scheme, leads to an optically constant head fraction after six recrystallizations. This diastereoisomeric salt is apparently optically pure, for additional crystallization fails to alter its specific rotation, −14.0°, melting point and crystal habit. The salt from the mother liquors is dextrorotatory, $[\alpha]_D$ + 8.3°.

From the decomposition of the optically constant (−)-III with dilute hydrochloric acid the corresponding (−)-hydrogen phthalate is obtained as a colorless glass. The absence of racemization during this decomposition is demonstrated by the recombination of the acid ester with brucine to yield the salt with undiminished rotation.

Reductive cleavage of the optically active hydrogen phthalates with lithium aluminum hydride occurs smoothly to form the dextro- and levorotatory carbinols in excellent yields. From (−)-II there is obtained (+)-methylethylphenylcarbinol, $[\alpha]_D$ + 17.45°, which is presumed to be optically pure on the basis of the optical constancy of its hydrogen phthalate. Partially resolved (+)-II from the mother liquors is cleaved to (−)-I, $[\alpha]_D$ − 14.56°. Racemization of the hydrogen phthalates during treatment with lithium aluminum hydride is excluded by the reaction cycle in which II, + 11.8°, is cleaved to I, −4.53°, and (−)-I, when reacting with phthalic anhydride *via* its potassium salt, is reconverted to II, +11.6°. The infrared spectra of the dextrorotatory, levorotatory and racemic carbinols are identical in all essential details.[5]

Experimental[6]

Methylethylphenylcarbinol (I, 2-Phenylbutan-2-ol).—Methyl ethyl ketone (72 g.) in 150 ml. of ether was added to an iced solution of phenylmagnesium bromide in 350 ml. of ether (24.4 g. of magnesium and 160 g. of bromobenzene). After the mixture had stood overnight at room temperature, it was hydrolyzed with iced dilute hydrochloric acid and worked up in the usual fashion. Vacuum distillation of the carbinol yielded 123 g. (82%) of I: b.p. 90–91° (4 mm.); $n^{25}D$ 1.5189; d^{25}_4 0.984.[7] This carbinol still contained traces of diphenyl which could be effectively removed by conversion of the alcohol to its hydrogen phthalate followed by regeneration of I with lithium aluminum hydride as described below. Distillation of the carbinol at atmospheric pressure invariably results in dehydration.

Hydrogen 2-Phenyl-2-phthalate (II).[8]—Methylethylphenylcarbinol (150 g.) was added dropwise to a vigorously stirred suspension of 39 g. of potassium sand in 2.5 l. of dry benzene at 75°. After four hours the hot benzene solution of the potassium salt of I was pumped under nitrogen pressure into 1.5 l. of benzene containing 148 g. of phthalic anhydride. The crude acid ester was isolated as previously described[2] and then dissolved in benzene. This solution on concentration and cooling deposited three crops of crystalline II totalling 119 g. (40%), m.p. 111–112° (dec.).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.80; H, 6.08; neut. equiv., 298. Found: C, 72.97; H, 6.28; neut. equiv., 298.

Fractional Crystallization of Brucine 2-Phenylbutyl-2-phthalate (III).—A solution of 100.5 g. of II and 133 g. of anhydrous brucine in 300 ml. of hot acetone was cooled slowly to room temperature and then stored in the refrigerator overnight. The crystalline mass which had formed was filtered off and redissolved in 700 ml. of fresh acetone. A systematic fractional crystallization was thus initiated and continued in which the head fraction of the brucine salt was dissolved each time in just enough fresh acetone to effect solution, followed by cooling to room temperature and standing overnight. After six recrystallizations the melting point of the brucine salt comprising the head fraction had risen from 133–135° to a constant value of 139–140° and its specific rotation had increased from +0.6° to −14.0°. Two recrystallizations of the salt caused no change in rotation. Evaporation of the filtrate from the last crystallization gave brucine salt with identical rotation. The fractional crystallization was continued until 21 g. (9%) of optically constant III had been obtained: $\alpha^{27}D$ −0.71°, *c*, 5.07. The crystalline cake from the mother liquors, spontaneously formed, had the rotation $\alpha^{22}D$ +0.40°, *c*, 4.82.

Optically Active Methylethylphenylcarbinol.—Optically constant III (20.5 g.) was dissolved in 80 ml. of ethanol and shaken with ether and 1% aqueous hydrochloric acid. The acidic aqueous layer was extracted with fresh ether, and the combined ether extracts were washed four times with water and dried over magnesium sulfate. The major part of the solvent ether was distilled on the steam-bath, and the remainder was removed by evaporation under reduced pressure: 8.5 g. (88%). Owing to the tendency of tertiary hydrogen phthalates to hydrolyze on standing in the presence of moisture, 3.1 g. of this acid ester was immediately added to 3 g. of lithium aluminum hydride in 200 ml. of anhydrous ether. The mixture was stirred for six hours at room temperature and then hydrolyzed with 40 ml. of water. The clear, supernatant ethereal solution of the carbinol was decanted from the precipitated salt, and the salt was washed several times with fresh ether. The combined ether solutions were washed with water, with two portions of dilute sodium hydroxide, again with water and then were dried over potassium carbonate. The ether was removed at the aspirator and (+)-methylethylphenylcarbinol was obtained by evaporative distillation[9] at 35° (1 mm.): 1.2 g. (77%); $[\alpha]^{22}D$ +17.45° (α = +17.18, *l* = 1); $[M]^{22}D$ 26.21°; $n^{25}D$ 1.5160; d^{25}_4 0.984.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.81; H, 9.31.

Partially Resolved (−)-Methylethylphenylcarbinol.—The brucine salt of the mother liquors was decomposed with dilute hydrochloric acid, and the resulting hydrogen phthalate was obtained in a viscous form (37 g.) which slowly crystallized. This was taken up in benzene from which on standing at room temperature there was deposited 13 g. of crystalline acid ester: m.p. 114–115°; $[\alpha]^{24}D$ +4.44°. Cooling and concentration gave two additional crops of crystalline material totalling 7 g. whose specific rotation, when combined, was +11.84°. The hydrogen phthalate (19.5 g.) remaining in solution could not be crystallized and was cleaved with 10 g. of lithium aluminum hydride in 450 ml. of ether. Evaporative distillation of the carbinol from this reaction gave 6.5 g. (66%) of (−)-I: $[\alpha]^{26}D$ −14.56°; $n^{25}D$ 1.5169.

(5) These spectra were obtained through the generous coöperation of Professor Ralph S. Halford of Columbia University.

(6) All melting points are corrected. Optical rotations of carbinols were measured without solvent. The rotations of the hydrogen phthalates and of the brucine salts were determined in absolute ethanol.

(7) A. Klages, *Ber.*, **35**, 3506 (1902), reported b.p. 102° (14 mm.); $n^{25}D$ 1.5158; d^{22}_4 0.9845 for I.

(8) Note added in proof: M. P. Balfe, J. Kenyon and E. M. Thain, *J. Chem. Soc.*, **386** (1951), have currently reported m.p. 113–115° for the racemic hydrogen phthalate.

(9) Evaporative distillations of the carbinols were carried out in a modified Hickman still equipped with a cold finger and central take-off well, in order to avoid any decomposition into olefin.

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On Cyclic Intermediates in Substitution Reactions. II. Steric Effects in the Alkaline Hydrolysis of the Epimeric 3-Chloro-6//7-cholestanedicarboxylic Acids[1]

BY DONALD W. WUJCIAK,[2] ROBERT L. FELLER[3] AND JOHN F. LANE

Part I[4] of this series presented a study of the

(1) Taken, in part, from a thesis submitted by Donald W. Wujciak to the School of Chemistry, Rutgers University, in partial fulfillment of the requirements for the Senior Honors Program, 1950.

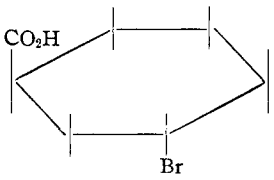
(2) Department of Chemistry, University of Minnesota.

(3) The Mellon Institute, Pittsburgh, Penna.

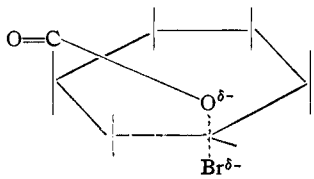
(4) J. F. Lane and H. W. Heine, THIS JOURNAL, **73**, 1348 (1951).

alkaline hydrolysis of some aliphatic bromoacids, in which the position of attachment of halogen ranged from α to γ, and which established that the reactivities increased in the order $\alpha < \beta \ll \gamma$. This increase in reactivity was interpreted as due to the increasingly strain-free character of the cyclic intermediate (lactone) formed.

While aliphatic γ-halogen acids may be expected uniformly to exhibit great reactivity toward alkaline hydrolysis, because of the essential strainlessness of the intermediate lactone, in a cyclic system, *e.g.*,

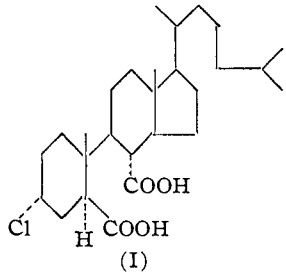


this enhanced reactivity should be displayed only by the *trans*-isomer, for which participation by the carboxylate ion involves the formation of a relatively strainless *cis*-lactone, *via* the transition state

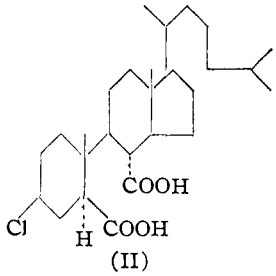


The structural influence on reactivity is quite analogous to that recently established[5] by Winstein and co-workers, for the isomeric 1-acetoxycyclohexyl-2-*p*-bromobenzenesulfonates. Here, participation by the acetoxyl group enhances the reactivity of the *trans* isomer over that of the *cis* isomer by a factor of 2.33×10^8.

The present paper deals with the relative reactivities in alkaline hydrolysis of two such isomeric cyclic acids: namely, the 3(α)- and 3(β)-chloro-6//7-cholestanedicarboxylic acids



(I)



(II)

Shoppee[6] has recently assigned reasonable configurations to these two acids, *viz.*, I to the "β" acid (m.p. 242°) of Windaus and Stein[7] and II to the "α" acid (m.p. 265°) of Windaus and von Staden[8] on the basis of their relationships to cholesteryl and cholestanyl chlorides. He has also given a lengthy discussion of the mechanism of their alkaline hydrolysis, the validity of which, in the light of the results obtained here, is open to some question.

(5) S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, **70**, 821 (1948).

(6) C. W. Shoppee, *J. Chem. Soc.*, 1032 (1948).

(7) A. Windaus and G. Stein, *Ber.*, **37**, 2629 (1904).

(8) A. Windaus and A. von Staden, *ibid.*, **54**, 1059 (1921).

Experimental

3(α) and 3(β)-Chloro-6//7-cholestanedicarboxylic Acids (I and II).—These acids were prepared from cholesterol by the conventional methods.[6,7,8] Acid I melted[9] at 242–243° (partial sublimation starting at 225°). Acid II melted at 266–268° (partial sublimation starting at 250°).

Anal. Calcd. for $C_{27}H_{45}O_4Cl$: Cl, 7.56. Found: I, Cl, 7.57; II, Cl, 7.76.[10]

Methods of Rate Measurement.—All measurements were carried out in a thermostated bath, the temperature of which was maintained within limits of ±0.02°. The rate of release of chloride ion from acid I at 30.3° (in solutions 0.001–0.002 *M* in I, 0.2 *M* in sodium bicarbonate and containing 6% dioxane) was followed electrometrically according to a recently described procedure of Swain and Ross.[11] Measurements on the acid II were conducted at 60.0° in more conventional fashion by withdrawing aliquot portions of solutions 0.004 *M* in II (as the ion) and either 0.085 *M* or 0.170 *M* in sodium hydroxide at various times, delivering them into excess of dilute nitric acid and then titrating the liberated chloride ion by the method of Volhard. (Acidification of aliquot portions of these alkaline solutions of II, after the reaction had come to completion, gave pure, sharply melting (217–218°) 3(α)-hydroxy-6//7-cholestanedicarboxylic acid, reported[6] m.p., 218–219°.)

Graphical treatments of typical rate data are shown in Figs. 1 and 2. A summary of the measurements on both acids follows.

Acid	Medium	No. of measurements	k_1 (sec.$^{-1}$)
I	0.2 *M* $NaHCO_3$ (6% dioxane) at 30.3°	8	$1.50 \pm 0.03 \times 10^{-3}$
II	0.170 *M* NaOH at 60.0°	2	$4.20 \pm 0.05 \times 10^{-6}$
	0.085 *M* NaOH +0.085 *M* $NaNO_3$ at 60.0°	2	$4.22 \pm 0.05 \times 10^{-6}$

Discussion

In interpreting the results it is of interest to convert the rates given in Table I to free energies of activation by means of the Eyring equation

$$-\Delta F^{\pm} = 2.303RT \log kh/kT$$

This gives $\Delta F^{\pm}_{I(303°)} = 21.5$ kcal.; $\Delta F^{\pm}_{II(333°)} = 27.6$ kcal. Although, strictly speaking, such parameters should be compared only at the same temperature, the literature[4,5,12] of solvolysis reactions of halides demonstrates that over a 30° range variations in $\Delta F^{\pm}$ are, at most, of the order of ±0.5 kcal. (*e.g.*, 20 e.u. $\geq \Delta S^{\pm} \geq$ − 20 e.u.). Hence, it may safely be inferred that in passing from II to its epimer I the barrier against ejection of chloride ion has been lowered by 6 ± 0.5 kcal., the reactivity enhanced by roughly ten-thousand fold. As pointed out in the introductory discussion this lowering of the barrier is most convincingly interpreted in terms of the ability of the carboxylate ion (at C_5) to participate in the displacement of the chlorine (at C_3) when the two groups are *trans* to each other. Whence the results may be regarded as a new and independent proof that the configurations are indeed those previously assigned by Shoppee[6] from other considerations.

Shoppee[6] concluded that the alkaline hydrolysis of I and II should proceed by the mechanism

(9) All melting points reported in this paper were determined on the Kofler micro hot-stage.

(10) Analysis by W. Mauser, Zürich, Switzerland.

(11) C. G. Swain and S. G. Ross, THIS JOURNAL, **68**, 618 (1946).

(12) E. D. Hughes and U. C. Shapiro, *J. Chem. Soc.*, 117 (1937); E. D. Hughes and K. A. Cooper, *ibid.*, 1183 (1937); A. R. Olson and R. J. Miller, THIS JOURNAL, **60**, 2687 (1938); A. F. Chadwick and E. Pacsu, *ibid.*, **65**, 392 (1943).

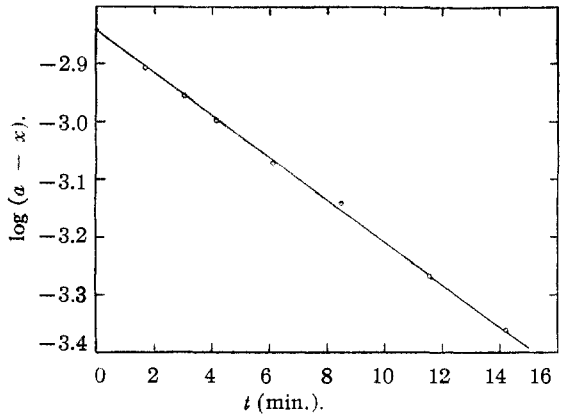


Fig. 1.—Evolution of chloride ion (x) with time at 30.3° in a solution 0.0015 M in 3(α)-chloro-6//7-cholestanedicarboxylate ion, 0.2 M in $NaHCO_3$ and containing 6% dioxane.

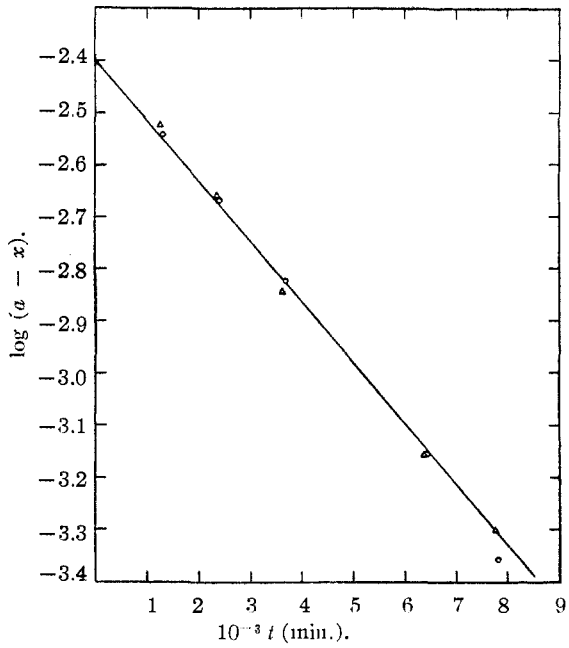


Fig. 2.—Evolution of chloride ion (x) with time at 60° in alkaline solutions 0.004 M in 3(β)-chloro-6//7-cholestanedicarboxylate ion: O, solution 0.170 M in NaOH; △, solution 0.085 M in NaOH and in $NaNO_3$.

S_N2 for (essentially) the following reasons: (a) if both I and II reacted by the (ionic) mechanism S_N1, the same mixture of epimeric 3-hydroxy-acids should result from each; (b) if intramolecular participation of carboxylate ion were operative in both hydrolyses, then the same hydroxy-acid should result in each case; (c) since, experimentally, each chloroacid gives a sterically pure hydroxyacid, formed with apparent Walden inversion at C_3, neither (a) nor (b) can provide the true explanation and the more reasonable assumption is hydrolysis by the mechanism S_N2.

Unfortunately this analysis overlooks the possibility (here demonstrated to be the fact) that the ions of both chloroacids can decompose by first-order mechanisms, but that for only one epimer (I) can participation by C_5–CO_2^- be effective.

The observed Walden inversions are of no little interest. Evidently they must be due to somewhat different influences operating for each isomer. Thus, inversion in the hydrolysis of I can probably be ascribed to initial formation of a lactonic acid (with Walden inversion) followed by alkaline cleavage of the lactone (without inversion). On the other hand, the complete inversion observed in the hydrolysis of II, which apparently proceeds by the (ionic) mechanism S_N1 is more likely connected either with shielding effects (of C_5–CO_2^- and departing Cl^-) which direct the entering hydroxide ion to the back of ring A, or with a greater thermodynamic stability for the *trans* (3(α)) hydroxy-acid.

Possible also is an intramolecular reaction involving C_3–CO_2^- in such a way as to produce (with inversion) initially a C_3–O–COC_3 lactone which subsequently cleaves (without inversion) to give the 3(α) hydroxy-acid. Inspection of molecular models shows that participation of C_3–CO_2^- in the hydrolysis of II would be possible, though attended by some strain and a very specific orientation of ring A relative to ring C. Participation by C_3–CO_2^- is sterically impossible in the hydrolysis of I.

While it is possible that some contribution by the mechanism S_N2 may have occurred under Shoppee's more alkaline conditions (4.5 N hydroxide) for the hydrolysis of II, its significance for this hydrolysis must remain questionable until experimentally verified. Certainly it is not at all necessary to assume it in accounting for the steric result.

That the mechanism S_N2 should operate under any conditions of alkalinity in the hydrolysis of I is hardly possible. The rate of such a process should be even less than that of the corresponding process for the hydrolysis of II (on account of interference by C_5–CO_2^- with a hydroxyl-ion trying to attack the face of ring A), hence should be even slower than the very sluggish first-order hydrolysis of II. Under no circumstances could it be expected to compete with the enormously rapid first-order hydrolysis of I.

A detailed study of the hydrolyses of these and other cyclic halogen acids under varying conditions of alkalinity and temperature is being undertaken in these laboratories and will be reported in subsequent papers of this series.

Acknowledgments.—The authors wish to express their thanks to the Rutgers University Research Council for a grant-in-aid in the year 1949 which assisted completion of a portion of this work and also to the White Laboratories, Inc., Newark, N. J., for supplying the cholesterol necessary for the preparation of the chloroacids.

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NEW COMPOUNDS

α,ω-Bis-γ-hydroxyvaleramidohexane

Hexamethylenediamine (58 g.) was added to γ-valerolactone[1] (100 g.) and warmed until solution took place.

(1) Obtained from Monsanto Chemical Co.