Acknowledgments.—The authors are indebted to Dr. Stanford L. Steelman, Dr. Dolores Patanelli, Dr. J. Brooks, and their coworkers for the endocrine data. Zearalenone was provided for these studies by the Commercial Solvents Corporation through arrangements made by Mr. M. Bachman. The authors also express their appreciation to Dr. W. Jones and his associates for the hydrogenations, to Mr. R. N. Boos and his associates for the microanalyses, and to Dr. B. Arison and coworkers for determination of the nmr spectra.

Relationship between Lipophilic Character and Hemolytic Activity of Testosterone and Testosterone Esters

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The relationship between lipophilic character and hemolytic activity was studied in a series of testosterone compounds. The lipophilic character was first expressed by means of the chromatographic R_m value, which was shown to be related to the partition coefficient between the mobile and the stationary phase of a chromatographic system. The R_m value was determined, for each compound, in two different chromatographic systems, respectively, containing in the mobile phase Me_2CO or MeOH. In both cases there was a highly significant parabolic relationship between R_m values and hemolytic activity. On the other hand this result could be expected from the linear relationship between the R_m values, respectively, determined with Me_2CO or MeOH in the mobile phase. The lipophilic character of the test compounds was also expressed by means of the π values. There was a linear relationship between the π values calculated from octanol–H_2O partition coefficients and the chromatographic R_m values. A parabolic relationship was therefore shown also between π values and hemolytic activity. The present results support previous findings, which suggest that the correlation between penetration of organic compounds through biological membranes and partition coefficient is not affected by the nature of the phases involved in the determination of the partition data.

The hemolytic activity of some neutral steroids was shown by Tateno and Kilbourne[1] and Palmer.[2] Weissmann and Keiser[3] in a series of 35 neutral steroids and bile acids pointed out that while the 5-β-H configuration was associated with hemolytic properties, the 5-α-H compounds were inactive and only a few Δ-4,5 steroids were active. Testosterone, which is a Δ-4,5 steroid, was found practically inactive,[1,3] while Palmer[2] observed some activity. Segaloff[4] described the hemolytic activity *in vitro* and *in vivo* of some testosterone esters. The hemolytic activity was interpreted as a consequence of the insertion of the steroids at the lipid-aqueous interface at the surface of the erythrocyte.[3,5] On the other hand, no direct relationship was found between hemolytic activity and water solubility.[3] However the acetate derivatives were found to be more active than their parent compounds.[3] An enhanced hemolytic activity was also found in the AcOH and BzOH esters of some steroidal sapogenins.[6] This could suggest the influence of the lipophilic character of the molecules, at least in a series of ester derivatives. Hansch, *et al.*,[7] found very good correlations between partition coefficient and penetration of organic compounds through biological membranes. In previous papers it was possible to show that reversed-phase tlc is a suitable method for the determination of the lipophilic character of drugs, as expressed by the R_m value.[8] Therefore, the main purpose of the present work was to study the relationship between R_m values and hemolytic activity of a series of testosterone esters, also, to study the influence, on the above relationship, of the phase system used for determining the lipophilic character.

Materials and Methods

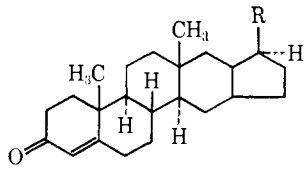
The testosterone compounds were kindly provided by drug companies (Organon N.V., Vister Vismara Terapeutici S.p.A., Istituto Luso Farmaco d'Italia s.r.l., Armour Erba Farmaceutici S.p.A, Essex Italia S.p.A.) and obtained from commercial sources (Prodotti Gianni, Milan). Their structures are reported in Table I. The chromatographic procedure for the determination of the R_m values was also used in order to check the purity of the compounds.

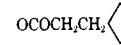
R_m Values Determination.—The lipophilic character of the test compounds was expressed by their chromatographic R_m values, which have previously been described.[8] The stationary nonpolar phase consisted of a silica gel G layer impregnated with silicone DC 200 (350 cSt) from Applied Sciences Laboratories. The impregnation was carried out by developing the plates in a 5% silicone oil solution in Et_2O. The polar mobile phase, saturated with silicone oil, was represented by H_2O in various mixture (v/v) with Me_2CO or MeOH. In particular the concentration of Me_2CO ranged from 42 to 74%, that of MeOH, from 54 to 86%. Two plates were simultaneously developed in a chromatographic chamber containing 200 ml of mobile phase. The steroids were dissolved in Me_2CO (3 mg/ml) and 1 μl of solution was spotted randomly on the plates in order to avoid any systematic error. The developed plates were dried and sprayed with an alkaline solution of $KMnO_4$. After a few minutes at 120° yellow spots appeared on an intensely pink background. The R_m values were calculated by means of the formula:

(1) I. Tateno and E. D. Kilbourne, *Proc. Soc. Exp. Biol.*, **86**, 168 (1954).
(2) R. H. Palmer, *Nature (London)*, **201**, 1135 (1964).
(3) G. Weissmann and H. Keiser, *Biochem. Pharmacol.*, **14**, 525 (1965).
(4) A. Segaloff, *J. Clin. Endocrinol. Metabol.*, **14**, 244 (1954).
(5) J. T. Dingle, "Lysosomes," A. V. S. de Reuck and M. D. Cameron Ed., Churchill, London (1963).
(6) R. Segal, M. Mansour, and D. V. Zaitschek, *Biochem. Pharmacol.*, **15**, 1411 (1966).
(7) (a) C. Hansch, A. R. Stewart, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, **1**, 205 (1965); (b) J. T. Penniston, L. Beckett, D. L. Bentley, and C. Hansch, *ibid.*, **5**, 333 (1969).
(8) (a) G. L. Biagi, A. M. Barbaro, M. F. Gamba, and M. C. Guerra, *J. Chromatogr.*, **41**, 371 (1969); (b) G. L. Biagi, A. M. Barbaro, M. F. Gamba, and M. C. Guerra, *ibid.*, **44**, 195 (1969).

TABLE I

STRUCTURE OF TESTOSTERONE AND ITS ESTERS



No.	Derivatives of testosterone	R	No.	Derivatives of testosterone	R
1	Testosterone	OH	8	Enanthate	$OCO(CH_2)_5CH_3$
2	Acetate	OAc	9	Caprylate	$OCO(CH_2)_6CH_3$
3	Propionate	$OCOC_2H_5$	10	Caprinate	$OCO(CH_2)_8CH_3$
4	Butyrate	$OCO(CH_2)_2CH_3$	11	17-β-Cypionate	
5	Isobutyrate	$OCOCH(CH_3)_2$	12	Phenylpropionate	$OCOCH_2CH_2C_6H_5$
6	Valerate	$OCO(CH_2)_3CH_3$	13	Hexahydrobenzoate	$OCOC_6H_{11}$
7	Isocaproate	$OCO(CH_2)_2CH(CH_3)_2$	14	Undecylenate	$OCO(CH_2)_8CH{=}CH_2$

$$R_m = \log\left(\frac{1}{R_f} - 1\right)$$

Hemolytic Activity Determination.—The procedure was based on those of Tateno and Kilbourne,[1] Weissmann and Keiser,[3] and Seeman and Weinstein.[9] Rat blood (0.8 ml) was obtained by cardiac puncture with 1-ml syringes containing 0.2 ml of Na citrate 3.8% and was immediately used. The erythrocytes were separated by centrifugation (5 min at 2.350*g*) and washed 3 times with a 0.9% NaCl solution buffered to pH 7.4 by 10 m*M* phosphate buffer. The washed erythrocytes were then suspended in this solution to a vol of 8 ml.

In order to test compounds a vol of 3.8 ml of phosphate-buffered saline was added to 0.2 ml of the above erythrocyte suspension to a final vol of 4 ml. EtOH solutions of the test compounds were finally added to the system in 1- to 10-μl amounts. In this way it was possible to obtain, for each compound, concentrations ranging from 0.25×10^{-4} to 2.5×10^{-4} *M*. At least 8–12 determinations were carried out for each concentration. Two series of control tubes were prepared. The assessment of 100% hemolysis was obtained by adding 3.8 ml of distd H_2O to 0.2 ml of erythrocyte suspension. The hemolytic activity of EtOH was determined by adding 1–10 μl of EtOH to 0.2 ml of erythrocyte suspension and 3.8 ml of phosphate-buffered saline. The hemolysis caused by EtOH in the added amounts was very low. On the other hand, Weissmann and Keiser[3] dissolved neutral steroids in EtOH and reported a control hemolysis varying from 0.4 to 1.4%. Obviously this does not rule out the possibility of a supraadditive synergism, between EtOH and steroids. However this hypothesis would be very difficult to prove owing to the very low water solubility of the tested compounds. Both control and test suspensions were incubated for 3 hr at 37°. After incubation all the tubes were centrifugated and the supernatants removed. The optical densities of these were measured at 540 mμ in the Bausch and Lomb colorimeter. The results were expressed as per cent of total hemolysis provoked by distilled H_2O, in the following way:

$$\frac{(\text{OD of sample} - \text{OD of EtOH control}) \times 100}{\text{OD of distilled } H_2O \text{ control}}$$

(9) P. Seeman and J. Weinstein, *Biochem. Pharmacol.*, **15**, 1737 (1966).

Results

R_m and π Values.—The partitioning of the testosterone compounds between the nonpolar stationary phase and the polar mobile phase affected their chromatographic migration in such a way, that they did not migrate until a certain concentration of Me_2CO or MeOH was reached in the mobile phase. On the other hand, above a certain Me_2CO or MeOH concentration in the mobile phase they tend to migrate with the solvent front. In any case, there is a range where, for each compound, the R_f values increase with the Me_2CO or MeOH concentration. Lower R_f values indicate shorter migrations and, therefore, molecules more lipophilic than those characterized by higher R_f values and longer migrations. As a consequence of the formula $R_m = \log [1/(R_f) - 1]$ negative and positive R_m values derive from R_f values, respectively, greater and smaller than 0.5. Therefore higher and/or positive R_m values indicate compounds more lipophilic than those represented by a lower and/or negative R_m value. The plots of Figures 1 and 2 show that for each compound there is a range of linear relationship between the R_m values and the concentration, respectively, of Me_2CO or MeOH in the mobile phase. According to Boyce and Milborrow,[10] the R_m values in the range of linearity were considered to be the most satisfactory ones, as over this range there are the maximum increments in the R_m value of each compound and among different compounds. By means of the least-squares method the equations of the straight lines were calculated from the R_m values in the linearity range. The equation of each straight line was used in order to calculate an R_m value corresponding to a 54% concentration of Me_2CO or MeOH in the mobile phase. In this way it was possible to obtain, for each compound, an R_m value in a standard system and in the range of maximum accuracy. The 54% concentration value was not chosen for any particular reason. The substantial parallelism of the straight lines of Figures 1 and 2 could permit the use of any other concentration. The R_m values calculated by means of the equation of the straight lines are reported in Table II as observed R_m values. They permitted the observation of the differ-

(10) C. B. C. Boyce and B. V. Milborrow, *Nature (London)*, **208**, 537 (1965).

TABLE II

CORRELATION BETWEEN π VALUES AND R_m VALUES OBTAINED WITH Me_2CO AND MeOH IN THE MOBILE PHASE. THE R_m (CALCD) VALUES WERE, RESPECTIVELY, OBTAINED FROM EQ 2 AND 3 OF TABLE IV

		R_m values (Me_2CO)			R_m values (MeOH)		
Compd	π values	Obsd	Calcd	Obsd − calcd	Obsd	Calcd	Obsd − Calcd
1	−1.160	−0.600	−0.471	−0.129	−0.020	0.039	−0.059
2	−0.270	−0.220	−0.219	−0.001	0.400	0.390	0.010
3	0.230	−0.050	−0.078	0.028	0.590	0.587	0.003
4	0.730	0.090	0.064	0.026	0.770	0.783	−0.013
5	0.530	0.090	0.007	0.083	0.730	0.705	0.025
6	1.230	0.250	0.206	0.044	1.020	0.980	0.040
7	1.530	0.400	0.291	0.109	1.190	1.098	0.092
8	2.230	0.560	0.489	0.071	1.450	1.374	0.076
9	2.730	0.700	0.631	0.068	1.630	1.571	0.059
10	3.730	0.960	0.914	0.046	1.960	1.965	−0.005
11	2.370	0.540	0.529	0.011	1.520	1.429	0.091
12	2.360	0.190	0.526	−0.336	1.060	1.425	−0.365
13	1.740	0.400	0.350	0.050	1.230	1.181	0.049
14	3.930	0.900	0.971	−0.071	2.040	2.043	−0.003

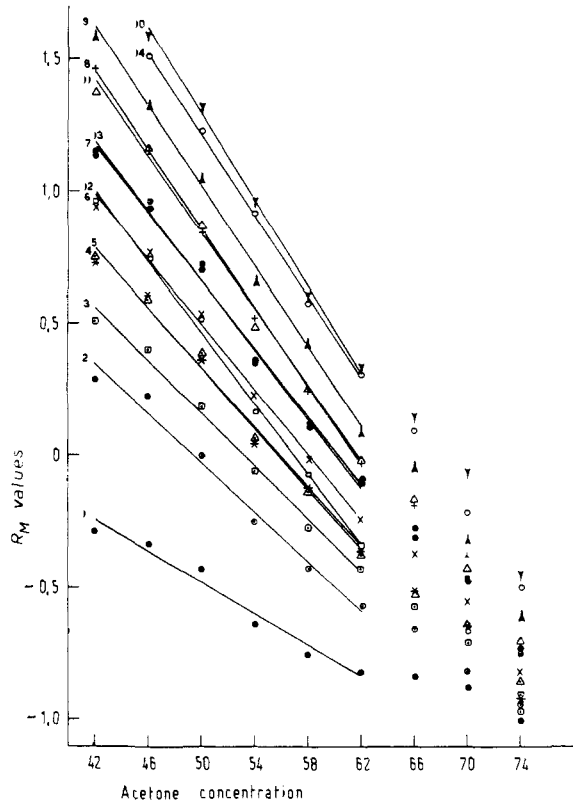


Figure 1.—Linear relationship between R_m values and acetone concentration in the mobile phase. Each point represents the mean of 8–12 values: (1) testosterone; (2) testosterone acetate; (3) testosterone propionate; (4) testosterone butyrate; (5) testosterone isobutyrate; (6) testosterone valerate; (7) testosterone isocaproate; (8) testosterone enanthate; (9) testosterone caprylate; (10) testosterone caprinate; (11) testosterone 17-β-cypionate; (12) testosterone phenylpropionate; (13) testosterone hexahydrobenzoate; (14) testosterone undecylenate.

ences due to the presence in the mobile phase of Me_2CO or MeOH at the same concentration.

As shown by eq 1 of Table IV there is a highly significant linear relationship between the R_m values calculated at 54% Me_2CO and those calculated at 54% MeOH.

The calculations of the π values of the testosterone compounds were kindly provided by Hansch[11] and reported in Table II. A linear relationship between π values and R_m values at 54% Me_2CO or MeOH is, respectively, shown by eq 2 and 3, from which were obtained the calculated R_m values of Table II.

Hemolytic Activity.—Some of the testosterone compounds could be tested with a dosewise approach in order to calculate a H_{50} value, that is, the molar concentration provoking a 50% hemolysis. This approach was not possible for some other compounds because of their low hemolytic activity. Therefore an effectwise approach was adopted for all the compounds, *i.e.*, all of them were tested at the same molar concentration of 1.50×10^{-4} M, which was selected because it caused a suitable hemolytic response for all the compounds. The results are reported in Table III as the log of the per cent of the total hemolysis found with distilled H_2O (log BR).

TABLE III

HEMOLYTIC ACTIVITY OF TESTOSTERONE AND ITS DERIVATIVES, AS EXPRESSED BY THE OBSERVED AND CALCULATED LOG BR VALUES. THE LOG BR (CALCD) VALUES WERE OBTAINED FROM EQ 5, 7, AND 9, RESPECTIVELY, FOR $R_m(Me_2CO)$, R_m(MeOH), AND π VALUES

Compd	Log BR observed	Log BR calcd (R_m, Me_2CO)	Log BR calcd (R_m MeOH)	Log BR calcd (π)
1	0.06	−0.06	0.03	0.10
2	1.00	1.08	1.01	0.95
3	1.00	1.42	1.33	1.31
4	1.74	1.63	1.57	1.58
5	1.69	1.63	1.53	1.48
6	1.94	1.78	1.80	1.77
7	1.94	1.85	1.87	1.85
8	1.92	1.84	1.88	1.90
9	1.71	1.75	1.80	1.84
10	1.24	1.41	1.49	1.46
11	1.90	1.84	1.86	1.89
12	1.81	1.74	1.82	1.89
13	1.69	1.85	1.88	1.88
14	1.63	1.51	1.38	1.34

Physicochemical Properties–Activity Relationship.—The equations which correlate structure and activity in the testosterone compounds are reported in Table IV. They were calculated from the R_m and log BR values of Tables II and III, by means of multiple regression analysis. Equations 4, 5, 6, and 7 were calculated with the R_m values determined, respectively.

(11) C. Hansch, personal communication.

with Me_2CO or MeOH in the mobile phase. By comparing eq 4 and 5 on the one hand with eq 6 and 7, respectively, on the other, it is evident that there is no significant difference in their correlation coefficients. This is clearly due to the linear relationship existing between the R_m values determined with a Me_2CO-containing mobile phase and those determined in presence of MeOH, as expressed by eq 1. In any case the best rationalization of the relationship between structure and activity is provided by eq 5 and 7, which explain, respectively, 91 and 90% of the variation in the biological activity, as obtained by R².[12] The relationship between π values and log *BR* data is described by eq 8 and 9, the latter of which shows a very good correlation coefficient. On the other hand eq 9 does not provide a better correlation than those shown by eq 5 and 7. The log *BR* values calculated from equations 5, 7, and 9 are reported in Table III.

Table IV

Regression Analysis of the Data of Tables II and III

No.	Equations	n	r	s
1	$R_{m(Me_2CO)} = -0.509 + 0.728\ R_{m(MeOH)}$	14	0.993	0.051
2	$R_{m(Me_2CO)} = -0.143 + 0.288\ \pi$	14	0.964	0.119
3	$R_{m(MeOH)} = 0.496 + 0.394\ \pi$	14	0.981	0.118
4	$\log BR = 1.289 + 0.766\ R_{m(Me_2CO)}$	14	0.622	0.431
5	$\log BR = 1.502 + 1.561\ R_{m(Me_2CO)} - 1.723\ R_{m^2(Me_2CO)}$	14	0.954	0.173
6	$\log BR = 0.922 + 0.537\ R_{m(MeOH)}$	14	0.594	0.443
7	$\log BR = 0.087 + 2.716\ R_{m(MeOH)} - 1.020\ R_{m^2(MeOH)}$	14	0.949	0.183
8	$\log BR = 1.192 + 0.209\ \pi$	14	0.577	0.450
9	$\log BR = 1.155 + 0.172\ \pi - 0.169\ \pi^2$	14	0.944	0.189

Discussion

The present data confirm the existence of a parabolic relationship between lipophilic character and penetration of molecules through biological membranes. The negative sign associated with the R_m^2 term of eq 5, 7, and 9 means that the hemolytic activity of testosterone compounds increases and decreases as the R_m and π values change and pass through an optimum. The lack of any significant difference between the correlation coefficients provided by eq 5, 7, and 9 shows that the nature of the phases involved in the determination of the partition data does not affect the results. This is explained on the one hand by the very high correlation between R_m values calculated with Me_2CO and MeOH, respectively, in the mobile phase and, on the other, by the high correlation between R_m and π values. These results support the findings of Collander[13] who pointed out that the penetration of organic compounds into *Nitella* cells was equally correlated with Et_2O–H_2O and olive oil–H_2O partition coefficients. In fact, Collander[13b] also found a linear relationship between the partition coefficients obtained with two different

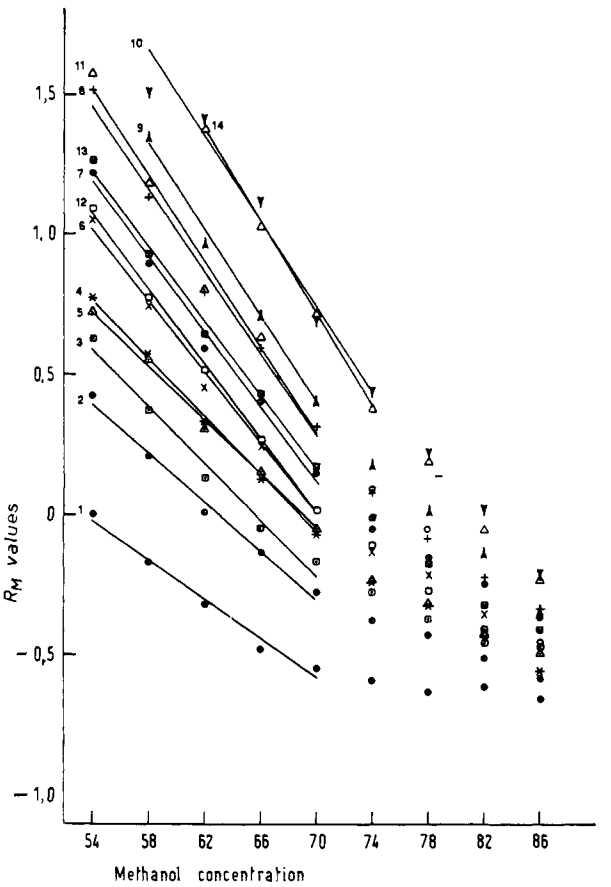


Figure 2.—Linear relationship between R_m values and methanol concentration in the mobile phase. Each point represents the mean of 8–12 values. The compounds are indicated as in Figure 1.

sets of solvents. More recently Iwasa, *et al.*,[14] found a very high correlation between π values and R_m values, a further support of Collander's findings. The correlation between R_m values and π values is very good, except for compound **12**. This is the phenylpropionate ester which from its π value seems to be more lipophilic than expected from its R_m values. This could be explained on the basis of some group interactions which interfere with the postulate of the additivity of π values.[7a] In the side chain of the phenylpropionate ester a $C_6H_5CH_2$ group is present. In benzylpenicillin, where the same $C_6H_5CH_2$ group is seen, it was possible to point out, in agreement with an analogous result of Bird and Marshall,[15] a similar disagreement between R_m and π value.[8a] However, at the present time insufficient data are available for any conclusion. The present work seems to suggest that the lipophilic character of the testosterone derivatives plays a major role in determining the disruption of the erythrocytes membrane. Seeman[16] distinguished between nonspecific and specific hemolysins. The nonspecific hemolysins exert their hemolytic effect because of their properties of surface-active or lipid-soluble compounds; in very low concentrations they stabilize the erythrocytes from hypotonic hemolysis. Specific hemolysins were considered to be those compounds which interact with a specific membrane component; they do not show the

(12) N. Draper and H. Smith, "Applied Regression Analysis", Wiley, New York, N. Y., 1966, p 26.

(13) (a) R. Collander, *Acta Physiol. Scand.*, **7**, 420 (1954); (b) R. Collander, *ibid.*, **13**, 363 (1947).

(14) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965).

(15) A. E. Bird and A. C. Marshall, *Biochem. Pharmacol.*, **16**, 2275 (1967).

(16) P. Seeman, *ibid.*, **15**, 1767 (1966).

above stabilizing effect at any concentration. In this sense vitamin A,[17] phenothiazine tranquilizers,[9,18a] local anesthetics,[18a] alcohols, and steroids[18b] are nonspecific hemolysins. In particular Seeman[18b] considered testosterone to be a nonspecific hemolysin. Polyene antibiotics and saponins, on the other hand, are examples of specific hemolysins.

This is in agreement with the present data, which show the influence of the lipophilic character on the hemolytic activity of nonspecific hemolysins such as testosterone esters. The lipophilic character should exert its effect also in the case of specific hemolysins. In fact it should influence the penetration to their site of action.

Finally, Milborrow and Williams[19] recently reexamined Collander's contribution on the penetration of *Nitella* cells by nonelectrolytes.[15] Collander[15] had suggested a linear relationship between penetration and partition coefficient. Actually Milborrow and Williams[19] showed the existence of a parabolic relationship between penetration and partition coefficient. This provides further support for our findings of a quadratic relationship between hemolytic activity and R_m values.

Acknowledgment.—We are grateful to Dr. Hansch for his helpful suggestions.

(17) J. A. Lucy and J. T. Dingle, *Nature (London)*, **204**, 156 (1964).

(18) (a) P. Seeman, *Biochem. Pharmacol.*, **15**, 1753 (1966); (b) *ibid.*, **15**, 1632 (1966).

(19) B. V. Milborrow and D. A. Williams, *Physiol. Plant.*, **21**, 902 (1968).

Steroidal Heterocycles. XIII.[1a] 4α,5-Epoxy-5α-androst-2-eno[2,3-*d*]isoxazoles and Related Compounds

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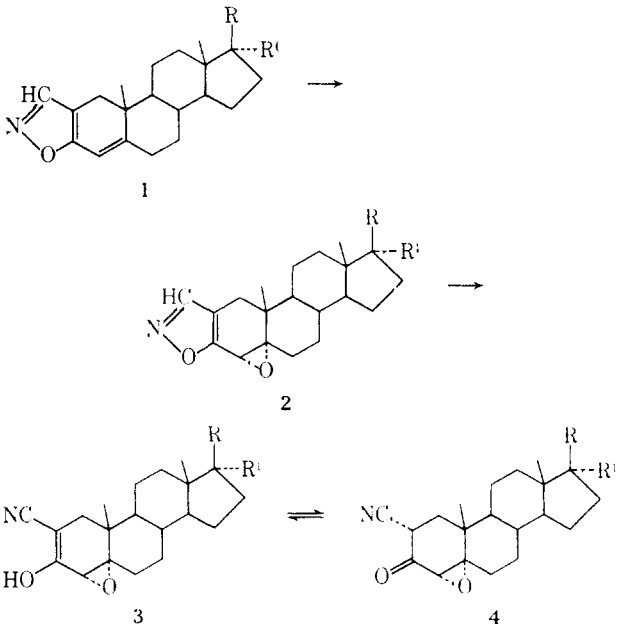
The preparation of a number of 4,5-epoxysteroido[2,3-*d*]isoxazoles from the corresponding Δ^4 compounds and their conversion into the corresponding 2-cyano derivatives and to 4,5-dihydroxy-, 5-hydroxy-4-oxo-, and 4-oxo derivatives are described. Several of these compounds were found to have unexpected adrenal cortical inhibitory activity.

Several compounds described in this paper, which were prepared as part of a continuing program in these laboratories involving the preparation and reactions of steroidal heterocycles,[1a] were found to inhibit adrenal cortical function. We have used them in attempts at molecular modification which has played such an important role in the development of better and safer drugs.[2]

Androsta-2,6-dieno[2,3-*d*]isoxazol-17β-ol (**1a**),[3] on treatment with either peracetic or perphthalic acid in C_6H_6, consistently yielded a mixture of 4α,5-epoxy-5α-androst-2-eno[2,3-*d*]isoxazol-17β-ol (**2a**) with starting material in a ratio of approximately 1:2. However, when a solution of isoxazole **1a** in $CHCl_3$ or CH_2Cl_2 was treated with either permaleic acid[4] or *m*-chloroperbenzoic acid[5] in the presence of a small amount of pyridine, **2a** was obtained in 80-90% yield.

Treatment of 4α,5-epoxy-5α-androst-2-eno[2,3-*d*]-isoxazol-17β-ol acetate (**2b**) with aq Me_2CO-H_2SO_4 yielded 5α-androst-2-eno[2,3-*d*]isoxazole-4β,5,17β-triol 17-acetate (**5a**) in 76% yield which was converted in Ac_2O-pyridine into the corresponding 4β-acetoxy compound (**5b**), also obtained directly on treatment of **2b** with aq AcOH-H_2SO_4. When a solution of **2b** in



a. R = OH; R' = H
b. R = OCOCH$_3$; R' = H
c. R = OH; R' = CH$_3$
d. R = OH; R' = C≡CH
e. R = OCOCH$_2$CH$_2$COOH; R' = H
f. R = OCOCH$_3$; R' = C≡CH

(1) (a) Paper XII: T. C. Miller, *J. Heterocycl. Chem.*, **3**, 338 (1966); (b) Albany Medical Center Hospital, Albany, N. Y.

(2) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Amer. Chem. Soc.*, **83**, 1478 (1961); B. Chance, "Amino Acids, Proteins, and Cancer Biochemistry," J. T. Edsall, Ed., Academic, New York, N. Y., 1960, p 191; L. L. Engel, A. M. Stoffyn, and J. F. Scott, "Hormonal Steroids," Vol. I, L. Martini and A. Pecile, Ed., Academic, New York, N. Y., 1964, p 291; M. Fisher, J. C. Sheehan, *et al.*, *Advan. Chem. Ser.*, **45**, 1-223 (1964); and other similar reviews.

(3) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, Robert L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(4) R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962).

(5) Technical Data, FMC Corp. Bulletin (1963); L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 135.