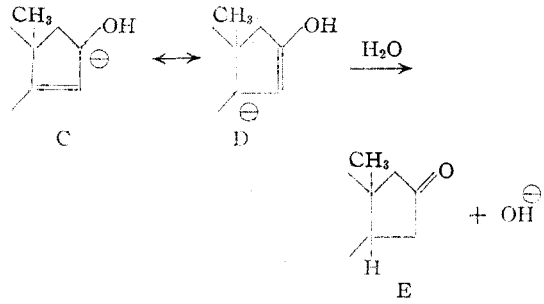
(9) In the Δ^{14-15}-etioallocholenic acid series it has been reported that the configuration of the 17-carbomethoxy group influences the ring configuration produced on hydrogenation, 17α-favoring the *cis* and 17β favoring the *trans* C:D ring; see Meyer, *Helv. Chim. Acta*, **29**, 718, 1908 (1946); Ruzicka, *et al.*, *ibid.*, **29**, 942, 2023 (1946); **30**, 395 (1947); Speiser and Reichstein, *ibid.*, **30**, 2143 (1947).

(10) This allylic alcohol was quite sensitive toward traces of acid, leading to interesting results which will be reported later.

(11) The finding by Johnson, Petersen and Gutsche [THIS JOURNAL, **69**, 2942 (1947)] that alkali increased the amount of *cis* hydrogenation with 3-methoxy-14,15-dehydro-17-equilenone, in which the double bond is not conjugated with the ketone group, would appear from the above to result from a partial shift of the double bond to the 15,16-position prior to hydrogenation. The corresponding 17-hydroxy derivatives are now being investigated.

(12) See Ott and Murray, Abstracts of 113th A. C. S. Meeting, Chicago, 1948; Bachmann and Dreiding, THIS JOURNAL, **72**, 1323 (1950).

(13) In the hydrogenation of relatively slowly reduced ketones such as I and III, alkali resulted in a definite acceleration in rate of reduction, while in the case of the hydrocarbon V a slower rate resulted.



After enolization to the ion B, hydrogenation is considered to lead to the reduced ion of which C and D represent two resonance extremes, and finally reaction *via* D with the solvent (or water) and ketonization leads to the saturated ketone E. Possibly the entire sequence of steps may take place on the catalyst surface. On the basis of this mechanism the final configuration at the ring juncture would be determined by the preference of ion D in accepting a proton. This preference should be related to the preferred configuration when the double bond shifts away from the bridgehead.[14] Johnson, Petersen and Gutsche[11] have shown with the 17-keto isomers of I and III that such a shift of the double bond from the 14–15 to the 15–16 position leads to the *cis* ring system.

In connection with any mechanism of hydrogenation, the role of the catalyst cannot be overlooked. In the *neutral* hydrogenation of I, where the *trans* isomer of II predominates, Linstead's[15] concept of steric hindrance resulting in oriented adsorption on the catalyst adequately accounts for the results, since the angular methyl group would favor adsorption from the opposite side of the molecule and hence lead to the *trans* structure. In agreement with this, the compound related to I but lacking the angular methyl group gave a mixture from which both *cis* and *trans* isomers could be isolated.[3a,16] In the *alkaline* hydrogenation of I adsorption from the rear might still be the favored orientation but would not determine the configuration of the reduction product.

(14) Modifications of the above mechanism in several details are possible and are not excluded by the facts known at present. It should also be pointed out that, since alkaline hydrogenation of Δ^4-3-keto steroids leads to a *cis* A:B ring system, the mechanism might imply that a shift of a double bond from a bridgehead of such a system with two six-membered rings also should lead to a *cis* configuration. Experimental evidence is needed on this point under mild conditions, although under the more severe conditions of Wolff-Kishner reduction Lardelli and Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949), isolated Δ^3-cholestene (*trans* A:B) among other products from cholestenone.

(15) Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(16) The reason for less stereospecificity in the neutral hydrogenation of III as compared to I is obscure, although it seems probable that it is a conjugative effect of the 3-methoxyl group. In this connection it is interesting to note that the methoxyl group exerts a powerful conjugative effect on the ultraviolet absorption of III (Wilds, *et al.*, THIS JOURNAL, **69**, 1985 (1947)), but has little effect on that of VI (as compared to V); and in the latter case the hydrogenation leads smoothly to the *trans* isomer.

The above mechanism for alkaline hydrogenation can also account satisfactorily for results with α,β-unsaturated ketones of the type XI, where the *trans* isomer is favored. Here the configuration would be established by ketonization of the intermediate analogous to D and should lead to the more stable *trans* configuration.

Experimental[17]

cis-16-Equilenone (II).—$\Delta^{1,1'}$-2'-Keto-2-methyl-3,4-dihydro-1,2-cyclopentenophenanthrene (14,15-dehydro-16-equilenone I) was purified with Raney nickel as described previously[3b] and 400 mg. of the ketone dissolved in 55 ml. of absolute alcohol was stirred with 80 mg. of powdered potassium hydroxide, 160 mg. of 30% palladium-on-carbon catalyst[18] and hydrogen at room temperature and atmospheric pressure. The theoretical amount of hydrogen was absorbed in about 5.5 hours. The solution was filtered, 0.5 ml. of hydrochloric acid added and most of the alcohol evaporated. The product, isolated by extraction with ether and crystallization from methanol amounted to a total of 359 mg. (89%) of *cis*-16-equilenone, m. p. 91–93.5°. Further recrystallization from methanol gave the pure ketone as white needles, m. p. 94.5–95°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.4; H, 7.2. Found: C, 86.2, 86.5; H, 7.0, 6.9.

The oxime, prepared in 72% yield in alcohol–pyridine, crystallized from alcohol as white needles, m. p. 165–166.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.2. Found: C, 81.3; H, 7.4.

Hydrogenation of 600 mg. of I with 200 mg. of the palladium catalyst in 60 ml. of dry *t*-butyl alcohol containing potassium *t*-butoxide from 0.1 g. of potassium gave in two crops 470 mg. (78%) of *cis*-16-equilenone, m. p. 92.5–95.5°.

Reduction of *cis*-(II) to *cis*-Equilenane.—Clemmensen reduction of 100 mg. of *cis*-16-equilenone as described earlier for the *trans* (II) isomer[4] gave an oil after extraction and evaporative distillation at 140–170° (0.3 mm.). Addition of 100 mg. of trinitrobenzene to this oil in absolute alcohol resulted in a total of 137 mg. (77%) of the crystalline derivative, melting in the range 106.5–112.5°. Recrystallization gave material melting at 113–114.5° alone or when mixed with the previously prepared derivative of known *cis*-equilenane.[4] The picrate also was prepared, m. p. and mixed m. p. 98.5–101°.

trans-3-Methoxy-16-equilenone (IV). (a) By Neutral Hydrogenation.—A solution of 500 mg. of sublimed and recrystallized $\Delta^{1,1'}$-2'-keto-2-methyl-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (14,15-dehydro-3-methoxy-16-equilenone III) in 30 ml. of dioxane was hydrogenated using 200 mg. of palladium-on-carbon catalyst as described earlier[3c]; it was necessary to add further 150 mg. of catalyst after five hours and the hydrogenation was stopped after 1.18 mole equivalents had been absorbed (42 hours). Repeated crystallization gave a total of 148 mg. (29%) of the *trans* isomer, most melting at 164–168° and undepressed when mixed with Isomer B (m. p. 169.5–171°) of Wilds and Close.[3c] None of the supposed Isomer A, m. p. 185–186°, could be isolated, and this must now be presumed to be a mixture.

The ultraviolet absorption of the pure *trans* ketone in 95% alcohol showed maxima at 231.5 mμ (log E_{molar} 4.81), 268.5 mμ (3.71), 278 mμ (3.75), 323 mμ (3.31) and 336 mμ (3.39); minima at 258 mμ (3.60), 272.5 mμ (3.67), 302.5 mμ (2.94) and 327 mμ (3.28); and an inflection at 287 mμ (3.59).

(17) All melting points are corrected; those marked vac. were determined in sealed Pyrex capillaries evacuated to 0.5 mm. or less. Microanalyses were carried out by Richard Hunt and Virginia Diekmann Miller.

(18) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

The oxime, obtained in 81% yield, crystallized from benzene–ethanol as fine white flakes, m. p. 236.5–238.5° (vac.).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.2. Found: C, 77.3; H, 7.0.

(b) **By Acidic Hydrogenation.**—Hydrogenation of 800 mg. of the ketone was carried out in 55 ml. of dioxane containing 0.5 ml. of acetic acid, using 320 mg. of the palladium catalyst and adding another 150 mg. after 24 hours (1.21 mole equivalents of hydrogen absorbed in 37 hours). The first crop of ketone, 457 mg., m. p. 159–164°, afforded 309 mg. (38%) of the *trans* isomer after two recrystallizations, m. p. 166.5–169°. When acetic acid was used alone as the solvent, reduction was not specific for the double bond and led to mixtures containing non-ketonic material.

cis-**3-Methoxy-16-equilenone** (IV).—Hydrogenation of 400 mg. of the methoxy ketone (III) suspended in 60 ml. of absolute alcohol containing 80 mg. of powdered potassium hydroxide and 160 mg. of the palladium catalyst was complete in 6.5 hours (one mole equivalent absorbed). Isolation of the ketone and crystallization from methanol–acetone gave 329 mg., m. p. 169.5–170.5° and 25 mg., m. p. 168.5–170.5°, for a total yield of 88%. Further recrystallization gave *cis*-3-methoxy-16-equilenone as fine white needles, m. p. 171–172°; mixed m. p. with *trans* isomer depressed to 137–155°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.5; H, 7.0.

The ultraviolet absorption spectrum in 95% alcohol showed maxima at 229 mμ (log E_{molar} 4.81), 265 mμ (3.77), 275 mμ (3.76), 319 mμ (3.27) and 334 mμ (3.37); minima at 258 mμ (3.69), 270 mμ (3.71), 299 mμ (2.85) and 325 mμ (3.20); and an inflection at 283 mμ (3.59).

The oxime (88% yield) was obtained as white needles from ethanol–benzene, m. p. 199–200.5° (vac.).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.2. Found: C, 77.6; H, 7.1.

cis-**3-Hydroxy-16-equilenone.** (a) **By Demethylation.**—Heating 300 mg. of the *cis*-methoxy ketone (IV) with hydrobromic and acetic acids as described for the *trans* isomer (Isomer B)[3c] afforded a total of 234 mg. (82%) of the phenolic ketone, m. p. 163.5–166.5°. After further recrystallization from methanol (Norit) the melting point was raised to 166.5–167.5° (mixed m. p. with the methoxy ketone 145–161°); this material appeared to contain solvent of crystallization (found: C, 74.1; H, 6.9). Evaporative distillation at 160–180° (0.001 mm.) and recrystallization from acetone–petroleum ether resulted in material of m. p. 160.0–160.7°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.2; H, 7.0.

(b) **By Alkaline Hydrogenation.**—Hydrogenation of 200 mg. of purified $\Delta^{1,1'}$-2′-keto-2-methyl-7-hydroxy-3,4-dihydro-1,2-cyclopentenophenanthrene,[3c] m. p. 258–261° (vac.), in 30 ml. of absolute alcohol, using 83 mg. of powdered potassium hydroxide and 100 mg. of palladium catalyst, required fifteen hours, an additional 100 mg. of catalyst being added at the end of seven hours. Isolation of the product and crystallization from methanol gave 88 mg., m. p. 161–164°, and 54 mg., m. p. 155–162°. By evaporative distillation (0.001 mm.) and recrystallization from methanol material was obtained melting at 164–165.5°; mixed m. p. with the sample from methanol in (a), 164.5–167°.

trans-**3-Methoxyequilenane** (VIII). (a) **From *trans*-3-Methoxy-16-equilenone.**—The best results for small-scale reductions under nitrogen by the Huang-Minlon procedure[7,18a] were obtained with the following apparatus modified from a design by Dr. A. Russell Jones. A separator (18 cm. over-all height) was constructed from a 10-ml. bulb to the top of which was sealed a standard taper joint for attaching a reflux condenser and at the bottom an inverted Y three-way stopcock, one lower arm of which was attached to the reaction flask by standard taper joints. A by-pass tube leading from this lower arm of the stopcock to the 10-ml. bulb permitted liquid to distil from the reaction flask to the upper bulb without being returned when the stopcock was closed. The third arm of the stopcock permitted periodic draining of the bulb as necessary. The reaction flask carried a side tube for a thermometer.

In the reaction flask of this apparatus were placed 150 mg. of *trans*-3-methoxy-16-equilenone (m. p. 166.5–169°), 9 ml. of diethylene glycol, 0.9 ml. of 85% hydrazine hydrate and 0.8 g. of potassium hydroxide pellets. Since after heating at 100–105° for one hour under a nitrogen atmosphere all of the ketone had not dissolved, 2 ml. of benzene was added and allowed to reflux for fifteen minutes, then distilled into the upper bulb. After another hour at 105° the temperature was raised slowly to 190–195° while water and excess hydrazine distilled into the upper bulb. Finally after three hours at 195°, the mixture was cooled, diluted, acidified and extracted with benzene and ether. After evaporating the extract the residue was remethylated using dimethyl sulfate and alkali. Evaporative distillation of the product at 140–170° (0.1 mm.) and crystallization from methanol afforded 105 mg. (74%) of *trans*-3-methoxyequilenane, m. p. 114.5–116°. Additional material isolated directly or as the trinitrobenzene derivative brought the total yield to 90%. Recrystallization of the first crop from benzene gave colorless needles, m. p. 120.3–121°.[19]

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 86.0; H, 8.2.

The trinitrobenzene derivative crystallized from absolute alcohol as fine orange crystals, m. p. 132.3–133°.

Anal. Calcd. for $C_{25}H_{25}N_3O_7$: C, 62.6; H, 5.3. Found: C, 62.5; H, 5.1.

(b) **From *dl*-Equilenin Methyl Ether.**—Similar reduction of 50 mg. of *dl*-equilenin methyl ether (m. p. 186–189°)[20] gave 26 mg. of *trans*-3-methoxyequilenane, m. p. 114–115.5°, and 14 mg. as the trinitrobenzene derivative. Recrystallization of the former gave material melting at 120.8–121.5° undepressed in m. p. when mixed with the sample from (a). The pure trinitrobenzene derivative, m. p. 132.2–133.0°, also was undepressed by the derivative from (a).

cis-**3-Methoxyequilenane** (*cis* VIII). (a) **From *cis*-3-Methoxy-16-equilenone** (IV).—Reduction of 100 mg. of this ketone by the Huang-Minlon procedure as described above afforded 66 mg. of product, m. p. 71–73°, with additional material from the filtrate and as the trinitrobenzene derivative bringing the total yield to 87%. Recrystallization from methanol–benzene (drying the product at 60°) gave a sample melting at 73.7–74.6°.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 86.0; H, 8.3.

The trinitrobenzene derivative crystallized as orange needles from absolute alcohol, m. p. 136.8–137.3°.

(b) **From *dl*-Isoequilenin Methyl Ether.**—Reduction of 150 mg. of this ketone as above gave 61 mg. of *cis*-3-methoxyequilenane, m. p. 68.5–71°. The recrystallized product melted at 72.2–73.3° alone and when mixed with the sample from (a).

The trinitrobenzene derivative melted at 136.1–136.7°, not depressed by the derivative from (a).

Anal. Calcd. for $C_{25}H_{25}N_3O_7$: C, 62.6; H, 5.3. Found: C, 62.5; H, 5.1.

14,15-**Dehydroequilenane** (V).—14,15-Dehydro-16-equilenone (I, m. p. 148–149°) was reduced by the Huang-Minlon procedure under nitrogen as described above, using

(18a) Clemmensen reduction was unsatisfactory with this compound.

(19) The optically active form of this compound has been prepared from *d*-equilenin methyl ether by Cohen, Cook, Hewett and Girard, *J. Chem. Soc.*, 653 (1934), and is reported to melt at 121–122°.

(20) We are indebted to Dr. W. S. Johnson for supplying 14,15-dehydroequilenin methyl ether and *dl*-isoequilenin methyl ether; see Johnson, Petersen and Gutsche, THIS JOURNAL, **69**, 2942 (1947).

a solution of 500 mg. of the ketone in 7 ml. of benzene, 4 ml. of 85% hydrazine hydrate, 20 ml. of diethylene glycol and 2.5 g. of potassium hydroxide. After refluxing for one hour, the temperature was raised to 190–200° with distillation of the volatile components, and held there for two hours. The product was isolated by extraction with ether and crystallized from methanol, giving 374 mg., m. p. 85–87°, and an additional 51 mg. melting slightly lower for a total of 90%. Recrystallization from methanol gave colorless needles, m. p. 87.5–88°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.30; H, 7.88.

The ultraviolet absorption spectrum in 95% alcohol showed maxima at 255 mμ (log E_{molar} 4.66), 285 mμ (4.10), 295 mμ (4.19) and 305 mμ (4.11); minima at 275 mμ (4.01), 287 mμ (4.09) and 300 mμ (4.05).

The trinitrobenzene derivative crystallized as lemon yellow needles from absolute alcohol, m. p. 120–121°. A mixed m. p. with the derivative of *trans*-equilenane showed depression to 109–116°.

Anal. Calcd. for $C_{24}H_{21}O_6N_3$: C, 64.42; H, 4.73. Found: C, 64.67; H, 4.59.

The picrate, orange-red elongated plates from absolute alcohol, melted at 110–110.8°.

Anal. Calcd. for $C_{24}H_{21}O_7N_3$: C, 62.20; H, 4.57. Found: C, 62.38; H, 4.39.

Hydrogenation of 14,15-Dehydroequilenane (V) to *trans*-Equilenane. (a) **Acidic Medium.**—Hydrogenation of 100 mg. of (V) in 15 ml. of absolute alcohol and 4 ml. of acetic acid, using 50 mg. of 30% palladium-on-carbon catalyst, was complete in 17 minutes. Crystallization of the product from methanol afforded 67 mg., m. p. 86–87°, 18 mg., m. p. 81–83° and 10 mg. m. p. 77–82°. Recrystallization from methanol gave colorless needles, m. p. 86.5–87.5° alone or when mixed with authentic *trans*-equilenane; a mixture with the starting 14,15-dehydro derivative (V) melted at 64–70°.

(b) **Alkaline Medium.**—Hydrogenation of 100 mg. of 14,15-dehydroequilenane in 15 ml. of absolute alcohol with 50 mg. of the palladium catalyst and 30 g. of powdered potassium hydroxide required 7.5 hours for completion. The product was crystallized from methanol giving 56 mg., m. p. 85–86°, 23 mg., m. p. 80–82°, and 13 mg., m. p. 72–73°. Recrystallization afforded *trans*-equilenane of m. p. 86–87°, showing no m. p. depression with an authentic sample.

3-Methoxy-14,15-dehydroequilenane (VI).—Huang-Minlon reduction of 250 mg. of 3-methoxy-14,15-dehydro-16-equilenone (III; m. p. 202–203°) under nitrogen by the procedure given above gave a dark brown solid which was dissolved in 10% potassium hydroxide and remethylated with dimethyl sulfate. Filtration gave 137 mg. (58%) of product, m. p. 115–119°. By recrystallization from methanol colorless crystals were obtained, m. p. 123–123.5°. The sample gave a m. p. depression (103–110°) when mixed with *trans*-3-methoxyequilenane.

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.10; H, 7.58.

The ultraviolet absorption spectrum in 95% alcohol showed maxima at 254 mμ (log E_{molar} 4.66), 263 mμ (4.65), 281 mμ (4.14), 292 mμ (4.27) and 303 mμ (4.25); minima at 259 mμ (4.58), 275 mμ (4.04), 284 mμ (4.13) and 298 mμ (4.15); and an inflection at 245 mμ (4.53).

The trinitrobenzene derivative formed orange platelets from absolute alcohol, m. p. 139.8–140.4°.

Anal. Calcd. for $C_{25}H_{23}N_3O_7$: C, 62.89; H, 4.85. Found: C, 63.01; H, 4.61.

Hydrogenation of 3-Methoxy-14,15-dehydroequilenane (VI) to *trans*-3-Methoxyequilenane.—The hydrogenation of 100 mg. of (VI) in 50 ml. of 95% alcohol with 50 mg. of 30% palladium-on-carbon catalyst was nearly complete in one-half hour. The product was crystallized from methanol, affording 80 mg., m. p. 116–117°, 12 mg., 110–112° and 5 mg., m. p. 105–111°. Recrystallization of the first crop raised the m. p. to 120–121° alone or in admixture with *trans*-3-methoxyequilenane prepared above from the 16-keto-derivative.

16-Hydroxy-14,15-dehydroequilenane (IX).—A solution of 100 mg. of lithium aluminum hydride in 50 ml. of dry ether was added to 200 mg. of 14,15-dehydro-16-equilenone dissolved in 10 ml. of dry benzene and 50 ml. of ether. After ten minutes at gentle reflux the reaction mixture was cooled, slowly hydrolyzed with 3 ml. of water[19] and extracted with three portions of ether. The extract was washed with saturated salt solution, dried over sodium sulfate and evaporated to give 195 mg. of material m. p. 160–164°. Two recrystallizations from ether did not change the m. p. Methanol or benzene as recrystallization solvents lowered and broadened the melting point range.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.09; H, 7.46.

The ultraviolet absorption spectrum in 95% alcohol showed maxima at 254 mμ (log E_{molar} = 4.67), 262 mμ (4.62), 283 mμ (4.13), 292 mμ (4.22) and 305 mμ (4.13); minima at 259 mμ (4.60), 275 mμ (4.00), 287 mμ (4.09) and 300 mμ (4.03); and an inflection at 245 mμ (4.54).

16-Hydroxy-*trans*-equilenane (Isomer A) (X).—*trans*-16-Equilenone (100 mg., m. p. 167–169°) in 50 ml. of ether was reduced with 50 mg. of lithium aluminum hydride in 50 ml. of ether as described above for (IX) and the product crystallized from methanol affording 95 mg. (95%), m. p. 181–183°. Further recrystallization gave pure Isomer A, m. p. 183.5–184.5°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.65; H, 7.99. Found: C, 85.55; H, 7.98.

The benzoate of Isomer A, prepared in 78% yield by heating for 12 hours with benzoyl chloride in benzene–pyridine solution, crystallized from alcohol containing a few drops of acetone as colorless prisms, m. p. 122–123°. A mixed m. p. with benzoic acid showed depression to 105–115°.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.23; H, 6.79. Found: C, 84.11; H, 6.78.

16-Hydroxy-*trans*-equilenane (Isomer B). (X).—Hydrogenation of 195 mg. of unrecrystallized 16-hydroxy-14,15-dehydroequilenone (IX; m. p. 160–164°) in 30 ml. of absolute alcohol with 100 mg. of 30% palladium-on-carbon required 90 minutes. Crystallization of the product from petroleum ether–benzene (2:1) gave a total of 164 mg. (82%), m. p. 120–123°. Further recrystallization from the same solvent pair gave Isomer B as fluffy needles, m. p. 123.5–124°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.65; H, 7.99. Found: C, 85.79; H, 8.00.

This compound in 95% alcohol showed absorption maxima at 231 mμ (log E_{molar} 4.91) and 286 mμ (3.68) with a minimum at 245 mμ (2.97).

The benzoate of Isomer B, prepared in 87% yield as for Isomer A, crystallized from methanol–acetone as colorless needles, m. p. 154–154.8°.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.23; H, 6.79. Found: C, 84.61; H, 6.72.

Oxidation of a solution of 100 mg. of Isomer B in 20 ml. of acetic acid with 70 mg. of chromium trioxide at 16–18° for one hour, then addition of methanol, concentration and extraction with ether gave the crude ketone which was crystallized from methanol. Further recrystallization of the product (32 mg., m. p. 154–161°) gave *trans*-16-equilenone, m. p. 163–166° alone or in admixture with an authentic sample.

Summary

The stereochemical course of hydrogenation of some derivatives of equilenane has been studied. Reduction of the 14–15 double bond of the α,β-unsaturated 16-keto derivatives under alkaline conditions led to the *cis* C:D ring fusion, while under neutral conditions the *trans* isomer was favored. Hydrogenation of the $\Delta^{14,15}$-16-hydroxy

or 16-desoxy compounds resulted in the *trans* isomer exclusively for the examples reported.

A mechanism to account for the effect of alkali on the hydrogenation of α,β-unsaturated ketones is proposed.

MADISON 6, WISCONSIN RECEIVED MAY 2, 1950

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

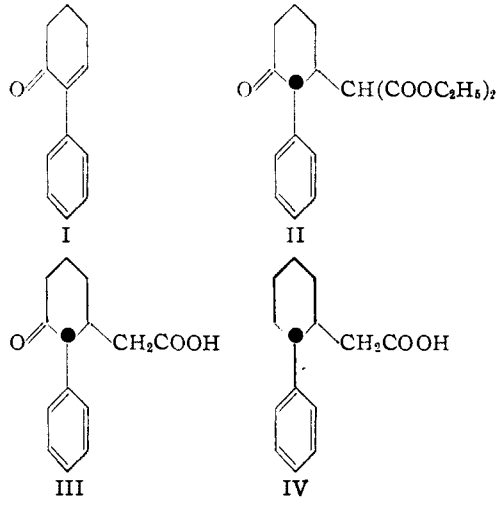
Reactions of 2-Arylcyclohexanones. IV. Michael Addition of Malonic Ester to 2-Phenyl-Δ^2-cyclohexenone

BY W. E. BACHMANN AND E. J. FORNEFELD[1]

Recently Bachmann and Wick[2] described the preparation of 2-phenyl-Δ^2-cyclohexenone (I) by dehydrobromination of the product formed by bromination of 2-phenylcyclohexanone. We have now carried out a Michael addition of diethyl malonate to the α,β-unsaturated ketone and obtained diethyl 3-oxo-2-phenylcyclohexanemalonate (II). As will be shown later, the reaction proceeded sterically in such a manner that the phenyl group and the malonic ester group became oriented in a *trans*-configuration. The reaction was unsuccessful when only small amounts of sodium ethoxide in ether or alcohol or when piperidine in boiling ethanol were used as the medium for the additions, but proceeded satisfactorily in the presence of an equivalent amount of sodium ethoxide and excess diethyl malonate. The successful addition of malonic ester to the unsaturated ketone is in contrast to the failure of diethyl malonate to add to ethyl α-phenylcinnamate, which also has the phenyl group next to the activating group.[3]

The substituted malonic ester II was converted into *trans*-3-oxo-2-phenylcyclohexaneacetic acid (III) by hydrolysis and decarboxylation in a boiling mixture of acetic acid and hydrochloric acid. Clemmensen reduction of the keto acid yielded *trans*-2-phenylcyclohexaneacetic acid (IV). The same acid was obtained when the substituted malonic ester II was subjected to Clemmensen conditions; hence *trans*-2-phenylcyclohexaneacetic acid IV can be obtained from 2-phenylcyclohexanone in a few steps. Confirmation of the structure and configuration of IV was obtained by cyclization of IV to the known *trans* 9-oxo-1,2,3,4-9,10,10a-octahydrophenanthrene. The reactions and intermediates offer promise in the construction of the morphine structure.

Linstead, Whetstone and Levene[4] condensed 2-phenylcyclohexanone with cyanoacetic ester at elevated temperatures and reduced the product to ethyl-2-phenylcyclohexanecyanoacetate. We obtained the last named compound from the ketone in one step at room temperature by carrying out the condensation in the presence of palladium and hydrogen according to the procedure employed by Alexander and Cope[5] on other ketones. Hydrolysis and decarboxylation of the product in a boiling mixture of acetic acid and hydrochloric acid gave *cis*-2-phenylcyclohexaneacetic acid in good yield.



I II III IV

Experimental

2-Phenyl-Δ^2-cyclohexenone (I).—It is essential to use pure 2-phenylcyclohexanone for good results. Following the procedure described,[2] a solution of 1.54 ml. of bromine (reagent grade) in 25 ml. of carbon tetrachloride (reagent grade) was added dropwise to a vigorously stirred, chilled (ice-bath) solution of 5 g. of 2-phenylcyclohexanone (m. p. 58–59°) in 30 ml. of carbon tetrachloride in a current of carbon dioxide. The crystalline bromoketone, which remained after the solution had been washed with water, dried and evaporated under reduced pressure below 30°, was heated with 50 ml. of 2,6-dimethylpyridine in a nitrogen atmosphere for twenty minutes, and the product was isolated as described.[2] After distillation at 0.1 mm. (bath temperature, 145–155°) and recrystallization from petroleum ether (60–75°) the 2-phenyl-Δ^2-cyclohexenone formed colorless needles; yield 3.5 g.; m. p. 93–94.5°.

In one run in which the bromoketone was recrystallized from acetone–petroleum ether, the 2-bromo-2-phenylcyclohexanone melted at 68.5–69° instead of the reported 103–104°. Apparently this represents another crystalline modification, for the melting point rose after several days and after recrystallization of the compound from methanol. It had the correct analysis and yielded the same unsaturated ketone as the higher-melting form.

Michael Addition of Malonic Ester.—To a solution of sodium ethoxide prepared from 0.66 g. of sodium in 50 ml. of absolute ethanol was added 23 g. of diethyl malonate

(1) From the Ph.D. dissertation of E. J. Fornefeld, 1950.

(2) Bachmann and Wick, THIS JOURNAL, **72**, 3388 (1950).

(3) Connor and McClellan, *J. Org. Chem.*, **3**, 576 (1939).

(4) Linstead, Whetstone and Levene, THIS JOURNAL, **64**, 2015 (1942).

(5) Alexander and Cope, *ibid.*, **66**, 886 (1944).