[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Nitrous Acid Deamination of 17β-Hydroxy-20-amino-C_{21} Steroids. Stereochemistry of D-Homoannulation. II

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The action of nitrous acid on 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa) yielded, stereospecifically, 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa), which could be equilibrated with alkali to a mixture containing *ca.* 70% of the $C_{17a\beta}$-CH_3 (equatorial CH_3) and 30% of the $C_{17a\alpha}$-CH_3 (axial CH_3) isomers. 3β-Hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa), previously obtained stereospecifically from the nitrous acid deamination of 3β,17α-dihydroxy-20α-aminoallopregnane (XIIIa), was equilibrated to the same mixture of C_{17a} epimeric D-homosteroids. A discussion of the stereochemistry of ring-D enlargement in the steroids based on these observations is presented.

We have recently reported on the course of the nitrous acid deamination of a steroidal 20-amino alcohol having a 17α-hydroxy configuration[2] and an asymmetric center at C_{20}, such as IA (Chart II). The present study is concerned with the deamination of a 20-amino alcohol having the 17β-hydroxy configuration, such as IIB (Chart II). Enough information is now available to permit a more detailed interpretation of the stereochemistry of the ring-D enlargement in this type of steroids.

3β,17β-Dihydroxy-20-oximido-17-isoallopregnane 3-monoacetate (VIIIb, Chart I) was prepared in nearly quantitative yield from 3β,17β-dihydroxy-17-isoallopregnan-20-one 3-monoacetate (VIIb),[3] a result which does not bear out the assumed general unreactivity of the C_{20}-carbonyl in $C_{17\alpha}$-oriented side chains in steroids.[4] 3β,17β-Dihydroxy-17-isoallopregnan-20-one *diacetate* (VIIc),[3,5,6] on the other hand, failed to yield an oxime even under rather drastic conditions.[7] Catalytic hydrogenation of the oxime 3-monoacetate VIIIb in acetic acid solution in the presence of platinum oxide, followed by mild hydrolysis with potassium carbonate, afforded in 54% yield a stereochemically pure amine diol regarded as 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa). The formation of a C_{20}-epimer of IXa in the reduction could not be demonstrated, although the results of the nitrosation experiments described below suggest that if the $C_{20\alpha}$-amine (*cf.* IIA, Chart II) is produced, the amount must be quite small. The configuration[8] assigned to the amine diol IXa at C_{20} is based on the results of the nitrosation experiments, interpreted in the light of a stereospecific mode of rearrangement of IXa, as discussed in the next section of this paper.

The action of nitrous acid on 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa) gave in 68% yield a $C_{21}H_{34}O_2$ keto alcohol to which structure and configuration Xa, *i.e.*, 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one, has been assigned. No other carbonyl compound was detected in the product of the nitrosation, which was explored also *via* a 2,4-dinitrophenylhydrazone derivative. That the keto alcohol obtained had a reactive methylene position was demonstrated by formation of 3β-hydroxy-17aβ-methyl-16-hydroxymethylene-D-homoandrostan-17-one (XV). That the methyl group at C_{17a} had the *more stable configuration*, that is the equatorial $C_{17a\beta}$-methyl conformation, was established by equilibration experiments in alkaline medium. The keto alcohol Xa gave on alkaline treatment a mixture of C_{17a}-epimers, consisting of approximately 70% of $17_{a\beta}$-methyl isomer (Xa) and 30% of 17aα-methyl isomer (XIa). These figures are based on the specific rotations of the pure isomers and of the equilibrium mixture and were confirmed by separation of the isomers by fractional crystallization. 3β-Hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa), available[2] also from the nitrosation of 3β,17α-dihydroxy-20α-aminoallopregnane (XIIIa), could likewise be converted to the same mixture of C_{17a}-epimers (Xa and XIa) on alkaline treatment. Comparisons among the steroisomeric series were also carried out with the 2,4-dinitrophenylhydrazones, the acetates Xb and XIb and the diones XII and XIV.

XV

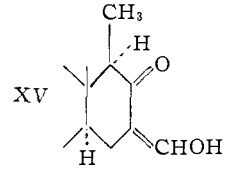


Table I summarizes the results of an examination of the infrared spectra of the D-homosteroids kindly performed by Miss F. Herling of the Sloan–Ketter-

(1) From part of the Ph.D. Thesis of S. Stafiej. Du Pont Postgraduate Teaching Fellow, 1954–1955.

(2) F. Ramirez and S. Stafiej, THIS JOURNAL, **77**, 134 (1955). In this reference, the 17-keto-17a-methyl-D-homosteroid obtained in the rearrangement of 3β,17α-dihydroxy-20α-aminoallopregnane (XIIIa, Chart 1) was tentatively assigned a 17aβ-methyl configuration (C_{17a}–CH_3 equatorial). It will now be shown that this inference was incorrect and that compounds XVIIa, XVIIb and XVIII of ref. 2 have a 17aα-methyl configuration (C_{17a}–CH_3 axial), as in XIa, XIb and XIV of Chart 1.

(3) (a) R. B. Turner, THIS JOURNAL, **75**, 3484 (1953); (b) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 185 (1943).

(4) (a) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); (b) L. F. Fieser, *ibid.*, **6**, 312 (1950). The oxime of Δ5-17-isoallopregnen-3β,17β-diol-20-one has been reported (H. E. Stavely, THIS JOURNAL, **62**, 489 (1940)).

(5) (a) R. B. Turner, *ibid.*, **75**, 3489 (1953); (b) L. Ruzicka, K. Gatzi and T. Reichstein, *Helv. Chim. Acta*, **22**, 626 (1939).

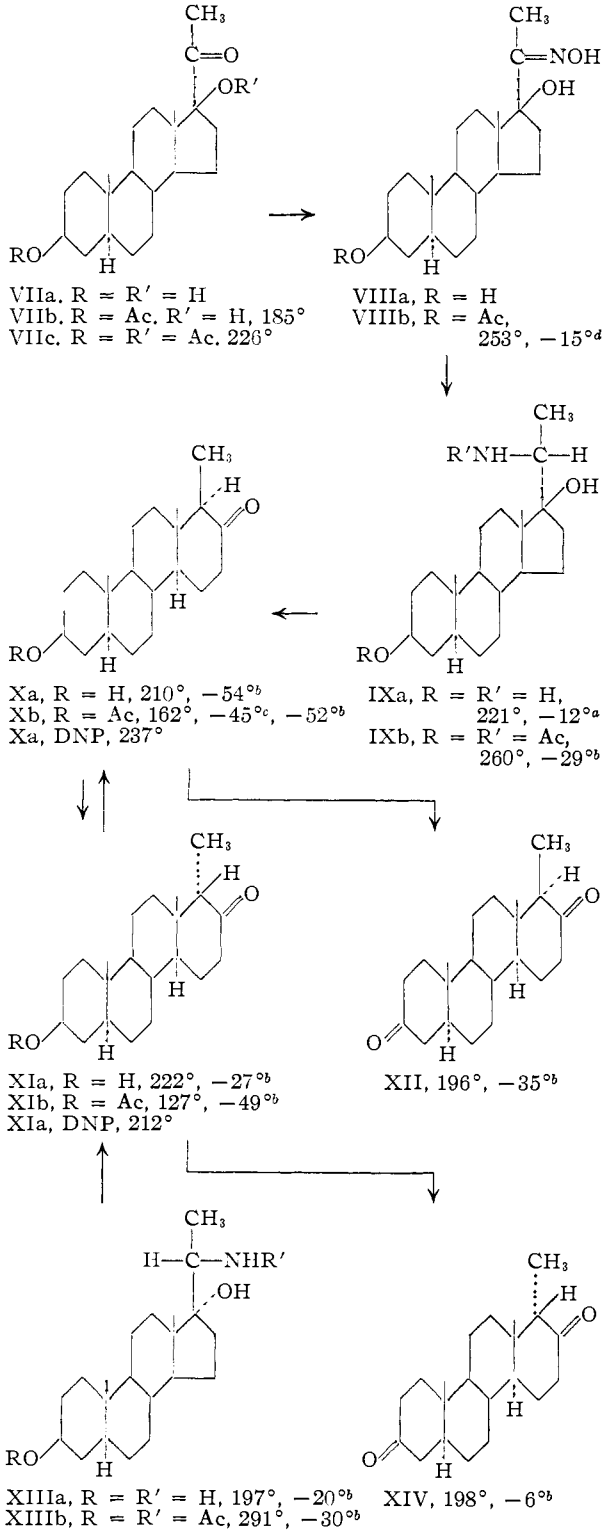
(6) (a) I. Salamon and T. Reichstein, *ibid.*, **30**, 1616 (1947); (b) A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2941 (1954).

(7) The 17β-hydroxy-20-keto steroids are available by the hydration of 17β-hydroxy-17α-ethynyl steroids utilizing mercuric salts (ref. 3 and H. E. Stavely, THIS JOURNAL, **63**, 3127 (1941)). The 17β-acetoxy-20-keto steroids are available from 17β-acetoxy-17α-ethynyl steroids by more convenient procedures (ref. 6). The acetoxy-ketones lead to D-homosteroids under hydrolytic conditions and thus could not be utilized in the present investigation.

(8) An independent assignment of configuration at C_{20} among 17α-hydroxy-20-amino steroids (1A, 1B, Chart 11) based on the known configurations of 17α-hydroxy-20-hydroxy steroids, is possible (ref. 2). For reasons discussed below, such an assignment is not possible in the 17β-hydroxy series (1IA, IIB, Chart I1).

CHART I

DNP = 2,4-dinitrophenylhydrazone; constants reported: m.p. (Kofler); $[\alpha]^{25}D$ taken in: [a] ethanol, [b] chloroform, [c] acetone, [d] pyridine.



ing Institute for Cancer Research. These data are fully consistent with the structures shown.

Several correlations with previously reported compounds can be made. From the catalytic hydrogenation (followed by CrO_3 oxidation) of 3β-hydroxy-17a?-methyl-Δ⁵-D-homoandrosten-17-one acetate ("neopregnenolone acetate"), Ruzicka and Meldahl[9] have obtained a 3β-hydroxy-17a?-methyl-D-homoandrostan-17-one acetate of m.p. 174–175° (no rotation given). This substance is probably identical with Xb (Chart I) and thus had a $C_{17a\beta}$-CH_3 configuration. Since "neopregnenolone acetate" was in turn made from what is now known to be 3β-hydroxy-17aβ-methyl-17aα-hydroxy-Δ⁵-D-homoandrosten-17-one 3-monoacetate[10] by a sequence of reactions involving replacement of the C_{17a}-OH by bromine and removal of the bromine with zinc dust in acetic acid, it seems that the over-all change involved retention of the C_{17a}-configuration. The alkaline hydrolysis of the 174–175° acetate was reported[9] to yield a 3β-hydroxy-17a?-methyl-D-homoandrostan-17-one, m.p. 222–224° (no rotation given), which has m.p. closer to that of the less stable isomer XIa than to the more stable isomer Xa. However, in the absence of rotation data a final conclusion is unwarranted. The 17a?-methyl-D-homoandrostan-3,17-dione obtained by oxidation of the 222–224° hydroxy ketone was said[9] to melt at 195–198° (no rotation given), which does not distinguish between XII and XIV. A hydroxymethylene derivative presumably identical with XV was also described.[9]

In the course of the present work, the recently reported conversion of 17α-aminomethyl-Δ⁵-androstene-3β,17β-diol to Δ⁵-D-homoandrosten-3β-ol-17a-one (ii → iv)[11] was repeated, with results which are similar to those obtained by the Swiss group.

Discussion

The course of the nitrous acid deamination of amino alcohols seems quite susceptible to steric strain in the transition state, which is assumed to be of a bridged-type.[12] The reaction thus appears to be particularly suitable for an exploration of the steric factors operating in the environment of the C_{17}- and C_{20}-positions of the steroid molecule.[4] The following stereochemical analysis of the possible course of the rearrangement of 17-OH, 20-NH_2 C_{21}-steroids *epimeric at both C_{17}- and C_{20}-positions* accommodates the observations made during the present study. Reference is also made to the situation encountered among 17-OH, 20-NH_2 C_{20}-steroids[11,13] having no asymmetry at C_{20}.

The results of the analysis are summarized in Table II with reference to Chart II and to Figs. 1a, 2a, 1 and 2.[14] For example, it can be seen from Table II that of the two possible modes of rear-

(9) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **23**, 364 (1940).

(10) (a) L. Ruzicka and H. F. Meldahl, *ibid.*, **21**, 1760 (1938); (b) **22**, 421 (1939); (c) R. J. Cremlyn, D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.*, 1847 (1953).

(11) H. Heusser, P. Th. Herzig, A. Furst and Pl. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

(12) (a) D. Y. Curtin and M. C. Crew, THIS JOURNAL, **77**, 354 (1955); (b) D. Y. Curtin and S. Schmuckler, *ibid.*, **77**, 1105 (1955), and previous references.

(13) (a) M. W. Goldberg, J. Sice, H. Robert and Pl. Plattner, *Helv. Chim. Acta*, **30**, 1441 (1947); (b) M. W. Goldberg and E. Wydler, *ibid.*, **26**, 1142 (1943); (c) M. W. Goldberg and R. Monnier, *ibid.*, **23**, 376 (1940); (d) N. L. Wendler, D. Taub and H. L. Slates, THIS JOURNAL, **77**, 3559 (1955).

(14) Only carbonyl products are considered in the stereochemical analysis of the deaminations. For conventions and nomenclature see ref. 4.

TABLE I

INFRARED SPECTRA OF D-HOMOSTEROIDS

Bands due to unperturbed cyclic methylene groups and bands due to C–H bending of acetate-methyl are not included

Frequency, cm.$^{-1}$	C=O (CS_2) 17-keto	CH_2 (CCl_4) C_{16}	CH_3 (CCl_4)
3β-Hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa)[a]	1713 (5.84 μ)	1420 (7.04 μ)	1388 (7.21 μ)
3β-Acetoxy-17aα-methyl-D-homoandrostan-17-one (XIb)[b]	1713	1424	1388
17aα-Methyl-D-homoandrostan-3,17-dione (XIV)	1717–1714[c]	1420[d] (broad)	1388
3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa)[a]	1715	1427	1389
3β-Acetoxy-17aβ-methyl-D-homoandrostan-17-one (Xb)[e]	1714	1426	1388
17aβ-Methyl-D-homoandrostan-3,17-dione (XII)	1717[c]	1425–1418[d]	1389
17-Keto-17aα-methyl-17aβ-hydroxy-D-homo[f]	1714–1713	1427–1425	1387–1386
17-Keto-17aβ-methyl-17aα-hydroxy-D-homo[f]	1722	1422–1421	1390
17a-Keto-17β-methyl-17α-hydroxy-D-homo[f]	1697[g] (5.89 μ)	.....	1379–1378

[a] O–H stretching at 3625 cm.$^{-1}$ (CS_2). [b] Acetate: C=O stretching at 1735 cm.$^{-1}$ (CS_2), C–O stretching at 1243 cm.$^{-1}$ (CS_2). [c] 3-Keto and 17-keto. [d] C_{16}, C_2 and C_4 methylenes. [e] Acetate: C=O stretching at 1727–1733 cm.$^{-1}$ (broad). C–O stretching at 1243 cm.$^{-1}$ (CS_2). [f] Reference compounds. [g] 17a-Keto.

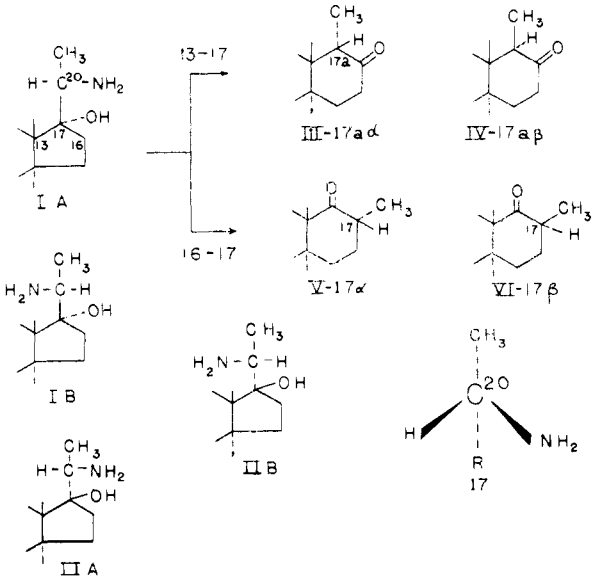
TABLE II

STEREOCHEMISTRY OF D-HOMOANNULATION OF AMINO ALCOHOLS

	Amino alcohol Chart II	Bond	Transition state[b]	Groups in opposition	D-Homosteroid Chart II	Obsd.
IAa[a]	17α-OH, 20α-NH_2 (IA)	13–17	Fig. 1a, R = CH_3	OH–CH_3; C_{16}–H	17-Keto, 17aα-CH_3 (III)[c]	IAa
IAb	17α-OH, 20α-NH_2 (IA)	16–17	Fig. 2a, R = CH_3	C_{13}–CH_3; OH–H	17a-Keto, 17β-CH_3 (VI)[c]	
IBa	17α-OH, 20β-NH_2 (IB)	13–17	Fig. 1a, R and H interchanged	OH–H; C_{16}–CH_3	17-Keto, 17aβ-CH_3 (IV)[d]	
IBb[a]	17α-OH, 20β-NH_2 (IB)	16–17	Fig. 2a, R and H interchanged	C_{13}–H; OH–CH_3	17a-Keto, 17α-CH_3 (V)[d]	
ia	17α-OH (i)	13–17	Fig. 1a, R = H	OH–H; C_{16}–H	17-Keto (iii)	(ia)
ib	17α-OH (i)	16–17	Fig. 2a, R = H	C_{13}–H; OH–H	17a-Keto (iv)	ib
IIAa	17β-OH, 20α-NH_2 (IIA)	13–17	Fig. 1, R = CH_3	C_{16}–CH_3; OH–H	17-Keto, 17aα-CH_3 (III)[c]	
IIAb[a]	17β-OH, 20α-NH_2 (IIA)	16–17	Fig. 2, R = CH_3	OH–CH_3; C_{13}–H	17a-Keto, 17β-CH_3 (VI)[c]	
IIBa[a]	17β-OH, 20β-NH_2 (IIB)	13–17	Fig. 1, R and H interchanged	C_{16}–H; OH–CH_3	17-Keto, 17aβ-CH_3 (IV)[d]	IIBa
IIBb	17β-OH, 20β-NH_2 (IIB)	16–17	Fig. 2, R and H interchanged	OH–H; C_{13}–CH_3	17a-Keto, 17α-CH_3 (V)[d]	
iia	17β-OH (ii)	13–17	Fig. 1, R = H	C_{16}–H; OH–H	17-Keto (iii)	(iia)
iib	17β-OH (ii)	16–17	Fig. 2, R = H	C_{13}–H; OH–H	17a-Keto (iv)	iib

[a] Sterically favored transition state. [b] The CH_3 at the C_{13}-carbon *faces* the group at C_{20} in Fig. 2a; the CH_3 at the C_{13}-carbon *points away* from the group at C_{20} in Fig. 2. [c] The CH_3 at C_{17a} or C_{17} is axial. [d] The CH_3 at C_{17a} or C_{17} is equatorial.

CHART II



rangement (IAa and IAb) of a 17α-hydroxy-20α-amino steroid (formula IA of Chart II), that one leading to a 17-keto-17aα-methyl-D-homosteroid (formula III of Chart II) *via* a transition state pictured in Fig. 1a, is sterically favored, since in the transition state the groups in direct opposition are considerably smaller.[12] It should be noted that as a result of an inversion of configuration[15] at C_{20} during the rearrangement, the methyl group at C_{17a} in the resulting D-homosteroid should adopt an α-configuration or *axial* conformation. This configuration should persist, provided that the mild conditions of the nitrosation reaction be insufficient to effect an equilibration at C_{17a}.

The experimental results of the present study are consistent with the deductions of Table II. Thus, the product of the nitrous acid deamination of the 3β,17α-dihydroxy-20α-aminoallopregnane (XIIIa ≡ IA) was shown to be the thermodynamically less stable 3β-hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa ≡ III). On the other hand, the product of the deamination of the amino alcohol regarded as 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa ≡ IIB) was shown to be the more stable 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa ≡ IV) (Table II, IAa and IIBa, respectively).

The structure and configuration of the resulting

(15) I. Bernstein and F. W. Whitmore, THIS JOURNAL, **61**, 1324 (1939).

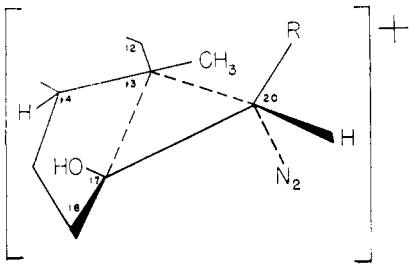


Fig. 1a.

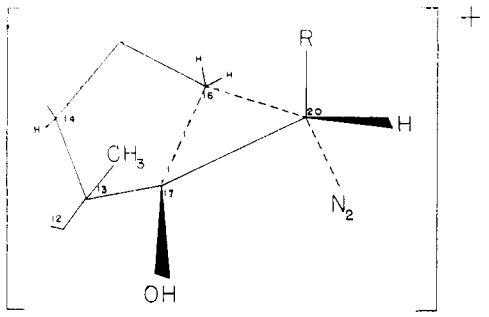


Fig. 2a.

D-homosteroids can be taken as evidence for the configuration at C_{20} in the starting amino alcohols *if the mechanistic considerations outlined above are accepted.* Thus, an amino alcohol having the 17β-hydroxy-20α-amino configuration would, on the basis of the mechanism, rearrange to a 17a-keto-17β-methyl-D-homosteroid (IIAb of Table II) in which the C_{17}-CH_3 is axial.[16] On this basis, the isolation of a D-homosteroid such as Xa (Chart I), in which the keto group is shown to be at C_{17} and the methyl group at C_{17a} and in the β-configuration, is compatible only with a $C_{20\beta}$-amino configuration of the $C_{17\beta}$-hydroxy steroid such as that assigned to IXa (Chart I).[17]

As previously shown,[2] an independent assignment of configuration at C_{20} can be made among 17α-OH,20-NH_2 steroids, such as IA and IB of Chart II, by an examination of optical rotation data. This assignment is based on comparisons with 17α-OH,20-OH steroids of analogous constitution. A satisfactory correlation between C_{20}- and C_{17}-configuration has been established[4] in the 17-normal series of pregnanes (17α-OH); an analogous correlation, however, is lacking in the 17-iso series (17β-OH).[18] Table III brings out a comparison of the contributions to the molecular rotation made by the hydroxylated C_{17}-center and the C_{20}-center in these steroids. It should be noted that the contribution to the molecular rotation made by

(16) If a 17β-hydroxy, 20α-amino steroid were to rearrange with migration of the 13–17 bond as in process 11Aa (Table 11), the resulting 17-keto, 17a-methyl-D-homosteroid would, on the basis of the mechanism, have the $C_{17a}\alpha$-CH_3 configuration; this configuration was shown to be preserved under the nitrosation conditions, in the IAa case.

(17) It should be noted from Table 11 that the less accessible cases 1Bb and 11Ab should furnish structures identical with those suggested by Klyne for the urane derivatives isolated from the urine of pregnant mares (W. Klyne, *Biochem. J.*, **43**, 611 (1948); R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 2719 (1939); W. Klyne, *Nature*, **166**, 559 (1950)).

(18) For references see Elsevier's "Encyclopedia of Organic Chemistry," Elsevier Publishing Co., Amsterdam, Series 11I, vol. 14, Supplement, p. 13, 343; *cf.* W. Klyne, *Chemistry & Industry*, 426 (1951).

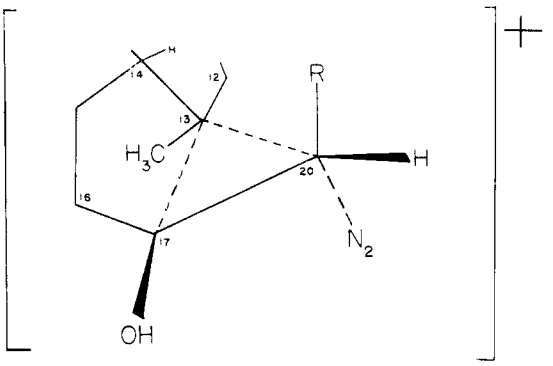


Fig. 1.

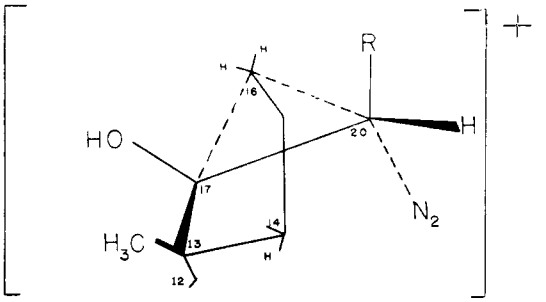


Fig. 2.

the C_{17}-center depends on the configuration at C_{20} (compare −61 (−29) with +86 (+59)). It can also be deduced that an acetamido group (NHAc) has a somewhat greater effect (−136), although in the same direction, than a similarly oriented acetoxy (OAc) group (−115). On this basis, and taking the configuration of the 17β-OH,20β-NH_2-steroid (IXb ≡ IIB) as established, a more satisfactory correlation is obtained if the 17β,20-diol of m.p. 235° reported by Salamon (see Table III) is regarded as having a $C_{20\alpha}$-OH configuration,[18] while the diol of m.p. 213° is considered to have a $C_{20\beta}$-OH configuration. Table III also includes contributions to the molecular rotation made by the C_{17a}-center among D-homosteroids.

An interesting situation involving the nitrous acid deamination of steroidal amino alcohols arises when C_{20} *is not asymmetric,* as in the 17α-hydroxy- and 17β-hydroxy-C_{20}-compounds i and ii studied by Heusser and co-workers.[11,13a] The 17α-hydroxy compound i was said to rearrange stereospecifically to a 17-keto-D-homosteroid iii, while the 17β-hydroxy compound ii yielded a 17a-keto-D-homosteroid iv. The recent work of Wendler, Taub and Slates[13d] (on compounds having an additional $C_{11\beta}$-OH) casts doubt on the conclusions of Heusser and co-workers. The American investigators demonstrated the formation of both 17a-keto- and 17-keto-D-homosteroid (iv and iii in a 6:1 ratio) in the deamination of a 17β-hydroxy-17α-aminomethyl steroid (ii). Both 17a-keto- and 17-keto-D-homosteroids were also produced in a 6:1 ratio from a 17α-hydroxy-17β-aminomethyl steroid (i). On the basis of these results, it appears that transition states iia and ia (Table II) are unfavorable relative to the corresponding iib and ib, in a manner not obvious from models. The operation of other factors implicit in the inherent difference between the 13–

TABLE III

ROTOPHORIC EFFECTS AT C_{17} AND C_{20} AMONG ACETYLATED 3,17,20-TRIOLS AND AMINEDIOLS[a,b]

Contribution of $C_\alpha = 1/2(M_D^\alpha - M_D^\beta) = 1/2\ [(+A+B)^\alpha - (-A+B)^\beta] = A$, where M_D refers to molecular rotations of epimers at *one* center

Compound	Rotophoric effect
3β,17α,20-Trihydroxyallopregnane-3,20-diacetate	$(C_{20\alpha}\text{-OAc})_{17\alpha\text{-OH}} = -115$
3β,17α-Dihydroxy-20-aminoallopregnane-3-acetate, N-acetyl	$(C_{20\alpha}\text{-NHAc})_{17\alpha\text{-OH}} = -136$
3β,17β,20-Trihydroxy-17-isoallopregnane-3,20-diacetate	$(C_{20\alpha}\text{-OAc})_{17\beta\text{-OH}} = +31(-31)$
3β,17,20α-Trihydroxyallopregnane-3,20-diacetate	$(C_{17\alpha}\text{-OH})_{20\alpha\text{-OAc}} = -61(-29)$
3β,17,20β-Trihydroxyallopregnane-3,20-diacetate	$(C_{17\alpha}\text{-OH})_{20\beta\text{-OAc}} = +86(+59)$
3β,17-Dihydroxy-20β-aminoallopregnane-3-acetate, N-acetyl	$(C_{17\alpha}\text{-OH})_{20\beta\text{-NHAc}} = +136$
Rotophoric Effects at C_{17a} in D-Homosteroids	
3β-Hydroxy-17a-methyl-D-homoandrostan-17-one acetate	$(C_{17a\alpha}\text{-Me})^{3\beta\text{-OAc}}_{17\text{-keto}} = +9$
3β-Hydroxy-17a-methyl-D-homoandrostan-17-one	$(C_{17a\alpha}\text{-Me})^{3\beta\text{-OH}}_{17\text{-keto}} = +43$
17a-Methyl-D-homoandrostan-3,17-dione	$(C_{17a\alpha}\text{-Me})^{3\text{-keto}}_{17\text{-keto}} = +45$

[a] Calculations based on data by: (a) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 21, 546 (1938), for substances O and J; (b) I. Salamon, *ibid.*, **32**, 1306 (1949), for 3β,17β,20a-trihydroxy-17-isoallopregnane (m.p. 235°) and 3β,17β,20b-trihydroxy-17-isoallopregnane (m.p. 213°) (*cf.* footnote 18); values in parentheses would be obtained if the diol m.p. 235° were regarded as $C_{20\beta}$-OH and the diol m.p. 213° as $C_{20\alpha}$-OH; (c) this paper. All rotations involve the same solvent for each epimeric pair; the uncertainty in M_D is about 8 units. [b] *Cf.* W. M. Stokes and W. Bergmann, *J. Org. Chem.*, **17**, 1194 (1952); **16**, 1817 (1951).

17 bond (equatorial to ring C) and the 16–17 bond, is evident among steroids lacking asymmetry at C_{20}.

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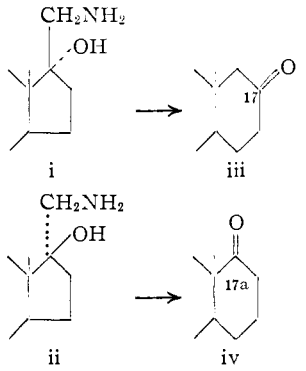

Experimental[19]

Preparation of 3β,17β-Dihydroxy-17-isoallopregnan-20-one 3-Monoacetate (VIIb)[3] and of 3β,17β-Dihydroxy-17-isoallopregnan-20-one Diacetate (VIIc)[3,5,6] from Δ⁵-Androsten-3β-ol-17-one Acetate (Dehydroepiandrosterone Acetate).—A mixture of 5.0 g. of dehydroepiandrosterone acetate, 500 mg. of palladium-on-charcoal catalyst (J. T. Baker, activity 950) and 250 ml. of ethanol was shaken in a hydrogen atmosphere (atmospheric pressure) for 18 hr. The filtered solution was concentrated to a small volume and treated with 200 ml. of methanol and 5.5 g. of potassium carbonate in 25 ml. of water. After a 2-hr. reflux period, the methanol was removed and the residue treated with water. The dry crude so obtained (4.35 g., m.p. 166–172°) gave, after one recrystallization from benzene–hexane, 4.0 g. (91%) of androstane-3β-ol-17-one, m.p. 172–174°; reported m.p. 174–175°,[20] 172–174°.[3b]

The conversion of androstan-3β-ol-17-one into 17α-ethynylandrostan-3β,17β-diol (m.p. 259–262°; reported 262.2–263.6,[21a] 255–257°[21b]) was performed, as described by Oliveto, *et al.*[21a] From 17α-ethynylandrostan-3β,17β-diol 3-monoacetate (m.p. 199–202°, 92% from the diol; reported m.p. 202–204°,[21a] 205–207°[21b]), 3β,17β-dihydroxy-17-isoallopregnan-20-one 3-monoacetate (VIIb)[3] (m.p. 184–186°; reported 181–183° and 191–193°,[3b] 173–175°[3a]) was obtained as described[3]; our observations in this preparation parallel those reported.[3]

From 17α-ethynyl-androstan-3β,17β-diol diacetate[6a] (m.p. 190–192°; 72% from the diol by refluxing with acetic anhydride–pyridine; reported m.p. 199–200°[21b]), 3β,17β-dihydroxy-17-isoallopregnan-20-one diacetate (VIIc)[3b,5,6] (m.p. 226–229°; reported 227–229°,[3b] 226–227°[5]) was obtained following the procedure of Salamon and Reichstein.[6a]

3β,17β-Dihydroxy-20-oximido-17-isoallopregnane 3-Monoacetate (VIIIb).—To a solution of 4.30 g. of monoacetate VIIb in 185 ml. of ethanol was added a solution of 9.25 g. of hydroxylamine hydrochloride and 9.35 g. of sodium acetate in 93 ml. of water. After 12 hours at its reflux temperature, the mixture was concentrated and filtered and the resulting crystalline material washed well with water and dried; yield of VIIIb, 4.36 g. (98%), m.p. 253–255°. The analytical sample of VIIIb had m.p. 255–257° (ethanol–water), $[\alpha]^{20}D$ −15 ± 2° pyridine (*c* 1) after drying at 68° *in vacuo*.

Anal. Calcd. for $C_{23}H_{37}O_4N$: C, 70.5; H, 9.5; N, 3.6. Found: C, 70.5; H, 9.5; N, 3.3.

3β,17β-Dihydroxy-17-isoallopregnan-20-one diacetate (VIIc) failed to form an oxime.

3β,17β-Dihydroxy-20β-amino-17-isoallopregnane (IXa).—A solution of 8.0 g. of 3β,17β-dihydroxy-20-oximido-17-isoallopregnane 3-monoacetate (VIIIb) in 400 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure for 41 hours, with 1.60 g. of platinum oxide catalyst. The catalyst was filtered off and most of the acetic acid removed under reduced pressure. The residue was dissolved in methanol and the solution treated with 20 g. of potassium carbonate in 175 ml. of water. The solution was refluxed for 2 hours, concentrated until crystals appeared, diluted with water (*ca.* 150 ml.) and cooled in ice. The crude material so obtained (6.22 g.) had m.p. 209–213°; the filtrate yielded upon further dilution with water 0.405 g. of material, m.p. 185–197°.

Repeated fractional crystallization of the 6.22 g. from methanol–water afforded 3.571 g. (53.5%) of pure amine diol IXa, m.p. 221–223°. The analytical sample of IXa,

(19) Microanalyses by Micro-Tech Laboratories, Skokie, Ill. The melting points were taken in a Kofler hot-stage microscope.

(20) L. Ruzicka, M. W. Goldberg and H. Brüngger, *Helv. Chim. Acta*, **17**, 1389 (1934).

(21) (a) E. P. Oliveto, L. Weber and E. B. Hershberg, THIS JOURNAL, **76**, 4482 (1954); (b) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937).

dried at 110° *in vacuo*, had m.p. 221–223° (methanol), $[\alpha]^{25}D$ −12 ± 1° EtOH (*c* 1), broad band at 3.0 μ (KBr), no bands at 5–6.2 μ.

Anal. Calcd. for $C_{21}H_{37}O_2N$: C, 75.2; H, 11.1; N, 4.2. Found: C, 74.8; H, 11.0; N, 4.1.

The mother liquids from the fractional crystallizations were combined and evaporated to dryness yielding 1.8 g. of crude amine diol (*vide infra*).

3β,17β-Dihydroxy-20β-acetamido-17-isoallopregnane 3-Monoacetate (IXb).—A solution of 0.167 g. of 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa, m.p. 220–222°) in 8 ml. of anhydrous pyridine containing 2 ml. of acetic anhydride was allowed to stand at room temperature for 24 hours. The solution was poured into cold 1 *N* sulfuric acid and the mixture extracted with chloroform. From the washed and dried chloroform extracts, crude acetate amide IXb of m.p. 252–256° was obtained on evaporation. One recrystallization from benzene afforded 183 mg. (90%) of pure IXb, m.p. 260–261°. The analytical sample of the same m.p. was dried at 110° *in vacuo* and had $[\alpha]^{25}D$ −29 ± 2° chf. (*c* 1), bands at 5.80 and 6.05 μ (chf.).

Anal. Calcd. for $C_{23}H_{41}O_4N$: C, 71.5; H, 9.8; N, 3.3. Found: C, 71.4; H, 9.6; N, 3.2.

3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa). (a).—A solution of 0.760 g. of 3β,17β-dihydroxy-20β-amino-17-isoallopregnane (IXa) in 10 ml. of acetic acid and 20 ml. of water was cooled to *ca.* 0° and treated dropwise over a 1.5-hour period, with a solution of 1.28 g. of sodium nitrite in 20 ml. of water. The temperature of the stirred solution was kept at 0° for 8 hours and at room temperature for 10 additional hours. The mixture was poured into water and extracted with diethyl ether. The washed (10% aqueous sodium carbonate) and dried (sodium sulfate) ether extracts were concentrated until crystals appeared; 220 mg. of Xa, m.p. 203–208°, was obtained in this manner. The ether filtrate was evaporated to dryness and the residue recrystallized once from methanol yielding 118 mg. of Xa of m.p. 208–212° and 103 mg. of Xa of somewhat lower m.p. (combined yield 61%). The analytical sample of Xa had m.p. 210–212° (benzene–hexane), $[\alpha]^{25}D$ −54 ± 1° chf. (*c* 1). The infrared spectrum are given in Table III.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.1; H, 10.8.

The 2,4-dinitrophenylhydrazone of Xa (43 mg. of Xa-DNP of m.p. 237–238° from 30 mg. of Xa of m.p. 210–212°) had m.p. 237–238° (chloroform–methanol).

Anal. Calcd. for $C_{27}H_{38}O_5N_4$: N, 11.2. Found: N, 11.1.

The mother liquids from the recrystallization of the ketone Xa obtained above were evaporated to dryness and the residue was treated with 2,4-dinitrophenylhydrazine reagent. Successive recrystallizations of the 2,4-dinitrophenylhydrazone (Xa-DNP) from chloroform gave 0.073 g., m.p. 225–238°, and 0.053 g., m.p. 237–238°. On this basis the total yield of ketone Xa from amino alcohol IXa was 68%.

(b).—The *crude* amine diol (1.8 g.) obtained in the reduction of oxime VIIIb was nitrosated as in (a), yielding 0.530 g. of D-homoketone, m.p. 208–211° identical with Xa, and an impure residue. This residue was treated with 2,4-dinitrophenylhydrazine reagent giving, after two recrystallizations from chloroform–methanol, 240 mg. of Xa-DNP of m.p. 232–236°.

3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one Acetate (Xb).—A mixture of 104 mg. of 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa) (m.p. 206–212°), 2 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand at room temperature overnight. The mixture was poured into 1 *N* sulfuric acid and extracted with ether. The product remaining after removal of the ether was recrystallized from methanol–water yielding 105 mg. (90%) of Xb, m.p. 159–164°. The analytical sample of Xb, dried at 56° *in vacuo*, had m.p. 162–164° (methanol–water), $[\alpha]^{26}D$ −45 ± 2° acetone (*c* 1), −51 ± 2° chf. (*c* 1). The infrared spectrum is given in Table III.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.5; H, 10.1.

17aβ-Methyl-D-homoandrostan-3,17-dione (XII).—A mixture of 160 mg. of 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa), 52 mg. of CrO_3, 3.2 ml. of acetic acid and 5 drops of water, was allowed to stand at room temperature for 18 hours. After addition of sodium bisulfite the mixture was diluted with water and filtered. The material so obtained was recrystallized from ethanol–water yielding 84 mg. (52%) of XII, m.p. 196–199°. The analytical sample of XII, dried at 110° *in vacuo*, had m.p. 196–199° (ethanol–water), $[\alpha]^{25}D$ −35 ± 1° chf. (*c* 0.83); infrared spectrum in Table III.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.9; H, 10.4.

The mixed m.p. between 17aβ-methyl-D-homoandrostan-3,17-dione (XII, m.p. 196–199°) and 17aα-methyl-D-homoandrostan-3,17-dione[2] (XIV, m.p. 197–200°) was 178–197°.

3β-Hydroxy-17aβ-methyl-16-hydroxymethylene-D-homoandrostan-17-one (XV).—To dry sodium methoxide (from 43 mg. of sodium) was added a solution of 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa, 200 mg.) in benzene (10 ml.) followed by a solution of purified ethyl formate (0.26 ml.) in benzene (13 ml.). The mixture was stirred at room temperature under nitrogen for 40 hours, and then poured into ice-water. The organic layer was extracted with 5% aqueous sodium hydroxide. The alkaline layer was combined with the original aqueous layer and extracted with ether. Acidification (concd. hydrochloric acid) of the alkaline layer gave a material which was extracted into ether. The washed (water) ether layer gave on evaporation 170 mg. of crude XV, m.p. 161–172°, which gave a very intense purple color with ferric chloride solution. The analytical sample of XV had m.p. 159–169° (ether).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 75.7; H, 9.8.

3β-Hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa).—XIa, m.p. 222–225°, $[\alpha]^{25}D$ −27 ± 1° chf. (*c* 1) was prepared from 3β,17α-dihydroxy-20α-aminoallopregnane (XIIIa) as described[2]; infrared spectrum in Table III.

The 2,4-dinitrophenylhydrazone of XIa (XIa-DNP) had m.p. 212–213° (chloroform–methanol).

Anal. Calcd. for $C_{27}H_{38}O_5N_4$: C, 65.0; H, 7.7; N, 11.2. Found: C, 64.7; H, 8.1; N, 11.4.

Equilibration of 3β-Hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa) with Alkali. (a).—A solution containing 75 mg. of XIa (m.p. 222–225°), 269 mg. of potassium hydroxide and 35 ml. of ethanol was refluxed for 13 hours, under nitrogen. The solution was concentrated to a small volume, treated with few drops of acetic acid and diluted with water. The precipitate was extracted with ether and the washed ether layer was evaporated to dryness yielding 75 mg. of product m.p. 186–210°.

A portion of the crude product (16 mg.) was used to determine the rotation, $[\alpha]^{25}D$ −48 ± 2° chf. (*c* 1). Utilizing the value of $[\alpha]^{25}D$ −54° for pure 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa) and $[\alpha]^{25}D$ −27° for pure 3β-hydroxy-17aα-methyl-D-homoandrostan-17-one (XIa) the mixture of isomers of m.p. 186–210° consisted of 77% Xa and 23% XIa.

The rest of the crude product (59 mg., m.p. 186–210°) was recrystallized from *benzene–hexane* giving 42 mg. (71%) of Xa, m.p. 210–212°, alone and mixed with the analytical sample of Xa. As previously described,[2] equilibration of XIa with methanolic potassium hydroxide afforded a mixture of isomers from which 10% of XIa, m.p. 218–221° could be recovered after several recrystallizations from *methanol*.

(b).—From 20 mg. of XIa (m.p. 222–225°) alkaline treatment as in (a) afforded 20 mg. of a mixture of isomers. Two recrystallizations from acetone–hexane gave 12 mg. of slightly impure Xa, m.p. 206–212°; this keto alcohol on acetylation, yielded 10 mg. of acetate Xb of m.p. 154–164° (one recrystallization from methanol–water) showing still the presence of some isomeric acetate XIb.

Equilibration of 3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one (Xa) with Alkali.—A solution containing 31 mg. of Xa, 120 mg. of potassium hydroxide and 18 ml. of ethanol was refluxed for 13 hours under nitrogen and worked up as for the 17aα-isomer. The crude residue (31 mg.) had m.p. 194–210°. A portion of the crude product (15 mg.) was used to determine the rotation, $[\alpha]^{25}D$ −45 ± 1° chf. (*c* 1). This corresponds to 66% of Xa and 34% of XIa in the crude product of the equilibration.

D-Homoandrostan-3β-ol-17a-one.[11]—The mixture of C_{17}-epimeric cyanohydrins (Schering Corporation) derived from dehydroepiandrosterone was acetylated and the resulting 17α-cyano-Δ⁵-androsten-3β,17β-diol diacetate (v) (m.p.

203–206°) was reduced with lithium aluminum hydride as described.[11] The 17α-aminomethyl-Δ⁵-androsten-3β,17β-diol (ii) (m.p. 215–220°) obtained was treated with $NaNO_2$ in aqueous acetic acid yielding Δ⁵-D-homoandrosten-3β-ol-17a-one (iv) (crude m.p. 178–180°). The acetate derived from iv was hydrogenated in the presence of Pt catalyst and the crude product oxidized with CrO_3–acetic acid and hydrolyzed with aqueous methanolic potassium carbonate as described,[11] yielding D-homoandrostan-3β-ol-17a-one, m.p. 192–195°, reported m.p. 193–195°.[11]

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

The Infrared Spectra of *p*-Benzoquinones

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The infrared spectra of twenty-two *p*-benzoquinones in the region 5 to 15 μ are reported and the relationship between them and the nature of the substituents is discussed.

Several studies have been made of the relationship between the structures of quinones and the location of their carbonyl stretching bands. Flett[1] has examined a number of anthraquinones and Hadži and Sheppard[2] have investigated several polycyclic quinones. Fuson and his school[3–6] have conducted extensive studies of the spectra of a large variety of quinones and have arrived at valuable correlations. This work, however, included consideration of only very few substituted *p*-benzoquinones and was limited to the measurement and discussion of the carbonyl stretching frequencies alone A more specific compilation of the carbonyl stretching frequencies of substituted *p*-benzoquinones has been given by Barchewitz, Tatibouët and Souchay[7] but again no reference was made to other infrared bands. It is the purpose of the present communication to report all the major bands between 5 and 15 μ of a series of twenty-two *p*-benzoquinones and to propose some tentative correlations on the basis of these observations.

Experimental

The quinones were specimens previously prepared in this Laboratory or were purified samples of commercially available materials. The spectra of solutions in carbon disulfide (*ca.* 0.1 *M*) or of mulls in mineral oil were recorded with a Perkin–Elmer Model 21 spectrophotometer using an NaCl prism. The spectra were calibrated by the use of a polystyrene film and atmospheric carbon dioxide.

Results and Discussion

The major bands observed between 5 and 15 μ are recorded in Table I (CS_2 solution) and in Table II (solid mull).

It has previously been observed that the spectra of certain benzoquinones[7,8] and naphthoquinones[5,8a] show two bands in the carbonyl stretching region. Our data provide further examples of such splitting of the carbonyl band.[9] It was originally proposed[5] that in the case of the naphthoquinones this phenomenon was due to unsymmetrical substitution giving rise to two non-equivalent resonating carbonyl systems. Subsequently, it was suggested[8a] that a more likely explanation was that the higher wave length band of the two had its origin in a C=C stretching vibration. We also find that the splitting cannot be due solely to the presence of different conjugated carbonyl systems, since no correlation between the symmetry of the quinones and the splitting of their carbonyl bands is apparent in the cases here investigated. However, it appears unlikely that the second bands may be attributed to the C=C vibrations in these cases, at least, since the bands, which occur between 5.97 and 6.14 μ, are at abnormally low wave lengths for such vibrations and also the solid spectra show bands at somewhat higher wave lengths (6.17–6.49 μ) which may readily be interpreted as arising from C=C vibration (*vide infra*). The origin of the splitting remains obscure, as does that of the analogous splitting of the carbonyl bands of some acid chlorides[10]; it may perhaps be due to vibrational interaction effects[2] but requires further study for its elucidation.

A well-defined relationship between the nature of the substituent groups and the position of the carbonyl bands emerges from a consideration of the spectra in both solution and the solid state.[11] The introduction of electron-donating groups, *viz.*, alkyl, methoxyl and hydroxyl, leads to an increase in the wave length of carbonyl absorption, the effect increasing as the number of such substituents becomes larger. Thus, for example, in the series of methyl derivatives 2, 5, 7, 13, 15 and 20, the carbonyl bands occur (i) in CS_2 at 6.01, 6.02, 6.02, 6.03, 6.03 and 6.08 and 6.09 μ, respectively, and (ii) in the solid state at 6.01, 6.02, 6.00 and 6.09, 6.05, 6.06 and 6.10 μ, respectively. It is of interest

(1) M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948).

(2) D. Hadži and N. Sheppard, THIS JOURNAL, **73**, 5460 (1951).

(3) M. L. Josien and N. Fuson, *Bull. soc. chim. France*, 389 (1952).

(4) M. L. Josien and N. Fuson, *Compt. rend.*, **234**, 1680 (1952).

(5) M. L. Josien, N. Fuson, J. M. Lebas and T. M. Gregory, *J. Chem. Phys.*, **21**, 331 (1953).

(6) N. Fuson, M. L. Josien and E. M. Shelton, THIS JOURNAL, **76**, 2526 (1954).

(7) P. Barchewitz, F. Tatibouët and P. Souchay, *Compt. rend.*, **236**, 1652 (1953).

(8) (a) M. L. Josien and J. Deschamps, *J. chim. phys.*, **52**, 213 (1955); (b) D. J. Cosgrove, D. G. H. Daniels, J. K. Whitehead and J. D. S. Goulden, *J. Chem. Soc.*, 4821 (1952).

(9) It is probable that in other cases splitting occurs but is not detected because the bands lie too close to be resolved under the conditions used. For example, although we and other workers[3–5,7] report a single carbonyl band for *p*-benzoquinone, yet others have observed two bands.[8]

(10) *Cf.*, for example, M. St. C. Flett, *Trans. Faraday Soc.*, **44**, 767 (1948).

(11) It is necessary to consider these independently, since, as has been noted previously with other series of quinones,[3] there is no consistent relationship between these bands in the different states.