3-Hydroxy-4,5-dimethoxy-β-phenethylamine Hydrochloride (I)—A solution of the benzyl ether IX (0.3 g.) in acetic acid (15 ml.) containing 0.1 g. of 10% palladized charcoal was shaken with hydrogen (26 p.s.i.) at room temperature for 90 min. After removal of the catalyst, the solution was evaporated and the residue crystallized from ethanol–benzene to give flat needles (0.195 g.), m.p. and mixed m.p. with an authentic sample[5] 178–179°; identical IR spectra.

REFERENCES

(1) A. R. Battersby, R. Binks, and R. Huxtable, *Tetrahedron Letters*, **1967**, 563; J. Lundström and S. Agurell, *ibid.*, **1968**, 4439.

(2) G. J. Kapadia and H. M. Fales, *Chem. Commun.*, **1968**, 1688.

(3) G. J. Kapadia, N. J. Shah, and T. B. Zalucky, *J. Pharm. Sci.*, **57**, 254(1968).

(4) S. Agurell and J. Lundström, *Chem. Commun.*, **1968**, 1638.

(5) E. Späth and H. Röder, *Monatsh. Chem.*, **43**, 93(1922).

(6) M. U. Tsao, *J. Am. Chem. Soc.*, **73**, 5495(1951).

(7) G. J. Kapadia and H. M. Fales, *Lloydia*, **31**, 430(1968).

(8) E. Leete and J. D. Braunstein, *Tetrahedron Letters*, **1969**, 451.

(9) A. J. Birch, "*Chemical Plant Taxonomy*," T. Swain, Ed. Academic Press, (1963), p. 141; M. Scribney and S. Kirkwood, *Nature*, **171**, 931(1953).

(10) I. Heilbron, "*Dictionary of Organic Compounds*," Oxford University Press, **3**, 1494(1965).

[5] Kindly supplied by Dr. John W. Daly (National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 17, 1969 from *Department of Pharmacognosy and Natural Products, College of Pharmacy, Howard University, Washington, DC 20001*

Accepted for publication May 5, 1969.

Presented to the Pharmacognosy and Natural Products Section, Academy of Pharmaceutical Sciences, APhA, Montreal meeting, May 1969.

The authors gratefully acknowledge the generous cooperation of Dr. Henry M. Fales, Molecular Disease Branch, National Heart Institute, Bethesda, Md. One of them (M.B.E.F.) thanks the National Science Foundation for the award of a Senior Foreign Scientist Fellowship.

* National Research Centre, Dokki, Cairo.

Structure and Conformation of the Cortisone Side Chain

A. COOPER* and W. L. DUAX

Abstract □ The results of a recent crystal structure analysis of the 4-chloro-derivative of cortisone have been used to describe the exact conformation of the C-17 side chain in this molecule. The results of this analysis are compared with those obtained from molecular orbital calculations, and from optical rotatory dispersion, circular dichroism, infrared and nuclear magnetic resonance measurements. The C-17 side chain shows no evidence of internal hydrogen bonding, either with the C-17 or with the C-21 hydroxyl groups, and it is shown that such hydrogen bonding is unfeasible, both in the crystal and in solution. Evidence regarding the preferred conformation of C-17 acyl side chains in general, is also presented.

Keyphrases □ Cortisone side chain—structure, conformation □ C-17 side chain conformation—4-chloro-derivative, cortisone □ Crystalline structure data—cortisone side chain conformation

The conformation and relative positions of the functional groups on the steroid molecules are of particular interest in steroid structure studies, in that they are thought to be the key to understanding the way in which steroids act upon their target organs (1). The configuration of the 17-side chain is less restricted than the rest of the steroid structure and is open to greater speculation. The authors have recently completed a detailed crystallographic structure analysis of the 4-chloro-derivative of cortisone (2) and are now able to accurately describe the geometry of the side chain of this corticosteroid.

EXPERIMENTAL

Conformation of the C-17 Side Chain—From molecular orbital calculations on cortisol, Kier (3) has predicted a side-chain conformation in which the carbonyl oxygen atom (O-20) is situated over the D-ring, and is equidistant from both C-13 and C-16 (Fig. 1*a*). Also, he predicted that the entire side chain, including C-17 and the α-oriented C-17 hydroxyl group, is planar.

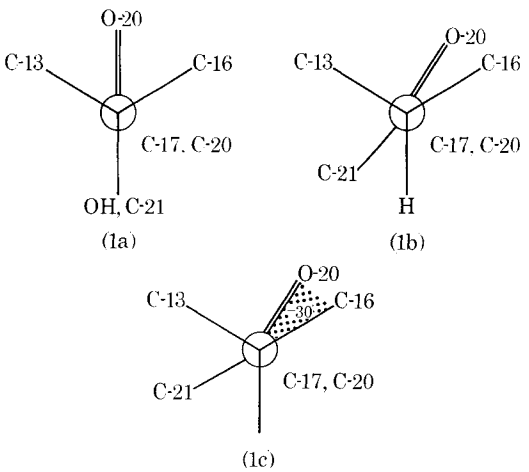


Figure 1—*Conformation of the C-17 side chain, showing Newman projections along the C-17–C-20 bond;* (a) *according to Kier (3);* (b) *according to Wellman and Djerassi (4);* (c) *the preferred conformation for the C-17 acyl side chains (6).*

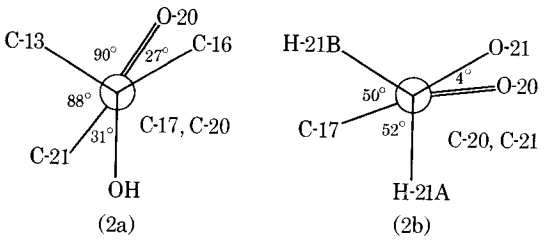


Figure 2—*Conformations in the side chain of cortisone, as determined in the X-ray structure investigation;* (a) *projection along the C-17–C-20 bond;* (b) *projection along the C-20–C-21 bond.*

On the other hand, Wellman and Djerassi (4), using optical rotatory dispersion and circular dichroism measurements, have assigned Fig. 1*b* as the preferred conformation for acetyl side chains when there is no 16β-ring D-substituent.

The present investigation confirms the latter assignment, in which our observed torsional angle C-16–C-17–C-20–O-20 is $-27°$. In fact, an examination of crystal structures of steroids, performed in this laboratory and by others, shows that the preferred conformation of steroids containing the acyl side chain at C-17 is as shown in Fig. 1*c*. Of the eleven examples available, the torsional angles for nine lie in the range 0–30°, and two in the range $-40°$ to $-45°$.

The exact conformations, obtained in this investigation, for the C-17–C-20 and C-20–C-21 bonds are given in Fig. 2. Obviously, this conformation about the C-17–C-20 bond, does not allow the 17α-hydroxyl group to be coplanar with the remainder of the side chain, as Kier predicted. It is seen that the side-chain atoms C-20, C-21, O-20, and O-21 are all within 0.02 Å. of the plane $0.7867x + 0.6136y + 0.0676z - 6.946 = 0$, and that the O-21 hydroxyl hydrogen atom (HO-21) lies 0.16 Å. out of this plane, with a torsional angle, C-20–C-21–O-21–HO-21, of 7°, instead of 0° in the case of coplanarity.

Although Kier's calculations do not agree precisely with the results of the present investigation, it is encouraging to note that the purely theoretical arguments employed by him produced a model in which the C-17–C-20 bond conformation was within about 30° of that actually observed. Since intramolecular interactions are of great importance in the extended Hückel treatment that he employed, Kier's adoption of the infrequently observed C_s (α-envelope) conformation, instead of the more usual distorted β-envelope conformation, as observed in this molecule, could make enough difference in the relationship between the carbonyl group and the D-ring, to bring the calculated conformation into closer agreement with that actually observed. In passing, it is worth noting that the authors' analysis of all accurately known steroid structures shows that the preferred D-ring conformation is almost halfway between C_2 (half-chair) and C_s (β-envelope) (5, 6).

Hydrogen Bonding—In view of the importance attached to the possibility of hydrogen bonding playing a major role in binding cortisone to possible receptors, this possibility is discussed in some detail.

The importance of the 21-hydroxyl group in assuring activity of the adrenocortical steroids is open to some speculation. For example, since 9α- and 12α-fluoro-11β-hydroxyprogesterone are approximately as active as cortisol in glucocorticoid activity (7, 8), the presence of the 21-hydroxyl group does not appear to be essential for this activity. The possibility of very weak receptor—C-21 hydroxyl-hydrogen bonding to assist in, or to enhance, an already existing receptor-steroid interaction, has been proposed (9).

A possible reason for the C-21 hydroxyl group not being a strong contributor to hydrogen bonding, is that it is already involved in intramolecular hydrogen bonding with O-20 or with the 17α-hydroxyl group. From IR and NMR studies (10), Cole and Williams dismiss the second of these factors, but attribute an increase of 3 $cm.^{-1}$ in the 20-carbonyl absorption frequency to a weak hydrogen bond between O-20 and the 21-hydroxyl hydrogen.

The results of this structure investigation of 4-chlorocortisone, as summarized in Fig. 3, immediately confirm that hydrogen bonding between the 17α- and the C-21 hydroxyl groups is impossible. However, at first sight, it would appear that O-20 to C-21 hydroxyl-hydrogen bonding is quite feasible. That this is not so, is apparent from an examination of the exact geometry of the atoms O-20–C-20–C-21–O-21–HO-21. As has already been mentioned, the first four of these atoms are coplanar, but the hydroxyl hydrogen lies 0.16 Å. out of this plane. This, in itself, is not sufficient reason to preclude hydrogen bonding. However, the distance O-20–HO-21, of 2.26 Å., is 0.56 Å. longer than expected for hydrogen bonding (11) and the angle O-20–HO-21–O-21, of 97°, is some 30° smaller than the minimum required for hydrogen bonding (12). The fact that, even if the hydroxyl hydrogen atom was coplanar with the remainder of the side chain, intramolecular hydrogen bonding in this region is unreasonable on purely steric grounds, is clearly evident in Fig. 4. Here, the van der Waals outline of the side chain of cortisone is compared with portion of the salicylic acid molecule. The geometry of salicylic acid has also been exactly determined by X-ray crystal-

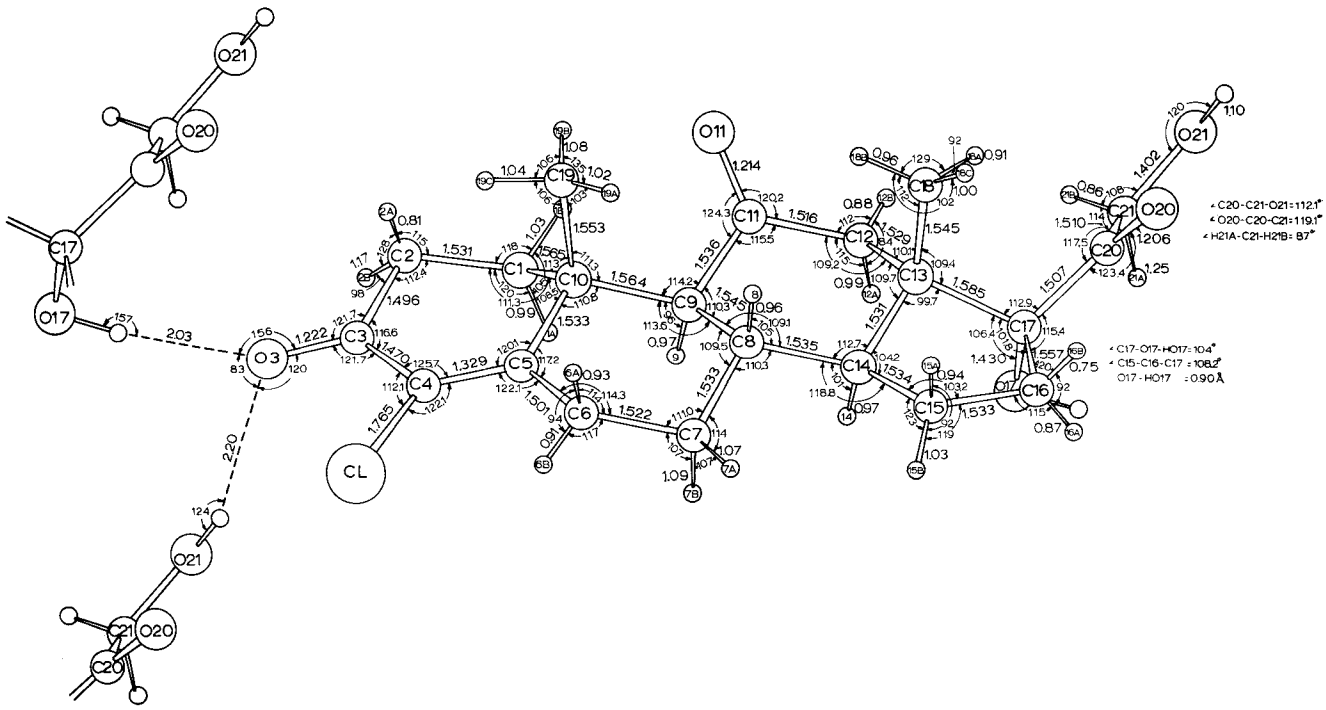
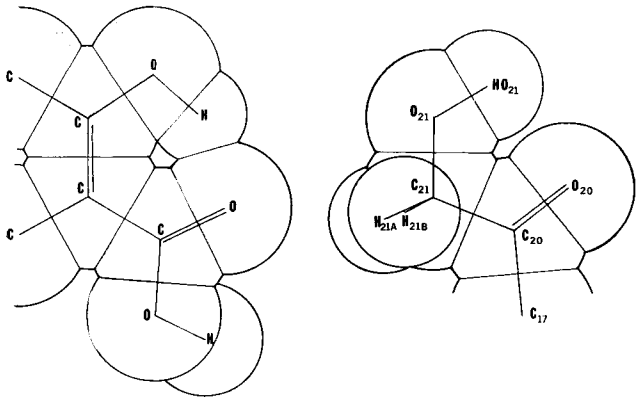


Figure 3—*Summary of interatomic bond distances and angles observed in 4-chlorocortisone. Intermolecular hydrogen bonding in the crystal is also shown.*



(4a) 4(b)

Figure 4—*Van der Waals outlines of* (a) *portion of salicylic acid, showing the presence of strong intramolecular hydrogen bonding;* (b) *the C-17 side chain of cortisone, showing the unfeasibility of intramolecular hydrogen bonding.*

lography (13), and intramolecular hydrogen bonding has been shown to exist. It is quite obvious that the additional atom in the hydrogen-bonding hexagon (Fig. 4*a*) has brought the atoms into the correct steric configuration for hydrogen bonding, but in cortisone (Fig. 4*b*) this cannot occur. The conclusion is that there is no intramolecular hydrogen bonding in the side chain of cortisone and that even in solution, the geometry of these atoms will not allow the necessary steric relationships to exist in order to effect it.

Intermolecular hydrogen bonding occurs in the cortisone crystals, between O-3 and the 17α-hydroxyl group of adjacent molecules, as shown in Fig. 3. There is a possibility of very weak hydrogen bonding involving O-3 and the C-21 hydroxyl group of an adjacent molecule, but the geometry of the "bond," as shown in Fig. 3, is at the limit of acceptable values.

REFERENCES

(1) I. E. Bush, *Pharmacol. Rev.*, **14,** 317(1962).

(2) W. Duax, A. Cooper, and D. A. Norton, *Acta Cryst.*, to be published.

(3) L. B. Kier, *J. Med. Chem.*, **11,** 915(1968).

(4) K. M. Wellman and C. Djerassi, *J. Am. Chem. Soc.*, **87,** 60(1965).

(5) C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, **24,** 13(1968).

(6) A. Cooper, to be published.

(7) J. Fried and A. Borman, *Vitam. and Horm.*, **16,** 303(1958).

(8) H. E. Herz, J. Fried, and E. F. Salvo, *J. Am. Chem. Soc.*, **78,** 2017(1956).

(9) J. Fried in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Eds., Pergamon Press, London, England, 1961, pp. 232–234.

(10) W. G. Cole and D. H. Williams, *J. Chem. Soc.* (*C*), **1968,** 1849.

(11) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, New York, N. Y., 1968.

(12) J. Donahue in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Eds., W. H. Freeman, San Francisco, Calif., 1968, pp. 443–465.

(13) M. Sundaralingham and L. H. Jensen, *Acta Cryst.*, **18,** 1053 (1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 9, 1969 from the *Medical Foundation of Buffalo, Buffalo, NY 14203*

Accepted for publication May 14, 1969.

This work was supported in part by U. S. Public Health Service grant No. CA 10906-02 from the National Cancer Institute.

* Present address: Computer Task Group Inc., Buffalo, NY 14221

Action of Adenosine Triphosphate on the Depressed Spontaneous Electrical Activity of the Dog Cerebral Cortex

G. BENZI, E. ARRIGONI, A. FERRARA, and P. MASCHERPA

Abstract □ The repeated suppression of the ventilation and the circulation of the brain in the dog, induces a high depression or a silence of electrical activity of the cortical and subcortical centers. The recovery of respiratory and circulatory conditions produces only a partial spontaneous reversion, which is particularly improved by adenosine triphosphate, selectively perfused into the circle of Willis.

Keyphrases □ Adenosine triphosphate (ATP) activity—cerebral cortex □ Cortical electrical activity depression—ATP effect □ EEG recording—ATP cortical effect

Many investigators have been interested in the modification of the normal or pathological electroencephalogram (EEG) induced by the systemic or local administration of drugs to experimental animals or man. However, a number of workers agree that electrical activity of the cortex is greatly modified by changes in blood CO_2 and O_2. An increase in CO_2 is associated with a shift in energy toward the fast side of the spectrum with a decrease in the total amount of energy; on the contrary a low P_{CO_2} induces a change in energy toward the slow side of the spectrum with an increase in the total amount of energy. A decrease in amplitude with an increase in frequency, as it occurs with high CO_2 values, does not necessarily indicate that less potential energy is being used, but it may indicate that the EEG recording apparatus is less efficient at high frequencies (1). Nevertheless, during a condition of short asphyxia by suspension of artificial ventilation, an actual decrease or suppression of the cerebral electrical activity can be induced; restoring artificial ventilation results in a normal EEG (2). The acute and severe anoxia induced by inhalation of 100% nitrogen gave progressive