[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

REACTIONS WITH α-ACETYL-4′-CHLOROSTILBENE[1]

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This communication describes attempts to synthesize for biological comparison with 3-chlorophenanthrene-9-alkamines of type VIII (1), the structural analogs of the stilbene series of type VII. An obvious starting material, the α-acetyl-4′-chlorostilbene was prepared readily, and in good yields by condensation, in acid medium, of phenylacetone with *p*-chlorobenzaldehyde. A possible alternative structure (2, 3, 4) of a 1-phenyl-4-*p*-chlorophenyl-3-buten-2-one (I) could be ruled out, because III could be oxidized to α-carboxy-4′-chlorostilbene (II) which we prepared from phenylacetic acid and *p*-chlorobenzaldehyde. Many attempts to arrive at the ω-bromomethylketone IV were without success.[3] Subsequently we attempted to prepare the homologs of VII, the propanolamines. The Mannich reaction of III and formaldehyde with benzylmethylamine or with piperidine gave the expected amino ketones Va and Vb in satisfactory yields. However, when ketone III and HCHO were allowed to react with dimethyl- or diethyl-amine, homogeneous and crystalline reaction products could be obtained only in small yields. Analytical data indicated that two moles of aliphatic amine had entered into the reaction giving compounds to which tentatively formula VI is assigned. Several attempts to reduce (PtO_2, Al isopropoxide) the amino ketones Va and Vb, failed.

EXPERIMENTAL[4]

α-Acetyl-4′-chlorostilbene[5] (III). To a solution of 66.0 g. (0.47 mole) of *p*-chlorobenzaldehyde in 200 ml. of dry benzene was added 67.5 g. (0.50 mole) of phenylacetone, and the ice-cooled mixture was saturated with hydrogen chloride gas. The solution turned pink immediately, and crystals began to separate. The reaction mixture was allowed to stand at 5° for 24 hours, and the crude crystalline mass was filtered off (72 g.). By concentration of

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[3] In a number of experiments under varied conditions (temperature, solvent, and brominating agent) two apparently homogeneous bromination products (m.p. 113–114°, m.p. 154–156°) could be isolated. Both of them, however, contained two bromine atoms, and were not investigated further. In only one experiment that could not be reproduced a monobromo ketone (m.p. 54–57°) was isolated. It was converted *via* the corresponding bromohydrin (m.p. 82–84°) to a piperidino alcohol of type VII.

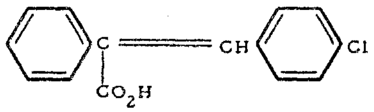
[4] All melting points given are corrected. The U.V. spectra were determined with a Beckman Quartz Spectrophotometer, Model DU. Microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

[5] No efforts were made to determine the configuration of this ketone. That it can be oxidized to acid II for which, by reasons of analogy, the *cis* form can be assumed, does not allow one to assign to the ketone the same configuration. The conditions of the oxidation (I_2) may have brought about a shift from *trans* to *cis*.

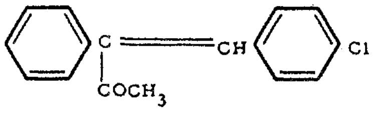
the mother liquor and resaturation with hydrogen chloride an additional amount (22 g.) of crystalline material was obtained. Recrystallization from ethanol yielded 78.0 g. (65%) of long colorless needles melting at 124–125°. The analytical sample melted at 126–127°; $\lambda_{\max}^{\text{abs alc.}}$ 300, 226 mμ (log ε 4.28, 4.14), *c*, 6.4×10^{-6} mole/l.

Anal. Calc'd for $C_{16}H_{13}ClO$: C, 74.8; H, 5.1.
Found: C, 75.1; H, 5.2.

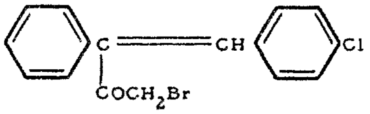
I



II



III



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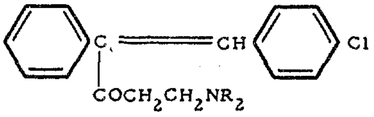
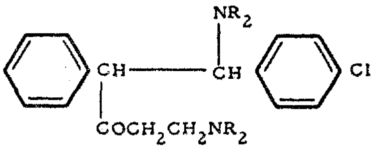
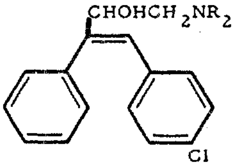


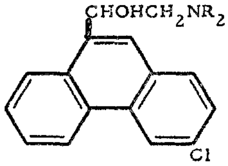
V a $NR_2 = N(CH_3)CH_2C_6H_5$
b $= NC_5H_{10}$



VI a $NR_2 = N(CH_3)_2$
b $= N(C_2H_5)_2$



VII



VIII

Semicarbazone of III. A mixture of 0.2 g. of III, 0.3 g. of sodium acetate trihydrate, 0.2 g. of semicarbazide hydrochloride, and 6 ml. of ethanol was heated at 100° for 25 minutes. The crystalline material obtained on cooling (0.2 g.) gave on recrystallization from absolute ethanol colorless prisms of m.p. 202–204°.

Anal. Calc'd for $C_{17}H_{16}ClN_3O$: C, 65.1; H, 5.1.
Found: C, 65.1; H, 5.3.

α-(1-Hydroxyethyl)-4'-chlorostilbene. A mixture of 7.7 g. of III in 100 ml. of a 0.5 *M* aluminum isopropoxide solution (in 2-propanol) was kept boiling for 2 hours. The greenish residue left upon evaporation of solvent was partitioned between ether and aqueous 10% sodium hydroxide. From the well-washed and dried ethereal solution there was obtained a yellow oil (5.5 g.) which solidified after seeding.[6] Recrystallization (Norit) from ligroin (b.p. 80–90°) gave 3.3 g. (42%) of small colorless needles of m.p. 69–70°; $\lambda_{\max}^{\text{abs alc.}}$ 262, 226 mμ (log ε 4.24, 4.18), *c*, 6.4×10^{-6} mole/l.

Anal. Calc'd for $C_{16}H_{15}ClO$: C, 74.3; H, 5.8.
Found: C, 74.3; H, 5.8.

α-Carboxy-4′-chlorostilbene (II). (*a*). A mixture of 10.0 g. (0.057 mole) of potassium phenylacetate, 8.0 g. (0.057 mole) of *p*-chlorobenzaldehyde, and 50 ml. of acetic anhydride was heated on the steam-bath for 19 hours. The resulting amber liquid, mixed with an equal amount of water, was heated to boiling and stirred vigorously. After cooling in ice 11.9 g. of yellow material (m.p. 165–182°) was filtered off, and gave after three crystallizations from ethanol 4.5 g. of colorless needles of m.p. 193–200°. Extraction of this material with 3 liters of dilute sodium hydroxide, acidification, and recrystallization gave 4.0 g. (27%) of colorless prisms melting at 202–203°.

Anal. Calc'd for $C_{15}H_{11}ClO_2$: C, 69.6; H, 4.3.
Found: C, 69.4; H, 4.4.

α-Carbomethoxy-4′-chlorostilbene. A mixture of 0.3 g. of II, 10 ml. of methanol, and 0.5 ml. of conc'd sulfuric acid was kept boiling for one hour. After dilution with water, and several recrystallizations of the precipitate from methanol the ester was obtained in colorless needles melting at 107–108.5°. Yield *ca.* 75%.

Anal. Calc'd for $C_{16}H_{13}ClO_2$: C, 70.5; H, 4.8.
Found: C, 70.2; H, 5.1.

(*b*). To a solution of 1.0 g. of III in 50 ml. of dioxane was added 10 ml. of a 10% aqueous sodium hydroxide solution and 10 ml. of an aqueous solution of 2.5 g. of potassium iodide and 1.2 g. of iodine. The mixture was heated at 60° for 4 hours, and diluted with 250 ml. of water. After 2 hours an orange-brown precipitate was filtered off, and the filtrate was acidified with hydrochloric acid. The tan-colored precipitate (0.3 g.) was triturated with cold ether and gave 0.15 g. of an acid of m.p. 195–201°. By recrystallization from glacial acetic acid colorless rods of m.p. 202–203° were obtained.

By adding this acid to a solution of excess diazomethane in methylene chloride, an ester was obtained which crystallized from methanol in colorless needles melting at 105–106°.

The mixture of the acids prepared according to (*a*) and (*b*) melted at 201–202°. The mixture of the respective methyl esters melted at 107–108°.

1-p-Chlorophenyl-2-phenyl-1,5-di(dimethylamino)pentan-3-one (VIa) *dihydrochloride.* A mixture of 5.14 g. (0.02 mole) of III, 1.63 g. (0.02 mole) of dimethylamine hydrochloride, 2.0 g. of paraformaldehyde, and 2 drops of conc'd hydrochloric acid in 90 ml. of benzene was heated to boiling. After 40 minutes a solid began to precipitate, and heating was continued for 2.5 hours. On cooling 4.6 g. of a colorless material (m.p. 164–172°) separated. Crystallization from ethanol yielded 1.9 g. (22%)[7] of colorless plates of m.p. 172–175°. The analytical sample melted at 178–180°.

Anal. Calc'd for $C_{21}H_{27}ClN_2O \cdot 2HCl$: C, 58.4; H, 6.8; N, 6.5.
Found: C, 58.7; H, 6.9; N, 6.7.

1-p-Chlorophenyl-2-phenyl-1,5-di(diethylamino)pentan-3-one (VIb) *dihydrochloride.* A mixture of 2.57 g. (0.01 mole) of III, 1.1 g. (0.01 mole) of diethylamine hydrochloride, 1.3 g. of paraformaldehyde, one drop of conc'd hydrochloric acid, 8 ml. of benzene, and 8 ml. of nitrobenzene was kept boiling for 2 hours. From the amber-colored solution there separated 0.25 g. of diethylamine hydrochloride. The filtrate was diluted with 125 ml. of ether, and a dark oil separated. The solvents were decanted, and the residue was treated with warm ethyl acetate whereby 0.35 g. (7.2%) of colorless material (m.p. 167–170°) was obtained. It crystallized from ethyl acetate in colorless needles which melted at 170–171°.

Anal. Calc'd for $C_{25}H_{35}ClN_2O \cdot 2HCl$: C, 61.5; H, 7.6; N, 5.7.
Found: C, 61.8; H, 7.9; N, 6.2.

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[6] Seed crystals were obtained by distilling a small sample of the oil in an oil-pump vacuum.

[7] Using 2 moles of amine rather decreased the yields.

α-(3-Benzylmethylamino-1-oxopropyl)-4′-chlorostilbene (Va) *hydrochloride.* A mixture of 2.57 g. (0.01 mole) of III, 1.58 g. (0.01 mole) of benzylmethylamine hydrochloride, 1.0 g. of paraformaldehyde, and 2 drops of conc'd hydrochloric acid in 45 ml. of benzene was kept boiling for 2.5 hours. The precipitate formed after cooling was recrystallized from absolute ethanol, yielding 2.6 g. (61%) of colorless needles of m.p. 177–178.5°. The average yield in a number of experiments was 70%. The analytical sample melted at 180–181°.

Anal. Calc'd for $C_{25}H_{24}ClNO \cdot HCl$: C, 70.4; H, 5.9; N, 3.3.
Found: C, 70.9; H, 5.7; N, 3.7.

α-(3-Piperidino-1-oxopropyl)-4′-chlorostilbene (Vb). A mixture of 2.57 g. (0.01 mole) of III, 1.22 g. (0.01 mole) of piperidine hydrochloride, 1.0 g. of paraformaldehyde, and 2 drops of conc'd hydrochloric acid in 45 ml. of benzene was kept boiling for 3 hours. The solid reaction product was recrystallized from ethanol giving 2.3 g. (59%) of colorless needles melting at 188–191°. Several recrystallizations from ethanol raised the m.p. to 192–193°.

Anal. Calc'd for $C_{22}H_{24}ClNO \cdot HCl$: C, 67.7; H, 6.5.
Found: C, 67.4; H, 6.5.

The *base* was obtained by extracting a suspension of the salt in dilute aqueous sodium hydroxide with ether. It crystallized from ethanol in colorless needles melting at 80–81°.

Anal. Calc'd for $C_{22}H_{24}ClNO$: C, 74.7; H, 6.8.
Found: C, 74.6; H, 6.8.

Oxidation of Vb hydrochloride. To a paste composed of 0.5 g. of Vb·HCl, 0.75 g. of potassium dichromate, and 2 ml. of water was added at 0°, 2 ml. of conc'd sulfuric acid. The mixture warmed up considerably, was kept at 75° for 15 minutes, and was finally poured onto ice and water. The crude acid (0.13 g.) obtained by alkaline extraction and subsequent acidification, melted at 218–234°. By vacuum sublimation and crystallization from ethanol, long colorless prisms were obtained which melted at 235–235.5°. The mixture with an authentic sample of *p*-chlorobenzoic acid of m.p. 235–235.5°, melted at the same temperature.

SUMMARY

Attempts to synthesize stilbene amino alcohols of type VII, carrying a chlorine in position 4′ and the alkamine chain in α, were unsuccessful. The desired monobromo compound — $COCH_2Br$ could not be obtained. In the Mannich reaction of III with the lower aliphatic tertiary amines two moles of amine entered into the reaction. With benzylmethylamine and piperidine, the expected amino ketones were formed. They did not yield any homogeneous reduction products.

BETHESDA 14, MD.

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