washed with dry EtOH and Et_2O to give the pure hydrochloride (0.358 g, 70%) of the desired Schiff base.

All the other Schiff bases were similarly prepared and are recorded in Table I.

Acknowledgments.—The authors are greatly indebted to Dr. H. B. Wood, Chief, Drug Development Branch, Cancer Chemotherapy National Service Center for his cooperation and for making the screening data available and to Mr. M. T. Jaokar for microanalyses. They are grateful to Dr. N. K. Dutta, Director, Haffkine Institute, Bombay, for providing facilities to carry out the present work.

Synthesis of Dideoxyzearalanone and Hydroxyl Derivatives

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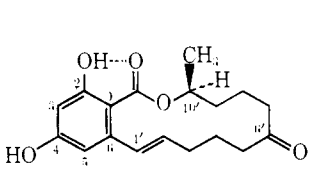
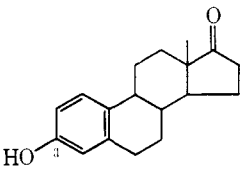
Received May 4, 1970

Syntheses are reported of 2,4-dideoxyzearalanone and each of the possible monophenolic derivatives of this compound. The preparation of 5-hydroxyzearalanone is also described. None of the new compounds exceeded the parent in respect to estrogenic activity.

The isolation of zearalenone (**1**) and a preliminary account of its marked uterotrophic activity and anabolic properties were reported by Stob and coworkers.[1] The structure of this fungal metabolite was deduced by chemical and spectroscopic means,[2] total syntheses of zearalenone have been announced[3] and its absolute configuration has also been determined.[4]



1



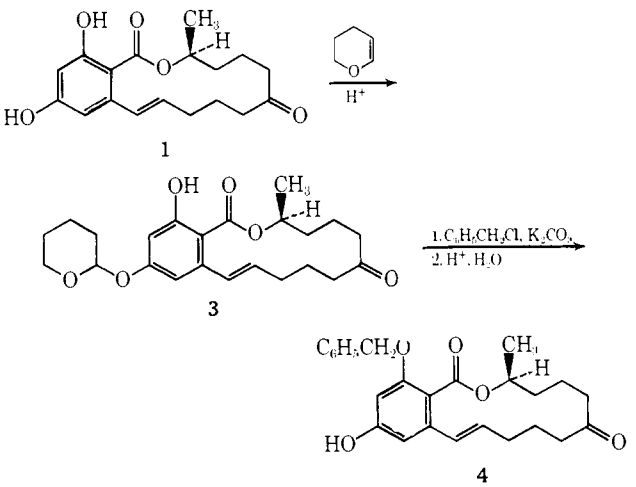
2

We have synthesized a number of structural variants of zearalenone in a joint project conducted several years ago with a group similarly engaged in the laboratories of the Commercial Solvents Corporation. The purpose of the present report is to summarize our findings in respect to the effect of phenolic OH addition or removal on the biological activity of the parent compound. This study was undertaken in a systematic way since the structural relationships of zearalenone to a typical estrogen such as estrone (**2**) are not obvious by inspection of models of their formulae. We selected as our synthetic goals the parent 2,4-dideoxyzearalanone (**6**) and each of the possible monosubstituted phenolic analogs, as well as 5-hydroxyzearalanone.

Chemistry.—Hydrogenolysis of the phenolic hydroxyls in zearalenone was possible using the technique of Musliner and Gates.[5] This involved preparation of the 1-phenyl-5-tetrazolyl ethers and their hydrogenolysis with 5% Pd–C which concurrently caused reduction of the olefin functionality. Our preferred conditions were 95% EtOH as solvent, and 3.5 kg/cm² at about 70° for 48 hr. These conditions are more drastic than those which were of general utility for Musliner and Gates.

In order to attain selective removal of the 2- and 4-hydroxyls of zearalenone it was necessary to prepare the required monophenyltetrazolyl derivatives. This was accomplished from the 2-benzyl and 4-tetrahydropyranyl ethers whose preparation is shown in Scheme I.

SCHEME I



The key reaction in this sequence was the selective monotetrahydropyranyl ether formation at C-4 in good yield using excess dihydropyran. This selectivity is attributed to the equilibrium nature of the reaction. Steric hindrance at C-2 and a loss of H bonding to the lactone CO are considered to disfavor derivatization of the 2-OH. It is also worth noting that benzyl ether formation is possible using K_2CO_3 in MeOH without any appreciable opening of the lactone ring. Formation of the phenyltetrazolyl ethers **5**, **7**, and **9** went well from the corresponding phenols using anhyd K_2CO_3 and 1-phenyl-5-chlorotetrazole in refluxing dry Me_2CO for 16 hr. The properties of these derivatives and of their

(1) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature (London)*, **196**, 1318 (1962).

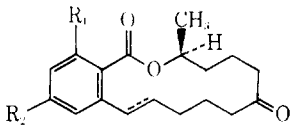
(2) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).

(3) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Chem. Commun.*, 225 (1967); N. N. Girotra and N. L. Wendler, *Chem. Ind. (London)*, 1493 (1967); D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968); I. Vlattas, I. T. Harrison, L. Tokes, J. H. Fried, and A. D. Cross, *J. Org. Chem.*, **33**, 4176 (1968). Total synthesis of dideoxyzearalane was reported by H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).

(4) C. H. Kuo, D. Taub, R. D. Hoffsommer, N. L. Wendler, W. H. Urry, and G. Mullenbach, *Chem. Commun.*, 761 (1967).

(5) W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, **88**, 4271 (1966). See also H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).

TABLE I



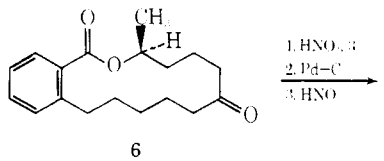
No.	R_1	R_2	C_1' and C_2'	Mp, °C	Cryst solvent	Formula	Analyses
5	PTO[a]	PTO	CH=CH	166–168	MeOH	$C_{32}H_{30}N_8O_6$	C, H, N
6	H	H	CH_2CH_2	89–91	Et_2O	$C_{18}H_{24}O_3$	C, H
7	PTO	THPO[b]	CH=CH	160–165	CH_2Cl_2–Et_2O	$C_{30}H_{34}N_8O_5$	C,[c] H, N
8	H	HO	CH_2CH_2	168–170	CH_2Cl_2–Et_2O	$C_{18}H_{24}O_4$	C, H
9	$PhCH_2O$	PTO	CH=CH	159–161	CH_2Cl_2–Et_2O	$C_{32}H_{32}N_8O_6$	C, H, N
10	HO	H	CH_2CH_2	101–104	Et_2O	$C_{18}H_{24}O_4$	C, H

[a] PTO, 1-phenyl-5-tetrazolyloxy. [b] THPO, 2-tetrahydropyranyloxy. [c] C: calcd, 65.92; found, 64.17.

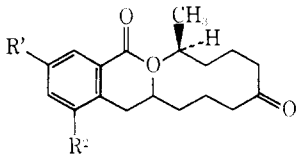
corresponding hydrogenolysis products are summarized in Table I.

The preparation of analogs monosubstituted with OH at C-3 and C-5 was accomplished from the dideoxy derivative **6** as summarized in Scheme II. As anticipated, nitration of **6** went primarily *para* to the alkyl group and to a lesser extent *ortho* to that function. Reduction of the pure 3-NO_2 analog (**11**) with 5% Pd–C and diazotization of the amine **12** led to the C-3 monohydroxy analog **13**. The C-5 monohydroxy analog **14** was obtained from a similar sequence using a mother liquor fraction containing the 5-NO_2 analog.

SCHEME II



6



11, R′ = NO_2; R^2 = H
12, R′ = NH_2; R^2 = H
13, R′ = OH; R^2 = H
14, R′ = H; R^2 = OH

5-Hydroxyzearalanone (**18**) was obtained *via* an aminozearalanone first prepared by E. B. Hodge of the Commercial Solvents Corp. and assigned by him structure **15** from physical data. Oxidation of **15** with Ag_2O–NH_4OH gave, after acidification, hydroxyquinone **16** best isolated as the acetate **17**, thereby providing chemical support for the assigned structure **15**. By shaking the Et_2O extract of **16** with aq $Na_2S_2O_4$, **18** was obtained directly. These conversions are summarized in Scheme III.

Biological Evaluation.—Estrogenic activities were estimated for the zearalenone analogs prepared in this study by a determination of their oral uterotrophic properties in rats using diethyl stilbestrol as the standard.[6] In this assay zearalenone (**1**) and its C_1'–C_2' dihydro derivative zearalanone show about 0.1% the activity of the standard. The dideoxy derivative **6** has less than 0.1 of the activity of zearalanone. 2-Deoxyzearalanone (**8**) retained about two-thirds of the activity of zearalanone (**1**); however, the other monohydroxy analogs showed less than 0.1 of the activity of zearalanone, while 5-hydroxyzearalanone had less than one-third of the estrogenic activity of the parent diol. Introduction of a third OH at either C-2[7] or C-4[8] in estradiol, leads to a sharp decrease in estrogenicity. Introduction of a third OH at C-1[9] in estradiol also causes a sharp drop in estrogenicity, unlike our finding that zearalanone is more active than the 2-deoxy derivative. We interpret the activating effect of the 2-OH in zearalanone to be the result of a conformational restriction which H bonding of the lactone imposes on the molecule.[10] We believe that the 4-OH of zearalanone corresponds to the 3-OH of estradiol in respect to its effect on intrinsic estrogenic activity.

Experimental Section[11]

6-(10-Hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcylic Acid μ-Lactone 4-(2-Tetrahydropyranyl) Ether (3).—A suspension of 8.0 g (25.6 mmoles) of **1** in 8 ml of dihydropyran and 4 drops of concd HCl was stirred at room temperature for 4 hr, an additional 8 ml of dihydropyran was then added, and the suspension was stirred overnight. The resultant solution was poured into saturated aq $NaHCO_3$ and extracted with EtOAc. The extract was washed with dil NaOH, H_2O, and NaCl solution, dried, and evaporated under reduced pressure. The 8.8 g of residue was dissolved in 450 ml of MeOH and cooled to 0°; 3.76 g of **3** was obtained, mp 146–149°. A second crop was obtained after concentration to *ca.* 150 ml, giving 4.20 g of **3**, mp 114–115°. Both of these fractions were 4-THP derivatives as judged by their spectra and both were suitable for further transformations. Repeated crystallization from MeOH of a portion of the first crop gave an analytical sample which melted at 159–160°. *Anal.* ($C_{30}H_{30}O_6$) C, H.

6-(10-Hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcyclic Acid μ-Lactone 2-Benzyl Ether (4).—A mixture of 500 mg (1.24 mmoles) of tetrahydropyranyl ether **3**, 400 mg (2.92 mmoles) of anhyd K_2CO_3, 0.42 ml (3.68 mmoles) of $PhCH_2Cl$, and 12.5 ml of anhyd MeOH was refluxed under N_2 for 16 hr, cooled, and filtered. The filtrate was discarded and the filter cake was washed repeatedly with $CHCl_3$. Evaporation of the washes yielded 535 mg of material which was crystallized from 45 ml of hot MeOH to give 300 mg (48%) of **4** as its 4-tetrahydropyranyl ether.

A solution of 250 mg (0.51 mmole) of this 4-tetrahydropyranyl ether in 50 ml of dioxane with 0.25 ml of 2.5 *N* HCl was heated

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(7) S. Gordon, E. W. Cantrall, W. P. Cekleniak, H. J. Albers, S. Maner, S. M. Stolar, and S. Bernatein, *Steroids*, **4**, 267 (1964).

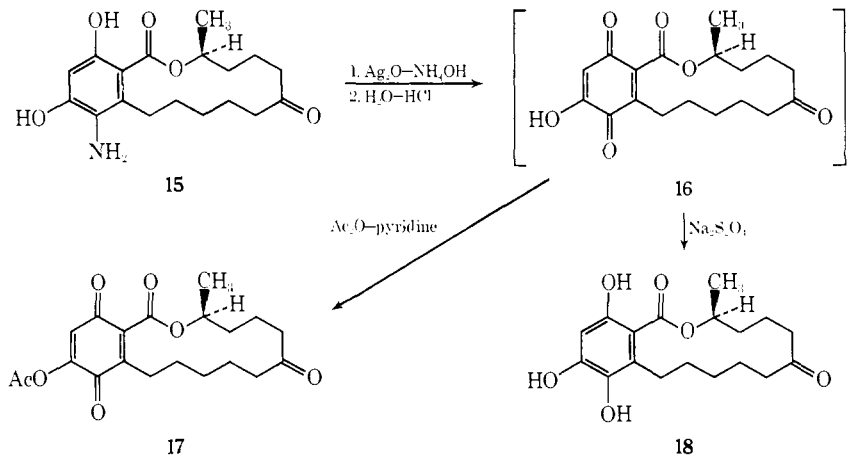
(8) C. Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 335 (1955).

(9) E. Hecker and G. Farthofer-Boeckh, *Biochem. Z.*, **338**, 628 (1963).

(10) Several other effects of conformational change on the chemistry and physical properties of zearalenone and its derivatives will be discussed in subsequent publications.

(11) Melting points were determined using a Koffler melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Nmr, uv, and ir data were in all cases consistent with the structures proposed.

SCHEME III



on the steam bath for 15 min, then poured onto ice. The aq suspension was extracted into EtOAc, washed, dried, and evaporated to yield 172 mg (81%) of **4**, suitable for further chemical transformations. Recrystallization from CH_2Cl_2–Et_2O gave an analytical sample, mp 165–167°. *Anal.* ($C_{25}H_{28}O_5$) C, H.

6-(10-Hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcyclic Acid μ-Lactone 2,4-Bis(1-phenyl-5-tetrazolyl) Ether (5). General Procedure for Tetrazolyl Ether Formation.—A mixture of 2.0 g (6 mmoles) of **1**, 2.17 g (12 mmoles) of 1-phenyl-5-chlorotetrazole, 2.4 g (24 mmoles) of anhyd K_2CO_3, and 18 ml of dry Me_2CO was stirred and refluxed under N_2 for 16 hr and filtered. The filtrate was evaporated under reduced pressure, the residue was swirled with C_6H_6 and taken to dryness under reduced pressure. Finally, the residue was dissolved in CH_2Cl_2 and concentrated to an oil. Addition of MeOH afforded 3.35 g (92%) of white crystals of **5**. Recrystallization from MeOH afforded the analytical sample of mp 166–168°. *Anal.* ($C_{32}H_{30}N_8O_5$) C, H, N.

2-(10-Hydroxy-6-oxoundecyl)benzoic Acid μ-Lactone (6). Hydrogenolysis Procedure.—A mixture of 2.5 g (4.12 mmoles) of bisphenyltetrazolyl ether (**5**), 0.5 g of 5% Pd–C, and 640 ml of 95% EtOH was shaken for 48 hr at 70° under H_2 at 3.5 kg/cm² and filtered and the filtrate evaporated under reduced pressure to afford 3.1 g of crude product. This was extracted with 25 ml of hot Et_2O and filtered quickly. A noncrystalline precipitate which formed in the solution at room temperature was filtered off. Further cooling and scratching of the Et_2O solution afforded a dense fibrous mass of crystalline **6**. Further recrystallizations (Et_2O) provided an analytical sample, mp 89–91°. *Anal.* ($C_{18}H_{24}O_3$) C, H.

Compounds **8** and **9** whose properties are described in Table I were prepared by the same hydrogenolysis conditions. However, it was necessary to resort to column chromatography to separate the products from phenyltetrazolone or to wash the latter out with dilute base. It is noteworthy that the THP group in **7** was usually cleaved during the hydrogenolysis so that **8** was obtained directly.

2-(10-Hydroxy-6-oxoundecyl)-5-nitrobenzoic Acid μ-Lactone (11).—To 5.0 ml of fuming HNO_3, cooled with ice to 3°, was added 2.0 g (6.93 mmoles) of dideoxy compound **6** in portions over a 15-min period with cooling and vigorous stirring. After an additional 30 min the solution was poured into about 70 ml of ice and H_2O. The resultant gum was taken up with EtOAc and this solution was washed with aq $NaHCO_3$, dried, and taken to dryness under reduced pressure. Crystallization (Et_2O) gave 0.632 g of **11** (27%). The analytical sample from Et_2O had mp 108–110°. *Anal.* ($C_{18}H_{23}NO_5$) C, H, N.

2-(10-Hydroxy-6-oxoundecyl)-5-aminobenzoic Acid μ-Lactone (12).—A mixture of 2.5 g (7.5 mmoles) of nitro compound **11**, 0.25 g of 5% Pd–C, and 250 ml of MeOH was shaken with H_2 at atmospheric pressure until 3 equiv had been absorbed. Filtration and evaporation of the filtrate under reduced pressure gave 2.18 g of white solid which was crystallized from MeOH in 5 crops to yield 1.74 g (76%) of **12**. An analytical sample was prepared from the same solvent, mp 139–140°. *Anal.* ($C_{18}H_{25}NO_3$) C, H, N.

2-(10-Hydroxy-6-oxoundecyl)-5-hydroxybenzoic Acid μ-Lactone (13).—A mixture of 4.05 g (13.4 mmoles) of amine **12**, 36.9 ml of H_2O, and 28.7 ml of concd H_2SO_4 was stirred vigorously giving an almost complete solution. Addition of 60–70 g of ice and vigorous stirring with ice bath cooling afforded a fine suspension. To this was added a solution of 0.943 g (15.5 mmoles) of $NaNO_2$ in 20.5 ml of H_2O. Stirring was continued for 20 min and then the solution was decanted from some undissolved material and decomposed by immersion in an oil bath preheated to 130° where it was allowed to reflux for 30 min. During this time the solution clouded, turned orange, and then lightened as a brown oil separated. The mixture was poured into cold H_2O, extracted with EtOAc and this solution after washing and drying was concentrated under reduced pressure to yield 3.4 g of a foam. Crystallization from CH_2Cl_2–Et_2O gave in 4 crops, 1.48 g (36%) of **13**. The analytical sample from the same solvent had mp 130–133°. *Anal.* ($C_{18}H_{24}O_4$) C, H.

2-(10-Hydroxy-6-oxoundecyl)-5-hydroxybenzoic Acid μ-Lactone (14).—Mother liquors from a large preparation of 5-NO_2 analog **11** on further crystallization from Et_2O gave a small fraction, mp 88–89° which according to glc was a 1:1 mixture of **11** and another compound; analytical data suggested it was a mixture of mononitro derivatives.

This fraction of mp 88–89° (2.0 g, 6.0 mmoles) was reduced in 200 ml of MeOH using 5% Pd–C and H_2 at atmospheric pressure. After 3 equiv of H_2 had been absorbed, the solution was filtered and concentrated. Treatment of the crude amine mixture under the same diazotization conditions used in preparing **13** from **12** afforded 1.27 g of foam. Peparative tlc on silica gel using 20% Et_2O in CH_2Cl_2 afforded **14**. Recrystallization from CH_2Cl_2–Et_2O provided the analytical sample, mp 124–127°. *Anal.* ($C_{18}H_{24}O_4$) C, H.

5-Acetoxy-3-(10-hydroxy-6-oxoundecyl)benzoquinone-2-carboxylic Acid μ-Lactone (17).—A solution of Ag_2O, from 0.5 g $AgNO_3$, in 5 ml of concentrated NH_4OH, was added dropwise over 1 min with stirring to a solution of 0.5 g (1.5 mmoles) of **15** in 5 ml of concentrated NH_4OH at 0°. After stirring for another 5 min, the reaction mixture was centrifuged and the blood red supernatant liquid added to a vigorously stirred ice-cold mixture of Et_2O and dil H_2SO_4. The phases were separated and the strongly acidic aq phase was extracted 2–3 more times with Et_2O. Upon combination of the extracts, washing with saturated aq NaCl, drying, and careful evaporation, a yellow gum was obtained which partially crystallized on standing. Careful titration with EtO_2 permitted isolation of the quinone **16** which could be recrystallized from MeOH. Isolation of the quinone was preferably carried out in the form of the acetate. Thus the gum was treated with 1.0 ml of Ac_2O and a *trace* of pyridine. After 5–10 min at room temperature, the volatile materials were removed with a gentle N_2 stream to give a crystalline residue. Recrystallization from MeOH or *i*-PrOH gave the quinone acetate **17** as bright yellow needles, mp 133–136°. *Anal.* ($C_{20}H_{24}O_7$) C, H.

5-Hydroxy-6-(10-hydroxy-6-oxoundecyl)-β-resorcyclic Acid μ-Lactone (18).—The Et_2O extract obtained in the preparation of **16** was shaken with 1 g of $Na_2S_2O_4 \cdot 2H_2O$ (per 0.5 g of starting **15**) in 50–100 ml of H_2O. The resultant off-color organic phase was then washed with saturated aq NaCl, dried, and evaporated under reduced pressure to give 0.3–0.4 g of solid. Recrystallization from EtOH gave pure triol **18**, mp 210–215° dec. *Anal.* ($C_{18}H_{24}O_6$) C, H.

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 toshow 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:

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