798. *Steroids. Part XLIII.* Comparison of the 16-Bromo-17-ketones and 16-Bromo-17-alcohols in the 3-Unsubstituted and 3β-Oxygenated 5α-Androstane Series.*

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The differences which Shoppee, Jenkins, and Summers reported between the chemical behaviour of the 16-bromo-17-ketones and 16-bromo-17-alcohols of the 3-unsubstituted 5α-androstane series on the one hand and that of their 3β-methoxy- and 3β-acetoxy-derivatives on the other are shown not to exist.

In 1954, we reported [1] the steric course of the bromination of 17-keto-steroids at position 16 and the preparation and properties of the epimeric 16-bromo-3β-acetoxy- and 16-bromo-3β-methoxy-5α-androstan-17-ones, and a number of 16-bromo-17-hydroxy-derivatives. Later, the corresponding reactions and derivatives were described for the 5,6-unsaturated 3α- and 3β-hydroxy-series.[2]

Shoppee, Jenkins, and Summers [3] recently carried out analogous reactions with (3-unsubstituted) 5α-androstan-17-one (I), and characterise their results as "strikingly different" from ours. They give the principal differences as "the variation, with the nature of the 3β-substituent, (i) of the rate of epimerisation of the 16α-bromo-17-ketones as disclosed by the occurrence of retention, as opposed to inversion of configuration at $C_{(16)}$, on reduction with sodium borohydride in methanol at 20°, (ii) the position of the equilibrium amongst the three pairs of epimeric ketones, and (iii) the production of 16β,17β-epoxides" [from the (*trans*)-16α-bromo-17β-alcohols in our work, as contrasted with the formation of the 17-ketone in the corresponding experiment of Shoppee and his co-workers].

Some of these conclusions appear to spring from a misunderstanding of our work; but certain real differences remain. The explanation suggested to account for the differences—conformational effects induced by the presence of a 3β-substituent in ring A and transmitted, by the long-range conformational mechanism envisaged by Barton,[4] to positions 16 and 17 in ring D—appeared to us to be *a priori* improbable; in fact, sterically more incisive changes such as the change from 3β- to 3α-substitution or the introduction of a 5,6-double bond had been found [2] to have no appreciable effect of this type. We therefore undertook some further experimental studies, including a repetition of certain experiments of Shoppee, Jenkins, and Summers.

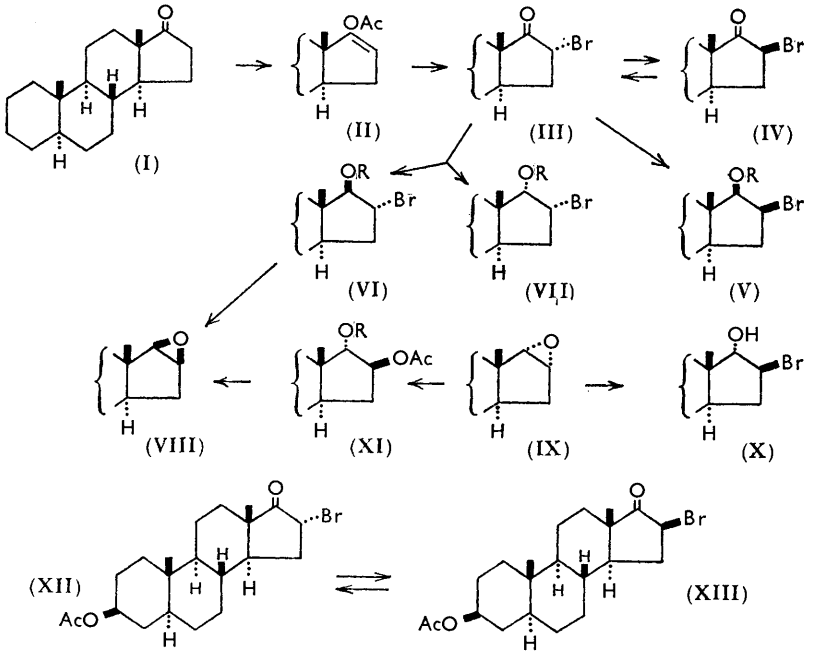
In their conclusion (i)—reduction of 16α-bromo-5α-androstan-17-one (III) with sodium borohydride without inversion at $C_{(16)}$, compared with extensive inversion in this reaction in the 3β-oxygenated series reveals differences in the rate of epimerisation of the starting bromo-ketones—Shoppee and his co-workers overlook the fact that their reaction was carried out in methanol–ether and ours in ethanol (misquoted [3] as methanol). We have previously stressed [1] how the solvent may influence critically the steric outcome of this reaction, and shown that, with lithium borohydride as the reagent, reduction of the 17-keto-group of the bromo-ketone (XII) proceeds with retention of configuration at $C_{(16)}$ in ether, but in ethanol gives a mixture of products epimeric at $C_{(16)}$. This alone accounts reasonably for the discrepancy noted by Shoppee, Jenkins, and Summers, but we have confirmed this explanation as follows:

Reduction of 16α-bromo-5α-androstan-17-one (III) [conveniently prepared by the

* Part XLII, *Coll. Czech. Chem. Comm.*, 1959, **24**, 1515.

[1] Fajkoš, *Chem. Listy*, 1954, **48**, 1800; *Coll. Czech. Chem. Comm.*, 1955, **20**, 312; 14th Internat. Conf. Union Pure Appl. Chem., Zurich, 1955.
[2] Fajkoš and Šorm, *Chem. Listy*, 1958, **52**, 505; *Coll. Czech. Chem. Comm.*, 1959, **24**, 766
[3] Shoppee, Jenkins, and Summers, *J.*, 1958, 3048.
[4] Barton, *Experientia*, 1955. Suppl. II, p. 121.

bromination of the enol acetate (II)] under the conditions used by Shoppee and his co-workers, *i.e.*, in methanol–ether (2 : 1), gave the bromohydrins (VI and VII; R = H) without epimerisation, but in ethanol the product was 16β-bromo-5α-androstan-17β-ol (V; R = H), identical with the material obtained by Shoppee, Jenkins, and Summers by a different route.[3] Sodium borohydride from three different commercial sources gave the same results, yields of the 16β-bromo-17β-alcohol (V; R = H) varying only between 64% and 70%. The supposed difference between the 3β-oxygenated and 3-unsubstituted series is thus illusory; it will be recalled that analogous behaviour was also shown by compounds of the 3α-substituted and 5,6-unsaturated series.[2]



Our earlier interpretation [1] had assumed that epimerisation at $C_{(16)}$ took place under the influence of the alkaline reagent before reduction of the keto-group; thus, 16α-bromo-3β-methoxy-5α-androstan-17-one, when kept in ethanolic sodium borohydride previously treated with acetone, gave the 16β-bromo-17-ketone in 40% yield; from its optical rotation, the crude product appeared to contain about 80% of the 16β-bromo-isomer. Shoppee, Jenkins, and Summers [3] exposed 16α-bromo-5α-androstan-17-one (III) to methanolic sodium hydroxide " equivalent to the alkalinity generated in reduction with sodium borohydride " and reported obtaining a product substantially free from bromine. We have examined the effect of acetone-treated sodium borohydride solutions and of 0·2% methanolic and ethanolic sodium hydroxide on Shoppee's 16α-bromo-5α-androstan-17-one (III) and on 3β-acetoxy-16α-bromo-5α-androstan-17-one (XII) as well as repeating our earlier experiments with the 3β-methoxy-derivative. In all these cases, the final optical rotation of the mixture corresponded to a content of about 75% of the 16β-bromo-17-ketone; the crude products contained the calculated amount of bromine, and on crystallisation yielded some of the pure 16β-bromo-epimerides. Since, moreover, the alkali-catalysed epimerisation at $C_{(16)}$ proved to be very rapid, the final rotation value being reached within 2 minutes, these results fully support our earlier interpretation [1] of the epimerisation during sodium borohydride reduction of the (thermodynamically labile) 16α-bromo-17-ketones. The *a priori* objection [3] that such a mechanism would also require the 16α-bromo-17-hydroxy-compounds to be isolated from the reduction of the (stable) 16β-bromo-ketones is based on a mistaken assumption as to the position of the equilibrium

between the two stereoisomeric bromo-ketones (see also below), and disregards the practical difficulty of isolating minor products from such mixtures.

Conclusion (ii) by Shoppee, Jenkins, and Summers,[3] that the position of equilibrium differs among the three pairs of 16-bromo-17-ketones, is based on a comparison of their findings with our results and involves a misinterpretation of the latter. In no case have we claimed that the epimeric mixtures obtained in our work are equilibrium mixtures; we stated only the compositions resulting under the experimental conditions. We have now equilibrated both epimerides of 16-bromo-5α-androstan-17-one (III) and (IV), and of 3β-acetoxy-16-bromo-5α-androstan-17-one (XII) and (XIII), under the conditions used by Shoppee and his co-workers, *i.e.*, in 4% hydrogen bromide in glacial acetic acid at 55°, the progress of the reaction being followed polarimetrically. The course of the reaction was the same analogous for both the 16α-bromo-ketones, and the final rotation corresponded to a mixture containing 73 ± 2% of the β-epimeride. Equilibration of both the 16β-bromo-ketones also took the same course, the final rotation values indicating 67 ± 2% of the 16β-bromo-derivative. The average equilibrium compositions, about 70% of the β-epimeride, are significantly different from the result recorded by Shoppee, Jenkins, and Summers (β 53 ± 3%, α 47 ± 3%), but reasonably close to the composition reached by alkaline equilibration (β about 75%; α 25%).*

Any differences in the conformation of ring D sufficient to affect the chemical behaviour of substituents in positions 16 or 17 would be expected to be reflected in the infrared spectra of the 16-bromo-17-alcohols. Nickon's findings[6] and our work on steroid bromohydrins[7] show that the O–H stretching frequency of these compounds depends on the steric relation of the bromo- and hydroxy-substituents in a regular and sensitive way. We have confirmed the preparations and determinations of configuration of the four 16-bromo-5α-androstan-17-ols (V, VI, and VII; R = H) and (X) described by Shoppee, Jenkins, and Summers[3] [a minor difference was that lithium aluminium hydride reduction of the bromo-ketone (III) in our hands gave both the 17β- and 17α-hydroxy-isomers, in agreement with our earlier results[1,2] in the 3-substituted series; both the acetates (VI and VII; R = Ac) were isolated by crystallisation after acetylation of the crude product]. The frequencies of the O–H stretching vibrations for the four 16-bromo-5α-androstan-17-ols are recorded in the Table, with similar data for a number of other,

5α-Androstane derivative	$\nu_{max.}$ (cm.$^{-1}$) (in CCl_4)	$\Delta\nu$ [a] (cm.$^{-1}$)
17β-Ol	3624	
3β-Acetoxy-17β-ol	3624	
16α-Bromo-17β-ol	3619	5
16α-Bromo-3β-methoxy-17β-ol	3617	7
16β-Bromo-17β-ol	3554	71
3β-Acetoxy-16β-bromo-17β-ol	3550	74
16β-Bromo-3β-methoxy-17β-ol	3552	72
17α-Ol	3626	
3β-Acetoxy-17α-ol	3625	
16β-Bromo-17α-ol	3618	8
16α-Bromo-17α-ol	3558	68
16α-Bromo-3β,17α-diol	3558, 3618 [b]	69

[a] Frequency shift referred to the 16-unsubstituted compounds. [b] 3-OH group.

3β-substituted compounds of the same type. No significant difference can be detected betweeen the 3-unsubstituted and the corresponding 3β-oxygenated compounds of the same type. Even the introduction of a double bond in position 5,6 causes no appreciable deviation (see ref. 7). The only infrared frequency recorded by Shoppee and his co-workers[3] for this group is that for the O–H vibration in 16α-bromo-5α-androstan-17β-ol

* The equilibrium mixture obtained by acid treatment of 16α-bromo-œstrone acetate is reported[5] to contain " predominantly " the 16β-epimeride.

[5] Fishman and Biggerstaff, *J. Org. Chem.*, 1958, **23**, 1190.
[6] Nickon, *J. Amer. Chem. Soc.*, 1957, **79**, 243.
[7] Horák and Fajkoš, *Coll. Czech. Chem. Comm.*, 1959, **24**, 1515.

(VI; R = H), which is given as 3632 cm.$^{-1}$, a shift of +8 cm.$^{-1}$ from that for the unsubstituted androstan-17β-ol. However, in Nickon's work and in our own substitution by bromine invariably caused a negative shift, as, indeed, do all other forms of hydrogen-bonding from their very nature. We therefore regard this value as erroneous. (In all other respects the infrared and rotational values recorded and discussed by Shoppee, Jenkins, and Summers [3] are substantially in accord with our earlier findings and discussion.[1,2])

Discrepancy (iii) referred to by Shoppee, Jenkins, and Summers [3]—conversion of 16α-bromo-5α-androstan-17β-ol (VI; R = H) into 5α-androstan-17-one (I) by alkali—is contrary to all experience in this field, whereby a *trans*-bromohydrin of this type is invariably converted into the epoxide. Indeed, from the 16α-bromo-17β-alcohol (VI; R = H) and methanolic potassium hydroxide under conditions used by Shoppee *et al.* we obtained a practically quantitative yield of 16β,17β-epoxy-5α-androstane (VIII); no infrared carbonyl absorption could be detected even in the crude product. The constitution of the epoxide was confirmed by independent synthesis from the 16α,17α-epoxide [3] (IX) through the diol monoacetate (XI; R = H) and its methanesulphonate (XI; R = Me·SO_2), the infrared spectra of the two products being identical. We cannot account for this difference in experimental findings.

Experimental

M. p.s were measured on a Kofler block. Samples for analysis were dried at 90°/0·002 mm. for 8 hr. Unless otherwise stated, $[\alpha]_D$ is for $CHCl_3$ solutions at 20°. Infrared spectra were measured for CCl_4 solutions on a Zeiss-Jena UR 10 double-beam spectrometer with lithium fluoride optics.

17-*Acetoxy*-5α-*androst*-16-*ene* (II).—5α-Androstan-17-one (10·75 g.), dried azeotropically with benzene, in isopropenyl acetate (70 c.c.) was treated with concentrated sulphuric acid (0·05 c.c.), and 30 c.c. of the mixture were distilled off during 2 hr. More isopropenyl acetate (70 c.c.) and sulphuric acid (0·05 c.c.) was then added and 70 c.c. were distilled off during 2 hr. The mixture was diluted with light petroleum (b. p. 40—60°; 1500 c.c.), filtered through alkaline aluminium oxide (activity I; 50 g.), and evaporated to dryness, and the residue crystallised from methanol to give 17-*acetoxy*-5α-*androst*-16-*ene* (8·0 g., 65%), m. p. 84—85°, $[\alpha]_D$ +36·5° (*c* 3·2) (Found: C, 79·6; H, 10·2. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

16α-*Bromo*-5α-*androstan*-17-*one* (III).—A solution of 17-acetoxy-5α-androst-16-ene (8·0 g.) in carbon tetrachloride (200 c.c.) was treated in 15 min. at 0°, with stirring, with bromine (4·1 g.) in carbon tetrachloride (50 c.c.). The mixture was washed with sodium thiosulphate solution, sodium hydrogen carbonate solution, and water, dried, and evaporated. The residue on repeated crystallisation from ethanol yielded 16α-bromo-5α-androstan-17-one (7·7 g., 87%), m. p. 196—197°, $[\alpha]_D$ +58° (*c* 2·4); Shoppee *et al.*[3] record m. p. 197°, $[\alpha]_D$ +58°.

Reduction of 16α-*Bromo*-5α-*androstan*-17-*one* (III) *with Sodium Borohydride*.—(*a*) A solution of 16α-bromo-5α-androstan-17-one (2·0 g.) in absolute ethanol (350 c.c.) was treated, at 0°, with sodium borohydride (580 mg.) and set aside at +4° for 15 hr. The mixture was worked up in the customary manner and the crystalline residue recrystallised from methanol to give 16β-bromo-5α-androstan-17β-ol (1·28 g., 64%), m. p. 122—123°, $[\alpha]_D$ +2° (*c* 2·7), $\nu_{max.}$ 3554 cm.$^{-1}$ (O–H stretching); Shoppee *et al.*[3] record m. p. 123°, $[\alpha]_D$ +3·5°. Treatment with acetic anhydride in pyridine afforded the *acetate* (V; R = Ac), m. p. 144°, $[\alpha]_D$ +61° (*c* 1·2) (Found: C, 63·3; H, 8·2; Br, 19·8. $C_{21}H_{33}O_2Br$ requires C, 63·5; H, 8·4; Br, 20·1%).

(*b*) The 16α-bromo-17-ketone (340 mg.) was reduced as under (*a*), and the crude product chromatographed on neutral aluminium oxide (activity III—IV; 30 g.) from light petroleum (b. p. 40—60°)–benzene (1 : 1), 30 c.c. fractions being taken. Fractions 2—6 afforded the 16β-bromo-17β-alcohol (233 mg.), fractions 9—13 androstan-17β-ol (80 mg.), m. p. and mixed m. p. 164—165°, $[\alpha]_D$ +13° (*c* 1·6).

(*c*) The 16α-bromo-17-ketone (340 mg.) in ether (25 c.c.) was treated with sodium borohydride (100 mg.) in methanol (12 c.c.) at 20° for 18 hr. as described by Shoppee *et al.*,[3] and worked up in the same manner, affording 16α-bromo-5α-androstan-17α-ol (215 mg.), m. p. 127—129° (from methanol), $[\alpha]_D$ −4° (*c* 1·3), $\nu_{max.}$ 3558 cm.$^{-1}$ (O–H stretching) {acetate, m. p. 206—207° (from methanol), $[\alpha]_D$ −5° (*c* 1·3)}, and 16α-bromo-5α-androstan-17β-ol (79 mg.), m. p.

93—95° (from methanol), $[\alpha]_D$ +2° (*c* 1·4), $\nu_{max.}$ 3619 cm.$^{-1}$ (O–H) stretching) {acetate, m. p. 144—145°, $[\alpha]_D$ −30° (*c* 1·2)}. Shoppee *et al.*[3] record, for an analogous experiment: 17α- (140 mg.), m. p. 125—126°, $[\alpha]_D$ −5° {acetate, m. p. 200—203°, $[\alpha]_D$ −5°}; 17β- (130 mg.), m. p. 90—94°, $[\alpha]_D$ +3°, $\nu_{max.}$ 3632 cm.$^{-1}$ (O–H stretching) {acetate, m. p. 142—144°, $[\alpha]_D$ −31°}.

Reduction of 16α-*Bromo*-5α-*androstan*-17-*one* (III) *with Lithium Aluminium Hydride.*—16α-Bromo-5α-androstan-17-one (830 mg.) in dry ether (150 c.c.) was treated at 0° with lithium aluminium hydride (400 mg.), and the mixture was set aside at 0° for 3½ hr., then worked up in the customary manner. The crude product was treated with acetic anhydride in pyridine, and the acetyl derivatives were fractionally crystallised from ethanol and ethyl acetate, to yield 17β-acetoxy-16α-bromo-5α-androstane (510 mg.), m. p. 143—145°, $[\alpha]_D$ −32° (*c* 1·8), together with the 17α-epimer (120 mg.), m. p. 203—206°, $[\alpha]_D$ −4° (*c* 1·9).

16β-*Acetoxy*-5α-*androstan*-17α-*ol* (XI; R = H).—16α,17α-Epoxyandrostane[3] (805 mg.) in acetic acid (12 c.c.) was heated to 100° under nitrogen for 2½ hr., the mixture diluted with water and worked up in the customary manner, and the crude product chromatographed on aluminium oxide (30 g.) from light petroleum (b. p. 40—50°)–benzene (2 : 1). Elution with benzene–ether (1 : 1) gave 248 mg. of crystals which on recrystallisation from methanol afforded 16β-*acetoxy*-5α-*androstan*-17α-*ol* (205 mg.), m. p. 174—175°, $[\alpha]_D$ −14° (*c* 2·08) (Found: C, 75·2; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·3%).

This product (150 mg.) with methanesulphonyl chloride (0·25 c.c.) in pyridine (2 c.c.) at 0° (2½ hr.) gave the *methanesulphonate* (150 mg.), m. p. 146—147° (from methanol), $[\alpha]_D$ 0° (Found: C, 63·9; H, 8·7; S, 7·5. $C_{22}H_{36}O_5S$ requires C, 64·0; H, 8·8; S, 7·8%).

16β,17β-*Epoxy*-5α-*androstane* (VIII).—(*a*) The foregoing methanesulphonate (150 mg.) in ether (4 c.c.) was refluxed with potassium hydroxide (150 mg.) in methanol (15 c.c.) for 1 hr., giving, after crystallisation from methanol, 16β,17β-*epoxy*-5α-*androstane* (87 mg.), m. p. 113—114°, $[\alpha]_D$ +40·2° (*c* 1·4) (Found: C, 83·1; H, 10·9. $C_{19}H_{30}O$ requires C, 83·2; H, 11·0%).

(*b*) 16α-Bromo-5α-androstan-17β-ol (270 mg.) was refluxed with potassium hydroxide (270 mg.) in methanol (28 c.c.) for 8 hr. and worked up in the usual manner. The crystalline residue, m. p. 112—114°, showed no infrared carbonyl absorption and contained no halogen. Crystallisation from methanol afforded 16β,17β-epoxy-5α-androstane (165 mg.), m. p. and mixed m. p. 114°, $[\alpha]_D$ +39·3° (*c* 1·7) (Found: C, 83·1; H, 10·8%).

Equilibration of the 16-*Bromo*-17-*ketones* (III, IV, XII, *and* XIII) *in Acid Solution.*—(*a*) 16α-Bromo-5α-androstan-17-one (155 mg.; $[\alpha]_D$ +58°) in acetic acid (9 c.c.) was treated with a 40% solution (1 c.c.) of hydrogen bromide in acetic acid and kept at 55°, the optical rotation being measured at hourly intervals. After 4 hr., $[\alpha]_D$ became constant at +106°, corresponding to 73 ± 2% of the β-epimeride in the mixture. {All calculations of composition are based on rotation values for the pure epimerides obtained in glacial acetic acid; these were identical with the values obtained in chloroform except for (XIII), which had $[\alpha]_D$ +97° (*c* 1·13) in acetic acid.} By the usual working-up the mixture gave a product of $[\alpha]_D$ +104° (70 ± 2% of β-epimeride) which on crystallisation from ethanol afforded 16β-bromo-5α-androstan-17-one (58 mg.), m. p. 126—127°, $[\alpha]_D$ +125°.

(*b*) 3β-Acetoxy-16α-bromo-5α-androstan-17-one (320 mg.) under the conditions described above gave a mixture of $[\alpha]_D$ +80° (71 ± 2% of β-epimeride); the crude crystalline product, $[\alpha]_D$ +79° (70 ± 2% of β-epimeride), on crystallisation from methanol gave 3β-acetoxy-16β-bromo-5α-androstan-17-one (125 mg.), m. p. 147°, $[\alpha]_D$ +94°.

(*c*) Under the same conditions, 16β-bromo-5α-androstan-17-one gave a final mixture of $[\alpha]_D$ +102° (67 ± 2% of β-epimeride); 3β-acetoxy-16β-bromo-5α-androstan-17-one gave a mixture of $[\alpha]_D$ +76° (65 ± 2% of β-epimeride).

Epimerisation of the 16α-*Bromo*-17-*ketones* (III) *and* (XII) *in Alkaline Solution.*—(*a*) Sodium borohydride (50 mg.) in ethanol (10 c.c.) was treated with acetone (0·5 c.c.) and, after 2 hr. at 15°, 16α-bromo-5α-androstan-17-one (200 mg.) in ethanol (5 c.c.) was added. Two minutes after mixing, $[\alpha]_D$ of the solution was +108°, corresponding to 76 ± 2% of the β-epimeride. The crude product (190 mg.), m. p. 110—120°, isolated in the usual way, had $[\alpha]_D$ +111° (80 ± 2% of β-epimeride) (Found: Br, 22·7%). Crystallisation from ethanol afforded pure 16β-bromo-5α-androstan-17-one (105 mg.), m. p. 127°, $[\alpha]_D$ +124°. In an analogous experiment, 3β-acetoxy-16α-bromo-5α-androstan-17-one gave an equilibrated solution of $[\alpha]_D$ +83° (77 ± 2% of β-epimeride) and, after working up, a crude product, m. p. 102—125°, $[\alpha]_D$ +85° (80 ± 2% of β-epimeride) (Found: Br, 19·5%). Crystallisation from ethanol afforded pure 3β-acetoxy-16β-bromo-5α-androstan-17-one, m. p. 146°, $[\alpha]_D$ +95°.

(*b*) To a 0·2% methanolic solution of sodium hydroxide (7 c.c.), the bromo-ketone (III) (100 mg.) in chloroform (1 c.c.) was added. After 20 min. at 15°, when the rotation of the solution was +105° (71 ± 2% of β-epimeride), the mixture was worked up in the usual way, to give a crude product, m. p. 110—125°, $[\alpha]_D$ +103° (68 ± 2% of β-epimeride) (Found: Br, 22·6%). The bromo-ketone (XII) in the same way gave a solution of $[\alpha]_D$ +79° (70 ± 2% of β-epimeride) and a crude product, m. p. 98—116°, $[\alpha]_D$ +79° (Found: Br, 19·1%). The pure β-bromo-ketones (IV) and (XIII) were again isolated by crystallisation of the crude products from ethanol. Closely similar results were obtained with ethanol as the solvent in the equilibration.

The author thanks Academician F. Šorm for his continued and active interest in this work.

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[*Received, April 8th,* 1959.]