Notes

Hydrogenation of Pyridinecarboxylic Acids with Platinum Catalyst

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The inhibiting effect of the pyridine nitrogen and the more basic piperidino nitrogen on the catalyst during hydrogenation is well known.[1] It has been shown that the pyridine compound must be present as a salt or that hydrogenation of the base must be carried out in acidic medium to overcome this catalyst poisoning.[2]

In some recent work in this laboratory[3] we found that uptake of hydrogen proceeded smoothly during conversion of the isomeric pyridinecarboxylic acids in water in the presence of rhodium catalyst. While the yield of 3-piperidinecarboxylic acid was low due to decarboxylation, nevertheless the theoretical amount of hydrogen was absorbed.

Since the carboxyl group should in effect tend to neutralize the inhibitory effect of the basic piperidino nitrogen, it appeared to be of interest to attempt hydrogenation of the same acids with platinum oxide in a neutral medium.

Low pressure reductions were indeed successful with picolinic and isonicotinic acids. Nicotinic acid underwent decarboxylation during hydrogenation as observed by us with rhodium and previously with ruthenium catalyst.[4] In this work, however, uptake of hydrogen was never more than 35% of theory, and only piperidine and starting material were obtained.

The neutralizing effect of the carboxy group was enhanced by the shielding effect in 2-position, picolinic acid being completely reduced in four to five hours compared to isonicotinic acid which was only 50% complete in the same length of time.

This study would suggest then that pyridines containing a carboxyl group, such as the isomeric pyridylacetic acids, could be hydrogenated with platinum oxide catalyst, eliminating the use of the acid medium so necessary with other pyridines.

Experimental

Piperidine-2-carboxylic Acid.—A mixture of 12.3 g. (0.1 mole) of picolinic acid in 150 cc. of water was hydrogenated under 2.5 atm. in the presence of 0.25 g. of platinum oxide. Uptake of hydrogen was complete in 4–5 hr. The solution was filtered and concentrated to dryness. The residue was then treated with absolute alcohol and filtered. On drying 12.7 g. (97%) of material was obtained; It melted at 276°.[5] A mixed melting point with an authentic sample was not depressed.

Piperidine-4-carboxylic acid was obtained in the same manner. Uptake of hydrogen was about 50% in 4–5 hr., but was complete in less than 18 hr. Yield of product melting at 336°[6] was 81.5%. A mixed melting point with isonicotinic acid (m.p. 317°) caused a drop to 230–240°, while a mixed melting point with an authentic sample was not depressed.

Hydrogenation of Nicotinic Acid.—Reduction was carried out in the same manner. However, uptake of hydrogen was about 35%, whether the reaction was carried out at room temperature or at 60°. The mixture was made basic and filtered. The alkaline solution was steam distilled into aqueous hydrochloric acid. The acid solution was then concentrated and the solid isolated. It weighed 2.0 g. (18%) and was identified as piperidine hydrochloride by its melting point and infrared spectrum. The alkaline solution after steam distillation was neutralized to pH 4.1 to recover nicotinic acid.

(1) E. B. Maxted and A. P. Walker, *J. Chem. Soc.*, 1093 (1948).
(2) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).
(3) M. Freifelder, R. M. Robinson, and G. R. Stone, *J. Org. Chem.*, **27**, 284 (1962).
(4) M. Freifelder and G. R. Stone, *ibid*, **26**, 3805 (1961).
(5) R. Willstätter, *Ber.*, **29**, 389 (1896), gives 274.5–275.5°.
(6) K. Freudenberg, *ibid.*, **51**, 1668 (1918), reports 325°.

C-6 Hydroxylated Steroids. III. A New Preparative Method[1]

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Current interest in metabolites having a C-6 hydroxyl function[2] has stimulated our efforts to establish a facile chemical approach to the synthesis of these compounds.

We have previously outlined a preparation of 9α-fluoro-6β,11β,17α,21-tetrahydroxypregn-4-ene-3,20-dione[3] which comprised the reaction of 21-acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione with trimethyl orthoformate to yield the crude $\Delta^{3,5}$-methyl enol ether. The latter

(1) For the previous paper in this series see, R. Littell and S. Bernstein, *J. Org. Chem.*, **27**, 2544 (1962).
(2) Leading references have been collected in ref. 1.
(3) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *J. Org. Chem.*, **26**, 974 (1961).

was then oxidized with monoperphthalic acid to afford the 21-acetate-6β-hydroxy-Δ^4-3-one which on treatment with aqueous methanolic potassium carbonate was converted into the desired tetrol. Extension of the enol ether–peracid reaction sequence to a variety of other compounds has shown (although the yields are low) that this method may have a broader utility than any of the previously described chemical approaches to C-6 hydroxylation.[4] In Table I are summarized the results obtained for representative members of a series of compounds which have been studied. It may be seen (Table I) that the attack of peracid on the enol ether (generally used in the crude form) does not give the 6β-hydroxy epimer exclusively, although this predominates in the reaction mixture. In most cases the isolation of the 6α-hydroxy epimer[5] was achieved by chromatography.

The mechanism involved in the formation of 6-hydroxy-Δ^4-3-ones from $\Delta^{3,5}$-enol ethers is not completely understood and the several possibilities warrant investigation.

Experimental[6]

The following examples are given to illustrate the various methods used in the preparation of compounds that are listed in Table I.

21-Acetoxy-3-methoxypregna-3,5-dien-20-one.—Four drops of 72% perchloric acid were added to a reaction mixture containing 2 g. of 21-acetoxypregn-4-ene-3,20-dione, 20 ml. of dry dioxane, 2 ml. of trimethyl orthoformate and 4 drops of absolute methanol. After 2 min. at room temperature, the reaction was terminated by the addition of 1 ml. of pyridine and then the reaction mixture was poured into water. The solid was collected by filtration and dried to give 2.1 g. of the crude enol ether. A portion (0.25 g.) of this material was crystallized from acetone–petroleum ether and afforded 0.19 g. of an analytically pure sample, m.p. 153–155°.

21-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione.—A solution of 1.85 g. of 21-acetoxy-3-methoxypregna-3,5-dien-20-one in 150 ml. of ether was oxidized with 20 ml. of an ethereal monoperphthalic acid solution (65 mg./ml.). After standing at room temperature for 20 hr., the reaction mixture was washed with a saturated aqueous sodium bicarbonate solution and then with a saturated saline solution. The residue obtained upon evaporation of the dried solution was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The eluates obtained with 6% acetone–methylene chloride (4 × 50 ml.) and 8% acetone–methylene chloride (4 × 50 ml.) were combined and evaporated. The residue was crystallized from acetone–petroleum ether to give 0.33 g. of the 6β-hydroxy compound, m.p. 190–192°.

21-Acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione, 21-Acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione, and 21-Acetoxy-6β,17α-dihydroxypregna-4,9(11)-diene-3,20-dione.—A suspension of 10 g. of 21-acetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione in 100 ml. of dioxane, 10 ml. of trimethyl orthoformate, and 0.1 ml. of absolute methanol was stirred rapidly and 8 drops of 72% perchloric acid were added to the reaction mixture. After 2 min. the dark green reaction mixture was rapidly filtered into a flask containing 2 ml. of pyridine. In this manner there was recovered 0.5 g. of unchanged starting material. The filtered solution (now light yellow in color) was poured into water and the precipitated material was collected and dissolved in ether. The solution was washed with a saturated saline solution and dried.

Removal of the ether *in vacuo* gave 9.1 g. of a glass which showed by infrared analysis a small amount of Δ^4-3-one. The addition of 100 ml. of ether to this residue dissolved the enol ether and left undissolved 0.1 g. of hydrocortisone acetate. The ether solution was treated with an ethereal monoperphthalic acid solution (70 ml., 65 mg./ml.) and the reaction mixture was kept at 0° for 68 hr., at which time the solid which had separated was collected by filtration, 0.575 g., m.p. 201–206°. Crystallization from acetone–hexane afforded 0.215 g. of 6β-hydroxyhydrocortisone 21-acetate, m.p. 204–206°, resolidifying and remelting at 222–224°.

The ether filtrate was washed with a saturated sodium bicarbonate solution and then with a saturated saline solution, dried and evaporated to give 7.6 g. of a crude residue. *One half* (3.8 g.) of this material was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The material eluted with 8% acetone–methylene chloride (4 × 100 ml.) was identified as hydrocortisone acetate. A second crystalline fraction was isolated from the late 10% acetone–methylene chloride (3 × 100 ml.) and the early 12% acetone–methylene chloride (6 × 100 ml.) eluates. Crystallization from ethyl acetate–heptane afforded an additional 0.20 g. of 21-acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione, m.p. 204–206°, resolidifying then remelting at 219–221°.

A third crystalline fraction was obtained from the late 15% acetone–methylene chloride (4 × 100 ml.), and 20% acetone–methylene chloride (8 × 100 ml.) eluates. Two crystallizations from acetone–hexane yielded 0.245 g. of 21-acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione, m.p. 212–214°.

The presence of 21-acetoxy-6β,17α-dihydroxypregna-4,9-(11)-diene-3,20-dione was detected in the above reaction mixture in varying amounts depending on the condition used for enol ether formation. Longer reaction time at this stage led to the formation of increased yields of this stripped product. It appeared in the 8% acetone–methylene chloride and 10% acetone–methylene chloride eluates as a crystalline material, and was eluted before 6β-hydroxyhydrocortisone 21-acetate, but after hydrocortisone acetate. Crystallization from ethyl acetate–heptane yielded the diene, m.p. 214–215°.

6β,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione (6β-Hydroxyhydrocortisone).—A suspension of 0.20 g. of 21-acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione in 20 ml. of methanol was briskly agitated by a stream of nitrogen. To this was added 0.32 ml. of methanolic 3.15 *N* sodium methoxide solution. Nitrogen agitation was continued for 30 min. and then 0.05 ml. glacial acetic acid was added. The reaction mixture was evaporated *in vacuo* and then refluxed briefly with 75 ml. of acetone and filtered. The acetone was then displaced with petroleum ether and there precipitated 0.12 g. of the tetrol, m.p. 241–243°. Another crystallization from acetone–petroleum ether yielded 0.097 g., m.p. 236–239°.

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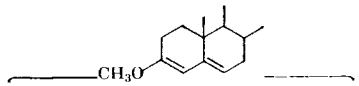
(4) (a) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954); (b) F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954); (c) S. Bernstein, W. S. Allen, C. E. Linden, and J. Clemente, *ibid.*, **77**, 6612 (1955); (d) S. Bernstein and R. Littell, *J. Org. Chem.*, **25**, 313 (1960); (e) S. Bernstein and R. Littell, *ibid.*, **26**, 3610 (1961).

(5) We have observed that peracid attack on $\Delta^{3,5}$-enol acetates[4a] also may give rise to a mixture of the epimeric 6-hydroxy compounds.

(6) Melting points are uncorrected. The ultraviolet spectra were determined in methanol and the rotations in the solvents specified. The petroleum ether fraction used had a b.p. 60–70°. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption and optical rotation data. We wish also to thank Louis B. Brancone and associates for the analyses.

TABLE I

DATA ON PREPARATION AND CHARACTERIZATION OF 6-HYDROXYLATED STEROIDS



Compound	M.p., °C.	[α]D (1% pyridine in chloroform)	λmax mμ (ε)	Product[b]	Method of isolation[a]	Yield,[c] %	M.p., °C.	[α]D[d]	λmax mμ (ε)
17β-Acetoxyandrost-4-en-3-one	176–180[e]	− 152	234 (19,500)	17β-Acetoxy-6β-hydroxyandrost-4-en-3-one[f]	C	33	210–212	+ 21 (C)	236 (14,600)
				17β-Acetoxy-6α-hydroxyandrost-4-en-3-one[g]		5	225–226	+ 8 (C)	241 (15,700)
17β-Hydroxyandrost-4-en-3-one		Not isolated		17β-Hydroxy-6β-hydroxyandrost-4-en-3-one[h]	C	20	213–215	+ 30 (C)	236 (13,700)
				17β-Hydroxy-6α-hydroxyandrost-4-en-3-one[i]		2	174–175	+ 9 (C)	241 (14,600)
16α,17α-Epoxypregn-4-ene-3,20-dione	192–194[j]	− 49.8	238 (19,800)	16α,17α-Epoxy-6β-hydroxypregn-4-ene-3,20-dione[k]	R	44	269–271		236 (13,500)
11α-Hydroxypregn-4-ene-3,20-dione		Not isolated		6β,11α-Dihydroxypregn-4-ene-3,20-dione[l]	C	8	248–251	+137 (C)	237 (12,800)
				6α,11α-Dihydroxypregn-4-ene-3,20-dione[m]		2	258–261	+162 (C)	242 (14,600)
16α-Hydroxypregn-4-ene-3,20-dione		Not isolated		6β,16α-Dihydroxypregn-4-ene-3,20-dione[n]	C	5	235–236	+ 75 (C)	235 (14,500)
21-Acetoxypregn-4-ene-3,20-dione	153–155[o]	+ 3.6	240 (19,700)	21-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione[p]	C	18	190–192	+107 (C)	236 (13,800)
				6β,21-Dihydroxypregn-4-ene-3,20-dione[q]			*211–212*	*+108 (C)*	*235 (14,900)*
21-Acetoxy-11β-hydroxypregn-4-ene-3,20-dione	201–206[r]	− 10.3	239 (20,900)	21-Acetoxy-6β,11β-dihydroxypregn-4-ene-3,20-dione[s]	R	10	212–216	+190 (P)	235 (16,000)
				6β,11β,21-Trihydroxypregn-4-ene-3,20-dione[t]			*245–248*		*237 (13,000)*
21-Acetoxy-17α-hydroxypregn-4-ene-3,20-dione	188–190[u]	− 91.6	239 (22,500)	21-Acetoxy-6β,17α-dihydroxypregn-4-ene-3,20-dione[p]	R	35	270–272	+ 49 (P)	236 (13,900)
				6β,17α,21-Trihydroxypregn-4-ene-3,20-dione[w]			*229–230*	*+ 39 (P)*	*236 (13,700)*
21-Acetoxy-17α-hydroxypregn-4-ene-3,11,20-trione	190–192[x]	+ 15.4	238 (18,200)	21-Acetoxy-6β,17α-dihydroxypregn-4-ene-3,11,20-trione[y]	R	7	267–268	+130 (P)	231 (15,400)
				6β,17α,21-Trihydroxypregn-4-ene-3,11,20-trione[z]			*241–242*	*+122 (P)*	*231 (14,300)*
21-Acetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione		Not isolated		21-Acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione[aa]	C	7	219–221	+100 (P)	236 (14,100)
				6β,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione[bb]			*236–239*	*+ 89 (P)*	*235 (13,800)*
				21-Acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione[cc]		4	212–214	+133 (P)	241 (15,400)
				6α,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione[dd]			*216–217*		
				21-Acetoxy-6β,17α-dihydroxypregna-4,9(11)-diene-3,20-dione[ee]		..	214–215	+ 57 (C)	235 (14,600)
				6β,17α,21-Trihydroxypregna-4,9(11)-diene-3,20-dione[ff]			*236–238*	*+ 34 (P)*	*235 (14,900)*

TABLE I (*Continued*)

[a] C = chromatography, R = recrystallization of the reaction mixture. [b] Compounds in italics were obtained by hydrolysis of the corresponding 21-acetates. [c] Yields of recrystallized material based on enol ether, except where not isolated, otherwise on Δ^4-3-one. [d] Solvent: C = chloroform, P = pyridine. [e] Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.67; H, 9.76. [f] Ref. 2, m.p. 211–212°, $[\alpha]D$ +27°, λ_{max} 236 mμ (log ε 4.14). [g] Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.55; H, 9.02. [h] C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954), m.p. 217–218°, $[\alpha]^{20}D$ +34°, λ_{max} 236 mμ (ε 13,800). [i] Calcd. for $C_{19}H_{28}O_3 \cdot {}^1/_2C_3H_6O$: C, 73.91; H, 9.53. Found: C, 73.91; H, 9.30. [j] Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.02; H, 8.97. [k] Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.63, 72.31; H, 8.26, 8.47. [l] D. H. Peterson and H. C. Murray, *J. Am. Chem. Soc.*, **74**, 1871 (1952), m.p. 245–248°, $[\alpha]^{24}D$ +144°. [m] B. Camerino, C. G. Alberti, A. Vercellone, and F. Ammannati, *Gazz. chim. ital.*, **84**, 301 (1954), m.p. 260–262°, $[\alpha]D$ +164°, λ_{max} 240 mμ (ε 12,220). [n] J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Res.*, **11**, 149 (1949), m.p. 230–232°, $[\alpha]D$ +75°. [o] Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.23; H, 9.14. [p] S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh, D. A. Lyttle, L. M. Reineke, and A. Weintraub, *J. Am. Chem. Soc.*, **75**, 408 (1953), m.p. 196–198°, $[\alpha]D$ +113°, λ_{max} 237 mμ (ε 13,900). [q] Ref. *p*, m.p. 198–202°, $[\alpha]^{23}D$ +101°. [r] Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.84; H, 8.79. [s] Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.05; H, 8.26. [t] R. Neher and A. Wettstein, *Helv. Chim. Acta*, **29**, 2062 (1956), m.p. 225–227°, $[\alpha]^{21}D$ +118°, λ_{max} 237 mμ (log ε 4.13). [u] Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.48; H, 8.70. [v] Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.08; H, 8.14, ref. *p*, m.p. 258–260°, $[\alpha]^{23}D$ +74°, λ_{max} 237 mμ (ε 14,100). [w] K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1331 (1954), m.p. 229–230°, $[\alpha]D$ +43.7°, λ_{max} 235 mμ (ε 13,100). [x] A. Ercoli, U. S. Patent 3,009,858, November 21, 1961, m.p. 189–192°, $[\alpha]D$ +20.5°. [y] Ref. 3, m.p. 246–248°. [z] Ref. *y*, m.p. 236–238°, $[\alpha]D$ +117°, λ_{max} 232 mμ (log ε 4.14). [aa] S. Bernstein and R. Littell, *J. Org. Chem.*, **27**, 2544 (1962), m.p. 208–210°, $[\alpha]^{25}D$ +107°, λ_{max} 236 mμ (ε 13,400). [bb] S. Bernstein and R. Littell, *ibid.*, **25**, 313 (1960), m.p. 241–243°, $[\alpha]D$ +90°, λ_{max} 234–235 mμ (ε 12,000). [cc] Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.07; H, 7.76. [dd] Ref. *bb*, m.p. 220–222°. [ee] Calcd. for $C_{13}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.91; H, 7.87. [ff] Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.56; H, 7.78.

Stereochemistry of Reactions of the Norbornyl Grignard Reagent

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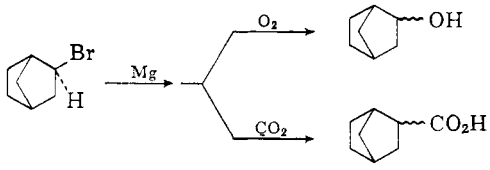
The stereochemistry of reactions of 2-bicycloheptyl Grignard reagents has not been thoroughly investigated. Interpretation of much of the earlier literature on reactions of bornyl Grignard reagents is complicated by the lack of adequate data on the structure and purity of some of the products involved.[2] More recently, Koch and Haaf[3] carbonated the Grignard reagent of norbornyl bromide and apparently obtained mainly *endo*-2-norbornanecarboxylic acid.

We undertook a more systematic study of reactions of the norbornyl Grignard reagent to evaluate the synthetic utility of this reagent. In particular, we studied the oxidation and carbonation reactions at two different temperatures (equation 1). The alcohols and acids (after conversion to methyl esters) were analyzed by gas-liquid chromatography. Table I summarizes the results.



(1)

TABLE I

exo–endo RATIOS OF PRODUCTS FROM REACTIONS OF NORBORNYL GRIGNARD REAGENT

	Reaction	
Temp.	Carbonation	Oxygenation
−78°	90:10	80:20
25°	70:30	79:21

The change in the *exo–endo* ratio of acids with temperature is of some interest. Since the yields at the lower temperature were lower, the possibility exists that carbonation was incomplete and that the *exo* Grignard reagent carbonated faster than the *endo* isomer.[4] A control experiment in which the length of the carbonation period at −78° was doubled led to the same ratio of acids in slightly higher yield. An attractive alternate rationale is that the *exo* and *endo* forms of the Grignard reagent exist in mobile equilibrium. The preponderance of *exo* acid in the product would be due to the fact that the transition state leading to it is of lower energy. Raising the temperature would be expected to shift the equilibrium toward *endo* Grignard as well as decrease the difference in transition state energies, thus leading to a smaller *exo–endo* ratio.

If the above explanation for carbonation is correct, it may be necessary to assume a different type of mechanism for oxidation, since the ratio of *exo–endo* alcohols did not change with temperature. Any possible explanation is complicated by the fact that there are two steps in which carbon–metal

(1) Abstracted from the Bachelor's thesis of G.T.K. (1962).

(2) For a summary and further references see C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, **77**, 6039 (1955).

(3) H. Koch and W. Haaf, *Ann.*, **638**, 111 (1960).

(4) It is assumed that carbonation is stereospecific with retention of configuration; *cf.* H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **83**, 2595 (1961).