Di-(4-morpholinyl)-methane was prepared from crude, dry morpholinylmethanol by a modification of the method of Zief and Mason.[9] One hundred and fifty grams of morpholinylmethanol was fractionally distilled at 1–2 mm. and the 92–96° fraction was redistilled, fractionally. Thus was obtained 89 g. of material boiling at 89–92° at 1 mm. pressure. After further purification by distillation the refractive index became $n^{20}D$ 1.4818.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.29; H, 9.45; N, 14.86.

Attempts to form a picrate gave yellow crystals which upon trituration with ether melted at 148–149° and were shown to be morpholine picrate by a mixture melting point with a known sample (m.p. 146–148°). Formation of the hydrochloride in dry ether solution gave material melting at 86–114° which upon recrystallization from isopropyl alcohol was shown to be morpholine hydrochloride (m.p. 175–176°; identification by the mixture melting point method).

(9) M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

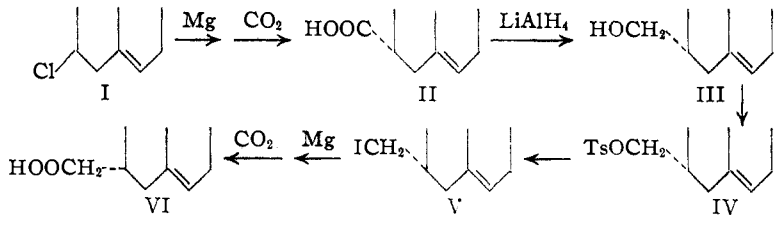
Derived Steroids. IV. 3-α-Cholesterylacetic Acid[1]

BY ROBERT H. BAKER AND QUENTIN R. PETERSEN

Nucleophilic replacement of groups at the 3-position of cholesteryl derivatives invariably leads to either 3-β or 6-derivatives. By contrast, electrophilic replacements of the 3-magnesiohalide group are shown to lead to α-products. The acid obtained by carbonation and also by degradation of other Grignard products has been converted with stereospecific reactions to cholesterylacetic acid which is different from the known β-acid.

Discussion

Previous papers from this Laboratory[2] have shown that the cholesteryl Grignard reagents react in a stereospecific manner with such a variety of reagents as acetaldehyde, acetyl chloride and carbon dioxide. These products were converted to common derivatives, *e.g.*, the carboxylic acid or methyl ketone which appear to be of a single configuration with respect to the 3-carbon atom. We have now extended the series of derivatives from cholesterylcarboxylic acid through reactions which do not involve the configuration at 3- to cholesterylacetic acid as illustrated.



This acid is compared with three cholesterylacetic acids prepared by Kaiser[3] in Table I. Specifically

TABLE I

CHOLESTERYLACETIC ACIDS

Position of Group and Δ		Acid M.p., °C.	Acid $[\alpha]^{25}D$	Methyl ester M.p., °C.
3-α	5,6	175	−31	73
3-β	5,6	213		108
6-	-*i*-	112	+32	
6-	4,5	174	+46	

it is an epimer of the 213° acid which, having been made by reaction of cholesteryl tosylate with sodiomalonic ester and subsequent hydrolysis and decarboxylation, must be of the β-configuration.[4]

Marker[5] treated cholesterylmagnesium chloride with both oxygen and carbon dioxide. The proportion of α- and β-cholesterol so formed was not determined accurately but certainly some α-product was formed. Although Marker[5] seemed to feel that the α- and β-acids were equal in amount, it now appears that it is almost wholly α, a few crystallizations being all that is necessary to bring it to purity.[2]

This preference of reagents to attack the cholesteryl Grignard reagent preferentially at the α-side of the molecule may be attributed to the fact that this is sterically the more open of the two possible paths. It seems possible that participation by the 5,6-double bond is responsible for the stereospecificity in this reaction as it is in the case of the production of β-derivatives from the mesomeric cation.[6] Actually it is clearly demonstrated by the work of Squire[7] that opposite configurations are obtained by carbonating cholestanyl or cholesteryl Grignard reagents.

There appears to be no possibility of configurational change at C-3 during the conversion of acid II to its homolog VI. The reduction with lithium aluminum hydride has been found to be quite safe in this respect[8] and it has been shown that a halomethyl group attached to an asymmetric carbon

(1) This work was supported by a grant from the Abbott Fund of Northwestern University.

(2) R. H. Baker and E. N. Squire, THIS JOURNAL, (a) **70**, 1487 (1948); (b) **70**, 4134 (1948); (c) **71**, 1383 (1949).

(3) E. Kaiser and J. J. Svarz, *ibid.*, **67**, 1309 (1945); **69**, 847 (1947); **71**, 517 (1949). We are indehted to Dr. Kaiser for a sample of his acid.

(4) C. W. Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946); R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948); S. Winstein and R. Adams, THIS JOURNAL, **70**, 838 (1948).

(5) R. E. Marker, T. S. Oakwood and H. M. Crooks, THIS JOURNAL, **58**, 481 (1936); R. E. Marker, O. Kamm, T. S. Oakwood and J. F. Laucius, *ibid.*, **58**, 1948 (1936).

(6) For one explanation of this reaction see J. D. Roberts, W. Bennett and R. Armstrong, *ibid.*, **72**, 3329 (1950).

(7) E. N. Squire, *ibid.*, **73**, in press (1951).

(8) R. H. Baker and Sidney H. Jenkins, Jr., *ibid.*, **71**, 3969 (1949); D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).

leads to no racemization upon conversion to the Grignard reagent.[9]

Experimental[10]

3-α-Cholesteryl Carbinol (III).—To 10.0 g. (24 millimoles) of 3-α-cholesterylcarboxylic acid dissolved in 500 ml. of boiling butyl ether was added at one time 10 g. (260 millimoles) of powdered lithium aluminum hydride. After 10 minutes hydrogen was no longer evolved and the suspension was allowed to cool. The mixture was decomposed with 20% potassium hydroxide during 12 hours. Extraction with five 200-ml. portions of ether and then crystallization from a mixture of Skellysolves B and F (petroleum ether, b.p. 60–70° and 30–60°, respectively) afforded 8.2 g., 85%, of white plates, m.p. 127–128°; $[\alpha]^{29}D$ −34° (*c* 2.6 in chloroform).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.44; H, 11.74.

3-α-Cholesteryl Carbinyl Tosylate (IV).—One gram (2.5 millimoles) of the powdered carbinol was mixed with 0.8 g. (4.2 millimoles) of *p*-toluenesulfonyl chloride and dissolved in the minimum quantity of pyridine. The solution was warmed momentarily to 50° and allowed to stand for two hours when crystals had formed. This tosylate was removed by filtration and was crystallized from absolute ethanol; yield 1.3 g., 95%; m.p. 148–149°; $[\alpha]^{29}D$ −13° (*c* 0.8 in chloroform).

Anal. Calcd. for $C_{35}H_{54}O_3S$: C, 75.76; H, 9.81. Found: C, 76.12; H, 10.00.

3-α-Cholesterylmethyl Iodide (V).—To 5.8 g. (10 millimoles) of the tosylate in 500 ml. of dry acetone was added 15 g. (100 millimoles) of sodium iodide. The solution was refluxed for 12 hours and the sodium *p*-toluenesulfonate was removed by filtration. Evaporation of the filtrate and separation from the excess sodium iodide by ether extraction gave a solution from which there was obtained colorless prisms. These were crystallized from methyl ethyl ketone to give 4.6 g. of iodide which could not be brought to analytical purity; m.p. 104.5–105°; $[\alpha]^{29}D$ −23° (*c* 3.7 in chloroform).

Anal. Calcd. for $C_{28}H_{47}I$: C, 65.86; H, 9.28. Found: C, 68.27; H, 9.92.

Repeated attempts to improve the purification and analytical techniques failed to produce better values than these.

3-α-Cholesterylacetic Acid (VI).—To 1.0 g. (40 millimoles) of powdered magnesium which had been previously baked under nitrogen was added 100 ml. of an ether solution containing 5 g. (10 millimoles) of 3-α-cholesterylmethyl iodide and a drop of methyl iodide. The mixture was stirred and refluxed under nitrogen for six hours during which time there was added dropwise an ether solution containing 0.6 ml. (10 millimoles) of methyl iodide. After an additional 18 hours of refluxing dry carbon dioxide was bubbled through the cloudy Grignard solution for five hours. The mixture was decomposed with 6 *N* hydrochloric acid and extracted with ether, 600 ml. The ether phase was extracted alternately with 300-ml. portions of water and 5% potassium hydroxide solution until 2 l. of extract had accumulated. The cholesterylacetic acid was precipitated by acidification with hydrochloric acid to the congo red end-point. It was crystallized from acetone to yield 2.8 g., 67%, m.p. 170–175°; $[\alpha]^{29}D$ −31° (*c* 1.9 in chloroform). The mixture m.p. with Dr. Kaiser's acid, m.p. 204–220°, reported 212–213°, was 163–166°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.27; neut. equiv., 429. Found: C, 81.71; H, 11.32; neut. equiv., 444, 452.

Methyl 3-α-Cholesterylacetate.—A solution of 0.7 g. (1.6 millimoles) of the acid in 100 ml. of dry methanol was treated with two drops of concd. sulfuric acid and refluxed for four hours. The product crystallized upon cooling, and it was recrystallized from methanol to yield 0.7 g. (97%), m.p. 79–79.5°; $[\alpha]^{29}D$ −32° (*c* 2.6 in chloroform).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.39. Found: C, 81.21; H, 11.12.

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(9) F. C. Whitmore and J. H. Olewine, THIS JOURNAL, **60**, 2570 (1938).

(10) Microanalyses by Misses M. Hines and J. Sorensen. Melting points are uncorrected.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

A New Synthesis of Hordenine and Other *p*-Dialkylaminoethylphenols and Some of Their Derivatives

BY CHAO-SHING CHENG, CLAUS FERBER, RAYMOND I. BASHFORD, JR., AND GERALD F. GRILLOT[1]

A series of *p*-dialkylaminoethylphenols including hordenine has been prepared by a new synthesis that includes the following steps: *p*-(β-hydroxyethyl)-anisole, *p*-(β-iodoethyl)-phenol and *p*-(β-dialkylaminoethyl)-phenol. The *p*-nitro- and the *p*-aminobenzoate esters of these dialkylaminoethylphenols have also been prepared and described. *p*-(β-Iodoethyl)-phenol has been converted to tyrosol and to the *p*-nitrobenzoate ester. The hydrochloride of the *p*-nitrobenzoate ester of di-*n*-butylaminoethylphenol is unusually low melting and appears to form a solvate with one molecule of benzene and toluene.

We have undertaken the preparation and study of a number of β-dialkylaminoethylphenols. The most important of these is *p*-(β-dimethylaminoethyl)-phenol called hordenine or anhaline which occurs in barley germs and in the cactus "Anhalonium fissuratium." Léger[2] isolated it from the former source and established its structure, which was independently confirmed by Gaebel.[3]

Syntheses of hordenine were developed by Barger,[4] Rosenmund,[5] Voswinkel,[6] Spaeth and Sobel,[7] and Kindler.[8] The yields of hordenine in these syntheses were usually poor but they did serve to confirm the structure assigned to this alkaloid.

In 1938 Buck, Baltzly and Ide[9] reported a synthesis of this compound starting with *p*-anisaldehyde and which proceeded through the following steps: aldehyde, azlactone, phenylpyruvic acid, pyruvic acid oxime, phenylacetonitrile, followed by the preparation of the methoxyphenylethyldimethylamine by catalytic reduction in the presence of an excess of diethylamine. The final step involved O-dealkylation with hydrochloric acid.

The synthesis that we have employed, not only for the *p*-dimethylamino-, but also for the diethylamino-, the di-*n*-butylamino-, the piperidino- and the morpholinoethylphenols, is theoretically more

(1) To whom all communications concerning this article should be addressed.

(2) Léger, *Compt. rend.*, **142**, 108 (1906); **143**, 916, 234 (1906); **144**, 488 (1907); *Bull. soc. chim.*, [3] **35**, 868 (1906); [4] **1**, 148 (1907).

(3) Gaebel, *Arch. Pharm.*, **244**, 441 (1906); *C. A.*, **1**, 437 (1907).

(4) Barger, *J. Chem. Soc.*, **95**, 2193 (1909).

(5) Rosenmund, *Ber.*, **42**, 4778 (1909); **43**, 306 (1910).

(6) Voswinkel, German Patent 248,385 (1911); *C. A.*, **6**, 3165 (1912).

(7) Spaeth and Sobel, *Monatsh*, **41**, 77 (1920).

(8) Kindler, *Arch. Pharm.*, **265**, 389 (1927); *C. A.*, **21**, 2668 (1927).

(9) Buck, Baltzly and Ide, THIS JOURNAL, **60**, 1789 (1938).