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STUDIORUM PROGRESSUS

Conformational Studies on *cyclo*Hexanones

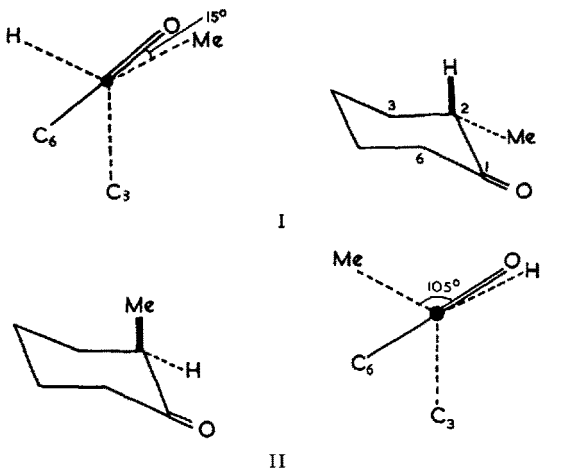
By W. KLYNE, London[1]

ROBINS and WALKER[2] have recently discussed the stabilities of some perhydro-1:4-dioxophenanthrenes prepared in their previous work[3]. They showed that the stability sequence of these diketones could be rationalized by making an allowance for nonbonded interaction between the oxygen atom of a *cyclo*hexanone carbonyl group and an equatorial (eclipsed) substituent on an adjacent carbon atom. This may be called the "2-alkyl ketone effect".

ROBINS and WALKER[4] subsequently pointed out that another conformational factor is also involved viz. the decrease in the non-bonded interaction energy associated with an axial alkyl group when a carbonyl group is present in the 3-position. This may be called the "3-alkyl ketone" effect.

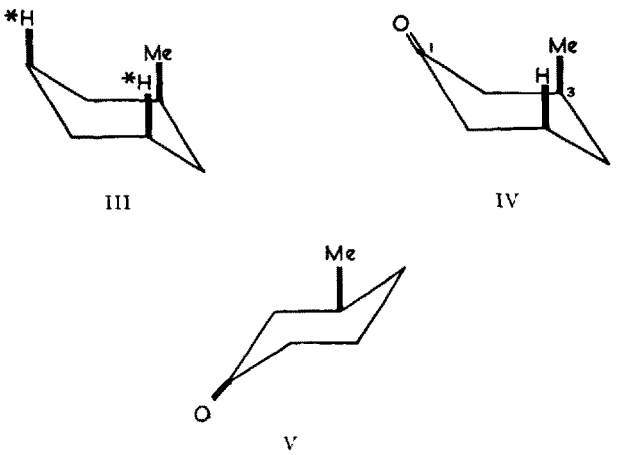
The purpose of the present paper is to discuss other evidence from a variety of alicyclic compounds which confirms the existence of these two separate effects, and gives further estimates of their magnitude.

Geometry.—The 2-alkyl ketone effect.—A methyl (or methylene) group substituted in an equatorial position on $C_{(2)}$ of *cyclo*hexanone is in an (almost) eclipsed position with respect to the oxygen of the carbonyl group (I). An axial methyl group is not (II). This is a special case of the general conformational problem of linked trigonal and tetragonal atoms (*cf.* MIZUSHIMA)[5]. COOKSON[6] has estimated the projected valency angles O= C_1-C_2-*X* to be 15° and 105° respectively for equatorial (I) and axial (II) substituents (*X*) in the 2-position.

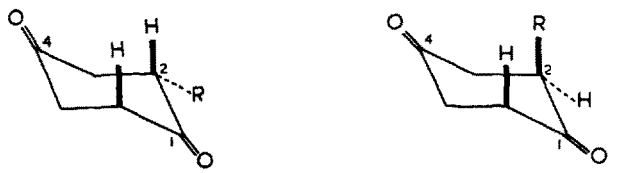


The 2-alkylketone effect resembles the steric factor involved in COREY's treatment[7] of the stereochemistry of α-bromoketones. The other factor discussed by COREY, viz. dipole repulsion – which is of great importance for the interaction of C–Br and C=O – is no doubt involved to a minor extent in the 2-alkyl-ketones.

The 3-alkyl ketone effect.—In a conformation such as (III) (methyl*cyclo*hexane in its unstable axial conformation) the 1:3-non-bonded interactions of the axial methyl group are with two axial hydrogen atoms marked '*'. In a compound such as 3(*a*)-methyl*cyclo*hexanone (IV) where C_1 is trigonal, one of these axial H-atoms is missing (*cf.* DREIDING[8]); the non-bonded interaction of the axial methyl group with the oxygen of the carbonyl at C_1 cannot be calculated, but since the interatomic distance Me – C to =O is large (ca. 3·8 Å), the interaction is presumably small. ROBINS and WALKER[4] therefore set the difference in non-bonded energy contributed by the methyl group between 3(*a*)-methyl*cyclo*hexanone (IV) and the 3(*e*)-methyl conformation (V) as something approaching one-half the energy increment for an axial methyl group in methyl*cyclo*hexane (ca 1·8 kcal.mole^{-1}; PITZER and BECKETT[9])—i.e. approximately 0·9 kcal. mole^{-1}.



In 2(*a*)methyl-*cyclo*hexane-1:4-diones (including the perhydro-1:4-dioxophenanthrenes of ROBINS and WALKER[3]) both 2-alkylketone and 3-alkylketone effects operate. Compare formulae (VI*A*) and (VI*B*).



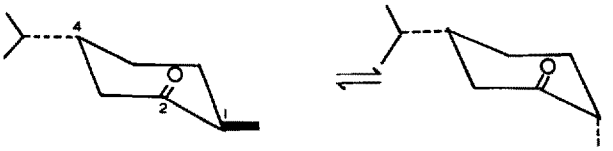
R = —CH_3 or —CH_2—

In the following discussion the possibility of boat conformations will not be considered, and small deformations of valency angles will be neglected.

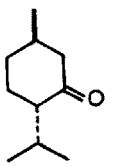
Monocyclic ketones.—The monocyclic terpene ketones, carvomenthone (VII) and *iso*carvomenthone (VIII), provide a valuable example for studying the 2-alkylketone effect alone. (I am indebted to Dr. J. WALKER for drawing my attention to these compounds.) The equilib-

[1] Postgraduate Medical School, London, W. 12.
[2] P. A. ROBINS and J. WALKER, J. chem. Soc. *1955*, 1789.
[3] P. A. ROBINS and J. WALKER, J. chem. Soc. *1954*, 3960.
[4] P. A. ROBINS and J. WALKER, Chem. and Ind. *1955*, 772.
[5] S. MIZUSHIMA, *Internal Rotations and the Structure of Molecules* (Academic Press, New York, 1954), p. 73.
[6] R. C. COOKSON, J. Chem. Soc. *1954*, 282.
[7] E. J. COREY, Experientia *9*, 329 (1953); J. Amer. chem. Soc. *75*, 2301, 3297, 4832 (1953); *76*, 175 (1954).
[8] A. S. DREIDING, Chem. and Ind. *1954*, 1419.
[9] K. S. PITZER and C. W. BECKETT, J. Amer. chem. Soc. *69*, 977 (1947).

rium between (VII) and (VIII) (JOHNSTON and READ[10]) represents an equilibrium between 2(*e*)- and 2(*a*)-methylketones. Here the 3(*a*)-alkylketone effect plays no part, since the large *iso*propyl group is presumably equatorial in both isomers.



VII VIII



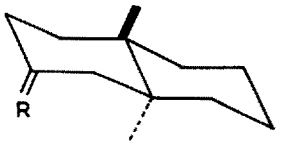
IX

The equilibrium is approximately 80% (*e*): 20% (*a*), i.e. $K = 4$. The difference in free energy between the two isomers can then be calculated as $\Delta F = -RT\ ln\ K = 0{\cdot}8$ kcal.mole^{-1}.

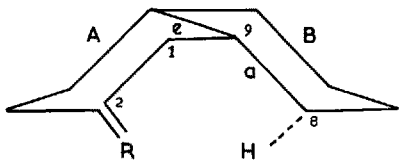
This value represents the difference in non-bonded energy between 2(*a*)- and 2(*e*)-methyl*cyclo*hexanones (I and II). PITZER and BECKETT[9] have calculated the energy difference between (*a*)- and (*e*)-methyl*cyclo*hexanes as ca. 1·8 kcal. mole^{-1}. The interaction between an equatorial methyl group and an adjacent carbonyl group is thus estimated as 1·8–0·8 = 1·0 kcal. mole^{-1}.

Menthone (IX) and *iso*menthone, in which the carbonyl group is adjacent to an *iso*propyl substituent, do not provide a suitable example for discussion at present.

2-Decalones.—Comparison of the *cis*- and *trans*-2-decalones with the related decalins provides an interesting illustration of the "3-alkylketone" effect acting alone.

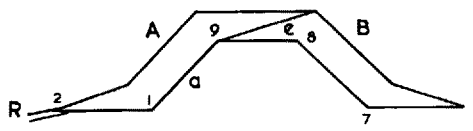


X *trans*



XI

(O–8αH = 3·1 Å)



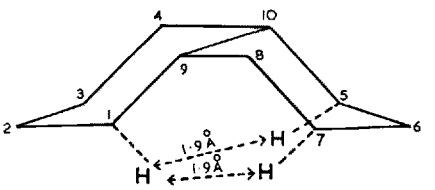
cis

XII

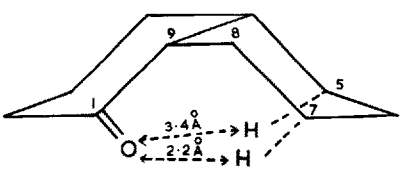
The difference in non-bonded energy between *cis*- and *trans*-decalins (X) and (XI) ($R = H_2$) has been represented by TURNER[11] as three skew-butane interactions present in the *cis*- but not the *trans*-isomer. These account well for the difference of 2·4 kcal.mole^{-1}.

In *cis*-2-decalone (preferred conformation (XI; R=O)[12] one of the three skew interactions is of the 3-alkylketone type—viz. that between the methylene group at $C_{(8)}$ (axial with respect to ring *A*) and the keto group at $C_{(2)}$ (*cf.* TAYLOR[13], DREIDING[3]). *trans*-2-Decalone (X; R = O) has no skew-butane interactions. The energy difference (*cis*- *minus trans*-2-decalone) should therefore be smaller than the energy difference (*cis*- *minus trans*-decalin). In fact the difference in heat of combustion between *cis*- and *trans*-2-decalone (2·2 kcal.mole^{-1}) is less than that between *cis*- and *trans*-decalins (4·7 kcal. mole^{-1}) (HÜCKEL[14]).

The alternative conformation (XII, R = O) for *cis*-2-decalone will not be favoured, since it shows three ordinary skew-butane interactions. 5β-Steroids must however take up this conformation because of fusion between rings *B* and *C*.



XIII



XIV

1-Decalones.—Some of the important interatomic distances for *cis*-decalin are shown in (XIII). The short (and equal) H–H distances 1α:5α and 1α:7α (both 1·9 Å) in skew-butane systems are noteworthy. If the two H atoms at C–1 are replaced by = O as in *cis*-1-decalone (XIV) the distance 0:5αH is 3·4 Å: this increased interatomic distance is the basis of the 3-alkylketone effect in (XIV).

It may be seen that the 0:7αH-distance is 2·2 Å; and the interaction here will be considerable. Hence although $C_{(1)}$–$C_{(9)}$–$C_{(8)}$–$C_{(7)}$ in (XIV) form a "skew butan-1-one" system (*cf.* TAYLOR[2] and DREIDING[3]) it seems reasonable in an approximate treatment to consider the interaction of $C_{(1)}{=}O : C_{(7)}H_2$ in (XIV) as roughly equivalent to $C_{(1)}H_2 : C_{(7)}H_2$.

The non-bonded energies of *cis*- and *trans*-1-decalones and some related steroids may be calculated using the

[10] R. G. JOHNSTON and J. READ, J. chem. Soc. *1935*, 1138.

[11] R. B. TURNER, J. Amer. chem. Soc. *74*, 2118 (1952).

[12] It is necessary to introduce a symbol to distinguish the two conformations (XI) and (XII) of *cis*-2-decalone; it suggested that the nature of the valency bond leading from the bridge-head in the direction of the principal substituent or function (ketone in decalones, double bond in octalins) be designated in the name; thus (XI) and (XII) are *cis*(*e*)- and *cis*-(*a*)-2-decalones respectively since the $C_{(9)}$: $C_{(1)}$ bonds are equatorial and axial respectively with reference to ring *B*.

[13] D. A. H. TAYLOR, Chem. and Ind. *1954*, 250.

[14] W. HÜCKEL, Liebigs Ann. Chem. *451*, 109 (1927). – G. F. DAVIES and E. C. GILBERT, J. Amer. chem. Soc. *63*, 1585 (1941) give the value 2·1 kcal. mole^{-1} for the decalins, but did not study the 2-decalones.

Table I.—Non-bonded energy differences in 1-decalones. All values of E are relative to the corresponding unsubstituted-*trans*-decalin as zero, in kcal.mole^{-1}. For steroids only the *A* and *B* rings are considered. Values of E calculated as follows: (a) Values for skeleton only—i.e. for decalins, following JOHNSON[1] and TURNER[2]. (b) Values for decalones, allowing + 1·0 kcal.mole^{-1} for 2-alkylketone effect and —0·9 kcal.mole^{-1} for 3-alkylketone effect (ROBINS and WALKER[3]).

	Interactions			E	
	Skew butane	2-Alkyl-ketone	3-Alkyl-ketone	(a)	(b)
trans-1-Decalone (XV, R = H)	0	1	0	0	1·0
cis-(*a*)-1-Decalone (XVI, R = H)	3	1	1	2·4	2·5
cis-(*e*)-1-Decalone (XVII, R = H)	3	0	0	2·4	2·4
9-Methyl-*trans*-1-decalone	4	1	0	3·2	4·2
9-Methyl-*cis*-(*a*)-1-decalone	5	1	1	4·0	4·1
9-Methyl-*cis*-(*e*)-1-decalone	5	1	0	4·0	5·0
10-Methyl-*trans*-1-decalone (XV, R = Me) also 4-Oxo-5α-steroid or 6-Oxo-5α-steroid	4	1	1	3·2	3·3*
10-Methyl-*cis*-(*a*)-1-decalone (XVI, R = Me) or 4-Oxo-5β-steroid (XVIII)	5	1	1	4·0	4·1
10-Methyl-*cis*-(*e*)-1-decalone (XVII, R = Me) or 6-Oxo-5β-steroid	5	0	1	4·0	3·1*

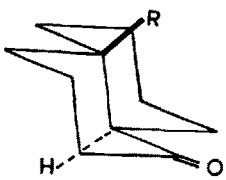
[1] W. S. JOHNSON, Experientia *7*, 315 (1951); J. Amer. chem. Soc. *75*, 1498 (1953).

[2] R. B. TURNER, J. Amer. chem. Soc. *74*, 2118 (1952).

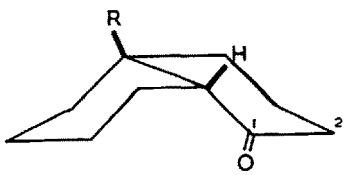
[3] P. A. ROBINS and J. WALKER, Chem. and Ind. *1955*, 772.

* Anomalous (see text).

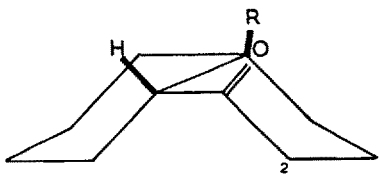
constants deduced by JOHNSON[15] and by ROBINS and WALKER[16] (see Table I).



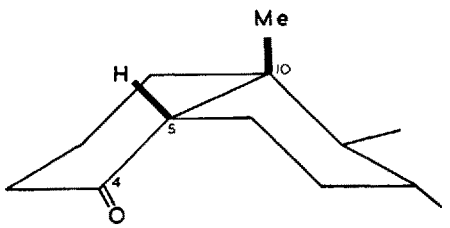
XV



XVI



XVII



XVIII

For the 1-decalones, HÜCKEL[17] found that the equilibrium mixture of the two isomers contained at least 95% *trans* (at 220°). For the 9-methyl-1-decalones Ross, SMITH, and DREIDING[18] have recently shown that equilibration over palladium-charcoal at 250° gives a mixture in which the *cis*-isomer predominates (60% *cis* : 40% *trans*). The energy values calculated in column *c* of Table I are qualitatively in accordance with this.

[15] W. S. JOHNSON, Experientia *7*, 315 (1951); J. Amer. chem. Soc. *75*, 1498 (1953).

[16] P. A. ROBINS and J. WALKER, J. chem. Soc. *1955*, 1789; Chem. and Ind. *1955*, 772.

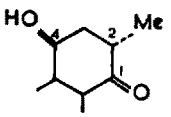
[17] W. HÜCKEL, Liebigs Ann. *441*, 1 (1925).

[18] A. ROSS, P. A. S. SMITH, and A. S. DREIDING, J. org. Chem. *20*, 905 (1955).

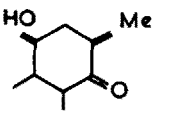
The experimental stability order for 6-oxosteroids (5α- more stable than 5β-) provides a good illustration of a fine balance in conformational effects. Energy differences calculated with allowances for the 2-alkylketone and 3-alkylketone effects as shown in Table I would imply that the 5β (A:B-*cis*) compounds should be of slightly lower energy content than the 5α (A:B-*trans*) isomers. In fact, the *latter* compounds are stable in isomerizing conditions. This anomaly can be corrected by assigning a value < 0·8 kcal. mole^{-1} to the 2-alkylketone effect[4].

No equilibrium data are available but WINDAUS[19] describes the transformation of *cis* → *trans* as irreversible (in 3:6-dioxo-5β-cholanic acid) and WIELAND and DANE[20] obtained a 70% yield of pure 3α-hydroxy-6-oxo-5α-cholanic acid from the 5β-isomer (*cf.* also PRELOG and TAGMANN[21]). The simpler example of LINSTEAD and WHETSTONE[22] is not immediately relevant here, since it concerns a perhydro-9-oxophenanthrene without an angle-methyl group.

Other perhydrophenanthrene ketones.—SARETT and coworkers[23] have shown that in perhydrophenanthrene derivatives of types (XIX) and (XX), one of the 2-epimeric methyl derivatives is appreciably more stable than the other; in the 1:4-diketones of types (XXI) and (XXII) the two epimers are of more nearly equal stability. (In fact in the presence of potassium carbonate,



XIX



XX

XXII preponderates.) SARETT therefore concluded provisionally that the *stable* epimer of the hydroxyketone

[19] A. WINDAUS, Liebigs Ann. Chem. *447*, 253 (1926).

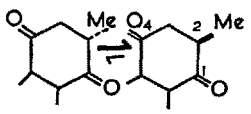
[20] H. WIELAND and E. DANE, Z. physiol. Chem. *212*, 41 (1932).

[21] V. PRELOG and E. TAGMANN, Helv. chim. Acta *27*, 1880 (1944).

[22] R. P. LINSTEAD and R. R. WHETSTONE, J. chem. Soc. *1950*, 1428.

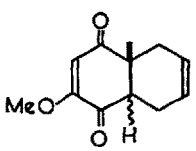
[23] R. M. LUKES, G. I. POOS, R. E. BEYLER, W. G. JOHNS, and L. H. SARETT, J. Amer. chem. Soc. *75*, 1707 (1953). – L. H. SARETT, W. F. JOHNS, R. E. BEYLER, R. M. LUKES, G. I. POOS, and G. E. ARTH, J. Amer. chem. Soc. *75*, 2112 (1953).

was the $2\alpha(e)$ compound (XIX) because non-bonded interaction between $2\beta(a)$-CH_3 and $4\beta(a)$-OH in the epimer (XX) would be greater than that between $2\beta(a)$-CH_3 and 4-carbonyl in (XXII). These examples support the idea that the "3-alkylketone" effect plays a part in determining the stabilities of 2-alkyl-1:4-diketones.

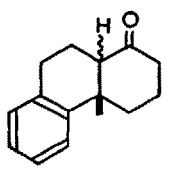


XXI/XXII

Other Examples.— A 1:4-dioxohexalin which shows stabilities of the same order in its *cis*- and *trans*-isomers is the compound (XXIII), one of the early stages in the Harvard steroid synthesis (WOODWARD, SONDHEIMER, TAUB, HEUSLER, and MCLAMORE[24]). This is however complicated by the presence of olefinic linkages in both rings.



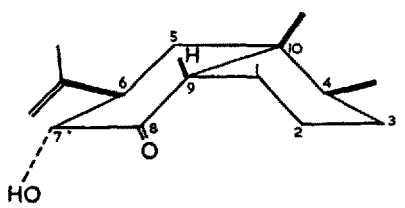
XXIII



XXIV

Another example where the *cis*-isomer predominates at equilibrium is provided by the oxo-octahydrophenanthrene derivatives of the general type (XXIV)[25].

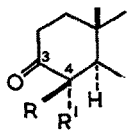
A further complex α-decalone which is stable in the *cis*-form is "hydroxydihydroeremophilone"[26] (XXIV*A*) which has recently been submitted to a detailed X-ray investigation by GRANT and ROGERS[27]. Here the 3-alkylketone effect (between $C_{(8)}$ and $C_{(4)}$) plays a part in favouring the stability of the *cis*-isomer; the principal factor is, however, the presence of substituents at $C_{(6)}$ and $C_{(7)}$ which are equatorial in (XXIV*A*) but would both be *axial* in the *trans*-isomer or in the alternative conformation of the *cis*-isomer. Some interaction between the carbonyl oxygen and the hydroxyl group may also be involved[27a].



XXIV*A*

(Dr. ROGERS has kindly informed the author that the carbonyl oxygen bond seems to be bent considerably out of the plane of $C_{(7)}$-$C_{(8)}$-$C_{(9)}$ towards the equatorial position.)

Triterpenoids and steroids. – *24-Nortriterpenoids.* – In these compounds (hedragonate type; XXV, *R* and *R'* = H and Me), if the single methyl group at C4 is axial it will be subject to 1:3-repulsion by the angle methyl group at C10 (*cf.* PITZER[28]; BECKETT, PITZER, and SPITZER[29]



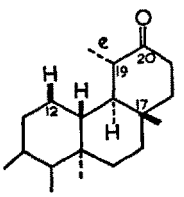
XXV

give 5·6 kcal.mole^{-1} as an "arbitrary" value for a 1:3-Me:Me interaction). We may therefore conclude that the stable (and only known) isomer is the $4\alpha(e)$-methyl compound (XXV, *R* = H, *R'* = Me).

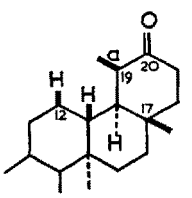
Support for this is forthcoming from molecular rotation arguments. The work of BARTON, IVES, and THOMAS[30] has shown that 3-ketones with *gem*-dimethyl at C4 (XXV, *R* = *R'* = Me) do not differ greatly in $[M]_D$ from those of type (XXV, *R* = *R'* = H) with no substituents at C4. It is therefore possible to calculate the contribution of the single methyl group at C4 in methyl hedragonate. $\Delta Me = M_D$ (methyl hedragonate[31]), $-M_D$ (methyl 3-oxoolean-12-en-28-oate) = (+ 463) – (+ 348) = + 115.

Date for the 30-nortaraxastan-20-ones- (see below)[32] show that (XXVI) is more dextrorotatory than (XXVII); the hedragonate is therefore analogous to (XXVI) and must have a 4α-methyl group (XXV, *R* = H, R' = Me).

30-Nortaraxastanes.— A further example showing how fine is the balance between axial and equatorial epimers in complex compounds is provided by the 30-nortaraxastan-20-ones of AMES, BETON, BOWERS, HALSALL, and JONES[33]. Arguments from reaction mechanisms and molecular rotations indicate that the axial 19β-methyl compound (XXVII) is more stable than the 19α-(*e*) epimer (XXVI)[23]. Repulsion between the two axial



XXVI
$[M_D]$ (+ 268)



XXVII
$[M_D]$ (+ 62)

methyl groups at C-17 and C-19 in (XXVII) might perhaps be expected to make this the less stable isomer. However, there is the further complication of interaction between the equatorial substituents at C-19 and C-12 ("4:5 effect" *cf.* KLYNE[33]). This just tips the balance in favour of (XXVII).

[24] R. B. WOODWARD, F. SONDHEIMER, D. TAUB, K. HEUSLER, and W. M. MCLAMORE, J. Amer. chem. Soc. *74*, 4223 (1952).

[25] D. ARIGONI and J. KALVODA (1955), cited by M. V. MIJOVIĆ, E. SUNDT, E. KYBURZ, O. JEGER, and L. RUZICKA, Helv. chim. Acta *38*, 237 (1955). – *Cf.* D. ARIGONI, J. KALVODA, H. HEUSSER, O. JEGER, and L. RUZICKA, Helv. chim. Acta *38*, 1857 (1955). – R. P. JACOBSEN, J. Amer. chem. Soc. *75*, 4769 (1953).

[26] Sir JOHN SIMONSEN and D. H. R. BARTON, *The Terpenes*, vol. 3 (Cambridge University Press, 1952), p. 212.

[27] D. F. GRANT and D. ROGERS, Chem. and Ind. *1956* (in press). (I am greatly indebted to Dr. D. ROGERS, Cardiff, for advance information about this paper.)

[27a] *Cf.* W. S. SVIRBELY and S. S. LANDER, J. Amer. chem. Soc. *72*, 3756 (1950) on 2-hydroxy*cyclo*hexanones.

[28] K. S. PITZER, Chem. Rev. *27*, 39 (1940).

[29] C. W. BECKETT, K. S. PITZER and R. SPITZER, J. Amer. chem. Soc. *69*, 2488 (1947).

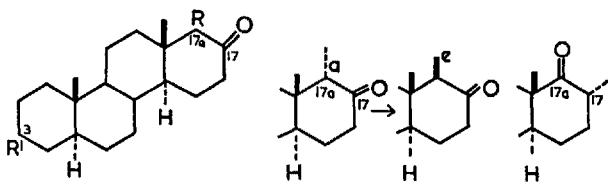
[30] D. H. R. BARTON, D. A. J. IVES and B. R. THOMAS, J. chem. Soc. *1954*, 903.

[31] D. H. R. BARTON and P. DE MAYO, J. chem. Soc. *1954*, 887.

[32] T. R. AMES, J. L. BETON, A. BOWERS, T. G. HALSALL, and E. R. H. JONES, J. Chem. Soc. *1954*, 1905.

[33] W. KLYNE, *Progress in Stereochemistry*, vol. 1 (Butterworth's, London 1954), p. 36.

D-Homosteroids.—RAMIREZ and STAFIEJ[34] have prepared epimeric 17*a*-methyl-17-oxo-*D*-homo steroids (general formula XXVIII, R = Me). These authors have shown that in the presence of alkali an equilibrium is set up between the 17*aα*(*a*)- and 17*aβ*(*e*)-methyl epimers (XXIX and XXX) in which the latter predominates (70% *e*:30% *a*). These proportions are of the same order as those for the carvomenthones (VII and VIII, 80% *e*:20% *a*).



XXVIII XXIX XXX XXXI

Comparison of molecular rotations with the compounds not carrying a methyl group at C-17*a* (GOLDBERG and WYDLER[35]) shows positive and negative changes due to the introduction of 17*aα*- and 17*aβ*-methyl groups respectively (Table II).

Table II.

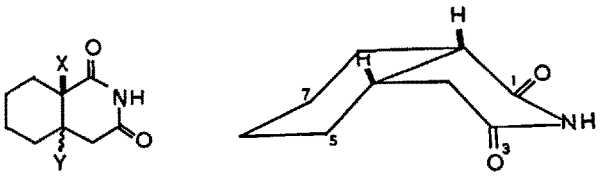
	$[M_D]$	ΔMe
17*aα*-Methyl-5α-*D*-homoandrostane-3:17-dione	− 19	+77
5α-*D*-Homoandrostane-3:17-dione	− 96	
17*aβ*-Methyl-5α-*D*-homoandrostane 3:17-dione	−110	−14

The 17-methyl-17*a*-oxo-*D*-homosteroids (urane derivatives; XXXI)—although not strictly analogous to the 24-nor-triterpenoids—have a general similarity in that, if the 17-methyl were *β* (axial) there would be a 1:3-Me(*a*):Me(*a*) interaction with C-18. It is therefore certain that the 17-methyl group in the uranes is α(*e*) as suggested previously[36].

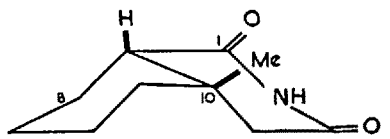
11-Oxo-9β-steroids.—These compounds[37] cannot profitably be considered here, since at least one ring must be a boat-form, on account of the presence of the *D*-ring.

1:3-Dione types.—BACHMANN, ROSS, DREIDING, and SMITH[38] have examined the stabilities of various decahydro*iso*quinoline-1:3-diones (general type, XXXII). These examples may be slightly complicated by the presence of the heteroatom (N) in one ring, which will modify some valency angles slightly. The relevant interactions are summarized in Table III.

In the compounds (XXXII; $X = Y$ = H) carrying no bridgehead substituents the *trans* compound is the more stable (equilibrium ca. 2 *trans*:1 *cis*). Here the preferred conformation for the *cis*-isomer must be (XXXIII).

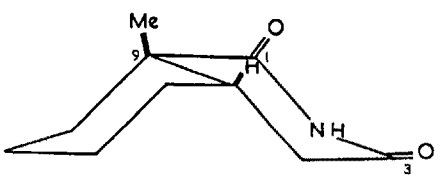


XXXII XXXIII

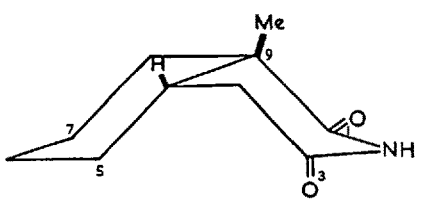


XXXIV

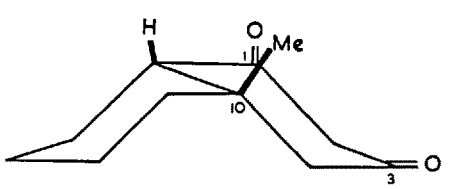
In the compounds carrying a methyl group at $C_{(10)}$ (XXXII:X = H, Y = Me) the *cis*-isomer (XXXIV) is the more stable (equilibrium ca. 2 *trans*:3 *cis*). Here the 2-alkylketone effect is just overbalancing one skew effect (0·8 kcal.mole^{-1}).



XXXV*A*



XXXV*B*



XXXVI

Table III.—Interactions in decahydro-1:3-dioxo*iso*-quinolines[37]

		Skew interactions in skeleton	2-Alkylketone effects	3-Alkylketone effects**
9H:10H	*trans**	0	1	0
	cis (XXXIII)	3	1	2
9H:10Me	*trans*	4	1	2
	cis (XXXIV)*	5	0	2
9Me:10H	*trans*	4	1	0
	cis (XXXV *A*)	5	1	0
	cis (XXXV *B*)*	5	1	2

* Stable isomer.

** These represent contributions to be *subtracted* from the skew interaction effects in the first column.

[34] F. RAMIREZ and S. STAFIEJ, J. Amer. chem. Soc. *77*, 134 (1955) Chem. and Ind. *1955*, 1180.

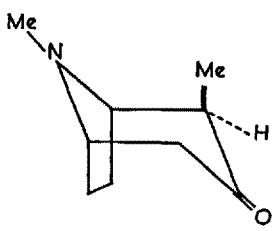
[35] M. W. GOLDBERG and E. WYDLER, Helv. chim. Acta *26*, 1142 (1943).

[36] W. KLYNE, Nature (London) *166*, 559 (1950). – W. KLYNE and C. W. SHOPPEE, Chem. and Ind. *1952*, 470. – R. J. W. CREMLYN, D. L. GARMAISE, and C. W. SHOPPEE, J. chem. Soc. *1953*, 1847.

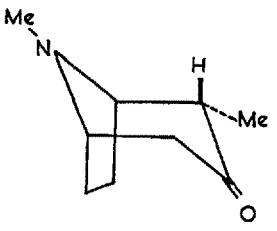
[37] P. BLADON, H. B. HENBEST, B. J. LOVELL, G. W. WOOD, G. F. WOODS, J. ELKS, R. M. EVANS, D. E. HATHWAY, J. S. OUGHTON, and G. H. THOMAS, J. chem. Soc. *1953*, 2921. – J. GRIGOR, W. LAIRD, D. MACLEAN, G. T. NEWBOLD, and F. S. SPRING, J. chem. Soc. *1954*, 2333. – A. CRAWSHAW, H. B. HENBEST, E. R. H. JONES, and A. A. WAGLAND, J. chem. Soc. *1955*, 3420. – K. HEUSLER and A. WETTSTEIN, Helv. chim. Acta *36*, 398 (1953).

[38] W. E. BACHMANN, A. ROSS, A. S. DREIDING, and P. A. S. SMITH, J. org. Chem. *19*, 222 (1954).

In the compounds carrying a methyl group at $C_{(9)}$ (XXXII; X = Me, Y = H) the *cis*-isomer is again the more stable (equilibrium, ca. 1 *trans*: 2 *cis*). In neither of the two possible conformations of the *cis* compound (XXXV*A* and XXXV*B*) is the eclipsed O:CH_2 effect decisive, since each must have one eclipsed grouping — (O:CH_3) in *A*, (O:CH_2'8]) in *B*; (O:CH_2[8]) is also eclipsed in the *trans*-isomer. The determining factor must then be the presence of two 3-alkylketone effects in (*cis*; XXXV*B*); these are between $C_{(5)}$ and the ketone groups at $C_{(1)}$ and $C_{(3)}$. Calculation in the usual manner from the equilibrium constant (at 250°C) indicates that each 3-alkylketone effect is worth rather less than 1 kcal.mole^{-1}.



XXXVII



XXXVIII

Another example—uncomplicated by the presence of a heteroatom in the ring—is the *homo*cyclic analogue of (XXXIV), the 1:3-dioxo-10-methyldecalin (XXXVI) of LINSTEAD and MILLIDGE[2]. Here again the *cis*-isomer is stable and the 2-alkylketone effect is able to overbalance one skew effect. The oxygen analogue of (XXXIV) (anhydride) has been found to give a 1:1 *cis*:*trans* equilibrium mixture[39].

Table IV.—2-Alkylketone effect. The following values are to be *added* to the contributions of the carbon skeleton.

Example	Formulae	E(2 AK) (kcal. mole^{-1})	References
ROBINS and WALKER's diketones	–	0·8–1·2	1
Carvomenthones	VII, VIII	1·0	2
17*a*-Methyl-17-oxo-*D*-homosteroids	XXIX, XXX	0·5	3
1:3-Dioxodecahydro*iso*-quinolines	XXXII (X=H; Y=Me)	>0·8	4
1:3-Dioxo-10-methyl-decalin	XXXVI	>0·8	5
6-Oxosteroids	XV, XVII	<0·8	6

[1] P. A. ROBINS and J. WALKER, Chem. and. and Ind. *1955*, 772.
[2] R. G. JOHNSTON and J. READ, J. chem. Soc. *1935*, 1138.
[3] F. RAMIREZ and S. STAFIEJ, J. Amer. chem. Soc. *77*, 134; Chem. and Ind. *1955*, 1180.
[4] W. E. BACHMANN, A. ROSS, A. S. DREIDING, and P. A. S. SMITH, J. org. Chem. *19*, 222 (1954).
[5] R. P. LINSTEAD and A. F. MILLIDGE, J. chem. Soc. *1936*, 478.
[6] See discussion in text page 123.

Methyltropinones. Another example from the heterocyclic field where the 2-alkylketone effect operates alone is provided by the methyltropinones of KOVÁCS, FODOR, and WEISZ[40]. The axial methyl-ketone (XXXVII) on oximation in alkaline conditions gives the oxime of the *equatorial* epimer (XXXVIII).

[39] R. P. LINSTEAD and A. F. MILLIDGE, J. chem. Soc. *1936*, 478.
[40] Ö. KOVÁCS, G. FODOR, and I. WEISZ, Helv. chim. Acta *37*, 892 (1954).

Table V.—3-Alkylketone effect. The following values are to be *subtracted* from the contributions of the carbon skeleton. The introduction of a 3-alkylketone effect in a polycyclic structure is equivalent to replacing one skew-butane by a skew-butan-1-one configuration.

Example	Formulae	E(3 AK) (kcal. mole^{-1})	References
3*a*-Methyl*cyclo*hexanone	III, IV	0·9	1
9-Methyl-1-decalones	–	1·2	2
1:3-Dioxodecahydro*iso*-quinolines	XXXII, (X=Me; Y=H	<1·0	3
1:3-Dioxodecahydro*iso*-quionlines	XXXII, (X=H, Y=H)	1·0	3

[1] P. A. ROBINS and J. WALKER, Chem. and Ind. *1955*, 772.
[2] A. ROSS, P. A. S. SMITH, and A. S. DREIDING, J. org. Chem. *20*, 905 (1955).
[3] W. E. BACHMANN, A. ROSS, A. S. DREIDING, and P. A. S. SMITH, J. org. Chem. *19*, 222 (1954).

Non-bonded Energy Contributions.—An attempt may now be made to summarize the values calculated for the non-bonded energy contributions of the 2-alkylketone (2 AK) and 3-alkylketone (3 AK) effects in different groups of compounds.

Whilst no claims to high accuracy can be made for the estimates in Tables IV and V, it appears that the 2-alkylketone and 3-alkylketone effects are each *of the order of* 1 kcal.mole^{-1}. It is hoped to apply these ideas in a future communication to the stability of hexahydroindanes and their oxo-derivatives.

Note added in Proof (Dec., 1955). J. SCHREIBER and A. ESCHENMOSER, Helv. chim. Acta *38*, 1529 (1955) have recently discussed the rates of oxidation of steroid alcohols to ketones with chromium trioxide, and the release of steric strain involved. Dr. A. DREIDING (private communication) has pointed out that their results can conveniently be considered in terms of the alkylketone effects.

Acknowledgements.—I am greatly indebted to Dr. JAMES WALKER and Dr. P. A. ROBINS (National Institute for Medical Research, London) for their kindness in sending me copies of their two papers before publication, and for a helpful discussion. I am also grateful to Dr. R. C. COOKSON (Birkbeck College, London), Dr. E. L. ELIEL (Notre Dame, Ind.), Dr. D. ROGERS (Cardiff), Dr. L. H. SARETT (Merck & Co., Rahway, N.J.), and especially Dr. A. DREIDING (Zürich) for their comments on the manuscript.

Zusammenfassung

Bei Stabilitätsbetrachtungen an Perhydro-1, 4-diketophenanthrenen haben ROBINS und WALKER[2] auf die Bedeutung der bindungsfreien («non-bonded») Wechselwirkung zwischen dem Carbonylsauerstoff eines Cyclohexanons und dem äquatorialen, gleichständigen («eclipsed») Alkylsubstituenten am benachbarten Kohlenstoffatom hingewiesen («2-Alkylketon»-Effekt). Ferner zeigten sie[4], dass noch ein anderer Konstellationsfaktor eine Rolle spielt, nämlich der «3-Alkylketon»-Effekt.

In der vorliegenden Mitteilung werden verschiedene Beispiele von monocyclischen Terpenen, Decalonen, 1, 3-Diketodecalinen (und ihren heterocyclischen Analogen), Steroiden und Triterpenen diskutiert, die diese beiden Effekte für sich oder in Kombination zeigen. In einzelnen Fällen stehen die verschiedenen Faktoren, die die relative Stabilität von äquatorialen und axialen Epimeren von Alkylcyclohexanonen bestimmen, in einem sehr empfindlichen Gleichgewicht.