diazomethane reactions have been described earlier in detail.[13,14] The same methods were found to be considerably more convenient than the classical gasometric procedures for following the rates of ethyl diazoacetate reactions. With this substance (prepared by the usual method[20] and distilled under reduced pressure before use) the change in concentration was followed by the change in optical density at 375 mμ (ε 15.7 in absolute ethanol).

**Deuterated Solvents. A. Deuteroethanol** ($C_2H_5OD$).—The following procedure is ideal for the preparation of $C_2H_5OD$ with maximum deuterium utilization but suffers from the relative inaccessibility of the starting material, ethyl orthocarbonate. A mixture of 140 g. (0.73 mole) of freshly distilled ethyl orthocarbonate,[21] 12.7 ml. (0.70 mole) of 99.75% deuterium oxide (Norsk Hydro) and one drop of concd. sulfuric acid was placed in a flask attached to a short Vigreux column and refluxed gently until it became homogeneous. The material with b.p. 78–82° (79 g.) was then collected and refractionated through a carefully-dried 50-cm. column packed with 2-mm. stainless-steel helices. The product had b.p. 78.5–79°, $n^{25}D$ 1.3583, and showed only very weak hydroxyl (O–H) and carbonyl absorption in the infrared. A saponification equivalent analysis indicated the presence of 1% or less of ethyl carbonate. The paraffin oil method of Robertson[22] indicated the presence of 0.5% of heavy water in the deuteroethanol.

*Anal.* Calcd. for $C_2H_5OD$: C, 51.03: H (total), 14.99. Found: C, 51.04; H (total) 14.88.

B. **Deuteroacetic Acid** ($CH_3CO_2D$).—Deuterium oxide (99.75%, 6.0 g., 0.30 mole) was refluxed for an hour with 35 g. (0.34 mole) of freshly distilled acetic anhydride. The mixture was fractionated and yielded 40 g. of $CH_3CO_2D$, b.p. 116–117°, $n^{25}D$ 1.3686–1.3689.

**Reaction of Ethyl Diazoacetate with Deuteroethanol.**—Mixtures of ethyl diazoacetate and $C_2H_5OD$ in molal ratios of 1:0.87, 1:1.74 and 1:8.7 were cooled in an ice-bath and a trace of concd. fluoboric acid added. Other acids such as hydrochloric, sulfuric, perchloric or *p*-toluenesulfonic acid were ineffective at the lower ratios since they appeared to react irreversibly with the diazo ester. The mixtures were allowed to stand overnight at room temperature, the excess alcohol was removed under reduced pressure and the residual ethyl ethoxyacetate fractionated (b.p. 50°, 10 mm.) through a semimicro column.[23] The mixtures were compared as to deuterium content by their infrared spectra (Fig. 3) and combustion analysis (Table III).

The infrared spectrum of the recovered ethyl ethoxyacetate obtained from a mixture of ethyl ethoxyacetate and deuteroethanol which was allowed to stand for several days in the presence of fluoboric acid is included in Fig. 3.

**Reaction of Ethyl Diazoacetate with Deuteroacetic Acid.**—The procedure was similar to that used for the deuteroethanol experiments except that no catalyst was used and the reactions were so slow that some heating was required. The products had b.p. 62° (10 mm.) after fractionation through a semi-micro column.[23] The infrared spectra of the products are given in Fig. 4 and the results of the combustion analyses are presented in Table III.

The reactions in benzene (90% by volume) were carried out similarly. The rates were slow and the mixtures were refluxed from 24–40 hr. The infrared spectra of the products are given in Fig. 4 and it is seen that there is no significant difference between the materials obtained in the presence or absence of benzene.

(20) E. B. Womack and A. B. Nelson, *Org. Syntheses*, **24**, 56 (1944).

(21) We are indebted to Dr. Robert E. McMahon for this material which was prepared by a modification of the method of H. Tieckelmann and H. W. Post, *J. Org. Chem.*, **13**, 265 (1948). The procedure will be published in detail elsewhere.

(22) G. R. Robertson, "Laboratory Practice of Organic Chemistry," 2nd Ed., The Macmillan Co., New York, N. Y., 1943, p. 177. We assume here that deuteroethanol and deuterium oxide behave the same as ordinary ethanol and water toward paraffin oil.

(23) C. W. Gould, G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

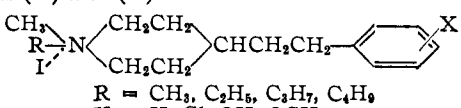
# Synthetic Curare Substitutes from Stilbazoline Bis-quaternary Ammonium Salts

BY ARTHUR P. PHILLIPS

RECEIVED FEBRUARY 15, 1952

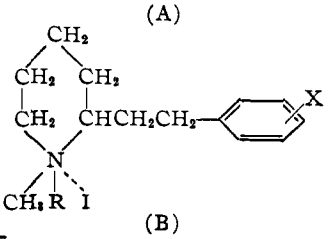
The structure of the alkyl groups attached to the nitrogens in 1,4′-bis-quaternary ammonium salts of 2- and 4-stilbazolines has been varied systematically, and the relationship between structure and curare-like activity has been examined. In the 4-stilbazolines the nature of the alkyls is critical and the completely methylated compound (I) represents maximum activity. Replacement of two methyl groups (one from each nitrogen) by ethyls (or higher alkyls) gives products devoid of curare-like activity, while a single ethyl at either nitrogen results in considerably diminished activity. In the 2-stilbazolines increasing alkyl group size does not diminish the antagonistic activity which these substances have in reversing the myoneural block of I or decamethylene-1,10-bis-trimethylammonium bromide (Syncurine).

An earlier paper[1] reported the discovery of powerful curare-like and related activities in certain 4- and 2-stilbazoline quaternary ammonium salts such as (A) and (B)



R = $CH_3$, $C_2H_5$, $C_3H_7$, $C_4H_9$
X = H, Cl, OH, $OCH_3$
$N(CH_3)_3I$, etc.

(A)



(B)

The 4-isomers (A) had a stronger curare-like potency, attaining a maximum in the bis-quaternary ammonium salt I (A, R = $CH_3$; X = $N(CH_3)_3I$). Reversal of the block of neuromuscular transmission in the cat, produced by these 4-isomers (best by I), was achieved by the 2-stilbazoline salts (B above) which showed only vestigial curariform activity, apparent only at much higher dosages than those required to produce reversal. Again in the latter series maximum activity, as an antagonist to the curare-like action of its 4-isomer, was found in the bis-quaternary ammonium salt X (B, R = $CH_3$, X = $N(CH_3)_3I$).

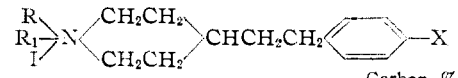
The effect of variation of the size of alkyl groups on the quaternary nitrogens on activity has been studied and the results are given in this work.

The compounds were made in the same general fashion as described earlier.[1] Condensation of 4-dimethylamino- and 4-diethylaminobenzaldehyde

(1) A. P. Phillips and J. C. Castillo, THIS JOURNAL, **73**, 3949 (1951).

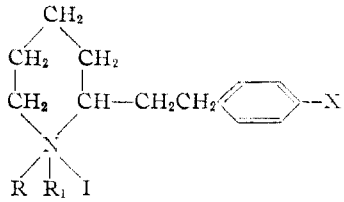
TABLE I

(A) 1,4'-Bis-quaternary ammonium iodides from 4-stilbazolines



| Compd. No. | R | $R_1$ | X | M.p., °C.[a-c] | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Iodine, % Calcd. | Iodine, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| I[d] | $CH_3$ | $CH_3$ | $(CH_3)_3NI$ | 183–185 | 40.7 | 40.4 | 6.1 | 6.1 | 47.9 | 47.9 |
| II | $CH_3$ | $C_2H_5$ | $C_2H_5(CH_3)_2NI$ | 191–193 | 43.0 | 42.7 | 6.5 | 6.1 | | |
| III | $CH_3$ | $n$-$C_3H_7$ | $n$-$C_3H_7(CH_3)_2NI$ | 166–167 | 45.0 | 45.0 | 6.9 | 7.0 | 43.3 | 43.3 |
| IV | $CH_3$ | $n$-$C_4H_9$ | $n$-$C_4H_9(CH_3)_2NI$ | 164–166 | 46.9 | 47.0 | 7.2 | 7.0 | 41.3 | 41.3 |
| V | $CH_3$ | $C_2H_5$ | $(CH_3)_3NI$ | 191–192 | 41.9 | 41.5 | 6.3 | 6.4 | 46.7 | 46.6 |
| VI | $CH_3$ | $CH_3$ | $C_2H_5(CH_3)_2NI$ | 185–186 | 41.9 | 42.2 | 6.3 | 6.1 | 46.7 | 46.6 |
| VII | $CH_3$ | $CH_3$ | $CH_3(C_2H_5)_2NI$ | 187–188 | 43.0 | 42.7 | 6.5 | 6.6 | | |
| VIII | $CH_3$ | $C_2H_5$ | $(C_2H_5)_3NI$ | 202–205 (dec.) | 45.0 | 44.6 | 6.9 | 6.7 | | |
| IX | $C_2H_5$ | $C_2H_5$ | $C_2H_5(CH_3)_2NI$ | 185–187 | 44.0 | 44.2 | 6.7 | 6.9 | 44.3 | 44.2 |

(B) 1,4'-Bis-quaternary ammonium iodides from 2-stilbazolines



| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| X[d] | $CH_3$ | $CH_3$ | $(CH_3)_3NI$ | 200–201 | 40.7 | 41.0 | 6.1 | 5.9 | 47.9 | 47.9 |
| XI | $CH_3$ | $C_2H_5$ | $C_2H_5(CH_3)_2NI$ | 205–206 | 43.0 | 43.0 | 6.5 | 6.4 | | |
| XII | $CH_3$ | $n$-$C_3H_7$ | $n$-$C_3H_7(CH_3)_2NI$ | 145–150[e] | 45.0 | 45.0 | 6.9 | 6.9 | 43.3 | 43.2 |
| XIII | $CH_3$ | $n$-$C_4H_9$ | $n$-$C_4H_9(CH_3)_2NI$ | 115–120[e] | 46.9 | 46.9 | 7.2 | 7.3 | 41.3 | 40.9 |
| XIV | $CH_3$ | $C_2H_5$ | $(CH_3)_3NI$ | 155–160 (dec.) | 41.9 | 41.5 | 6.3 | 6.5 | 46.7 | 46.6 |
| XV | $CH_3$ | $CH_3$ | $CH_3(C_2H_5)_2NI$ | 191–192 | 43.0 | 42.7 | 6.5 | 6.3 | | |
| XVI | $CH_3$ | $C_2H_5$ | $(C_2H_5)_3NI$ | Viscous glass[e] | 43.7[f] | 43.3 | 7.0 | 7.0 | | |

[a] All melting points are uncorrected. [b] The products were recrystallized from mixtures of methanol and ethyl acetate or ether. [c] Yields were all about 90–100%. [d] Known compound, see reference 1. [e] These salts were obtained only as glass-like solids and their melting points were not sharp. [f] These calculated figures are for the mono-hydrate; the compound was hygroscopic.

with 2-methylpyridine methiodide[2] and 4-methylpyridine methiodide[3] gave the 4'-dialkylamino-2 and 4-stilbazoles, which upon catalytic hydrogenation[4] gave the corresponding 2- and 4-stilbazoline hydriodides. The 2- and 4-stilbazolines, as the bases, were treated with various alkyl iodides to yield the 1,4'-bis-quaternary ammonium salts. Examination of the structures and substituents (listed in Table I) shows that this sequence of reactions gives symmetrical 1,4'-alkylation as the last step; methyl iodide gives the 1,4'-bis-methiodide, butyl iodide gives the 1,4'-bis-butiodide.

In a few instances it was desired to have a single larger group, such as ethyl, in either the 1- or the 4'-position. To accomplish this, alternative synthetic routes were adopted.

To place a single ethyl on the 1-(piperidino) nitrogen, 4-dimethylaminobenzaldehyde was condensed with 2- or 4-methylpyridine ethiodide and the product was hydrogenated catalytically as described previously.[4] The base stilbazoline, liberated from its hydriodide salt, on alkylation with methyl iodide gave a bis-quaternary ammonium salt (V or XIV) bearing a single ethyl on the piperidine nitrogen.

To introduce a single ethyl on the 4'-anilino nitrogen, the 4'-dimethylaminostilbazoline hydriodide, in which the more strongly basic piperidino is tied up as the acid salt, was alkylated with ethyl iodide quaternizing the weaker anilino nitrogen. Liberation of the piperidino group with alkali and alkylation of this with methyl iodide gave the bis-quaternary salt (VI) with the single 4'-ethyl group.

**Pharmacology.**—In the bis-quaternary ammonium salts of the 4-stilbazoline series maximum curare-like activity was found when all alkyl groups were methyl (I). When two methyls, one from each of the quaternary ammonium groups, were replaced by higher alkyls as in the 1,4'-bis-ethiodide (II), the 1,4'-bis-propiodide (III), and the 1,4'-bis-butiodide (IV) curare-like activity was abolished, while these more heavily alkylated bis-salts acted as strong antagonists to reverse the myoneural blocking action of I. Since curariform activity was absent even in the 1,4'-bis-ethylated compound II, the unsymmetrical mono-ethyl (1 or 4') derivatives V and VI were prepared. With these it was found that the presence of a single ethyl group considerably diminished activity but did not eliminate it. The 4'-monoethyl compound VI had about one half the activity of I, while the 1-monoethyl compound V, although only one-twentieth as potent as I, had a much longer duration of action.

The bis-quaternary ammonium salt (X) of the 2-stilbazoline series, although nearly devoid of curare-like action, manifested powerful antagonistic activity in preventing or reversing the myoneural blocking action of either I or the decamethylene-1,10-bis-trimethylammonium bromide (Syncurine) (C)

(2) A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).
(3) A. P. Phillips, *ibid.*, **14**, 302 (1949).
(4) A. P. Phillips, THIS JOURNAL, **72**, 1850 (1950).

Modification of the structure of X by the introduction of larger alkyl groups as in the 1,4′-bis-ethiodide (XI), the 1,4′-bis-butiodide (XIII) and the tetraethyl salt (XVI) gave compounds of essentially the same potency as antagonists of I and (C). The antagonistic activity of the more heavily alkylated derivatives was accompanied in some cases by a slight additive curariform activity, thus making these members less desirable for use than X.

A detailed pharmacological report will be published elsewhere.

**Acknowledgment.**—The author is indebted to S. W. Blackman for the microanalytical results reported, and to Drs. E. J. de Beer and C. H. Ellis, and to J. C. Castillo, R. V. Fanelli and A. L. Wnuck who kindly supplied the pharmacological data summarized here.

## Experimental

These compounds were prepared in simple modifications of the procedures described previously.[1] Details for all the bis-quaternary ammonium salts are summarized in Table I. Preparations for new intermediates and for compound VI are given below.

**4-(4′-Dimethylamino)-stilbazole Ethiodide.**—This was prepared by the condensation[3] of 4-methylpyridine ethiodide and 4-dimethylaminobenzaldehyde. Bright red crystals were obtained by recrystallization from methanol; yield 100%; m.p. 255–260° (dec.).

*Anal.* Calcd. for $C_{17}H_{21}N_2I$: C, 53.7; H, 5.6. Found: C, 54.0; H, 5.6.

**1-Ethyl-4-(4′-dimethylamino)-stilbazoline Hydriodide.**—Catalytic hydrogenation[4] of the 4-(4′-dimethylamino)-stilbazole ethiodide gave the stilbazoline hydriodide as white crystals from methanol–ether mixtures; yield 90%; m.p. 127–128°.

*Anal.* Calcd. for $C_{17}H_{29}N_2I$: C, 52.6; H, 7.5; I, 32.8. Found: C, 52.5; H, 7.3; I, 32.9.

**2-(4′-Dimethylamino)-stilbazole Ethiodide.**—This compound was obtained by the condensation[3] of 2-methylpyridine ethiodide with 4-dimethylaminobenzaldehyde and after recrystallization from methanol gave 100% of bright red crystals; m.p. 258–259°.

*Anal.* Calcd. for $C_{17}H_{21}N_2I$: C, 53.7; H, 5.6. Found: C, 53.6; H, 5.6.

**1-Ethyl-2-(4′-dimethylamino)-stilbazoline Hydriodide.**—Catalytic hydrogenation[4] of the 2-(4′-dimethylamino)-stilbazole ethiodide gave the stilbazoline hydriodide; white crystals from methanol–ether; m.p. 145–146°; yield 97%.

*Anal.* Calcd. for $C_{17}H_{29}N_2I$: C, 52.6; H, 7.5. Found: C, 52.7; H, 7.6.

**1-Methyl-4-(4′-methylethylamino)-stilbazoline 1,4′-Bismethiodide (VI).**—A mixture of 1.3 g. (0.0035 mole) of 1-methyl-4-(4′-dimethylamino)-stilbazoline hydriodide[4] and 5 cc. (large excess) of ethyl iodide was refluxed on a steam-bath for four hours. Excess ethyl iodide was evaporated and the residue was washed repeatedly with ether by decantation. The viscous residue was stirred up with 10 cc. of saturated aqueous potassium carbonate solution and the insoluble crystalline precipitate was filtered off by suction, washed with saturated aqueous potassium carbonate, and finally washed once with a little cold water. The product, 1.6 g. (90%), was 1-methyl-4-(4′-dimethylamino)-stilbazoline 4′-monoethiodide, and this when refluxed in methanol with excess methyl iodide gave 80% of VI as white crystals from methanol–ethyl acetate; m.p. 185–186°.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, SCHERING CORPORATION]

# Catalytic Isomerization of Spirostans to Furostenols[1]

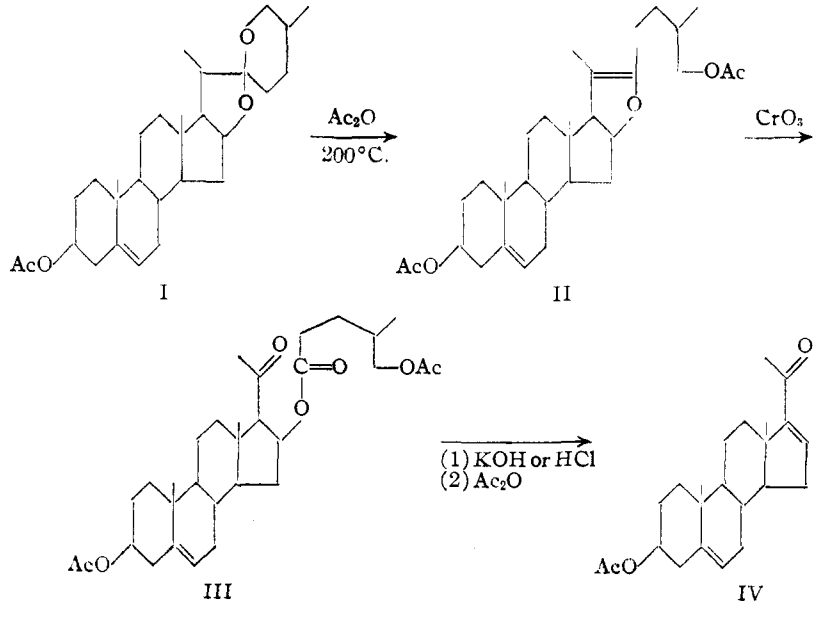
BY DAVID H. GOULD, HEINZ STAEUDLE AND E. B. HERSHBERG

RECEIVED AUGUST 3, 1951

Catalysts of the Lewis acid type have been found which permit the isomerization of spirostans to furostenols in acetic anhydride solution at the boiling point rather than at 200°.

In order to convert diosgenin acetate (I, 22-iso-5-spirostan-3β-ol acetate) into 5,16-pregnadien-3β-ol-20-one acetate (IV) according to scheme (1),[2] it must first be isomerized to the pseudo compound, 5,20(22)-furostadiene-3β,26-diol diacetate (II). The conditions of this reaction reported by Marker and Rohrmann[2] involved the use of acetic anhydride at elevated temperature and

(1)




(1) Presented at the XIIth International Congress of Pure and Applied Chemistry, New York City, September 11, 1951.

(2) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947); R. E. Marker and E. Rohrmann, *ibid.*, **61**, 3592 (1939).