The phenylhydrazone is insoluble in alkali and gives no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.71; H, 5.99; N, 13.25. Found: C, 75.96; H, 6.02; N, 13.02.

When excess aniline was added to an alcoholic solution of the isatin and the mixture heated on the steam-bath for several days, the unreacted isatin was quantitatively recovered.

When benzylamine was added to a methanolic solution of N-benzyl- or N-phenyl-4,5,6,7-tetrahydroisatin and the resulting mixture heated on the steam-bath for several hours a white precipitate gradually appeared. Upon cooling and filtering a 70% yield of N,N'-dibenzyloxamide was obtained in each case; m.p. 215° alone and mixed with authentic specimens. With isobutylamine, 70% yields of N,N'-diisobutyloxamide were obtained with both of these isatins; m.p. 166.5–167° alone and when mixed with separately synthesized specimens.

When N-phenyl-N'-benzyloxamide was treated with benzylamine in methanol under similar conditions it was recovered quantitatively.

Preparation of the Quinoxaline Derivatives. (a) **6-Phenyl-7,8,9,10-tetrahydro-indolo[2,3-b]quinoxaline (IXa).**—A mixture of 1.6 g. of N-phenyl-4,5,6,7-tetrahydroisatin, 0.9 g. of *o*-phenylenediamine, 8 ml. of water and 3 ml. of glacial acetic acid was refluxed for two hours. After cooling, the upper layer was decanted from the brown oil which was washed with water and then dissolved in hot methanol. From the cooled solution 0.5 g. (24%) of yellow crystals deposited. The quinoxaline crystallized from methanol in yellow prisms, m.p. 159–160°.

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.27; H, 5.69; N, 14.05. Found: C, 79.94; H, 5.88; N, 14.27.

(b) **6-Phenyl-8-methyl-7,8,9,10-tetrahydro-indolo[2,3-b]-quinoxaline (IXb).**—From 1.5 g. of N-phenyl-6-methyl-4,5,6,7-tetrahydroisatin, 1.0 g. of *o*-phenylenediamine, 4 ml. of glacial acetic acid and 10 ml. of water, 0.3 g. (15%) was obtained by the procedure described above. The quinoxaline crystallized from methanol as yellow needles, m.p. 199–200°.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.51; H, 6.07; N, 13.42. Found: C, 80.55; H, 6.19; N, 13.50.

2,6(or 2,2)-Diglyoxalamidecyclohexanone.—A solution prepared from 2.3 g. of sodium and 50 ml. of absolute ethanol was added with stirring to a mixture of 9.8 g. of cyclohexanone and 11.7 g. of ethyl oxamate cooled to below 10°. The resulting suspension was stirred for several hours and then allowed to stand overnight. The mixture was diluted with 100 ml. of water and neutralized with dilute hydrochloric acid in the cold. The solid product which separated was collected and recrystallized from acetone; yield 6.0 g., m.p. 185–186° (foaming). The product produced no coloration with ferric chloride solution and was cleaved readily to oxamic acid by acid or base.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.00; N, 11.67. Found: C, 50.02; H, 4.98; N, 11.77.

4(or 6)-Methyl-2-ketocyclohexylglyoxalamide.—A solution prepared from 2.3 g. of sodium and 50 ml. of anhydrous ethanol was added with stirring to a mixture of 11.2 g. of 3-methylcyclohexanone and 11.7 g. of ethyl oxamate. During the addition the temperature was kept below 10°. Stirring was continued until the contents of the flask reached room temperature and then it was allowed to stand overnight. The mixture was diluted with 50 ml. of water and made neutral by the addition of dilute hydrochloric acid in the cold. The white solid which formed was collected and recrystallized from methanol; yield 6.9 g., m.p. 147–148°. The glyoxalamide showed no color reaction with ferric chloride and attempts to hydrolyze to the known 4-methyl-2-ketocyclohexylglyoxylic acid produced only oxamic acid.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.01; H, 7.10; N, 7.65. Found: C, 58.98; H, 7.00; N, 7.58.

UNIVERSITY HEIGHTS
NEW YORK 53, N. Y.

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Dipole Moments and Conformations of Androstane-3,17-dione and of Etiocholane-3,17-dione

BY HAROLD R. NACE AND RICHARD B. TURNER

RECEIVED MARCH 16, 1953

The dipole moments of androstane-3,17-dione and of etiocholane-3,17-dione, derived from dielectric constant measurements of benzene solutions of these substances are 3.1 and 3.5 *D*, respectively. Assuming an "all chair" conformation of the A/B/C ring system in each derivative, the dipole moments of the two compounds should be identical, and equal to 3.04 *D*. The discrepancy between the observed and calculated values for etiocholane-3,17-dione suggests the presence, at equilibrium, of about 16% of the ring A "boat" form, which possesses a dipole moment of 5.28 *D*.

The greater thermodynamic stability of the "chair" conformation of cyclohexane with respect to the "boat" modification is well known and is supported by several independent lines of evidence. Pertinent to the present discussion are dipole moment measurements of Le Fèvre and Le Fèvre[1] for cyclohexane-1,4-dione. The moments calculated for the "chair" and "boat" forms of this substance are, respectively, zero and 4.1 *D*, as compared with an experimentally determined value (benzene solution) of 1.2 *D*. Simple calculations employing the squares of the dipole moments indicate that in solution the "chair" form predominates to the extent of about 91% at equilibrium.[1] The energy difference between the "chair" and "boat" conformations of cyclohexane in the gas phase (25°) has been estimated by Beckett, Pitzer and Spitzer[2] to be of the order of 5.6 kcal. in favor of the more stable "chair" structure.

Information regarding fused ring systems, although not as extensive as that for cyclohexane and its derivatives, is in general agreement with the idea that "chair" structures are more stable than the corresponding "boat" conformations. Detailed X-ray analyses of cholesteryl iodide, 3β,5α-dichlorocholestane, and related products[3] support this conclusion. An important contribution to the structural theory of fused rings is the demonstration of Bastiansen and Hassel,[4] based upon electron diffraction studies, that *cis*-decalin possesses the

---

[1] C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1696 (1935).

[2] C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, 69, 2488 (1947).

[3] D. Crowfoot, "Vitamins and Hormones," R. S. Harris and K. V. Thimann, Vol. II, Academic Press, Inc., New York, N. Y., 1949, p. 409.

[4] O. Bastiansen and O. Hassel, *Nature*, 157, 765 (1946).

"2-chair," rather than the "2-boat" conformation. Extension of the Pitzer treatment to this case indicates an energy difference of at least 8.8 kcal. in favor of the "2-chair" structure.[5]

On the basis of this and other evidence constructions I and II have been proposed,[6] respectively, for the androstane and for the etiocholane ring systems, which constitute the basic nuclear structures of the two main classes of steroids. Support for these formulations is drawn from extensive correlations of the properties of various steroid derivatives in terms of the proposed conformations and the concept of polar and equatorial bonds.[7] Little evidence of a direct nature, however, can be cited as rigorously establishing conformations assigned to A/B *cis* derivatives (*cf.* II). X-Ray data for coprostane[8] and for desoxycholic acid,[9] which indicate a shortening and thickening of these molecules as compared with A/B *trans* compounds, are suggestive, but not decisive. The X-ray evidence in any event applies only to the crystals and gives no information regarding conformations in solution where intermolecular forces are minimized. Dipole moment measurements of a number of steroids, including several bile acid derivatives, have been reported by Kumler and his associates,[10,11] but their data are not readily interpretable in terms of structure II, owing to the presence of non-oriented dipoles in the compounds examined. We have, therefore, investigated the dipole moment of etiocholane-3,17-dione, which does not suffer from this ambiguity. Kumler's work on androstane-3,17-dione[10] was also repeated using benzene rather than dioxane as the solvent. Our results and the methods of calculation are described below.

Experimental

Dielectric constants of the several solutions were determined at 200 kc./sec. with a capacitance-conductance bridge that has been described elsewhere.[12] The test cell consisted of three coaxial nickel cylinders in a glass jacket.[13] With the three terminal arrangement used, the variable capacitance was 25.4 $\mu\mu$f. in air and the fixed capacitance 1.9 $\mu\mu$f., as determined by calibration with benzene purified as described below (ϵ^{25} 2.274). In order to obtain a very open scale for balancing the small capacitance changes of interest, a special capacitance circuit consisting of a General Radio Type 722 precision variable capacitor and 70 $\mu\mu$f. fixed air capacitor in series was employed.

Materials.—Benzene (Merck and Co., Inc., A. C. S. Reagent Grade) was dried over calcium hydride and distilled through a five-inch column packed with glass helices and equipped with a total-reflux, partial take-off head. The fraction boiling at 80° (761 mm.), d^{25} 0.8727 and $n^{25}\text{D}$ 1.4973, was collected; reported values:[14] d^{25} 0.8737 and $n^{25}\text{D}$ 1.4979.

Androstane-3,17-dione.—This material was prepared from dehydroepiandrosterone by standard procedures.[15] After several recrystallizations from acetone and ether–petroleum ether, the product melted at 132–133°.

Etiocholane-3,17-dione.—The A/B *cis*-dione was obtained by catalytic hydrogenation of Δ^4-androstene-3,17-dione over palladium black.[16] The purified material (ether–petroleum ether) melted at 132–133.2°.

Results

For the dilute solutions studied, both the density change, Δd, and the dielectric constant increment, $\Delta\epsilon$, were linear functions of weight per cent. solute, W, within experimental error. The best values of $\Delta\epsilon/W$ and of $\Delta d/W$ were therefore used to calculate the solute polarization, P_2, and the dipole moment, μ, by the relations

$$P_2 = \frac{3}{(\epsilon_1+2)^2}\left(\frac{M_2}{d_1}\right)\left(\frac{\Delta\epsilon_{12}}{W}\right) - \frac{(\epsilon_1-1)}{(\epsilon_1+2)}\left(\frac{M_2}{d_1}\right)\frac{1}{d_1}\left(\frac{\Delta d_{12}}{W}\right) + \frac{(\epsilon_1-1)}{(\epsilon_1+2)}\left(\frac{M_2}{d_1}\right)$$

and

$$\mu = 0.0127\sqrt{(P_2 - P_{\text{E}2})T}$$

In these equations, which are forms of the general expressions thoroughly discussed by Pohl, Hobbs and Gross,[17] the subscripts 1 and 2 refer to solvent and solute, M is the molecular weight, d the density and T the absolute temperature. The solute electronic polarization $P_{\text{E}2} = 81.2$ calculated by Kumler[10] for androstane-3,17-dione was used for both compounds. Measured solution dielectric constants ϵ_{12}, densities d_{12}, and weight per cent. W, are listed in Table I.

TABLE I

MEASUREMENTS IN BENZENE AT 25°

W	ϵ_{12}	d_{12}
	Androstane-3,17-dione	
1.15	2.313	0.8743
0.92	2.307	.8731
0.60	2.295	.8728
0.29	2.283	.8727
	Etiocholane-3,17-dione	
1.27	2.334	0.8736
0.90	2.316	.8736
0.65	2.304	.8732
0.28	2.287	.8727

The calculated values for the dipole moments were 3.1 D for androstane-3,17-dione[18] and 3.5 D for etiocholane-3,17-dione.

Discussion

Examination of molecular models[19] shows that

---

[5] R. B. Turner, THIS JOURNAL, **74**, 2118 (1952); *cf.* D. H. R. Barton, *J. Chem. Soc.*, 340 (1948).

[6] D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950); *cf.* L. Ruzicka, M. Furter and M. W. Goldberg, *Helv. Chim. Acta*, **21**, 498 (1938), and reference 10.

[7] D. H. R. Barton, *Experientia*, **6**, 316 (1950).

[8] J. D. Bernal, D. Crowfoot and I. Fankuchen, *Trans. Roy. Soc. (London)*, **239**, 135 (1940).

[9] V. Cagliotto and G. Giacomello, *Gazz. chim. ital.*, **69**, 245 (1939).

[10] W. D. Kumler, THIS JOURNAL, **67**, 1901 (1945).

[11] W. D. Kumler and I. F. Halverstadt, *ibid.*, **64**, 1941 (1942); W. D. Kumler and G. M. Fohlen, *ibid.*, **67**, 437 (1945).

[12] R. H. Cole and P. M. Gross, Jr., *Rev. Sci. Instruments*, **20**, 252 (1949).

[13] Obtained from J. C. Balsbaugh, The Massachusetts Institute of Technology, Cambridge, Mass.

[14] "Selected Values of Properties of Hydrocarbons," National Bureau of Standards Circular C461 (1947), p. 43.

[15] *Cf.* R. E. Marker, THIS JOURNAL, **58**, 480 (1936).

[16] *Cf.* A. Butenandt, *Z. physiol. Chem.*, **248**, 205 (1937).

[17] H. A. Pohl, M. E. Hobbs and P. M. Gross, *Annals N. Y. Acad. Sciences*, **40**, Art. 5, 390 (1940).

[18] Kumler[10] reported a value of 3.25 D for this compound in dioxane at 25°. The difference can probably be ascribed to solvent effects.

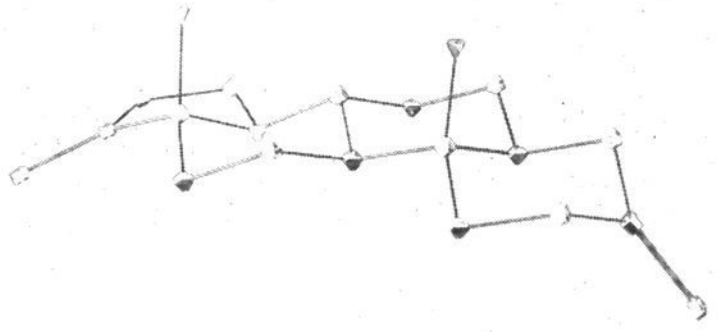
[19] Models designed by Barton consisting of aluminum tetrahedra connected by flexible steel rods (see plates) were employed for these constructions. The advantage of these models lies in the fact that angle strain associated with the *trans* C/D ring fusion can be absorbed throughout the system in a manner simulating strain distribution in actual molecules.

the angles (φ) between the C_3 and C_{17} carbonyl groups of the stable "all-chair" conformations of androstane-3,17-dione (I) and of etiocholane-3,17-dione (II) are identical and equal to 118°. The values of the angles, given by the relation

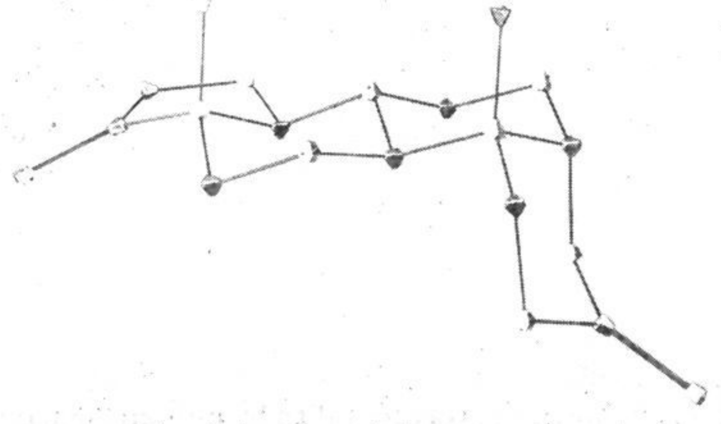
$$\cos\varphi = \cos\alpha_1\cos\alpha_2 + \cos\beta_1\cos\beta_2 + \cos\gamma_1\cos\gamma_2$$

were obtained by direct measurement of the direction cosines ($\cos\alpha_1$, etc.) of the carbon–oxygen double bonds with respect to a fixed system of coördinates. The resultant dipole moments, $\mu_{\rm I} = \mu_{\rm II} = 3.04\ D$, were calculated in the ordinary way, by employing for the moment of the 3-keto group that of cyclohexanone (2.90 D),[20] and for the moment of the 17-keto group that of cyclopentanone (3.00 D).[21] Comparison of the calculated values with those determined experimentally—3.1 D for androstanedione and 3.5 D for etiocholanedione—reveals a discrepancy of 0.5 unit between the calculated and observed moments for the latter compound. This divergence is greater than the limits of error of the method and must, therefore, be regarded as real. The following explanation may be advanced in connection with this observation.

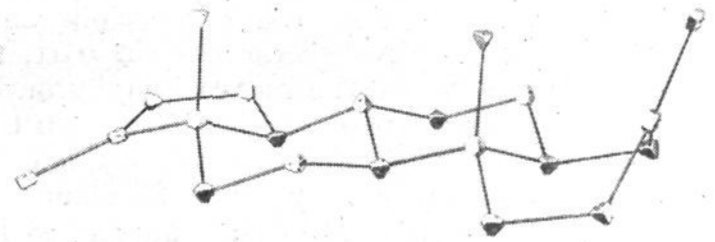
Since the observed dipole moment represents a weighted average of the moments of all contributors to the equilibrium state, the presence of small amounts of any geometrical form possessing a very high or a very low moment, relative to that of the major component, will be reflected in corresponding changes in the experimental value. Of various conformations of etiocholane-3,17-dione, the most likely secondary structure, from an energetic point of view, is the ring A "boat" form IV. The dipole moment calculated for this conformation is 5.28 D (φ = 53°), as compared with a value of 3.04 D for the "all-chair" structure (II). From these data and the measured moment (3.5 D), the equilibrium composition of etiocholane-3,17-dione in benzene solution may be calculated as 84% of II and 16% of IV. These results are to be compared



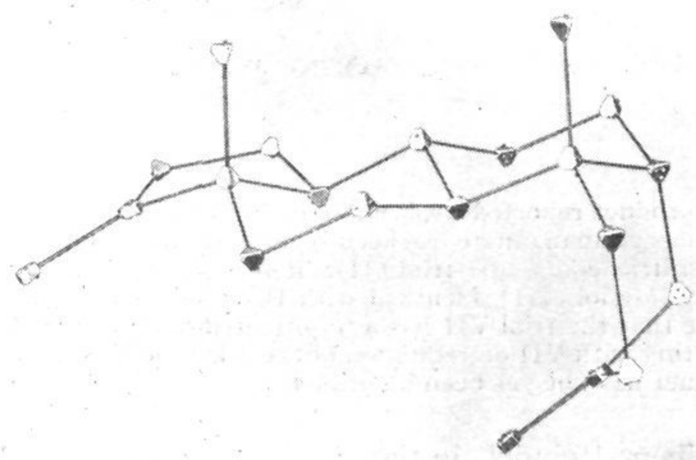
I



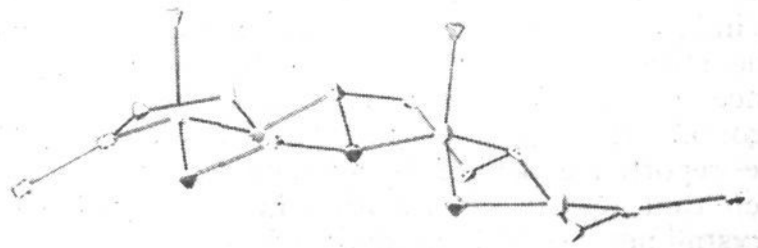
II



III



IV



V

---

(20) I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 1982 (1942).

(21) H. L. Donle and G. Volkert, *Z. physik. Chem.*, **B8**, 60 (1930).

with values of 91 and 9%, respectively, obtained for the "chair" and "boat" conformations of cyclohexane-1,4-dione by LeFèvre and LeFèvre (see above) in the same solvent. The relatively smaller contribution of the boat structure of cyclohexane-1,4-dione may be attributed, at least in part, to dipole repulsions between the two carbonyl groups, which in this case are proximate in space. On the basis of the above arguments any appreciable concentration of the high energy "2-boat" structure V (σ = 148°, μ = 1.70 D) would appear to be excluded.

Similar consideration of the conformations of androstane-3,17-dione indicates that the ring A "boat" structure (III) in this case (φ = 105°) should possess a dipole moment of 3.58 D. The presence of 10–15% of this form will hence be much less effective in weighting the average dipole moment than is the corresponding "boat" structure IV of etiocholane-3,17-dione. This conclusion is in accord with the experimental findings.

Acknowledgment.—The authors are grateful to Prof. Robert H. Cole for assistance and advice. H. R. N. is indebted to the Corporation of Brown University for a Faculty Summer Research Grant which made possible a portion of this study.

PROVIDENCE, R. I.
HOUSTON, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Permanganate Oxidation of Ergosterol

BY MARY FIESER, ADOLFO QUILICO,[1] ALEX NICKON,[2] WILLIAM E. ROSEN, E. JAMES TARLTON AND LOUIS F. FIESER

RECEIVED APRIL 18, 1953

A product reported by Reindel in 1928 to be formed in high yield by oxidation of ergosterol in methylcyclohexane with aqueous permanganate has been separated into an O_3- and an O_5-component. The O_3-product has been identified as $\Delta^{7,14,22}$-ergostatriene-3β,5α,6α-triol (II); it forms a diacetate, a maleic acid adduct, and on reduction it affords $\Delta^{8(14)}$-ergostene-3β,5α,6α-triol (III), identical with the product of hydrogenation of $\Delta^{7,22}$-ergostadiene-3β,5α,6α-triol (VII). Further evidence that the triol VII has a 6α-oriented hydroxyl group was obtained by comparison of the triol with the 6β-epimer VI, resulting with VII on reduction of the 6-ketone V: epimer VII forms an acetonide, whereas VI does not. The O_5-oxidation product has not yet been identified.

When Reindel initiated a program of independent research at Munich, Windaus turned over to him the problem of investigating the then little studied ergosterol.[3] Shortly afterwards, the sterol rose to a position of key interest with the discovery by Windaus, Hess and Pohl at Göttingen[4] and by Rosenheim and Webster in England[5] that on irradiation it acquires high antirachitic potency, but Windaus only authorized work at Göttingen on the structure of ergosterol at the urgent insistence of members of his vitamin D research group.[6] In Reindel's third paper on ergosterol,[7] he reported experiments conducted with A. Frölich that resulted in isolation in good yield of a crystalline, neutral product of oxidation. The nature of the product was not established, but the results were communicated with the idea that "they might later be of use in elucidation of the structure of ergosterol." This hope was not realized, and a quarter of a century has gone by with no further reference in the literature to the oxidation product.

We were intrigued with the novel method of oxidation used and the high yield of crystalline product. Reindel and Frölich[7] added aqueous permanganate solution to a hot solution of ergosterol in methylcyclohexane, shook the mixture for 12 hours, and processed the resulting three-phase system by a briefly described procedure that is not clear to us. They reported isolation of a small amount of an unidentified lower fatty acid derived from fission of the side-chain double bond and of a crystalline neutral product for which they suggested the formulas $C_{26}H_{40-42}O_4$, on the basis of the formula $C_{27}H_{42}O$, at the time attributed to ergosterol (now $C_{28}H_{44}O$); the analytical data also fit the formulas $C_{28}H_{46-48}O_4$. Several ester derivatives were prepared and analyzed and hydrogenation was studied, but some of the results appeared anomalous and no definite conclusions were reached.

After considerable experimentation (A.Q.), a reproducible procedure was worked out for oxidation of ergosterol in 4-g. lots in hot methylcyclohexane with a hot aqueous solution of three oxygen equivalents of permanganate (Reindel and Frölich used six equivalents); when less oxidizing agent was used, starting material was found in the reaction mixture. The precipitated manganese dioxide was reduced with sulfur dioxide, the methylcyclohexane was eliminated by steam distillation and evaporation, and the reaction product was obtained in a crystalline filterable form by digestion with methanol. Under the best conditions found, crystalline, ergosterol-free product corresponding approximately to that of Reindel and Frölich was regularly obtained in 80% yield by weight. This material, however, was found to be unhomogeneous, and by fractional crystallization it was separated into a main O_3-component and a secondary O_5-component, of composition and properties indicated in Table I. The analyses and optical rotations indicate that the oxidation affords a mixture of about

---

(1) On leave of absence from the Politecnico di Milano.

(2) National Institutes of Health Predoctoral Fellow, 1950–1952.

(3) F. Reindel, E. Walter and H. Rauch, *Ann.*, **452**, 34 (1927), footnote 1. See also F. Reindel and E. Walter, *ibid.*, **460**, 212 (1928).

(4) A. Windaus and A. F. Hess, *Nachr. Ges. Wiss., Göttingen*, 175 (1926); R. Pohl, *ibid.*, 185 (1926).

(5) O. Rosenheim and T. A. Webster, *Biochem. J.*, **21**, 389 (1927).

(6) Incident related by Dr. Werner Bergmann.

(7) F. Reindel, *Ann.*, **466**, 131 (1928).