Coprostanyl Cathylate (J.E.H.).—Treatment of 0.5 g. of coprostanol,[18] m.p. 108.5–110°, α_D +27° Chf, in 12 cc. of pyridine with 1 cc. of ethyl chlorocarbonate (25°, overnight) and fractionation of the resulting mixture by chromatography afforded 0.20 g. (34%) of cathylate, m.p. 107–109°, $\alpha^{25}D$ +23.6 ± 2° Di (depresses starting material).

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 78.43; H, 11.32.

Epicoprostanyl Cathylate (J.E.H.).—Cathylation of 0.5 g. of epicoprostanol,[18] m.p. 109.5–110°, $\alpha^{25}D$ +32° Chf, by the procedure described for coprostanol gave, after chromatography, 0.30 g. (51%) of cathylate, m.p. 101–103° (depression with epicoprostanol), $\alpha^{23}D$ +42.4 ± 0.5° Chf, +49 + 2° Di.

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 78.63; H, 11.30.

Androstane-3β,17β-diol Dicathylate (M.A.R.).—Cathylation of 380 mg. of androstane-3β,17β-diol (m.p. 158–160°) gave a crude product, m.p. 100–110°; on chromatography 10:1 petroleum ether–benzene eluted 250 mg. (44%) of white plates, m.p. 130–132°. Recrystallization from methanol did not change the m.p.; $\alpha^{22}D$ ± 0 Chf; infrared spectrum, no absorption in the region 2.7–3.0 μ.

Anal. Calcd. for $C_{25}H_{40}O_6$ (436.57): C, 68.77; H, 9.24. Found: C, 68.94; H, 9.46.

Lithocholanyl Alcohol (M.W.K.).—Lithocholic acid (m.p. 183–185°) was reduced by placing 2 g. of acid in the thimble of a soxhlet extractor and 2 g. of lithium aluminum hydride and 350 cc. of ether in a boiling flask fitted with a sealed stirrer. After a reaction period of 6 hr., the acid was all dissolved. After destruction of excess reagent by addition of small pieces of ice, the mixture was acidified with dilute sulfuric acid and the product collected by ether extraction. The crude diol, 1.9 g., m.p. 170–172°, gave crystals from dilute methanol, m.p. 176–178°, $\alpha^{27}D$ +35 ± 2° CH_3OH.

Anal. Calcd. for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.80; H, 11.55.

The dicathylate resulted from reaction of the diol (1 g.) in dioxane (10 cc.)–pyridine (2 cc.) with ethyl chlorocarbonate (2 cc.) as described above. The product, obtained as a semi-solid after considerable scratching (1.38 g.), formed shiny crystals from methanol, m.p. 74–75°. After several recrystallizations the sample melted at 75–76°, $\alpha^{25}D$ +41 ± 2° Di.

Anal. Calcd. for $C_{30}H_{50}O_6$ (506.70): C, 71.11; H, 9.95. Found: C, 71.16; H, 10.07.

The infrared spectrum showed no hydroxyl band and the substance was recovered unchanged after treatment with chromic acid in acetic acid at 25° for 18 hr.

Attempts to prepare a monocathyl derivative did not lead to conclusive results.

Δ⁵-Cholestene-3β,4β-diol Dicathylate (M.A.R.).—A solution prepared from 0.5 g. of Δ⁵-cholestene-3β,4β-diol (m.p. 176–177°, $\alpha^{27}D$ −62 ± 0.3° Chf), 15 cc. of pyridine and 2 cc. of ethyl chlorocarbonate was let stand 10 hr. at 25° and poured into water. The reaction product was eluted from alumina by petroleum ether and then crystallized from methanol; it formed leaflets, m.p. 147–149°; yield 0.5 g. (74%); $\alpha^{22}D$ −79.8 ± 0.5° Chf, λ infrared 5.78, 7.80 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.81; H, 10.22.

Δ⁴-Cholestene-3β,6β-diol Dicathylate (M.A.R.).—Reaction of 0.1 g. of Δ⁴-cholestene-3β,6β-diol (m.p. 256–257°, $\alpha^{22}D$ +7.6 ± 0.4° Py) in 15 cc. of pyridine with 0.4 cc. of ethyl chlorocarbonate for 10 hr. and dilution with water gave a solid product that on crystallization from methanol afforded 0.11 g. (80%) of white leaflets, m.p. 168–170°, $\alpha^{22}D$ −19.6 ± 0.6° Chf, λ infrared 5.80, 7.90 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.68; H, 9.78.

Δ⁵-Cholestene-3β,7β-diol Dicathylate (M.A.R.).—A solution of 0.4 g. of 7β-hydroxycholesterol (m.p. 174–176°, $\alpha^{26}D$ 0 ± 0.7° Chf) in 10 cc. of pyridine was treated with 0.8 cc. of ethyl chlorocarbonate (cooling) and let stand 6 hr. at 25°. The material that precipitated on dilution crystallized from methanol in needles, m.p. 82–84°; yield 0.3 g. (55%). Two further crystallizations from aqueous acetone gave needles, m.p. 93–95°, λ infrared 5.80, 7.90 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.78; H, 10.11.

Cathylation of 7α-hydroxycholesterol (m.p. 186–187°, $\alpha^{22}D$ −89 ± 0.6° Chf) gave a product that could not be obtained crystalline even after chromatography. A homogeneous fraction eluted from alumina by 10:1 petroleum ether–benzene had the constants $\alpha^{22}D$ −79.8 ± 0.4° Chf, λ infrared 5.80, 7.90 μ. The absence of absorption in the hydroxyl band region indicates that the substance is the dicathylate.

Cathylation of coprostane-3β,6α-diol[19] (m.p. 195–196°, α_D +23 ± 0.4° Chf) also gave a non-crystalline product that appears to be a dicathylate: eluted by 10:1 petroleum ether–benzene, $\alpha^{20}D$ +4.5 ± 0.5° Chf, λ infrared 5.80, 7.90 μ (no absorption around 2.8 μ).

(19) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

β-Dialkylaminoethyl Esters with Adrenergic Blocking Activity

BY T. A. GEISSMAN, HARRY HOCHMAN AND ROY T. FUKUTO

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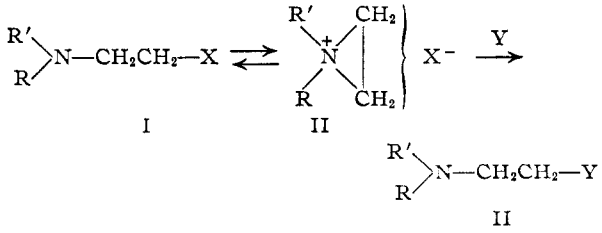
A number of derivatives of β-dialkylaminoethanols have been prepared and compared chemically and pharmacologically with the corresponding β-dialkylamino ethyl chlorides. It was found that sulfonic acid esters of the ethanols possess adrenergic blocking ability. It has been shown that suitable constituted carboxylic esters can react with displacement of the acyloxy grouping, but none of these showed appreciable adrenergic blocking ability. A color reaction of potential usefulness in the estimation *in vivo* of adrenergic blocking agents was studied briefly.

The ability of certain N,N-disubstituted β-haloethylamines (I) (for example, N,N-dibenzyl-β-chloroethylamine) to block excitatory responses to epinephrine and to sympathetic nerve stimulation may be related to their conversion *in vivo* into ethylenimonium intermediates (II) followed by the reaction of these with tissue elements.[1]

Studies on the relationship between structure and physiological activity in compounds of this type[1a,1c] have indicated the importance of structural factors



(1) (a) M. Nickerson and W. S. Gump, *J. Pharm. Exp. Ther.*, **97**, 25 (1949); (b) M. Nickerson, *Pharm. Rev.*, **1**, 27 (1949); (c) J. F. Kerwin, G. C. Hall, M. Nickerson, W. S. Gump, R. A. McLean, E. J. Fellows and G. E. Ullyot, *Science*, **113**, 315 (1951). See also, B. B. Brodie, L. Aranow, E. Titus and J. Axelrod, *Federation Proc.*, **10**, 283 (1951).

which influence (a) the rate of formation and (b) the subsequent reactivity of the imonium ion.[2] The study of a series of compounds of the type shown as I, differing in the nature of the groups R and R′ will, even if X remains constant (*e.g.*, X = Cl), be complicated by changes in the rate of formation of II, its persistence in the blood stream, and by changes in the selectivity of such a series of compounds for specific tissue sites. On the other hand, if R and R′ are held constant in a series differing only in X, the range of variability where X is a halogen atom is clearly limited (the fluoro compound has not been reported). Since the property of the halogen atom in making possible the reaction I ⟶ II is evidently its displaceability by intramolecular attack of the nucleophilic β-nitrogen atom, the use of groups X (in I), other than halogen, which are susceptible of nucleophilic displacement would be expected to lead to compounds having adrenergic blocking activity. The present report concerns the extension of the series by the introduction of other groups X into two selected examples of I.

The above expectations regarding adrenergic blocking activity of analogs of I were confirmed by the preparation of a series of arylsulfonic esters of the alcohols I, R = R′ = $CH_2C_6H_5$; X = OH; and I, R = α-$C_{10}H_7$, R′ = C_2H_5, X = OH. These esters (Table I) show the characteristic behavior

TABLE I: $(R)(R')N—CH_2CH_2—X\cdot HX$

No.	R	R′	X	$t_{1/2}$ (min.)[a] with $S_2O_3^=$
1	$C_6H_5CH_2$	$C_6H_5CH_2$	$OSO_2C_6H_5$	0.5[b] (37°)
2	$C_6H_5CH_2$	$C_6H_5CH_2$	$OSO_2C_6H_4CH_3(p)$	.75 (37°)
3	$C_6H_5CH_2$	$C_6H_5CH_2$	OSO_2-β-$C_{10}H_{10}$	.5 (37°)
4	$C_6H_5CH_2$	$C_6H_5CH_2$	$OSO_2C_6H_4Br(p)$	
5	$C_6H_5CH_2$	$C_6H_5CH_2$	$OCO\cdot C_6H_2(CH_3)_3$	No measurable reaction (37° and 85°)
6	$C_6H_5CH_2$	$C_6H_5CH_2$	$OCOC_6H_2Br_3$	No measurable reaction (37°); 2000 (85°)
7	$C_6H_5CH_2$	$C_6H_5CH_2$	OSO_3H[c]	$.36 \times 10^4$ (37°), 500 (85°)
8	α-$C_{10}H_7CH_2$	C_2H_5	$OSO_2C_6H_4CH_3(p)$	.50[d] (37°)

[a] Half-life calculated from the first-order velocity constant of the reaction with sodium thiosulfate at the indicated temperature. [b] R = R′ = $C_6H_5CH_2$; X = Cl, $t_{1/2}$ = 20 min. (37°). [c] High-melting (zwitterion?) form. [d] R = α-$C_{10}H_7CH_2$; R′ = C_2H_5; X = Cl, $t_{1/2}$ = 5 min. (37°).

of the corresponding β-halogen compounds[3]: they possess adrenergic blocking activity,[4] they consume thiosulfate,[5] they combine with 4-*p*-nitrobenzylpyridine to produce quaternary salts which yield deeply-colored ions when treated with alkali,[6] and they react with dibenzylamine to yield N-tetrasubstituted ethylenediamines.

(2) Current ideas regarding the nature of the *in vivo* reaction include the suggestion that Y may be an amino, sulfhydryl or other nucleophilic grouping of a tissue protein.

(3) Most of the comparisons are based upon examination of derivatives of β-dibenzylaminoethanol the chloride hydrochloride being "Dibenamine").

(4) The authors are grateful to Dr. E. J. Fellows, Smith, Kline and French Laboratories, for the pharmacological tests. The details will be published elsewhere.

(5) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946), see also M. Nickerson, ref. 1b.

(6) E. Koenigs, K. Kohler and K. Blindow, *Ber.*, **58B**, 933 (1925); O. Mumm and G. Hingst, *ibid.*, **56B**, 2301 (1923); Th. Decker, *ibid.*, **38**, 2493 (1905).

β-Dibenzylaminoethyl hydrogen sulfate, an ester closely related to the sulfonic esters, was also prepared and studied. The reaction of β-dibenzylaminoethanol with chlorosulfonic acid in chloroform led to the formation of a crystalline compound which gave analytical figures which agreed with the composition III. When this substance was rubbed with water, or recrystallized from hot ethanol, it was transformed into a higher-melting substance (IV) having a molecule of water less than III. The low- and high-melting forms showed the same reactions; no means was found for reconverting IV into III. It is probable that IV is the anhydrous zwitterion

$$(C_6H_5CH_2)NCH_2CH_2OSO_3H\cdot H_2O$$
III

$$(C_6H_5CH_2)\overset{+}{N}HCH_2CH_2OSO_3^-$$
IV

Both forms reacted with dibenzylamine in boiling chloroform to yield N,N,N′,N′-tetrabenzylethylenediamine, and reacted slowly with thiosulfate. The ester was inactive as an adrenergic blocking agent.

The discovery of adrenergic blocking activity in carboxylic esters (I, X = OCOR) would appear to be unlikely since the displacement of a carboxylate ion in the reaction I ⟶ II is very improbable. β-Dibenzylaminoethyl benzoate[7] is not an adrenergic blocking agent and does not consume thiosulfate. It appeared possible, however, that the ester of a sufficiently strong carboxylic acid might undergo the desired displacement; or that an ester moiety so constituted that attack on the carboxyl carbon atom would be inhibited might undergo displacement of the desired kind. The displacement of benzoate and substituted benzoate ions from the corresponding methyl esters by the action of sodium methoxide has been described,[8] and Hauser has discussed analogous reactions.[9] The β-dibenzylaminoethyl esters of 2,4,6-tribromobenzoic (V) and 2,4,6-trimethylbenzoic acids have now been prepared; they showed no adrenergic blocking ability and neither consumed thiosulfate at a measurable rate at 37°. At 85°, however, while the trimethyl derivative was still inert toward thiosulfate, the tribromo derivative reacted slowly, suggesting that the expulsion of the tribromobenzoate ion took place. This observation is in general accord with the finding[6] that the stronger acid (pK_A tribromo = 3.9×10^{-2}; pK_A trimethyl = 3.8×10^{-5}) reacts more readily by displacement of the acid anion. Additional evidence for the displacement reaction was obtained when it was found that the tribromobenzoate (V) reacted with methanol at 150° to yield methyl β-dibenzylaminoethyl ether

$$(C_6H_5CH_2)_2NCH_2CH_2OCOC_6H_2Br_3 + CH_3OH$$
$$(C_6H_5CH_2)_2NCH_2CH_2OCH_3 + Br_3C_6H_2COOH$$

The use of sodium methoxide in methanol led only to β-dibenzylaminoethanol, indicating that the rate of saponification by attack of methoxide on the carbonyl carbon atom is a relatively more rapid reaction than the obviously slow (*cf.* thiosulfate

(7) V. O. Gabel, *Bull. soc. chim.*, [5] **1**, 1006 (1934).

(8) J. F. Bunnett, M. M. Robison and F. C. Pennington, THIS JOURNAL, **72**, 2378 (1950).

(9) C. R. Hauser, J. C. Shivers and P. S. Skell, *ibid.*, **67**, 409 (1945).

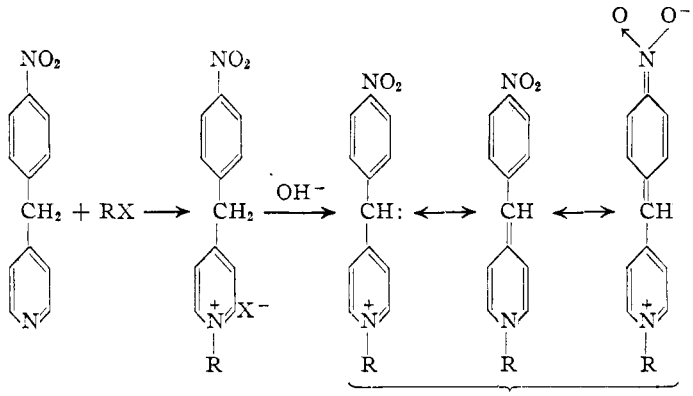
reaction) displacement of the anion, a reaction which presumably, but not demonstrably, occurs by intramolecular attack of the amino nitrogen atom.

The preparation of the sulfonic and carboxylic esters listed in Table I was most conveniently carried out by the reaction of the appropriate β-dialkylaminoethyl chloride hydrochloride (or in a few cases, the iodide hydriodide) with the dry silver salt of the appropriate sulfonic or carboxylic acid in an inert solvent such as chloroform. The addition of ether, after the removal of silver halide, precipitated the ester, usually as an oil; crystallization could often be induced by scratching, but numerous preparations failed to yield crystallizable materials although there was evidence in many such cases (silver halide formation, thiosulfate consumption by the oily product) that the desired compound was in hand. The non-crystallizable products were not examined in detail.

$$R_2NCH_2CH_2Cl\cdot HCl + R'SO_2OAg\ (R''COOAg)$$
$$R_2NCH_2CH_2OSO_2R'\cdot R'SO_3H\ (R_2NCH_2CH_2OCOR'')^{10}$$

A number of alternative routes to the sulfonic acid esters of β-dibenzylaminoethanol were examined. (1) Treatment of the amino alcohol with benzenesulfonyl chloride in ether solution at ordinary temperature resulted in the benzenesulfonic acid salt of the amino alcohol as the only crystalline product isolated. (2) When the same reactants where heated at 150–160° in the absence of a solvent, β-dibenzylaminoethyl chloride hydrochloride (Dibenamine) was formed. (3) The interaction of the amino alcohol with methanesulfonyl chloride in chloroform–acetone solution yielded only the hydrochloride of the amino alcohol, in contrast to the experience of Wendler and Tishler,[11] who prepared the mesyl ester of dimethylaminopropanol-2 under the same conditions. (4) The reaction of ethylene glycol bis-benzenesulfonate (in large excess) with dibenzylamine led only to the bis-benzenesulfonic acid salt of N,N,N′,N′-tetrabenzylethylenediamine. (5) The reaction of the amino alcohol with *p*-toluenesulfonic acid at 160–200° afforded a moderate yield of the *p*-toluenesulfonate of the amino alcohol (as the *p*-toluenesulfonic acid salt), but the method was unsatisfactory in analogous cases.

Estimation of Dibenamine in Solution.—Koenigs and others[6] have described the formation of deeply-colored substances by the action of alkylating agents on γ-(*p*-nitrobenzyl)-pyridine. Since, in the estimation of Dibenamine and its congeners in physiological fluids and tissues what it is necessary to measure is alkylating ability, it appeared that the use of this reaction might lead to the development of a method for the assay of these drugs. The reaction between an alkylating agent, such as methyl iodide, and α- or γ-(*p*-nitrobenzyl)-pyridine, followed by the addition of alkali, may be formulated as



VI, RX = CH_3I
VII, RX = $(C_6H_5CH_2)_2NCH_2CH_2Cl$

When Dibenamine was allowed to react with γ-(*p*-nitrobenzyl)-pyridine the expected dibenzylaminoethylpyridinium salt (VII) was formed. This reacted with alkali to produce a deep blue salt (λ_{max} 556 mμ, log ε 4.48), visually and spectrophotometrically (Fig. 1) very similar to that derived from the methyl analog (VI) (λ_{max} 548 mμ, log ε 4.52).

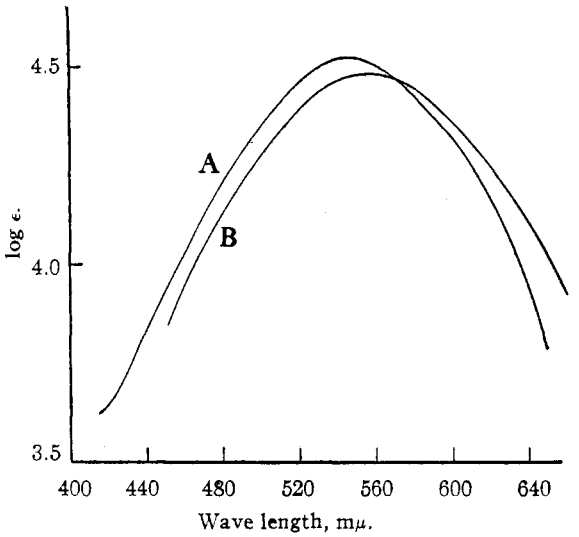


Fig. 1.—Absorption spectra of the methines derived from the alkylpyridinium salts VI (A, R = CH_3) and VII (B, R = $CH_2CH_2N(CH_2C_6H_5)_2$). See text for details of measurements.

Measurements of the development with time of the colored ions formed in solutions of Dibenamine and its analogs and γ-(*p*-nitrobenzyl)-pyridine disclosed the interesting fact that while the initial *rates* of color development with variations in the groups R of I bore a parallelism to the rates of reaction with thiosulfate, the *maximum* color development was about the same within a series in which R and R′ remained the same and X was varied. This result is to be expected if the active alkylating agent is the imonium ion, derived by a first-order, rate determining reaction from the parent I, and dissipated by concurrent reactions with the substituted pyridine (leading to the colored ion) and with the solvent (leading to compounds, such

(10) The carboxylic esters were obtained as hydrochlorides.
(11) N. L. Wendler and M. Tishler, THIS JOURNAL, **71**, 374 (1949).

as the alcohol, undetected by the spectrophotometric measurement).[12]

Tables II and III contain the data for the two series of compounds examined.

TABLE II

$(C_{10}H_7CH_2)(C_2H_5)NCH_2X\cdot HY$

X	Y	% reaction[a] at time (min.) 15	30	45	60	max.
Cl	Cl	3.6	7.6	10.5	12.5	13.6
$OSO_2C_6H_5$	$OSO_2C_6H_5$	10.8	13.1	13.6	14.1	14.4
OSO_2-*p*-tol	OSO_2-*p*-tol	10.6	12.1	13.2	(13.2)	14.3
OSO_2-α-naph.	OSO_2-α-naph.	10.5	11.7	13.1	13.9	14.1
$OCOCCl_3$	Cl	0.0	0.0	0.0	0.0	0.0

[a] As percentage of the extinction (at 550 mμ) given by the colored ion derived from an amount of the pure quaternary salt equal to the amount of I used.

TABLE III

$(\alpha\text{-}C_{10}H_7CH_2)(C_2H_5)NCH_2CH_2X\cdot HY$

X	Y	% reaction[a] at time (min.) 15	30	45	60	max.
Cl	Cl	4.7	8.7	12.0	13.6	19.4
Cl	$C_6H_5SO_3$	3.9	7.6	11.4	13.7	18.7
Cl	*p*-Tol-SO_3	3.8	8.1	11.1	13.7	19.2
OSO_2-*p*-tol	OSO_2-*p*-tol	7.3	10.8	13.7	15.0	19.0
$OCOCCl_3$	Cl	0.0	0.0	0.0	0.0	0.0

[a] As percentage of the extinction (at 550 mμ) given by the colored ion derived from an amount of the pure quaternary salt equal to the amount of I used.

Experimental

N,N-Dibenzyl-β-chloroethylamine hydrochloride was prepared by the action of thionyl chloride on dibenzylaminoethanol, prepared according to the method of Gabel.[7]

N-Ethyl-N-(α-naphthylmethyl)-β-chloroethylamine hydrochloride[13] was prepared by the action of thionyl chloride on the corresponding alcohol. The latter was prepared as follows: A mixture of 220 g. of α-naphthylmethyl chloride,[14] 55 g. of ethylaminoethanol, 190 g. of potassium carbonate, 50 ml. of water and 300 ml. of 95% ethanol was refluxed for two hours and then kept at room temperature overnight. The ethanol solution was decanted from the inorganic salts, concentrated by distillation, diluted with water and extracted with chloroform. Dry hydrogen chloride was passed into the chloroform extract and the resulting amine hydrochloride was precipitated by the addition of dry ether. The product weighed 160 g. and melted at 136–138°.

N,N-Dibenzyl-β-iodoethylamine Hydriodide.—A solution of 20 g. of N,N-dibenzyl-β-chloroethylamine hydrochloride and 25 g. of sodium iodide in 200 ml. of dry acetone was refluxed, with stirring, for 24 hours. The solid material, which contained the bulk of the product, was removed and to the acetone filtrate was added dry ether to precipitate the remainder. The combined solids were extracted with hot, absolute ethanol from which the iodo compound crystallized on cooling. The yield of pale yellow, crystalline material was 30.5 g., m.p. 178–179° dec.

Anal. Calcd. for $C_{16}H_{19}NI_2$: C, 40.10; H, 4.00; neut. equiv., 239.6. Found: C, 39.82; H, 4.21; neut. equiv., 239.

N-Ethyl-N-(α-naphthylmethyl)-β-iodoethylamine hydriodide (7 g.) was prepared in an analogous way from the corresponding chloro compound (5 g.); it formed pale yellow prisms, m.p. 166.5–167° dec.

Anal. Calcd. for $C_{15}H_{19}NI_2$: C, 38.56; H, 4.10; neut. equiv., 233.6. Found: C, 38.31; H, 4.12; neut. equiv., 236.

Silver Salts of Sulfonic Acids.—These were prepared by the addition of the required amount of silver carbonate or silver oxide to an aqueous solution of the appropriate sulfonic acid. The silver salts were nicely crystalline substances which could be recrystallized from water. Table IV summarizes the pertinent data.

TABLE IV

R-SO_3Ag

R	Ag calcd., %	Ag found, %
C_6H_5	40.70	40.76
p-$C_6H_4CH_3$	38.66	38.55
β-$C_{10}H_7$	34.24	34.17
p-C_6H_4Br	31.37	31.49
CH_3	53.15	53.34
NH_2	44.95[a]	44.77

[a] Dihydrate.

Preparation of N,N-Dialkyl-β-sulfonyloxyethylamines (as the Sulfonic Acid Salts).—The following procedure was followed, minor variations occasionally being necessary in dealing with products difficult to crystallize: A mixture of 20 g. of N,N-dialkyl-β-chloroethylamine hydrochloride, somewhat over two equivalents of the required silver sulfonate and 200 ml. of dry chloroform or acetone was refluxed vigorously for 18–22 hours. The hot solution was filtered through filter-aid and the clear filtrate concentrated and diluted with dry ether until turbidity resulted. The product usually separated as an oil when the solution was allowed to stand. Crystallization was induced by scratching and cooling. The product was redissolved in chloroform, filtered to remove traces of silver chloride, and crystallized by the addition of ether.

The properties and analytical data for the compounds listed in Table I are given in Table V.

In many cases the reaction between a β-chloroethylamine hydrochloride and a silver sulfonate proceeded only to the stage at which the sulfonic acid salt of the chloroethylamine was formed. In other cases uncrystallizable oils were obtained. In still other experiments the sulfonic acid salt of the amino alcohol was produced. The descriptions of these unsuccessful experiments are omitted.

β-Dibenzylaminoethyl Hydrogen Sulfate Monohydrate (Compd. No. 7).—Ten grams of β-dibenzylaminoethanol was dissolved in 50 ml. of dry chloroform and a solution of 6 g. of chlorosulfonic acid in 50 ml. of chloroform was added slowly. The clear, colorless solution which resulted was refluxed for two hours, cooled, and diluted with dry ether. An oil was precipitated. The ether–chloroform solution was decanted and the oil covered with dry ether. Scratching induced crystallization of the oil, and subsequent recrystallization from chloroform–ether took place readily. The product (12 g.) formed colorless needles, m.p. 73–75°.

Anal. Calcd. for $C_{16}H_{19}NSO_4\cdot H_2O$: C, 56.32; H, 6.19. Found: C, 56.20; H, 6.19.

When the m.p. 73–75° compound was recrystallized from hot ethanol the product, obtained in quantitative yield, formed colorless leaflets, m.p. 208–210°.

Anal. Calcd. for $C_{16}H_{19}NSO_4$: C, 59.82; H, 5.96. Found: C, 59.40; H, 6.05.

When either the 73–75° or the 208–210° compound was refluxed with a chloroform solution of dibenzylamine, N,N,N′,N′-tetrabenzylethylenediamine, m.p. 94–95°, was formed. The diamine was prepared from N,N-dibenzyl-β-chloroethylamine in the same way; reported[15] m.p. 95°.

Silver 2,4,6-Tribromobenzoate.—2,4,6-Tribromobenzoic acid[16] (14.38 g.) was dissolved in a mixture of 9 ml. of 6 *N* ammonium hydroxide and 100 ml. of water. An aqueous solution of 6.23 g. of silver nitrate was added and the white solid which separated was collected, washed with water and methanol and dried. The yield was 16 g.

Silver 2,4,6-Trimethylbenzoate.—A solution of 5.16 g. of silver nitrate was added to a solution of 5.10 g. of 2,4,6-trimethylbenzoic acid in 7 ml. of 6 *N* ammonium hydroxide and 20 ml. of water. The precipitated salt was collected, washed with water and methanol and dried; yield 6.5 g.

β-Dibenzylaminoethyl 2,4,6-Tribromobenzoate (Compd. No. 6).—A mixture of 8.0 g. of silver 2,4,6-tribromobenzoate

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TABLE V

Cpd. (Table I)		1	2	3	4	8[a]
M.p., °C.		119–120.5	144–146	125–127[b]	107–110	103.5–105
Carbon, %	Calcd.	62.32	63.55	67.13	49.28	62.69
	Found	62.05	63.03	66.88	48.75	62.86
Hydrogen, %	Calcd.	5.42	5.87	5.63	4.40	5.99
	Found	5.80	6.04	5.70	4.45	6.17
Sulfur, %	Calcd.	11.86	11.30			
	Found	11.87	11.13			
Nitrogen, %	Calcd.	2.60				
	Found	2.59				
Neut. equiv.	Calcd.	269.5	283.5	349	373	277.5
	Found	271	281	350	377.5	277

[a] Prepared from the iodo-hydriodide. [b] Crystallizes from acetone with one molecule of solvent.

and 2.54 g. of N,N-dibenzyl-β-chloroethylamine hydrochloride in 200 ml. of chloroform was refluxed with stirring for 48 hours. The mixture was filtered while hot, the filtrate concentrated to 50 ml., cooled in ice, shaken with two 75-ml. portions of aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and the chloroform removed *in vacuo*. When petroleum ether was added to the residual oil the product crystallized. After recrystallization from ether–petroleum ether the ester melted at 91–92°; the yield was 4.75 g.

Anal. Calcd. for $C_{23}H_{20}NO_2Br_3$: C, 47.40; H, 3.47. Found: C, 47.34; H, 3.63.

The hydrochloride, prepared by treating an ether solution of the ester with dry hydrogen chloride, melted at 194–195°.

Anal. Calcd. for $C_{23}H_{21}O_2Br_3Cl$: C, 44.70; H, 3.43. Found: C, 44.87; H, 3.62.

β-Dibenzylaminoethyl 2,4,6-Trimethylbenzoate (Compd. No. 5).—Thirteen grams of silver 2,4,6-trimethylbenzoate and 7.8 g. of N,N-dibenzyl-β-chloroethylamine hydrochloride were stirred and heated in 200 ml. of refluxing chloroform for 24 hours. The filtrate was concentrated to 75 ml. and treated with dry hydrogen chloride. The addition of ether caused the separation of an oil. This crystallized when scratched, and after recrystallization from chloroform–ether the hydrochloride melted at 155–157°.

Anal. Calcd. for $C_{27}H_{30}NO_2Cl$: C, 73.65; H, 7.13. Found: C, 73.27; H, 7.37.

Reactions of β-Dibenzylaminoethyl 2,4,6-Tribromobenzoate. A. With Dibenzylamine.—A solution of 0.5 g. of β-dibenzylaminoethyl 2,4,6-tribromobenzoate and 0.5 g. of dibenzylamine in 10 ml. of chloroform was boiled under reflux for 24 hours. The original ester and dibenzylamine were recovered.

B. With Sodium Methoxide in Methanol.—To a solution of 0.2 g. of sodium in 15 ml. of absolute methanol was added 0.45 g. of β-dibenzylaminoethyl-2,4,6-tribromobenzoate. The solution was refluxed for 96 hours, evaporated to dryness, and the residue treated with water and ether. The dried ether solution was treated with hydrogen chloride; β-dibenzylaminoethanol hydrochloride (0.25 g., m.p. 172–175°) precipitated. Acidification of the alkaline solutions yielded a trace of 2,4,6-tribromobenzoic acid. No attempt was made to isolate methyl 2,4,6-tribromobenzoate. The β-dibenzylaminoethanol hydrochloride depressed the m.p. of a sample of the hydrochloride of β-dibenzylaminoethyl methyl ether to 130–137°.

C. With Methanol.—A solution of 0.2 g. of the amino ester in 3 ml. of dry methanol was heated (sealed tube) for 48 hours at 140–150°. The basic material was converted into the hydrochloride as in B, yielding 0.10 g. of a crystalline product, m.p. 143–145°. A mixed melting point determination with β-dibenzylaminoethyl methyl ether hydrochloride, m.p. 145–146°, showed the identity of the two samples. The authentic material was prepared by treatment of N,N-dibenzyl-β-chloroethylamine with sodium methoxide in methanol.

Anal. Calcd. for $C_{17}H_{21}NOCl$: C, 69.98; H, 7.61. Found: C, 70.19; H, 7.83.

β-Dibenzylaminoethyl 2,4,6-trimethylbenzoate was unaffected by treatment with dibenzylamine in boiling chloroform and by sodium methoxide in boiling methanol.

Rate of Reaction with Thiosulfate.[17]—A weighed sample of the compound (as the hydrochloride or other salt) in 40 ml. of ethanol was brought to 37.1° and added to 200 ml. of a standard solution of water, ethanol, sodium bicarbonate and sodium thiosulfate, also at 37.1°. The final reaction mixture had the approximate composition: ethanol, 70% by volume; water, 30%; sample, 4×10^{-4} *M*; sodium thiosulfate, 1.6×10^{-3} *M*; sodium bicarbonate, 1.6×10^{-3} *M*. At measured intervals, 75-ml. aliquots were removed, cooled quickly, acidified, and titrated with standard biiodate solution (0.024 *N*). First-order rate constants were calculated from the titration data. Blank determinations showed that the titer of the thiosulfate solution remained constant at 37.1 and 85° over the periods of time covered by the rate runs. High precision was not sought nor required for the present purposes, and comparisons of our results with those reported for selected compounds[17] showed satisfactory agreement.

4-(*p*-Nitrobenzyll)-pyridine has been described.[6,18] Its preparation in a pure state depends upon the accessibility of pure 4-benzylpyridine, which is formed along with the 2-isomer by the reaction of benzyl chloride with pyridine at elevated temperatures.[18,19] For the preparation of small amounts of the pure 4-isomer, it was found more convenient to proceed by way of the readily purified isonicotinic acid,[20] and thence to 4-benzoylpyridine[21] and 4-benzylpyridine. The reduction of 4-benzoylpyridine was most conveniently carried out by the use of Huang-Minlon's modification of the Wolff–Kishner reduction.[22] Nitration of the 4-benzylpyridine was carried out in the manner described,[18,23] the nitro compound having m.p. 70–71.5° (reported[23] 74°).

4-(*p*-Nitrobenzyl)-pyridine methiodide was prepared as described by Koenigs, *et al.*[6]

4-(*p*-Nitrobenzyl)-pyridine β-Dibenzylaminoethochloride.—A solution of 100 mg. of 4-(*p*-nitrobenzyl)-pyridine and 200 mg. of N,N-dibenzyl-β-chloroethylamine hydrochloride in 5 ml. of absolute ethanol was heated at 75° for 48 hours. The addition of ether to the orange solution caused a yellow crystalline solid to separate. Recrystallized from ethanol–ether, the compound formed nearly colorless needles, m.p. 205–206° dec.

Anal. Calcd. for $C_{28}H_{29}N_3O_2Cl_2 \cdot H_2O$: C, 63.62; H, 5.91. Found: C, 63.79; H, 5.96.

Rate of Alkylation of 4-(*p*-Nitrobenzyl)-pyridine.—To 100 ml. of 70% ethanol, brought to 37.6°, were added 2 ml. of 0.01 sodium bicarbonate, 20 ml. of 0.01 *M* ethanolic 4-(*p*-nitrobenzyl)-pyridine and 2 ml. of a 0.01 *N* ethanolic solution of the amino alcohol derivative to be studied. At measured time intervals 5-ml. aliquots of this solution were transferred to a cuvette containing 5 ml. of 70% ethanol and

(17) The choice of conditions for these determinations was dictated by our desire to be able to compare our compounds' behavior directly with that of a series of β-chloroethylamines, the rates of reaction of which were disclosed to us in private communications from Dr. G. E. Ullyot.

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0.5 ml. of 0.1 *N* ethanolic potassium hydroxide. The solution was mixed and the optical density at 550 mμ measured in a Coleman Model 11 Universal Spectrophotometer. The extent of conversion of the pyridine to the pyridinium compound was calculated with the aid of the molar extinction coefficient determined by measurements made in the same way on pure 4-(*p*-nitrobenzyl)-N-β-dibenzylaminoethyl pyridinium chloride.

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LOS ANGELES, CALIFORNIA

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Steroidal Sapogenins. XX.[1a] Synthesis and Reactions of the Epimeric Δ^5-22-Isospirosten-3β,7-diols[1b]

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Alkaline hydrolysis with alumina of 7α-bromo-Δ^5-22-isospirosten-3β-ol acetate (Ia) produced Δ^5-22-isospirosten-3β,7α-diol 3-monoacetate (IIa), which upon chromium trioxide oxidation afforded Δ^5-22-isospirosten-3β-ol-7-one 3-acetate (IIIa). **The latter** could also be obtained by oxidation of Ia or most advantageously from Δ^5-22-isospirosten-3β-ol acetate (diosgenin **acetate)** by N-bromosuccinimide bromination–alumina hydrolysis–chromium trioxide oxidation without purification of **intermediates.** Lithium aluminum hydride reduction of the 7-ketone IIIa led to Δ^5-22-isospirosten-3β,7β-diol (IVa). The **configuration of the** epimeric diols II and IV was established by a comparison of the molecular rotation differences with **analogous derivatives** in the cholesterol series and by the course of pyrolysis experiments of the respective dibenzoates. **The 3β,7α-dibenzoate** IId led predominantly to $\Delta^{2,4,6}$-22-isospirostatriene (VI), while the epimeric 3β,7β-dibenzoate IVb **afforded** $\Delta^{6,7}$-22-isospirostadien-3β-ol benzoate (V).

Two methods have been recorded[1,3] for the synthesis of $\Delta^{5,7}$-22-isospirostadien-3β-ol (7-dehydrodiosgenin) (V). Since this substance represents the starting material in the synthesis[4,5] of the adrenal hormone cortisone from the plant sapogenin diosgenin it appeared of interest to study the applicability of the classical Windaus 7-dehydrocholesterol synthesis[6] to the sapogenin series and to characterize the intermediates.

Δ^5-22-Isospirosten-3β-ol-7-one acetate (IIIa), the key intermediate in such a synthesis has previously been prepared[7] in poor yield by direct chromium trioxide oxidation of Δ^5-22-isospirosten-3β-ol acetate or its 23-bromo derivative. In the present work it has been possible to increase the yield in this reaction to over 40%[8] by employing two alternate procedures. In either instance, the starting material was 7α-bromo-Δ^5-22-isospirosten-3β-ol acetate (Ia)[3] which without purification could be oxidized directly to IIIa with chromium trioxide in aqueous acetic acid. Alternately, the bromo derivative Ia was hydrolyzed in carbon tetrachloride solution (directly from the Wohl–Ziegler bromination[3]) with aluminum oxide to yield in *ca.* 50% over-all yield (based on Δ^5-22-isospirosten-3β-ol acetate) pure Δ^5-22-isospirosten-3β,7α-diol 3-monoacetate (IIa) which could then be oxidized to the ketone IIIa. A similar reaction sequence could be carried out with the 3-benzoate leading to Δ^5-22-isospirosten-3β,7α-diol 3-monobenzoate (IIc); for further characterization the free diol IIb and the dibenzoate IId were prepared. A small amount of the 7β-hydroxy epimer (IV) was also produced in the hydrolysis reaction.

In agreement with the observation of Fieser, *et al.*,[6] in the cholesterol and stigmasterol series lithium aluminum hydride reduction of the 7-keto derivative IIIa afforded predominantly the 7β-hydroxy isomer IVa, further characterized by its 3,7-dibenzoate IVb. The molecular rotation differences (Table I) both with respect to the differences between the two pairs of epimers (ΔM_D epimers) or the C-7 unsubstituted parent compound (ΔM_D parent compound) are in excellent agreement with the corresponding cholesterol derivatives. This coincidence in the rotation measurements automatically correlates the configuration of the presently described epimeric Δ^5-22-isospirosten-3β,-7-diols (II, IV) with the Δ^5-cholestene-3β,7-diols. The present assignments of configurations are based on the conclusions of Fieser and Fieser,[6,9] and of Barton[10] in the cholesterol series employing as additional chemical evidence the now generally accepted concept of thermal *cis*-elimination,[10] rather than on the proposed revision of configurational assignments made by Schaltegger and Müllner.[11] Thus in agreement with the results in

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(1b) Presented on the program of the Division of Organic Chemistry, A. C. S. meeting, Milwaukee, Wis., April, 1952.

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