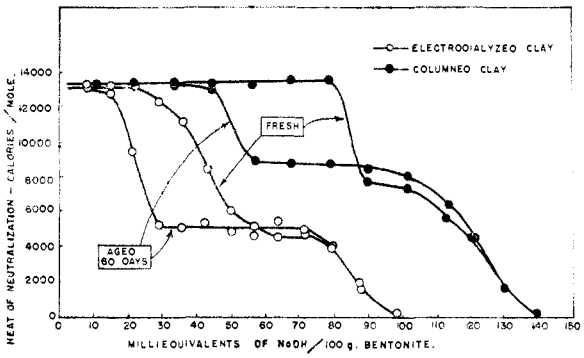

Fig. 2.—Heat of neutralization of electrodialyzed bentonite and bentonite exchanged with hydrogen in an Amberlite IR 120 column.

ized in Fig. 2. The ΔH values were calculated on the basis of molar quantities of alkali added in each step of the neutralization process. For example, when 1 ml. of 0.165 N NaOH (0.0165 millimole) is added to an acid system a certain quantity of heat is evolved. This amount of heat multiplied by $(0.0000165)^{-1}$ gives the amount of heat which would be evolved by the reaction of a mole of NaOH with a given portion of the hydrogen ions in the clay system. The ΔH values do not represent the total heat of neutralization but, rather, the quantity of heat evolved in each successive step in the neutralization process. In plotting these data, the quantity of alkali is expressed in terms of the number of milliequivalents of NaOH per 100 g. of oven-dried bentonite. By determining the total area under the ΔH curves it is possible to express the mean heat of neutralization. The electrodialyzed clay gave values of 8,000 calories per mole for the freshly prepared samples, and 6,700 calories per mole for the aged samples. The columned clay gave values of 10,400 calories and 9,400 calories per mole for the fresh and aged samples, respectively.

In Fig. 3 are the potentiometric titration data for the same system. A glass electrode and a sleeve type calomel cell were used in these titrations.

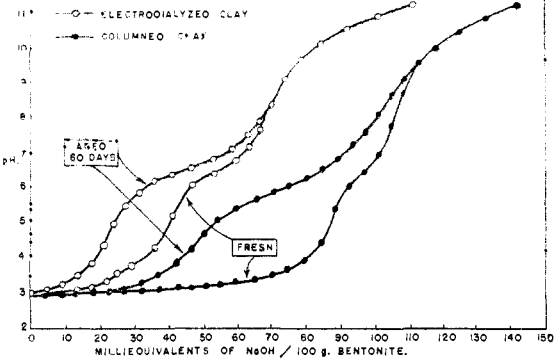

Fig. 3.—Potentiometric titration of electrodialyzed bentonite and bentonite exchanged with hydrogen in an Amberlite IR 120 column.

Discussion

The experimental data obtained in this work show further indication of the existence of two types of available hydrogen in the hydrogen–bentonite system. In the acid-clay from the electrodialysis and column procedures, the early portions of alkali react with hydrogen ions which are completely ionized. During the latter part of the neutralization process, the hydrogen ions show a much different character. The lower heat of reaction shows that these secondary hydrogen ions are less highly ionized, possible less available geometrically, and that considerable energy is required for the hydration of these ions. These two types of hydrogen ions correspond to the plateaus in the ΔH curves.

Considerable heat is evolved by the addition of NaOH beyond the stoichiometric end-point which follows the second plateau in the ΔH curves. This is attributed to the greater degree of covalency of the hydrogen ions which are neutralized only at an alkalinity above pH 9.0. It is doubtful if this heat is associated with the physical adsorption of NaOH which is described by Kayser and co-workers.[8] Apparently, up to 75 milliequivalents of NaOH beyond the stoichiometric end-point can be physically adsorbed. Since this is probably a van der Waals adsorption, the heat of adsorption would likely be too small to detect by the present method.

A significant contrast between the electrodialyzed and columned bentonite is shown by the end-point in the titration curves. For the electrodialyzed clay, the primary end-points require one-half and one-third as much of base as is required for total neutralization of fresh and aged samples, respectively. In the case of the columned clay, the primary end-points require 80 and 50% as much base as is required for the total neutralization of fresh and aged samples, respectively.

Although the total amount of titratable hydrogen ion remains essentially the same, aging produces pronounced effects upon the ratio of primary to secondary hydrogen ions in the clay systems. The curves in Figs. 2 and 3 represent the maximum change in this respect which the hydrogen–clay underwent in 60 days. These data suggest that in the aging process the highly reactive hydrogen ions, which are probably concentrated to a considerable extent in the adsorbed ion layer of the colloidal micelles, migrate into the micelle and occupy positions which are geometrically closer to the negatively charged points on the clay lamina, the base-exchange sites. These ionic migrations provide experimental evidence for Pauling's electrostatic valence principle which was applied to clays by Hendricks.[9] The principle states that ionic systems are statistically neutral on the smallest possible scale. In freshly prepared hydrogen–bentonite, the hydrogen ions have not reached their most stable positions. Due to the small ionic radius of the hydrated proton it is conceivable that if enough base-exchange sites are available, most of the hydrogen ions in the hydrogen–clay system would eventually migrate into the laminar structure of these layer silicates, whereupon they would attain their maximum covalency.

(8) F. Kayser, J. M. Bloch and G. Gommery, *Bull. soc. chim. France*, 462 (1951).

(9) S. B. Hendricks, *Ind. Eng. Chem.*, **37**, 625 (1945).

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3β,17α-Dihydroxynorcholanic Acid Lactone

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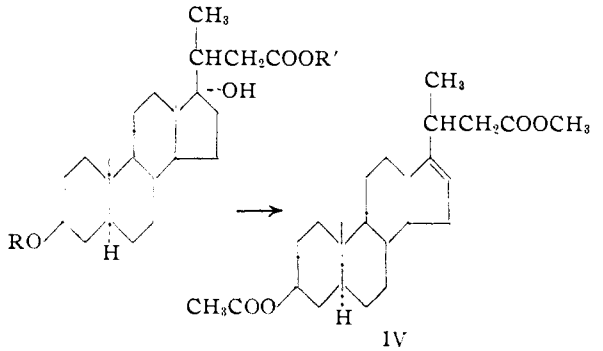
Recently we reported the isolation of a new by-product of the oxidation of sitosterol acetate

dibromide, 3β-acetoxy-17α-hydroxynor-5-cholenic acid lactone.[1] We now describe the reduction of the 3-hydroxy derivative to give a mixture of the corresponding norcholanic and allonorcholanic lactones and the conversion of the latter to the known 3β-hydroxyallonorcholanic acid.[2] As in our previous work,[1] the allonorcholanic lactone was opened with alkali to give the hydroxy acid (I). The 3-acetate methyl ester (III) was dehydrated with thionyl chloride to the Δ^{16}-norcholenate (IV) and reduction of the latter gave the allonorcholanate (V).

The Δ^{16}-norcholenate (IV) had an absorption band at 12.20 microns in the infrared (Nujol mull)[3] which is typical of the structure $R_2C{=}CHR$. Neither III nor V had absorption in this region.



IV

I, R = H, R′ = H
II, R = H, R′ = CH_3
III, R = CH_3CO, R′ = CH

V. Methyl-3β-acetoxy-allonorcholanate

Experimental[4]

3β,17α-Dihydroxyallonorcholanic Acid Lactone.—A suspension of 12 g. of 3β,17α-dihydroxynor-5-cholenic acid lactone [m.p. 282–283°; $[\alpha]^{22}D$ −94.4° (2% in $CHCl_3$)][1] was hydrogenated at atmospheric pressure and room temperature using 1.2 g. of platinum oxide catalyst. The reduction was stopped when 1055 ml. of hydrogen had been consumed (35 minutes). Since the product was completely in solution at the end of the hydrogenation, the catalyst was removed by filtration and the volume of the filtrate reduced to 100 ml. The solution was poured into water and the resulting precipitate filtered, washed neutral with water and dried to give 12.0 g. of a mixture of the isomeric saturated lactones, m.p. 220–263°. The crude product from several hydrogenations (44.0 g.) was recrystallized twice from acetone to give 23.0 g. of 3β,17α-dihydroxyallonorcholanic acid lactone (needles) melting at 284.0–285.4°; $[\alpha]^{20}D$ −16.4° (2% in $CHCl_3$). (Surprisingly, a mixture with a sample of the unhydrogenated hydroxy lactone showed no depression in the melting point.) The acetone filtrates were held for the isolation of the other saturated lactone below.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.20; H, 10.25.

3β-Acetoxy-17α-hydroxyallonorcholanic Acid Lactone.—The allolactone (above) (4.0 g.) was acetylated by refluxing two hours with 40 ml. of acetic anhydride. The crude product (4.38 g.) melting at 239.0–241.5° was recrystallized from methanol and acetone to give 3.08 g. of 3β-acetoxy-17α-hydroxyallonorcholanic acid lactone (long needles), m.p. 240.6–242.6; $[\alpha]^{22}D$ −21.1° (2% in $CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 75.00; H, 9.80.

3β,17α-Dihydroxynorcholanic Acid Lactone.—The acetone mother liquor from the crystallization of the crude hydrogenation mixture, after removal of the bulk of the hydroxy allolactone, was concentrated to dryness. An 8.0-g. portion of this material was dissolved in hot benzene, concentrated to a low volume and while hot, an equal volume of naphtha (b.p. 90–120°) was added. After cooling to 25°, the crystals were filtered and washed with a mixture of equal parts of benzene and naphtha to give 5.5 g.; m.p. 211–220°. This material was dissolved in hot acetone, concentrated to a heavy slurry of crystals, cooled and filtered to give an additional yield of 1.4 g. hydroxyallolactone, m.p. 279–282°. The mother liquor upon concentrating to dryness (3.7 g.) melted at 213.5–224.0°. A solution of this residue in 200 ml. of benzene was chromatographed using 20 g. of 60–100 mesh Florisil.[5] The column was eluted with benzene and the eluate collected in 300-ml. fractions which were each concentrated to dryness. The first two fractions contained only a slight trace of oil, and the next seventeen fractions contained only a new lactone, melting sharply at 234.5–235.5°. Further elution of the column gave a mixture of the two isomers. The sharp melting fractions were combined (1.53 g.), dissolved in hot acetone and concentrated to a low volume. The acetone was completely replaced with ethyl ether by distillation, concentrated to a heavy slurry of crystals, cooled to 5° and filtered to give 1.2 g. of 3β,17α-dihydroxynorcholanic acid lactone (needles), m.p. 234.6–236.4°; $[\alpha]^{20}D$ −15.2° (2% in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.69; H, 10.30.

3β,17α-Dihydroxyallonorcholanic Acid (I).—A solution of 18.2 g. of 3β,17α-dihydroxyallonorcholanic acid lactone in 1300 ml. of 5% ethanolic potassium hydroxide was refluxed for two hours and the mixture poured into 5 l. of water. Dilute hydrochloric acid was added to the solution of the potassium salt until it was just faintly acid to litmus and the precipitated free acid filtered, washed neutral and air-dried. The crude acid (19.0 g.) was dissolved in hot methanol, treated with activated carbon, and concentrated to a low volume. The methanol was replaced with ethyl ether by distillation and the ether solution concentrated to a heavy slurry of crystals. After cooling to 5°, the crystals were filtered to give 13.8 g. of I, $[\alpha]^{22}D$ −1.58 (2% in methanol). When the melting point capillary was inserted at 260°, the acid immediately melted and bubbled up the tube, solidified and finally remelted at the melting point of the hydroxy allolactone (282.0–284.0°).

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.80; H, 10.50.

Methyl 3β,17α-Dihydroxyallonorcholanate (II).—The silver salt of the hydroxy acid (I) was prepared by a modification of the method of Allen and Wilson.[6] To a solution of 15.0 g. of the acid (I) and 2.81 g. of 87% potassium hydroxide in 200 ml. of methanol and 200 ml. of water was added a solution of 7.4 g. of silver nitrate in 50 ml. of water with agitation and the suspension of silver salt stirred for 10 minutes. Methyl iodide (57 g.) was added, and after stirring for 15 minutes the mixture was filtered. The filter cake was extracted with hot methanol and the extracts added to the original filtrate. The combined liquids were concentrated to a small volume, poured into water and filtered to give 14.5 g. of crude ester (II). The crude ester (3.0 g.) was recrystallized from methanol to give 2.0 g. of fine needles, $[\alpha]^{22}D$ −0.4° (2% in methanol). When the sample was inserted in the melting point bath at 125°, it melted at 150–153° with bubbling, resolidified at approximately 170° and finally remelted at 282–284°. When heated, the methyl ester apparently lost the elements of methanol to regenerate the lactone.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.33. Found: C, 73.40; H, 10.70.

Methyl 3β-Acetoxy-17α-hydroxyallonorcholanate (III).—A solution of 13.5 g. of the methyl ester (II) in 67 ml. of dry pyridine and 13.5 ml. of acetic anhydride was warmed at 60° for one hour, allowed to stand overnight and then poured into water. The precipitate was filtered, washed thoroughly with water and dried. The crude product was recrystallized from methanol to give 10.7 g. of (III), m.p. 196.0–198.4°; $[\alpha]^{21}D$ −10.25° (2% in $CHCl_3$). When the

(1) A. I. Ryer and W. H. Gebert, THIS JOURNAL, **74**, 41 (1952).

(2) P. A. Plattner and J. Pataki, *Helv. Chim. Acta*, **26**, 1241 (1943).

(3) R. B. Barnes, R. C. Gore, R. W. Stafford and V. Z. Williams, *Anal. Chem.*, **20**, 402 (1948).

(4) All melting points are corrected. Microanalysis and microrotations by Edwin Conner and staff of these laboratories.

(5) Obtained from the Floridin Company, Warren, Pennsylvania.

(6) C. F. H. Allen and C. V. Wilson, *Org. Syntheses*, **26**, 52 (1946).

melting point sample, after melting, was heated to 250° and cooled, the resolidified material remelted at 236–238° [lactone acetate].

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.08; H, 9.95.

Methyl 3β-Acetoxyallonor-16-cholenate (IV).—A solution of 11.3 g. of the acetoxy ester (III) in 114 ml. of dry pyridine was cooled in an ice–salt-bath and 11.4 ml. of redistilled thionyl chloride added. The mixture was allowed to stand for two hours in an ice–salt-bath and for one hour at room temperature, then poured into ice-water and stirred for one hour. The crystals were filtered and washed neutral with water to give 10.9 g., m.p. 94–170°. The crude product was dissolved in hot methanol, the solution concentrated to 55 ml., cooled and filtered to give 8.0 g., m.p. 103–180°. These crystals were dissolved in 300 ml. of ethyl ether, the volume reduced to 100 ml., cooled and the crystals filtered to give 1.6 g. of needles, m.p. 236–238°. A second crop of needles (0.25 g.) with the same melting point was obtained from the mother liquor at a volume of 35 ml. A mixture of these needles with a sample of the acetoxy lactone showed no depression in the melting point. It is apparent that relactonization occurs during the dehydration reaction. The mother liquor after removal of the lactone acetate was concentrated to dryness and the residue recrystallized several times from methanol and ethanol to give 3.1 g. of IV (fine needles) melting at 120.6–123.4°; $[\alpha]^{21}D$ +2.0° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.83.

Methyl 3β-Acetoxyallonorcholanate (V).—A solution of 2.0 g. of the unsaturated acetoxy ester (IV) dissolved in 300 ml. of absolute alcohol was hydrogenated at 760 mm. and 25° using 0.6 g. of 10% palladium-on-charcoal. The reduction was stopped when 109 ml. of hydrogen had been consumed (22 minutes). Fine needle-like crystals were formed during the reduction. The mixture of catalyst and crystals was removed by filtration and the filter cake washed thoroughly with chloroform to remove the sterol. The filtrate was concentrated to a small volume, the chloroform replaced completely with ethanol by distillation and the volume reduced to 40 ml. After cooling to 5°, the crystals were filtered to give 1.70 g. of V (needles), m.p. 157.5–159.0°. After recrystallization from acetone and methanol the analytical sample melted at 159.4–160.8°; $[\alpha]^{25}D$ +11.0° (2% in $CHCl_3$). This product corresponds in its properties to the methyl 3β-acetoxyallonorcholanate described by Wieland and Miescher[7] and by Plattner and Pataki.[2]

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.50; H, 9.95.

3β-Hydroxyallonorcholanic Acid.—The acetoxy ester (V) was saponified by refluxing with 2% methanolic potassium hydroxide. After recrystallization from ethyl acetate and acetone, the product melted at 226.0–226.8°; $[\alpha]^{24}D$ +22.8° (1% in ethanol). These constants agree with those reported by Plattner and Pataki.[2]

Acknowledgment.—We wish to thank Dr. W. B. Tarpley and Miss C. Vitiello of our Chemical Research Division for the infrared data herein reported.

(7) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **30**, 1876 (1947).

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β-Glycerol Ethers Isomeric with Mephenesin

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In a search for drugs that exhibit muscle-paralyzing activity more intense and with a longer duration of action than mephenesin (3-*o*-toloxy-1,2-propanediol), numerous compounds have been synthesized wherein variations were made in the nature and distribution of substituents in the aromatic nucleus, and modifications were made in the hydroxylated side chain.[1] Among the previously reported compounds are three isomers of mephenesin, 3-*m*-toloxy-1,2-propanediol, 3-*p*-toloxy-1,2-propanediol and 3-benzyloxy-1,2-propanediol, all of which have the formula $C_7H_7OCH_2CHOHCH_2OH$, but no reference has been made to the preparation of the corresponding β-glycerol ethers. This paper describes the preparation and physical constants of the four isomeric β-glycerol ethers having the formula $C_7H_7OCH(CH_2OH)_2$. These compounds are of interest not only because of their structural relationship to mephenesin but also because of their similarity to the anticonvulsant drug 2,2-diethyl-1,3-propanediol (DEP). The results of pharmacological studies carried out with these compounds will be reported elsewhere.

Synthesis of the 2-toloxy-1,3-propanediols was accomplished through the lithium aluminum hydride reduction of the corresponding toloxymalonic esters following the procedure described by Chaikin for the reduction of ethyl phenoxymalonate.[2] Since ethyl benzyloxymalonate could not be readily prepared by direct condensation of ethyl chloromalonate and sodium benzylate, 2-benzyloxy-1,3-propanediol was synthesized by the condensation of benzyl chloride and the sodium salt of 5-hydroxy-2-phenyl-*m*-dioxane followed by hydrolysis of the cyclic acetal.

The melting point of each of the 2-toloxy-1,3-propanediols is lower than that of the corresponding 3-toloxy-1,2-propanediol. However, the 2-benzyloxy derivative was isolated as a solid whereas the 3-benzyloxy compound has been reported to be a liquid.[3] The β-glycerol ethers reported here have water solubilities comparable to those of the corresponding α-glycerol ethers, with the exception of 2-*m*-toloxy-1,3-propanediol, which possesses an abnormally high water solubility.

Experimental[4]

Ethyl Toloxymalonates.—The three isomeric ethyl toloxymalonates were prepared by condensation of ethyl chloromalonate with the appropriate sodium cresolate in absolute ethanol following the procedure described for ethyl *m*-toloxymalonate by Niederl and Roth.[5]

2-Toloxy-1,3-propanediols.—The diols were obtained by reduction of the corresponding toloxymalonic esters with lithium aluminum hydride[2] followed by acid hydrolysis of the aluminate. The *o*-toloxy compound was purified by fractionation under diminished pressure, the meta- and para-isomers by crystallization from benzene–ligroin solution.

5-Benzyloxy-2-phenyl-*m*-dioxane (VII).—To a well-stirred suspension of 4.3 g. (0.11 mole) of sodium amide in 200 ml. of anhydrous toluene, there was added portionwise 18.0 g. (0.1 mole) of 1,3-benzylidene glycerol[6] and the mixture was refluxed until the evolution of ammonia had ceased. A solution of 16.0 g. (0.12 mole) of benzyl chloride in 50 ml. of anhydrous toluene was added over a period of 15 minutes and refluxing continued for six hours. The mixture was cooled, washed with two 50-ml. portions of water, dried over sodium sulfate and concentrated *in vacuo*.

(1) For a listing of the pertinent references in this field, see: B. J. Ludwig, W. A. West and W. E. Currie, THIS JOURNAL, **74**, 1935 (1952).

(2) S. W. Chaikin, *ibid.*, **70**, 3522 (1948).

(3) J. C. Sowden and H. O. Fischer, *ibid.*, **63**, 3244 (1941).

(4) All temperatures reported are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, New York.

(5) J. B. Niederl and R. T. Roth, THIS JOURNAL, **62**, 1154 (1940).

(6) H. Hibbert and N. M. Carter, *ibid.*, **51**, 1608 (1929).