Participation of Water in the N→O Migration of Acyl Groups with Inversion of Configuration

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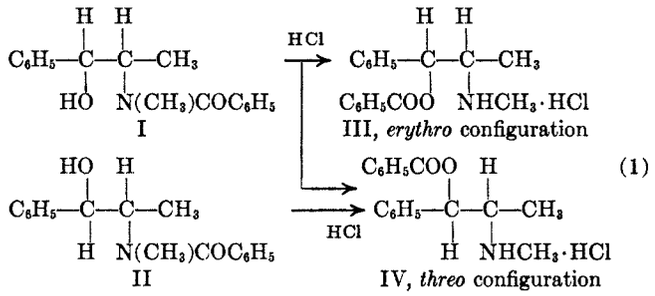
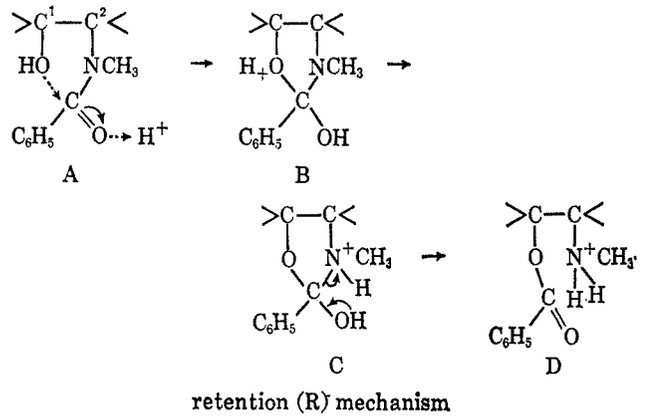
Acid-catalyzed N→O acyl migrations in N-benzoylephedrine and the diastereomeric N-benzoyl-ψ-ephedrine were carried out in an aqueous system enriched in the O^{18} isotope. Amino ester product with inverted configuration at the carbon bearing the acyloxy group had an enriched content of O^{18}, while that in which configuration was retained had a normal content of the isotope. The results support the concept that N→O acyl migration in derivatives of 2-aminoalkanols may take place by two competitive mechanisms, one leading to inversion, the other to retention, of configuration at the hydroxyl-bearing carbon atom, with water participating in the inversion process only.

A previous communication from this laboratory[1] reported the results of acid-catalyzed N→O acyl migrations in N-benzoyl-(−)-ephedrine (I) and the diastereomeric N-benzoyl-(+)-ψ-ephedrine (II) (eq 1). The

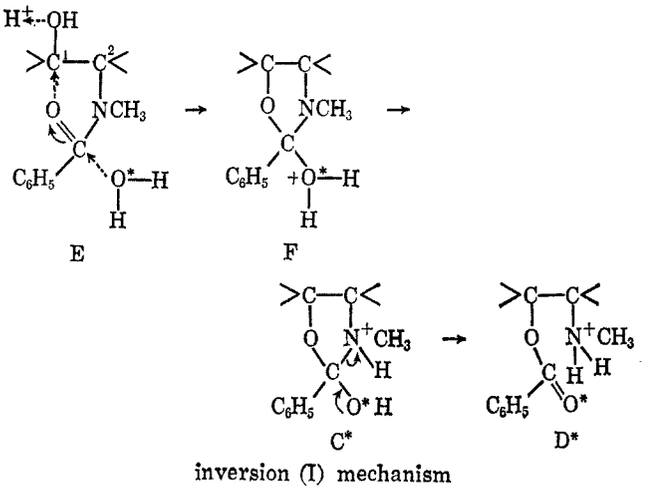


(1)

data seemed best explained on the basis that rearrangement in aqueous media may occur by two mechanisms, one leading to retention, the other to inversion,



retention (R) mechanism

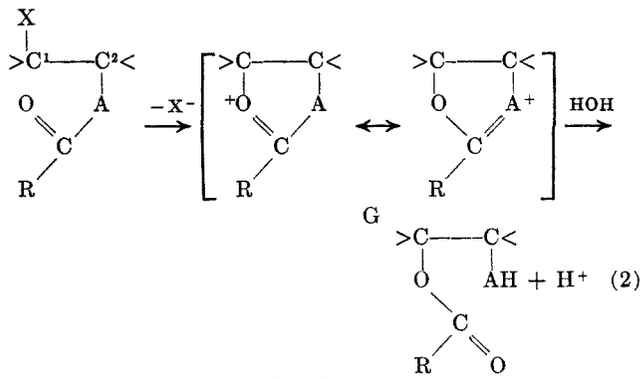


inversion (I) mechanism

of configuration at the hydroxyl-bearing carbon atom, with steric factors determining to a large extent the distribution of molecules rearranging by the competing mechanisms.

An essential difference between the postulated paths of reaction is that water is a reactant in the I mechanism only, with its oxygen (O*) bonding at carbonyl carbon either in concert with or subsequent to a backside attack of carbonyl oxygen at carbon one.[2]

There is strong analogy between the I mechanism and that accepted for certain replacement reactions with a neighboring group mechanism, shown in generalized form in eq 2 and carried out under somewhat different experimental conditions, in which inversion of configuration occurs at a carbon atom adjacent to one bearing an acyloxy or acylamino group. Although this and other analogies[3] enhance the credibility of the proposition, it was considered of importance to obtain direct evidence of the participation of water in the inversion process before attempting to interpret the results of future studies.[4]



(2)

a,[5] A = O; R = CH_3; X = Br
b,[6] A = O; R = CH_3; X = p-$CH_3C_6H_4OSO_2$
c,[7] A = O; R = CH_3; X = p-$BrC_6H_4OSO_2$
d,[8] A = NH; R = C_6H_5; X = p-$CH_3C_6H_4OSO_2$

(1) L. H. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949).

(2) Should the attack of carbonyl oxygen at carbon one precede that of water, an analog of G (eq 2) would be the immediate precursor of F.

(3) *Inter alia*, K. Koczka and G. Fodor, *Acta Acad. Sci. Hung.*, **13**, 89 (1957).

(4) It could be argued, perhaps with difficulty but also irrefutably, that acyl migration with inversion might occur by an alternative mechanism without obvious analogy, and that the oxygen atoms of the acyloxy group have the identities of those of the hydroxyamide.

(5) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2787 (1942); S. Winstein and R. M. Roberts, *ibid.*, **75**, 2297 (1953).

(6) S. Winstein, H. V. Hess, and R. E. Buckles, *ibid.*, **64**, 2796 (1942); S. Winstein, C. Hanson, and E. Grunwalt, *ibid.*, **70**, 812 (1948); S. Winstein, E. Grunwalt, R. E. Buckles, and C. Hanson, *ibid.*, **70**, 816 (1948).

(7) S. Winstein, E. Grunwalt, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(8) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949); S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

In the present work, N→O acyl migration was effected in I by heating with 5% hydrochloric acid prepared from water enriched in the O^{18} isotope (O* in I mechanism). The rearrangement product was separated into a *threo* fraction (IV, 76%) representing material which had undergone inversion at C-1 and an *erythro*-rich fraction (24%) composed of 88% III, in which configuration had been retained at this center, and 12% IV. Fusion of each fraction with dry pyridine hydrobromide at 220° provided efficient cleavage of the benzoyloxy group at the O-alkyl bond (eq 3).

$$C_6H_5CHCH(CH_3)NHCH_3\cdot HCl + C_5H_5N\cdot HBr \longrightarrow \underset{\displaystyle OCOC_6H_5}{\overset{|}{}}$$

$$C_6H_5COOH + C_6H_5\underset{\displaystyle C_5H_5NBr}{\overset{|}{CH}}CH(CH_3)NHCH_3\cdot HCl \quad (3)$$

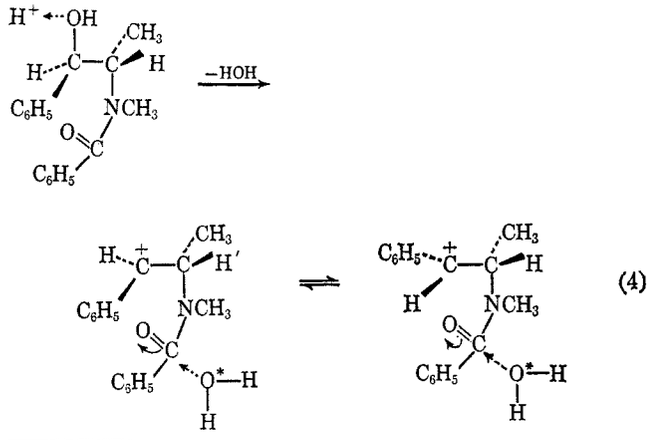
decomposition products?

The benzoic acid so formed was separated from nonacidic by-products under essentially anhydrous conditions by precipitating as ammonium benzoate from a benzene solution, then decomposing the salt into its constituents by boiling with toluene.

Acyl migration was also effected in II in the O^{18}-enriched system, and from the product (IV) in which there was complete retention of configuration, benzoic acid was obtained as described.

By mass spectrometric analysis the following values of the expression $10^2 \times C_6H_5CO^*O/C_6H_5COO$ were obtained for the three specimens of acid and, hence, from the rearrangement products from which they were derived: *threo* fraction from I, 1.7 ± 0.1; *erythro*-rich fraction from I, 0.6 ± 0.1; product from II, 0.4. The results are in agreement with the values 1.9 ± 0.1, 0.6, and 0.4, respectively, calculated on the basis of the stereochemical composition of each source, the O^{18} isotope fraction (1.7 ± 0.1%) in the water employed, and the proposed mechanisms.

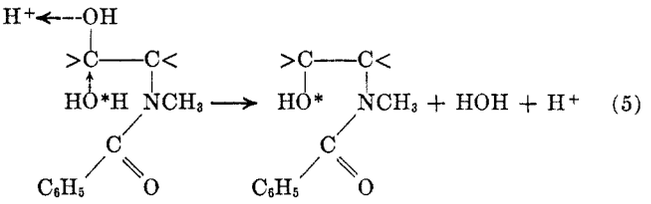
The findings rule out any possibility that the stereochemical results in the ephedrine series are related to the formation of a flattened carbonium ion at C-1 sufficiently long lived to permit bond formation between carbonyl oxygen and that atom in either of two ways as the ion rotates about its linkage with C-2 (eq 4).[9] In such a case, product with the original as well as with inverted configuration would show isotopic enrichment.



(4)

(9) Speaking against this possibility, *a priori*, is the fact that in the ψ-ephedrine series the reaction yields but one product.

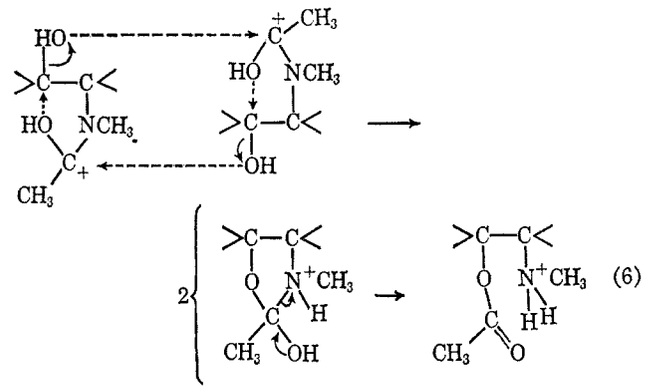
The results do not eliminate the possibility that inversion results from the attack of a proton at hydroxyl and a backside approach of water at carbon one (eq 5).



(5)

The resulting hydroxyamide could then rearrange according to the R mechanism[10] and yield product with isotopic enrichment. However, this alternative seems ruled out by the consideration that ephedrine, itself, and, possibly of more importance, N-mesitoylephedrine, in which it has not been possible to bring about N→O acyl migration,[11] are configurationally unaffected by the experimental conditions.

Although water participates in acyl migration with inversion when a component of the system, its presence is not necessary for the occurrence of the process, as is shown by the formation of O-acetyl-(+)-ψ-ephedrine hydrochloride by the action of heat on dry, crystalline N-acetyl-(−)-ephedrine hydrochloride.[12] Under such conditions, where the protonated hydroxyamide molecules are in close proximity in the solid or fused state, it would appear possible for the hydroxyl group of one molecule to act as electron donor to the carbonyl carbon of another in a pairing of molecules (eq 6) or in a type of chain reaction involving a number of molecules.



(6)

Experimental Section

Water enriched in O^{18} was purchased from Bio-Rad Laboratories. Mass spectrometric analysis showed the fraction of this isotope to be 1.7 ± 0.1%. Hydrochloric acid was prepared by passing hydrogen chloride over the agitated surface of the water until the content of gas was 10.1 g/100 ml as determined by titrimetry.

Pyridine hydrobromide was prepared by mixing the calculated quantities of reagent pyridine and 48% hydrobromic acid and removing the water by azeotropic distillation with benzene. It was stored *in vacuo* over silica gel.

(+)-*threo*-1-Chloro-1-phenyl-2-(N-methylbenzamido)propane (V).—Five grams of (+)-*threo*-1-chloro-1-phenyl-2-methylaminopropane hydrochloride, mp[13] 193.5–195° dec, $[\alpha]^{25}D$ +116°

(10) The possibility has been considered that inversion takes place prior to acyl migration: G. Fodor, V. Bruckner, J. Kiss, and G. Ohegyi, *J. Org. Chem.*, **14**, 337 (1949).

(11) L. H. Welsh, unpublished work.

(12) L. H. Welsh, *J. Am. Chem. Soc.*, **69**, 128 (1947).

(13) Varies with rate of heating; capillary specimen immersed in bath at a temperature 10° below the melting point and rising at an average rate of 1°/min.

(*c* 5, H_2O) (lit.[14] mp 201°, $[\alpha]^{20}D$ +116.6°), prepared from thionyl chloride and (−)-ephedrine hydrochloride,[14] was added to a solution of 2.80 ml (1.05 equiv) of benzoyl chloride in 50 ml of U.S.P. chloroform in a separatory funnel. Sodium bicarbonate (5.50 g, 2.9 equiv) and 50 ml of water were added and the mixture was shaken until effervescence ceased (4 min) and occasionally during 5 min thereafter. The extract was filtered and the aqueous phase was extracted twice more with 50-ml portions of chloroform. Solvent was removed on the steam bath and the residue was powdered and triturated with 100 ml of 30–60° petroleum ether. The system was chilled to −10° and the crude material (6.36 g, 97.3%) was filtered off and boiled with 190 ml of *n*-hexane. The hot solution was filtered to remove a small amount of fine, white solid and cooled slowly to −10°, and the product was filtered off: 5.74 g (87.4%), mp 89–91°, $[\alpha]^{22}D$ +146.5° (*c* 1.5, U.S.P. $CHCl_3$). After two additional recrystallizations the colorless rods showed mp 90.5–91.5°, $[\alpha]^{21}D$ + 147.0°.

Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 70.96; H, 6.23; N, 5.13.

This procedure is a significant improvement over that used to prepare the racemic substance;[15] the reaction requires only a few minutes instead of 48 hr and the yield from it is some 12% higher.

O-Benzoyl-(−)-ephedrine Hydrochloride (III).—One and one-half grams of V was refluxed with 7.5 ml of 2 *N* hydrochloric acid. The system became homogeneous after 6 min and was boiled for an additional 9 min. The cooled solution was quantitatively transferred to a separator with small portions of 2 *N* acid and extracted six times with 20-ml portions of chloroform. The residue from the filtered extracts was recrystallized by dissolving in 5 ml of absolute ethanol and adding 20 ml of absolute ether: 1.51 g (95%), $[\alpha]^{24}D$ +73.5° (*c* 1.5, H_2O). After three more recrystallizations it showed mp[13] 191.5–193° dec, $[\alpha]^{24}D$ +73.8° (*c* 1.5, H_2O) and +92.5° (*c* 1.5, U.S.P. $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.82; H, 6.30; N, 4.65.

The reaction[16] is probably complete when the system becomes homogeneous. Prolonged refluxing, as used[15] in preparing the racemic substance, lowers the yield by hydrolyzing the product.

On undergoing O→N acyl migration,[1] III quantitatively yielded I, which, without purification, showed mp 110–110.5°, $[\alpha]^{24}D$ −54.8° (*c* 4, U.S.P. $CHCl_3$) (lit.[1] mp 110–110.5°, $[\alpha]^{20}D$ −54.8°).

O-Benzoyl-(+)-ψ-ephedrine Hydrochloride (IV).—Two grams of II and 30 ml of 5% hydrochloric acid were refluxed together for 7 min. The clear solution was cooled for 2 hr at 2° and the crystals were filtered off, washed with a little cold 5% acid, and dried, yielding 2.19 g (96%). After recrystallization from absolute ethanol (15 ml/g, 90% recovery), it showed mp[13] 208.5–209.5° dec, $[\alpha]^{25}D$ −16.2° (*c* 1.5, H_2O) and −44.3° (*c* 1.5, U.S.P. $CHCl_3$). All values were unchanged by additional recrystallization.

Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; Cl, 11.59; N, 4.58. Found: C, 67.02, 67.00; H, 6.26, 6.41; Cl, 11.47; N, 4.54.

By O→N acyl migration IV quantitatively yielded II, which, without purification, showed mp 137–137.5°, $[\alpha]^{26}D$ +134.3° (*c* 3, U.S.P. $CHCl_3$) (lit.[1] mp 137–137.5°, $[\alpha]^{20}D$ +135.2°).

N→O Acyl Migration in O^{18}-Enriched Water.—In a 250-ml erlenmeyer flask 3.20 g of I and 25 ml of isotopically enriched water were heated under reflux in the presence of a few tared glass beads. Through the condenser 25 ml of the enriched 10% hydrochloric acid was added at a rate that did not interrupt boiling. Refluxing was continued for 5 min longer than the 5.5 min required to obtain homogeneity. The solution was quickly cooled, seeded with IV, and kept at 2° for 3 hr, and the crystals were filtered off and washed with three 5-ml portions of ice-cold enriched 5% acid with which the reaction flask had been rinsed. The filter cake was sucked dry then kept *in vacuo* over silica gel and sodium hydroxide for 3 days, yielding 2.68 g, $[\alpha]^{26}D$ −42.9° (*c* 1.5, U.S.P. $CHCl_3$), corresponding to a composition[17] of 99% IV and 1% III (*threo* fraction from I).

The combined filtrate and washings were quantitatively transferred to a separator with the aid of three 5-ml rinses with enriched 5% acid and extracted with six 85-ml portions of chloroform. The powdered residue from the filtered extracts was triturated thoroughly with 10 ml of absolute ether (to remove *ca.* 30–40 mg of benzoic acid formed by hydrolysis of III and IV), then filtered off and washed well with ether. After drying for 5 days *in vacuo* over silica gel the fraction (0.860 g) showed $[\alpha]^{26}D$ +74.8° (*c* 1.5, U.S.P. $CHCl_3$), corresponding to 87.8% III and 12.2% IV[17] (*erythro*-rich fraction from I). The infrared spectrum of the material agreed with that of a prepared mixture of this composition.[18]

The total yield of III and IV was 97.5%. That highly reproducible results can be obtained with the procedure is shown by the additional data from duplicate runs in ordinary 5% acid: *threo* fraction 2.70 g (99.4% *threo*), 2.70 g (99.1% *threo*); *erythro*-rich fraction 0.844 g (87.3% *erythro*), 0.853 g (87.7% *erythro*); total yield 97.5 and 97.9%.

The rearrangement of II was carried out in enriched acid as described for the preparation of IV.

Cleavage of Ester Hydrochlorides with Pyridine Hydrobromide.[19]—One gram of *threo* fraction from I was intimately mixed with 1.57 g (3 equiv) of the pyridine salt in an 18 × 150 mm test tube. After standing for 48 hr *in vacuo* over silica gel, the mixture was packed into a firm mass, and the tube, with the mixing rod, was immersed to a depth of 65 mm in a 700-ml silicone bath maintained at 220 ± 2°. The mass was worked with the rod until liquefaction was complete, after which the system was maintained at bath temperature for 1 hr. A gentle evolution of gas, apparently hydrogen halide, occurred during the first 30 min.

The same procedure was followed with the *erythro*-rich fraction from I and the product from II, except in the former case a 0.840-g sample and a proportionately smaller amount of pyridine salt were used.

The tube was cooled, the resulting largely crystalline mass was triturated thoroughly with 10 ml of absolute ether, and the extract was decanted. The extraction was repeated twice, and the filtered extracts were evaporated cautiously (to avoid condensation of moisture) until the brown, semicrystalline residue had no odor of ether. The crude product was dissolved in a little benzene, solvent was removed by warming, and the residue was transferred to a 25-ml erlenmeyer flask with a total of 10 ml of benzene. Anhydrous ammonia was passed over the surface of the swirled solution until precipitation was complete. The fine, white crystals of ammonium benzoate were filtered off, washed thoroughly with benzene and then with petroleum ether, and air dried for several hours before being left over silica gel for 48 hr. Yields from the three specimens of amino ester salts were in the range of 76–79%.

The ammonium benzoate was heated in a 25-ml erlenmeyer flask with 8 ml of dry toluene so that the vapors refluxed near the mouth of the vessel. After 30 min there remained but a small amount of fine solid which did not disappear with continued boiling. It was filtered off and washed with benzene. Evaporation of the filtrate, with warming, until there was no odor of solvent gave a white residue of benzoic acid which was dried for 24 hr over silica gel. Yields from the three specimens of ammonium salt amounted to 96–98%. The products melted at 122.5–123° and each gave an infrared spectrum[18] identical with that of standard benzoic acid.

Attempts to obtain benzoic acid from III and IV by hydrogenolysis with palladium–charcoal and by pyrolysis at 400° were unsuccessful.

Mass Spectrometric Analyses.—A Consolidated Electrodynamics Corp. Model 21-103 C analytical mass spectrometer was used in measurements on the water and benzoic acid specimens.

(14) H. Emde, *Helv. Chim. Acta*, **12**, 384 (1929).

(15) H. Pfanz and H. Wieduwilt, *Arch. Pharm.*, **288**, 563 (1955).

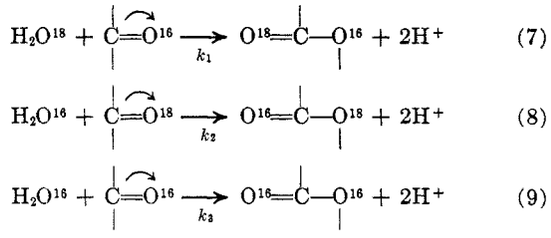
(16) This migration of the benzoyl group in V, with the participation of water and replacement of halogen at C-1 with inversion, evidently occurs by a process related to that shown in eq 2 and to the I mechanism. This requires bringing the phenyl and methyl groups on C-1 and C-2 into a *cis* relationship in the transition state, a situation not realized in N→O acyl migration in II, which, unlike V, has the alternative of rearranging by the sterically highly favored R mechanism.[1]

(17) Specific rotations of III and IV in chloroform vary appreciably with concentration. A standard curve was used in determining composition.

(18) Determined by Mr. Oscar R. Sammul of this laboratory.

(19) The basis of this reaction is the work of D. Klaman [*Monatsh.*, **83**, 1398 (1952)] who used pyridine hydrochloride with simple esters. In applying the procedure to the present substances, preliminary studies with the hydrochloride gave maximum yields of *ca.* 63% at an optimum temperature of *ca.* 220°. Using the hydrobromide at this temperature raised the range to 75–80% as determined by an efficient analytical method. No significant difference was noted between yields from pure III and IV.

The theoretical value of the ratio, $C_6H_5CO^*O/C_6H_5COO$, in product of inverted configuration (*threo* fraction from I) is based on the following equations.



(7)

(8)

(9)

The relative amounts of the three benzoyloxy species formed in the reactions will be in the same proportion as the relative rates of the reactions. In calculating the relative rates, the relative concentrations of total isotopic species of water and of carbonyl oxygen in the hydroxyamide are constant[20] and may be disregarded. If it is assumed that there is no isotope effect, *i.e.*, that the specific reaction rates, k_1, k_2, and k_3, are equal, each relative rate, v, or abundance of benzoyloxy species, may be represented as equal to the product of isotopic abundances.

(20) In view of the low value of the ratio of hydroxyamide to water (1:230), one can ignore the effect of change in the original abundance of O^{18} in the aqueous system owing to the formation of water of normal isotopic composition in the displacement of the hydroxyl group at C-1.

For eq 7, $v_1 = (0.017 \pm 0.001) \times 0.998 = 0.017 \pm 0.001$, $^{18}O{=}CO^{16}$; for eq 8, $v_2 = (0.983 \pm 0.001) \times 0.002 = 0.002$, $^{16}O{=}CO^{18}$; for eq 9, $v_3 = (0.983 \pm 0.0001) \times 0.998 = 0.981 \pm 0.001$, $^{16}O{=}CO^{16}$.

In mass spectrometry, $^{18}O{=}C{-}O^{16}$ and $^{16}O{=}C{-}O^{18}$ are equivalent; hence, the theoretical value, 0.019 ± 0.001, of the ratio, $C_6H_5CO^*O/C_6H_5COO$, is based on the sum of the abundances of the two species.

The theoretical value ($0.006 = 0.019 \times 0.12 + 0.004 \times 0.88$) for the ratio of benzoyloxy species in the *erythro*-rich fraction from I is derived from that calculated for inverted substance, the value 0.004 characteristic of normal benzoic acid and expected in substance formed *via* the R mechanism, and the polarimetrically determined composition of the fraction.

Acknowledgments.—The author is grateful for a critical review of the manuscript provided by the late G. Forrest Woods, Professor of Chemistry, University of Maryland. For microanalyses, he acknowledges his indebtedness to Dr. W. C. Alford and his associates, Microanalytical Laboratory, National Institutes of Health. For helpful discussions on mass spectrometry, he wishes to thank Mr. E. E. Hughes, Analytical Chemistry Division, National Bureau of Standards, who also performed the analyses.

Preparation and Reactions of Ferrocenyl(trichloromethyl)carbinol and of Metal Derivatives of Ferrocene

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The syntheses of some new derivatives of ferrocene employing condensation and metalation reactions are described. Ferrocenyl(trichloromethyl)carbinol has been prepared by four methods: from ferrocene by a Friedel–Crafts reaction with chloral, from chloromercuriferrocene and chloral with aluminum chloride, from ferrocenylmagnesium bromide and chloral, and from ferrocenecarboxaldehyde and chloroform. The ferrocenylmagnesium bromide was prepared from lithioferrocene and magnesium bromide. The carbinol was converted into α-methoxyferroceneacetic acid by treatment with potassium hydroxide in methanol. The methoxy acid was also prepared in one step from ferrocenecarboxaldehyde, bromoform, and methanolic potassium hydroxide. Lithioferrocene reacts normally with ethylene oxide, propylene oxide, and styrene oxide, but not with chloral, and a halogen–metal interchange reaction occurs with 3,3,3-trichloro-1,2-epoxypropane.

It has been shown that ferrocenecarboxaldehyde enters into many condensation reactions typical of aromatic aldehydes.[2,3] In the present work, a new condensation reaction was studied, namely the one-step conversion of an aromatic aldehyde to an α-methoxyarylacetic acid by treatment with bromoform and methanolic potassium hydroxide.[4] From ferrocenecarboxaldehyde (I) the α-methoxyferroceneacetic acid (II) was formed in 73% yield. Almost all α-methoxyphenylacetic acids are strong plant-growth regulators, but the α-methoxyferroceneacetic acid was found to be inactive when tested on bean plants;[5] strongly indicating that plants metabolize the ferrocenyl group more readily than the phenyl group.

Ferrocenecarboxaldehyde was found to react with chloroform, using potassium *t*-butoxide in *t*-butyl alcohol as the base, to form ferrocenyl(trichloromethyl)-carbinol (III), the intermediate in the one-step synthesis of α-methoxyferroceneacetic acid (II). On treatment with methanolic potassium hydroxide, III gave the α-methoxyferroceneacetic acid (II) in 57% yield.

The reaction of ferrocene with a twofold excess of chloral in the presence of aluminum chloride was investigated as an alternative route to the trichloromethylcarbinol (III). Methylene chloride was used as the solvent. The best yield obtained was 21% of theory. Two per cent of the disubstitution product, 1,1′-di(2,2,2-trichloro-1-hydroxyethyl)ferrocene, was obtained and 60% of the starting ferrocene was recovered. In this reaction, the solvent and the amount of aluminum chloride employed are critical; with carbon disulfide as the solvent, only traces of products could be isolated. With methylene chloride as the solvent, too little aluminum chloride results in no reaction, and more than the optimum amount (0.25 mole/mole of chloral) resulted in the formation of an olefin as the major product in 15% yield. The olefin is tentatively assigned the formula (2,2-dichlorovinyl)-ferrocene (IV). The mechanism by which this is formed probably involves the intermediate formation of (1,2,2,2-tetrachloroethyl)ferrocene and the subse-

(1) American Cyanamid Teaching Fellow, 1960–1961.
(2) K. Plesske, *Angew. Chem. Intern. Ed. Engl.*, **1**, 323 (1962).
(3) M. D. Rausch, *Can. J. Chem.*, **41**, 1289 (1963).
(4) W. Reeve and E. L. Compere, *J. Am. Chem. Soc.*, **83**, 2755 (1961).
(5) We are indebted to Dr. J. W. Mitchell and co-workers of the U. S. Department of Agriculture, Beltsville, Md., for studying the plant growth regulating properties of this compound.