lated and dried as before, weighed 1.3 g. and had an infrared spectrum identical to the analytically pure sample prepared by procedure 1.

Acknowledgment.—The authors extend their thanks to Mr. N. B. Colthup for assistance in the interpretation and assignment of infrared spectra, to Miss E. C. Eberlin for the thermogravimetric analyses, to Dr. J. E. Lancaster for n.m.r. studies, and to the Microanalytical Department for elemental analyses.

Ortho Substitution Rearrangement *vs.* Elimination Reaction of Ring-substituted Benzyldimethylethylammonium Ions[1]

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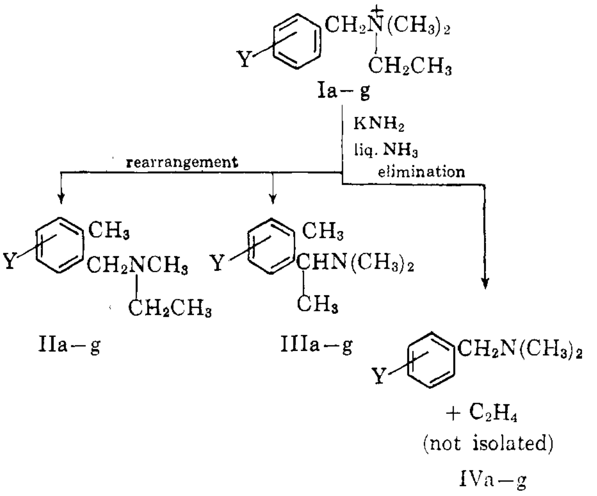
Treatment of 2-, 3-, and 4-methoxy- and -fluoro-substituted benzyldimethylethylammonium iodides with potassium amide in liquid ammonia was found to afford varying mixtures of the corresponding benzyldimethylamines and the two possible ortho substitution rearrangement products. The 2- and 4-methoxy substituents favored rearrangement almost to the exclusion of elimination. The 3-methoxy substituent had no appreciable effect, compared to the unsubstituted compound. The 2- and 3-fluoro substituents favored elimination. The rearrangement products consisted mainly of the corresponding methyl derivatives but contained smaller amounts of the methylene derivatives. These results are of interest from the theoretical and synthetic standpoints.

Recently[2] the benzyldimethylethylammonium ion (Ia) and certain other benzyldimethylalkylammonium ions having β-hydrogen were shown to undergo both the ortho substitution rearrangement and an elimination reaction with sodium amide in liquid ammonia. The relative extents of these two types of reaction were observed to depend on the nature of the alkyl group in the side chain. We have now found that the relative extents of the two types of reaction are also dependent on substituents in the aromatic ring. Thus treatment of quaternary ammonium ions Ia–g with five[3] molecular equivalents of potassium amide in liquid ammonia afforded various proportions of the rearrangement and elimination products. The former type of product consisted of mixtures of isomeric amines IIa–g and IIIa–g and presumably ethylene (Scheme A).



Ia. Y = H
Ib. Y = 2-OCH$_3$
Ic. Y = 2-F
Id. Y = 4-OCH$_3$
Ie. Y = 4-F
If. Y = 3-OCH$_3$
Ig. Y = 3-F

Scheme A

In Table I are summarized the proportions of rearrangement products to elimination products and calculated yields of products. These proportions were determined by vapor phase chromatography. A sample of the crude amine product from each reaction was passed through a short, nonselective column which separated the elimination product IV from the rearrangement products II and III, but which did not separate isomers II and III. The composition of the mixture was estimated from this chromatogram. When possible, the proportions of products were determined more accurately by comparison of the areas under the peaks corresponding to elimination and rearrangement products with the areas under these peaks of a known mixture of pure elimination product and a mixture of essentially pure rearranged amines II and III, obtained by distillation of the crude reaction product. Each analysis was reproducible to within 2%.

From the results shown in Table I and the weights of the crude amine products were calculated the yields of rearrangement product mixtures containing amines of types II and III and the yields of the elimination products of type IV (see Table I). In the reactions of the methoxy-substituted quaternary ions, only the above mentioned products were detected, the total yields being 88–93%. However, in the reactions of the fluoro-substituted quaternary ions, the amine products were con-

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(1) Supported by the Army Research Office (Durham).

(2) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 1542 (1962).

(3) Although only one molecular equivalent of the alkali amide is required, this large excess was employed to reduce possible concentration effects during the course of addition of the quaternary halide.

TABLE I

PROPORTIONS OF REARRANGEMENT PRODUCTS TO ELIMINATION PRODUCTS AND CALCULATED YIELDS OF PRODUCTS

Quaternary iodide	Substituent, Y	Proportions, mole % rearrangement: elimination	Total yield[a]	Calculated yields, %	
				Mixtures of II and III	Benzyldimethylamines
Ia[b]	H	71:29	89	63	25
Ia[c]	H	72:28	92	66	26
Ib	2-OCH_3	99:1.2	88	87	1
Ic	2-F	6:94 to 10:90[d]			
Id	4-OCH_3	94:6	93	87	5
Id[c]	4-OCH_3	94:6	93	87	5
Ie	4-F	84:16 or 76:24[d,e]			
If	3-OCH_3	75:25[d]	91	65–71	20–24
Ig	3-F	1:99 to 2:98[d]			

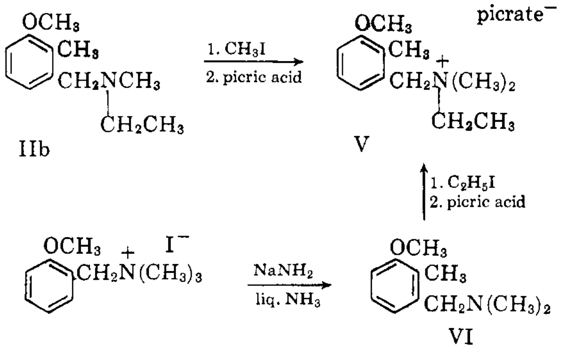
[a] Total yield of crude amine product based on the average molecular weight of the mixture. [b] Treatment of salt Ia with 3 molecular equivalents of sodium amide afforded these products in the proportions 82:18 and 81:19 (see ref. 2). [c] Repeat experiment. [d] Estimated value; not accurately determined. [e] Two possible estimated proportions are given because it was not distinguished which two of the three rearrangement product isomers were the ortho substitution products (see Experimental).

taminated with volatile and nonvolatile materials, so that such calculations have little significance.

As in the earlier work in which the side chain was varied,[2] the rearrangement product from quaternary ions Ia, Ib, and Id consisted of methyl derivatives IIa, IIb, and IId together with methylene derivatives IIIa, IIIb, and IIId in the approximate ratio 4:1. This ratio was estimated by vapor phase chromatography using various columns. The amounts of these isomers in the products of the other quaternary ions were not estimated for various reasons (see Experimental).

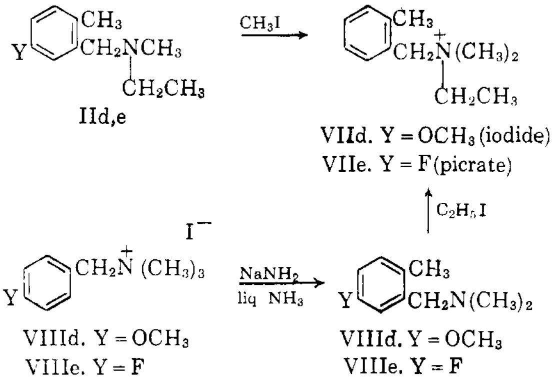
The larger and smaller rearrangement isomer peaks in the chromatogram of the crude product from salt Ia were shown to be amines IIa and IIIa, respectively, by their enhancement on addition of samples of independently synthesized amines IIa and IIIa.[2]

The structure of major rearrangement product IIb was established by independent synthesis of the picrate of its methiodide through amine VI, whose structure has been definitely established[4] (Scheme B). Insufficient rearrangement product of quaternary ion Ic was obtained for its structure to be proved.



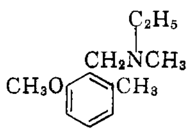
Scheme B

Similarly, the structures of the predominant rearrangement products from quaternary ions Id (Y = 4-OCH_3) and Ie (Y = 4-F) were established as IId and IIe (Scheme C). The structures of amines VIIId and VIIIe employed in this synthesis were established in this laboratory[4] and by Gaughan,[5] respectively.

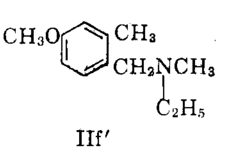


Scheme C

Although only one methyl and one methylene derivative may be obtained on rearrangement of the 2- and 4-substituted quaternary ions, two of each of these types of derivatives may be produced on rearrangement of a 3-substituted quaternary ion, depending on whether the ring is attacked at the position *ortho* to the substituent or *para* to the substituent. For example, the rearrangement of quaternary ion If may afford the two methyl derivatives IIf and IIf′ and also the two corresponding methylene derivatives. Actually, three of these four possible isomers were detected by vapor phase chromatography, and the fourth is



IIf



IIf′

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(4) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

(5) E. J. Gaughan, Ph.D. dissertation, Fordham University, New York, N. Y., 1961.

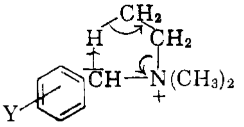
presumed to have been present. Their structures were not definitely established. Quaternary ion Ig afforded insufficient rearrangement product for study.

The structures of the elimination products, the substituted benzyldimethylamines IVb–g, were established by showing that they had the same vapor phase chromatography retention times as samples of the authentic compounds. Amines IVb–g had been intermediates in the synthesis of quaternary ammonium iodides Ib–g.

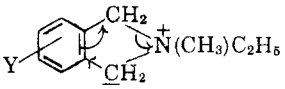
Discussion

Table I shows that the introduction of the methoxy group into the 2- or 4-position of the benzyldimethyl-ethylammonium ion greatly favored rearrangement, whereas the introduction of fluorine into the 2- or 3-position greatly favored elimination. The introduction of methoxy into the 3-position and apparently the introduction of fluorine into the 4-position had little effect on the relative extents of the two types of reaction, though the result with the fluoro compound was complicated by side reactions.

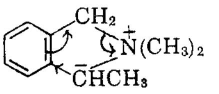
These results are of interest in connection with the mechanisms of the two types of reaction. The reactive intermediate in the elimination reaction is evidentally benzyl carbanion I′.[2] The intermediate in the rearrangement reactions are methyl and methylene carbanions I″ and I‴[6] which afford rearranged amines of types II and III, respectively.



I′



I″



I‴

The reasons for the observed effects of substituents on the relative extents of the two types of reaction are not clear, since several factors may act on the relative rates of rearrangement and elimination. It appears that one important factor may be the influence of substituents on the stability of benzyl carbanion I′. Electron-withdrawing substituents may favor I′ at the expense of methyl and methylene carbanions I″ and I‴ and thus repress rearrangement and possibly favor elimination. Electron-releasing substituents might be expected to have the opposite effect.

The present results extend the usefulness of the ortho substitution rearrangement in synthesis. The reactions of the 2- and 4-methoxy quaternary ions Ib and Id furnish a convenient method for synthesis of the corresponding rearranged amines IIb and IId, which appear difficult to prepare by other methods. Although these amines are obtained contaminated with the isomeric amines IIIb and IIId, they are readily isolated as derivatives. The method should be applicable to the synthesis of other 2-methyl-3-methoxy- and 2-methyl-5-methoxybenzylmethylalkylamines and possibly to synthesis of related amines having 2- and 4-alkyl substituents in the aromatic ring. Also, the method might be expected to give better yields of methoxy-substituted 2-benzazocines from ring enlargement of the appropriate 1,1-dimethyl-2-phenylpyrrolidinium ions than that (41%) obtained recently from the unsubstituted quaternary ion, which afforded about as much elimination product as rearrangement product.[7] Actually, sodium amide is probably to be preferred to potassium amide for all of these syntheses, since the unsubstituted quaternary ion Ia had given relatively more rearrangement product with the former reagent than with the latter (see Table I, footnote *b*).

Experimental[8]

Substituted Benzyldimethylamines (IVb–g; See Table II).—These amines were prepared by treatment of the appropriate benzyl chloride with a fivefold excess of dimethylamine in acetonitrile for 5 days at room temperature. The methoxy-substituted benzyl chlorides had been prepared from the appropriate benzyl alcohol and thionyl chloride; these chlorides were used without purification.

Substituted Benzyldimethylethylammonium Iodides (Ia–g; See Table III).—These quaternary ammonium iodides were prepared from the appropriate benzyldimethylamines by treatment with ethyl iodide in acetonitrile essentially as described previously for the unsubstituted compound.[2]

Reaction of Substituted Benzyldimethylethylammonium Iodides with Potassium Amide in Liquid Ammonia (See Table IV).—To a stirred solution of 0.67–0.70 mole of potassium amide in 1.0 l. of liquid ammonia[9] was added, during 2.5 hr., 0.135–0.140 mole of the quaternary iodide in small portions. After stirring for one more hour, excess ammonium chloride was added to neutralize the remaining potassium amide. The ammonia was evaporated with stirring as 500 ml. of ether was added. The resulting ether suspension was filtered and the filtrate extracted with 2 *N* hydrochloric acid. The acid extract was made basic with solid sodium hydroxide and the resulting amine mixture extracted with ether. The ether extract was dried over magnesium sulfate and the ether was removed on a rotary evaporator at room temperature under about 150 mm. of pressure, leaving colorless crude amine product in 88–93% yield.

Distillation of all but a 1-g. sample of the crude rearrangement product afforded pure samples of the mixtures of rearranged amines of type II and type III. Quaternary ions Ic and Ig did not afford enough rearrangement product for distillation. The distilled samples were analyzed (see

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[6] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

[7] G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962).

[8] Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Dr. Ing. Schoeller, Kronach, West Germany.

[9] C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

TABLE II

RING-SUBSTITUTED BENZYLDIMETHYLAMINES (IVg)

Ring subst.	Designation of amine	Yield, %	Boiling point/ pressure, mm.	Empirical formula	Elemental analysis or reported b.p. Calcd., % C	H	N	Found, % C	H	N
2-OCH_3	IVb	56[a]	92–93°/6.5		113° at 20 mm.[b]					
2-F	IVc	52	61.5–63°/5.8	$C_9H_{12}FN$	70.55	7.89	9.14	70.89	7.87	9.20
4-OCH_3	IVd	70[a]	76–77°/0.9		110–111° at 16 mm.[c]					
4-F	IVe	26[d]	61–62°/6.5	$C_9H_{12}FN$	70.55	7.89	9.14	70.18	7.80	9.04
3-OCH_3	IVf	45[a]	99–101°/8.8		105° at 13 mm.[b]					
3-F	IVg	94	62–62.5°/7.0	$C_9H_{12}FN$	70.55	7.89	9.14	70.40	7.99	9.28

[a] Over-all yield for conversion of the benzyl alcohol to the benzyldimethylamine. [b] E. Stedman, *J. Chem. Soc.*, 1902 (1927). [c] M. M. Tiffeneau, *Bull. soc. chim. France*, [IV] 9, 825 (1911). [d] Benzene, rather than acetonitrile, used as reaction solvent.

TABLE III

RING-SUBSTITUTED BENZYLDIMETHYLETHYLAMMONIUM IODIDES (a–g)

Ring subst.	Designation of salt	Yield, %	Melting[a] point	Empirical formula	Calcd., % C	H	N	Found, % C	H	N
H	Ia	95	119.5–120°[b]							
2-OCH_3	Ib[c]	..	97.5–98°[d]	$C_{18}H_{22}N_4O_8$[c]	51.18	5.25	13.27	51.43	5.12	13.40
2-F	Ic	94	131–132°	$C_{11}H_{17}FIN$	42.73	5.54	4.53	42.84	5.80	4.64
4-OCH_3	Id	95	109–110°	$C_{12}H_{20}INO$	44.87	6.28	4.36	45.00	6.34	4.68
4-F	Ie	96	147.5–148°	$C_{11}H_{17}FIN$	42.73	5.54	4.53	42.93	5.61	4.86
3-OCH_3	If	94	174–175.5°	$C_{12}H_{20}INO$	44.87	6.28	4.36	45.17	6.18	4.58
3-F	Ig	97	142–143°	$C_{11}H_{17}FIN$	42.73	5.54	4.53	42.59	5.62	4.52

[a] Melting point of analytical sample. Salts of slightly lower melting point were, in some cases, used in the reactions. [b] Reported m.p. 119.5–120°; see ref. 2. [c] Characterized as the picrate; used as the very hygroscopic iodide. [d] Melting point of the picrate.

TABLE IV

BOILING POINTS AND ANALYSES OF REARRANGEMENT PRODUCT MIXTURES

Initial ring subst.	Amines in distilled mixture	Boiling point/ pressure, mm.[a]	Empirical formula	Calcd., % C	H	N	Found, % C	H	N
H	IIa, IIIa	97–97.5°/17[b]							
2-OCH_3	IIb, IIIb	84°/0.80	$C_{12}H_{19}NO$	74.57	9.91	7.25	74.35	9.82	7.30
4-OCH_3	IId, IIId	122.5–123.5°/6.5	$C_{12}H_{19}NO$	74.57	9.91	7.25	74.65	9.89	7.23
4-F	IIe, IIIe, one other	88.5–89°/6.0	$C_{11}H_{16}FN$	72.89	8.90	7.75	72.69	8.99	7.79
3-OCH_3	Four isomers	118–120°/6.3	$C_{12}H_{19}NO$	74.57	9.91	7.25	74.44	9.90	7.30

[a] Boiling point of a middle fraction; distillation through a 10-in. Vigreux column. [b] Reported b.p. 97–97.5° at 17 mm.

Table IV) and used in the accurate determination of the composition of the crude product (see below).

Vapor phase chromatography of a sample of each crude amine product using a 0.6-meter column of 20% polypropylene glycol on Chromosorb W gave a peak for the substituted benzyldimethylamine (type IV) and a peak for the mixture of rearranged amines of types II and III. The relative amounts of the two types of products in the mixture were determined by comparison of the areas, measured with a planimeter, under these peaks to the areas under the corresponding peaks in a chromatogram of a mixture of known composition of these two types of products.

Vapor phase chromatography of samples of each crude amine product using various 2-meter columns showed the presence of the minor (type III) rearrangement products in the reaction products from salts Ia, Ib, and Id. Each of these products was estimated to contain the type II and type III amines in the ratio 4:1. Amines IIa and IIIa had been independently synthesized previously and were shown to be identical to the major and minor rearrangement products of salt Ia by vapor phase chromatography and by isolation of derivatives.[2] The product from salt Ic contained insufficient rearrangement product for positive detection of the minor isomer. The products from salts If and Ig were expected to contain four rearrangement product isomers. Of these, three were detected in the chromatogram of the product of salt If; the three peaks had areas in the ratio 60:42:8.[10] No such isomers were positively detected in the small amount of presumed rearrangement product of amine Ig. The rearrangement product mixture from amine Ie contained, unexpectedly, three isomers in the approximate ratio 52:41:7. Two of these were assumed to be ortho substitution rearrangement products, and the structure of the major product was proved. The methpicrate of the third isomer was isolated, but the structure was not determined (see below). It was not determined which of the major products was amine IIe. The minor product was assumed to be IIIe.

Isolation of Derivatives V, VIId, and VIIe.—A 2-g. sample of the distilled mixture of amines IIb and IIIb was treated overnight with excess methyl iodide. The resulting oil was triturated with ether and dissolved in warm ethanolic picric acid. Cooling and scratching afforded crystalline 3-methoxy-2-methylbenzyldimethylethylammonium picrate (V) which, after two recrystallizations from 95% ethanol. melted at 119–119.5°.

Anal. Calcd. for $C_{19}H_{24}N_4O_8$: C, 52.29; H, 5.54; N, 12.84. Found: C, 52.35; H, 5.47; N, 12.86.

Similarly, a 2-g. sample of the distilled mixture of amines IId was treated with methyl iodide. Trituration with ethyl acetate gave crystalline 5-methoxy-2-methylbenzyldimethylethylammonium iodide (IVd) which, after three recrystallizations from acetonitrile, melted at 165–165.5°.

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[10] Compare with the fact that the two possible rearrangement product isomers of 3-methoxybenzyltrimethylammonium ion are formed in the ratio 64:36, the more predominant product being the isomer resulting from rearrangement into the position adjacent to the methoxy group. W. Q. Beard, Jr., D. N. Van Eenam, and C. R. Hauser, *J. Org. Chem.*, **26**, 2310 (1961).

Anal. Calcd. for $C_{19}H_{22}INO$: C, 46.57; H, 6.62; N, 4.18. Found: C, 46.70; H, 6.54; N, 4.43.

As described above for preparation of derivative V, a sample of the distilled mixture of amines IIe and IIIe, which had been shown to contain a considerable amount of a third isomer, was treated with methyl iodide and the resulting oil treated with picric acid. This treatment afforded a mixture of two types of crystals, which were separated mechanically. One type of crystals was recrystallized five times from 95% ethanol to give 5-fluoro-2-methylbenzyldimethylethylammonium picrate (VIIe), m.p. 134–135°.

Anal. Calcd. for $C_{18}H_{21}FN_4O_7$: C, 50.94; H, 4.99; N, 13.20. Found: C, 50.75; H, 4.87; N, 13.26.

The second type of crystals from this separation was assumed to be the picrate of the methiodide of the unidentified rearrangement product isomer. After two recrystallizations from 95% ethanol, it melted at 195.5–197°.

Anal. Calcd. for $C_{18}H_{21}FN_4O_7$: C, 50.94; H, 4.99; N, 13.20. Found: C, 50.81; H, 5.21; N, 13.27.

Independent Synthesis of Derivatives V, VIId, and VIIe.—Ortho substitution rearrangement of 2-methoxybenzyltrimethylammonium iodide as described[4] gave 3-methoxy-2-methylbenzyldimethylamine (VI), b.p. 78–80° at 0.7 mm., reported b.p. 111–113° at 9.5 mm.[4] This amine was treated overnight with excess ethyl iodide. The resulting oil was triturated with ether and treated with ethanolic picric acid to give quaternary picrate V which, after six recrystallizations from 95% ethanol, melted at 115.5–118°. A mixture of this material and the sample of picrate V obtained as described above melted at 117–119°. The infrared spectra of the two samples were superimposable.

Ortho substitution rearrangement of 4-methoxybenzyltrimethylammonium bromide as described[4] gave 5-methoxy-2-methylbenzyldimethylamine, b.p. 77–78.5° at 0.65 mm., reported b.p. 106–108.5° at 7.3 mm.[4] Treatment overnight with ethyl iodide afforded derivative VIId. After two recrystallizations from a mixture of acetonitrile and anhydrous ether, this material melted at 165–165.5°, undepressed on admixture with derivative VIId obtained as described above.

Ortho substitution rearrangement of 4-fluorobenzyltrimethylammonium chloride as described[5] gave 5-fluoro-2-methylbenzyldimethylamine (VIIIe), b.p. 77–78° at 6.2 mm., reported b.p. 57–60° at 3–4 mm.[5] Vapor phase chromatography of this amine on several columns gave no evidence of any isomeric impurity. This amine was treated overnight with ethyl iodide and the resulting oil treated with ethanolic picric acid. This treatment afforded quaternary picrate VIIe which, after three recrystallizations from 95% ethanol, melted at 134.5–135°, undepressed on admixture with derivative VIIe obtained as described above

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Norsteroids. IV. The Benzilic Acid Rearrangement of 3-Hydroxy-5α-cholest-3-en-2-one and 2-Hydroxy-5α-cholest-1-en-3-one[1]

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Received July 18, 1962

Treatment of 3-hydroxy-5α-cholest-3-en-2-one or of 2-hydroxy-5α-cholest-1-en-3-one with potassium hydroxide in *n*-propyl alcohol gives a single benzilic acid rearrangement product, A-nor-5α-cholestan-2-ol-2-carboxylic acid. This product indicates a common intermediate for the rearrangement of the isomeric diosphenols. Further transformations of the hydroxy acid are described.

Of the various ring contraction methods available for the preparation of ring-norsteroids, the benzilic acid rearrangement of diosphenols is particularly useful because of its stereospecificity. Thus, the 2,3-diosphenol derived from bismethylenedioxyprednisone rearranged to a single A-nor-2-hydroxy-2-carboxylic acid, which was then converted to A-norcortisone.[2]

Similarly, treatment of 2-bromolanosta-1,8-diene-3-one with alcoholic potassium hydroxide presumably led to the corresponding diosphenol (which was not isolated) which then rearranged to give a single ring contraction product, A-norlanost-8-en-2-ol-2-carboxylic acid.[3] The reaction of 2,2-dibromocholestan-3-one with aqueous or alcoholic alkali also probably proceeded through the diosphenol (spectroscopic evidence was obtained for its presence) to give A-norcholestan-2-ol-2-carboxylic acid, which was not characterized but was directly cleaved with lead tetraacetate to A-norcholestan-2-one.[4]

The rearrangement of 2,2-dibrom-4,4-dimethylcholestan-3-one and of 2,2-dibrom-3-oxotrinordammara-24:20 ξ_2-olide to the corresponding A-nor-2-hydroxy-2-carboxylic acids has also been reported.[5] In all of the above examples of the rearrangement only a single hydroxy carboxylic acid was isolated, and no evidence was given for the presence of isomers.

The work reported here describes a study of the rearrangement of the isomeric diosphenols, 3-hydroxy-5α-cholest-3-en-2-one (I), Diosphenol A, and 2-hydroxy-5α-cholest-1-en-3-one (II), Diosphenol B. These diosphenols had previously been prepared and characterized by several groups.[6] This work[6] also established the fact that the two diosphenols and the diketone were interconvertible in the presence of acid or base,

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[1] Grateful acknowledgment is made to the National Science Foundation for grant NSF-G5926, which financed this study.

[2] R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **81**, 2822 (1959).

[3] R. G. Curtis and R. Schoenfeld, *Australian J. Chem.*, **8**, 258 1955).

[4] T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1573 (1958).

[5] R. Hanna, C. Sandris, and G. Ourisson, *ibid.*, 1454 (1959).

[6] (a) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938); (b) L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944); (c) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).