[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

REACTIONS WITH α-CARBOXY-4-CHLOROSTILBENE[1]

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Received March 25, 1952

This investigation was undertaken with the intention of synthesizing for biological studies stilbene derivatives of type X, structural analogs of 3-chlorophenanthrene-10-alkamines (XI) which had shown relatively high antimalarial activity (1). An obvious starting material was α-carboxy-4-chlorostilbene (IV) which was readily prepared from *p*-chlorophenylacetic acid and benzaldehyde. When the acid chloride II was treated with diazomethane, instead of the expected diazoketone a pyrazoline derivative was formed to which we assign tentatively formula I (2, 3). It is noteworthy that acid IV as well as acid IX gave with diazomethane the methyl esters in the regular manner. For an alternative route to the alkamines X we attempted to prepare α-acetyl-4-chlorostilbene from acid IV. When the amide III was dehydrated with phosphorus pentoxide, cyanide V was obtained which, on treatment with methylmagnesium iodide, gave the stereoisomeric cyanide VIII. The same transformation (V → VIII) was accomplished by treating a solution of V in carbon tetrachloride with bromine. By ultraviolet illumination VIII was reconverted to V. Cyanide VIII, moreover, is readily obtained by condensation of *p*-chlorobenzylcyanide with benzaldehyde (4). Both cyanides gave on hydrolysis (glacial acetic acid, hydrochloric acid, 150–160°) acid IV. Cyanide VIII gave, in addition, a small amount of the 4-chlorostilbene VII. By reasons of analogy (5–8) we assumed for acid IV a *cis*-stilbene configuration. The acid produces, on decarboxylation, besides the main product VII, small amounts of the lower-melting unstable isomer VI which is apparently the primary product. By boiling VI in nitrobenzene with a crystal of iodine (9), VII was readily formed. Thus, to VI a *cis*- and to VII a *trans*-structure may be ascribed. We obtained the *trans*-acid IX by illumination of the *cis*-acid IV (as the ethyl ester). Of the cyanides, on the other hand, the *trans*-form VIII is the more stable isomer and can be converted by illumination with ultraviolet light to the *cis*-form V. We carried out similar transformations on the analogous chlorine-free stilbene derivatives, and confirmed finally our steric assignments by comparison of the ultraviolet spectra of the appropriate derivatives.

EXPERIMENTAL[3]

cis-α-Carboxy-4-chlorostilbene (IV). A mixture of 45.9 g. (0.23 mole) of potassium *p*-chlorophenylacetate, 24.5 g. (0.23 mole) of benzaldehyde, and 153 ml. of acetic anhydride

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[1] This paper was presented before the 115th National Meeting of the American Chemical Society in San Francisco, California, March 27–April 1, 1949.

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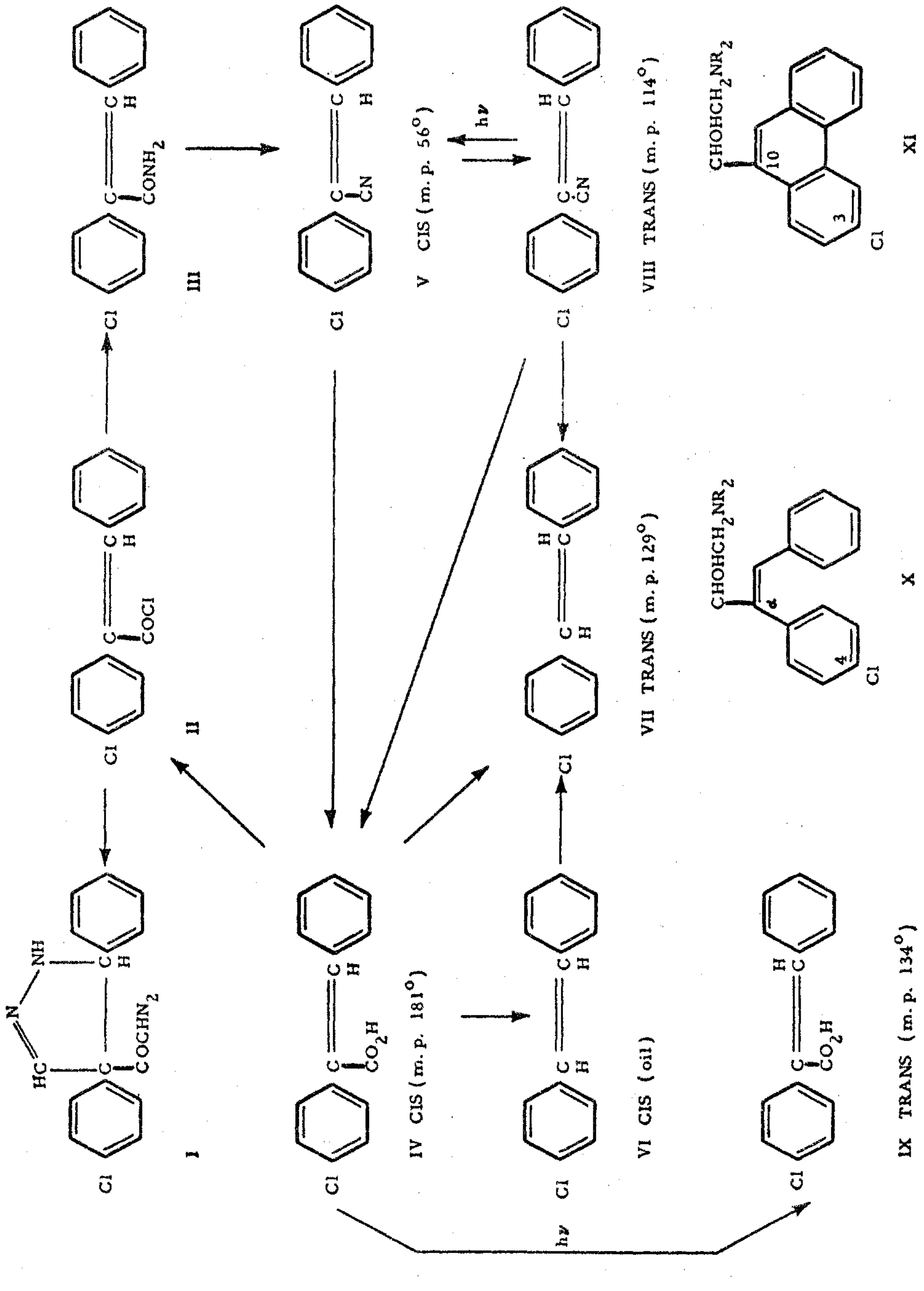
[3] All melting points given are corrected. The U. V. spectra were determined with a Beck-


I
II
III
IV CIS (m.p. 181°)
V CIS (m.p. 56°)
VI CIS (oil)
VII TRANS (m.p. 129°)
VIII TRANS (m.p. 114°)
IX TRANS (m.p. 134°)
X
XI
hν

was heated at 100° for 16 hours. The yellow solution was poured into 400 ml. of water and the mixture heated to boiling with vigorous stirring. After cooling 53 g. of yellow material was filtered off. Crystallization from ethanol (Norit) gave 30.8 g. (52%) of colorless needles which melted at 180–181°. λ_{max} 282, 226 mμ (log ϵ 4.13, 4.30).

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

Found: C, 69.7; H, 4.3.

cis-4-Chlorostilbene-α-carbonyl chloride (II). A mixture of 10.4 g. of IV and 15 ml. of thionyl chloride was heated to solution. Refluxing was continued for 35 minutes and excess thionyl chloride was removed under reduced pressure, leaving a pale-green solid. Crystallization from ligroin gave 9.7 g. (87%) of almost colorless prisms which melted at 77–78°.

Anal. Calc'd for $C_{15}H_{10}Cl_2O$: C, 65.0; H, 3.6.

Found: C, 64.7; H, 3.8.

cis-α-Carbomethoxy-4-chlorostilbene. (*a*). A sample of II was added to an excess of methanol. The solution was concentrated and cooled whereby colorless needles of m.p. 86–88° were obtained. λ_{max} 283, 224 mμ, (log ϵ 4.26, 4.38).

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

Found: C, 70.5; H, 5.0.

(*b*). To a cooled solution of diazomethane (from 3.4 g. of nitrosomethylurea) in 100 ml. of ether was added 0.5 g. of IV. The solution was allowed to warm to room temperature. After two hours the ether was evaporated. The crystalline residue gave, after recrystallization from methanol, 0.27 g. (51%) of long colorless needles of m.p. 87.5–88.5°. The mixture of the two samples gave no depression of melting point.

cis-α-Carbethoxy-4-chlorostilbene. (*a*). The ester was prepared from the acid chloride and ethanol. Colorless needles, m.p. 56–57°.

(*b*). A mixture of 14.0 g. of IV, 65 ml. of absolute ethanol, and 4 ml. of conc'd sulfuric acid was refluxed for 6 hours. The precipitate obtained upon cooling was recrystallized from ethanol, yielding 14.4 g. (93%) of colorless needles, m.p. 55–55.5°.

Anal. Calc'd for $C_{17}H_{15}ClO_2$: C, 71.2; H, 5.3.

Found: C, 71.1; H, 5.4.

The pyrazoline derivative (I) *from II and diazomethane.* To a cooled solution of diazomethane (from 18.8 g. of nitrosomethylurea) in 360 ml. of methylene chloride was added 4.5 g. of II. Gas was evolved, and the solid dissolved gradually. The solution was kept at 0° for three hours and at room temperature for 14 hours. After evaporation of the solvent a yellow oil remained which solidified on seeding. By trituration with 2-propanol followed by crystallization from methanol, 2.2 g. (42%) of yellow prisms were obtained which melted at 89–93°. On several crystallizations the melting point rose to 95.5–97°.

Anal. Calc'd for $C_{17}H_{13}ClN_4O$: C, 62.9; H, 4.0; N, 17.2.

Found: C, 62.8; H, 4.1; N, 15.2.[4]

cis-α-Carboxamido-4-chlorostilbene (III). A cooled solution of crude II (from 4.0 g. of acid) in 75 ml. of dry benzene was saturated with ammonia gas. Ammonium chloride was filtered off, and the filtrate was evaporated to dryness leaving 3.7 g. of a pink-colored solid. By crystallization from absolute ethanol 2.6 g. (65%) of pale-yellow crystals melting at 133–135° was obtained. Another crystallization (Norit) yielded colorless needles of m.p. 134.5–135.5°. λ_{max} 280, 223 mμ, (log ϵ 4.29, 4.38).

Anal. Calc'd for $C_{15}H_{12}ClNO$: C. 69.9; H, 4.7.

Found: C, 70.0; H, 4.8.

cis-α-Cyano-4-chlorostilbene (V). A mixture of 20 g. of III, 35 g. of phosphorus pentoxide,

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man Quartz Spectrophotometer, Model DU. All the compounds shown in the introduction (Figs. 1–4) were measured in absolute ethanol at the same concentration *c*, 6.4 × 10^{-6} mole/l. The microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

[4] In spite of the apparent homogeneity of the compound, in repeated analyses the value for N was found too low.

and 100 ml. of xylene was kept boiling for one hour. The yellow solution was decanted and the residue extracted with 15 ml. of hot xylene. The combined xylene solutions left upon evaporation under reduced pressure a red oil which soon solidified. Recrystallization from methanol gave 11.3 g. (61%) of colorless prisms melting at 56–57.5°. λ_{max} 295, 234 mμ, (log ϵ 4.20, 4.39).

Anal. Calc'd for $C_{15}H_{10}ClN$: C, 75.2; H, 4.2.

Found: C, 75.2; H, 4.6.

trans-α-Cyano-4-chlorostilbene (VIII). (*a*). To a solution of 11.3 g. of V in 25 ml. of dry ether at 0° was added, over a period of 30 minutes, a solution of methylmagnesium iodide (from 7.3 g. of methyl iodide). After stirring for 30 minutes the reaction mixture was poured into 100 ml. of 25% ammonium nitrate solution mixed with ice, and extracted with ether. The dried ethereal solution gave upon evaporation crystalline material which melted after recrystallization from absolute ethanol at 113–114.5°. Yield, 8.7 g. (77%). λ_{max} 316, 232 mμ, (log ϵ 4.44, 4.23).

Anal. Calc'd for $C_{15}H_{10}ClN$: C, 75.2; H, 4.2; N, 5.8.

Found: C, 75.1; H, 4.4; N, 5.8.

The trans-nitrile (VIII) remained unchanged when refluxed with excess ethereal methylmagnesium iodide.

(*b*). To a cooled solution (0°) of 0.5 g. of V in 15 ml. of carbon tetrachloride was added 0.32 g. of bromine. After 30 minutes the solution was allowed to rise to room temperature and to stand overnight. No decolorization took place. The solvent was evaporated under reduced pressure. A colorless solid (m.p. 111–113.5°) remained which gave on recrystallization from methanol colorless prisms (0.35 g.) of m.p. 113–114°.

The mixtures of samples prepared according to (*a*) and (*b*), and of these samples with a standard sample [prepared from *p*-chlorobenzyl cyanide, benzaldehyde, and sodium ethoxide (4)], melting at 112–113.5°, showed no depression in melting point.

Conversion of VIII to V. A solution of 3.0 g. of VIII (m.p. 112.5–113.5°) in 30 cc. of dry benzene was subjected for 36 hours to illumination by a General Electric R. S. Sunlamp (275 w), placed approximately two inches from the quartz flask, whereby a temperature of about 60° was maintained. The solution was agitated continuously with a magnetic stirrer. The colorless solution left, on evaporation *in vacuo*, an oil which was redissolved in benzene-petroleum ether and allowed to stand. Two crystalline fractions (0.1 g. of m.p. 112–114°, and 0.05 g. of fine needles of m.p. 230–235°, dec.) were filtered off, but not further investigated. The oily residue from the mother liquor crystallized immediately upon seeding with V. By repeated crystallization from methanol 1.33 g. (44%) of prisms, melting at 55–57° were obtained. The mixture with cyanide V (obtained by dehydration of amide III) showed no m.p. depression.

cis-α-Carboxy-4-chlorostilbene (IV). (*a*). *By hydrolysis of cis-α-cyano-4-chlorostilbene* (V). A mixture of 1.0 g. of V, 4 ml. of glacial acetic acid, and 4 ml. of conc'd hydrochloric acid was heated in a sealed tube at 165° for 6½ hours. The mixture was poured into 25 ml. of water and filtered. The collected precipitate was treated with 50 ml. of warm 5% sodium hydroxide solution. The acid obtained by acidification of the filtered alkaline solution gave, on recrystallization from methanol, colorless needles which melted at 180–181°. The mixture with acid IV, described above, melted at 180.5–182°.

(*b*) *By hydrolysis of trans-α-cyano-4-chlorostilbene* (VIII) A mixture of 1.5 g. of VIII 10 ml. of glacial acetic acid, and 5 ml. of conc'd hydrochloric acid was heated in a sealed tube at 150° for 18 hours. The mixture was cooled and filtered. The brown-colored material was extracted several times with 5% aqueous sodium hydroxide. From the resulting solution a colorless acid was precipitated which after recrystallization appeared to be identical (m.p., mixture m.p.) with the acid described above. The solid residue of the alkaline extraction was sublimed in an oil-pump vacuum. The sublimate melted at 123–126° and after recrystallization from petroleum ether (b.p. 65°) at 129–130°. The mixture with VII, obtained as described below, melted at 129–130°.

Decarboxylation of α-carboxy-4-chlorostilbene (IV). A mixture of 4.0 g. of acid IV, 2.0 g.

of cupric carbonate, and 20 ml. of quinoline was heated at 225–230° for 25 minutes. The reaction mixture was stirred with 500 ml. of dilute hydrochloric acid and extracted with ether. The washed and dried ethereal solution left, on evaporation, a brown-colored, semi-solid mass. This material was triturated several times with small portions of low-boiling petroleum ether. The crystalline residue (1.30 g. of m.p. 109–113°), and a crystalline fraction (0.25 g. of m.p. 119–125°), obtained by concentration of the petroleum ether solution, were combined and recrystallized from petroleum ether, yielding 1.0 g. of colorless leaflets melting at 125–127°. Another recrystallization raised the m.p. to 129–130°; lit. (4) m.p. 129°.

Anal. Calc'd for $C_{14}H_{11}Cl$: C, 78.3; H. 5.2.

Found: C, 78.6; H, 5.5.

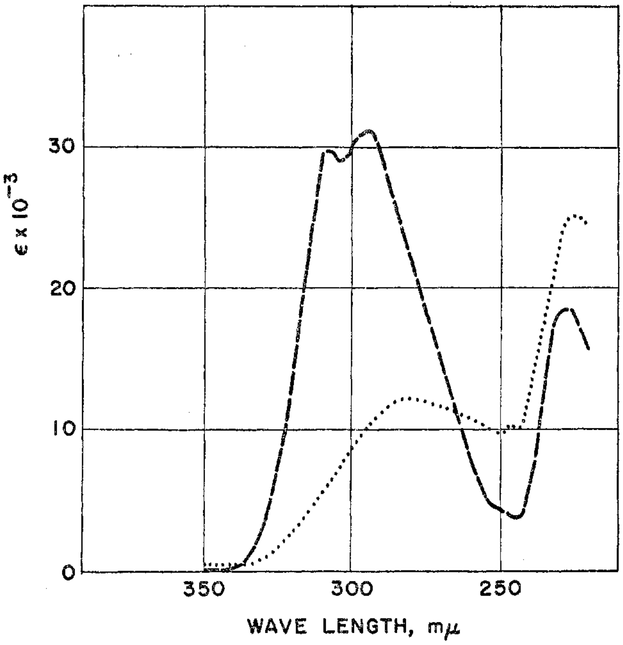

FIGURE 1. ULTRAVIOLET SPECTRA OF THE STILBENES. — — — *trans*-Stilbene; ······*cis*-Stilbene

The original petroleum ether mother liquor left on evaporation a brown oil which was distilled slowly in an oil-pump vacuum. The first fractions gave a colorless oil (n_D^{25} 1.615) which solidified on cooling to clusters of small prisms and remelted between −10° and 0°;[5] yield *ca.* 0.5 g. A mixture of 0.15 g. of the oil, 2 ml. of nitrobenzene, and a small crystal of iodine was boiled for 2 minutes. The nitrobenzene was driven off with steam leaving 0.13 g. of lightly colored crystals of m.p. 116–125°. Sublimation raised the m.p. to 127–129°.

trans-α-Carboxy-4-chlorostilbene (IX). A solution of 9.4 g. of the ethyl ester of IV in 120 ml. of dry benzene was illuminated in the manner described above. The clear colorless solution left upon evaporation under reduced pressure a colorless oil which could not be induced to crystallize. It was boiled for 2 hours with a solution of 4.5 g. of sodium hydroxide in 100 ml. of 80% ethanol. The resulting pale yellow solution was diluted with one liter of water and acidified with hydrochloric acid. The yellow precipitate was filtered and recrys-

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[5] This material was possibly contaminated with the *trans* form. The end-fractions contained about one-third of the crystalline *trans* form.

tallized from 50 ml. of 80% ethanol. About 4.0 g. of crude *cis* acid (m.p. 170–179°) was recovered. The filtrate was diluted with water and the precipitate was dried and recrystallized twice from petroleum ether (b.p. 65–67°). Yield, 2.7 g. (32%); m.p. 132.5–134.5°. Another recrystallization gave colorless needles of m.p. 134–135°. λ_{max} 295, 228 mμ, (log ε 4.38, 4.08).

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

Found: C, 69.9; H, 4.4.

trans-α-Carbomethoxy-4-chlorostilbene. Compound IX (0.4 g.) was added at 0° to 35 ml. of an ethereal diazomethane solution (from 2 g. of nitrosomethylurea). The solution was allowed to stand for one-half hour, and evaporated to dryness. The colorless solid obtained was washed with sodium carbonate and recrystallized from methanol; yield, 0.3 g. (71%), elongated prisms, m.p. 91–93°. λ_{max} 288 mμ, (log ε 4.39).

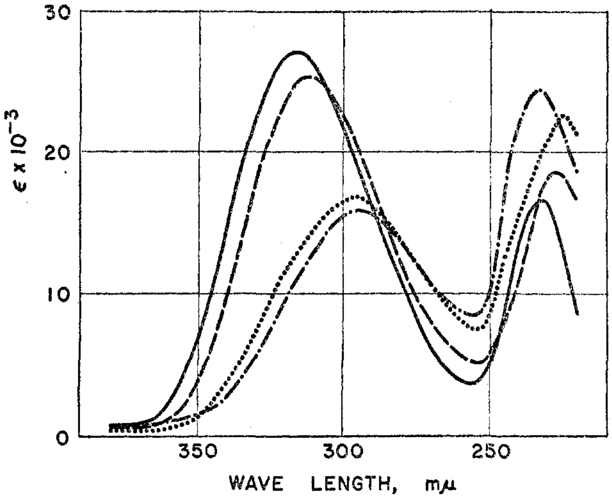

FIGURE 2. ULTRAVIOLET SPECTRA OF THE CYANOSTILBENES. ——— *trans*-4-Chloro-α-cyanostilbene; — — — *trans*-α-Cyanostilbene; —·—*cis*-4-Chloro-α-cyanostilbene; ······ *cis*-α-Cyanostilbene

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

Found: C, 70.6; H, 5.1.

In an esterification with methanol and sulfuric acid only 15% of the expected ester was obtained after 8 hours. The mixture with the corresponding *cis* compound of m.p. 87–89°, melted at 66–72°.

trans-α-Carboxamido-4-chlorostilbene. A mixture of 0.5 g. of IX and 5 ml. of thionyl chloride was refluxed for 15 minutes. The crude oily chloride was treated with conc'd ammonium hydroxide, the lumps formed were broken up, and the mixture was allowed to stand for one hour. The crude amide (0.5 g., m.p. 157–177°) gave, after crystallization from ethanol, colorless rods melting at 191.5–192°. λ_{max} 292 mμ, (log ε 4.43).

Anal. Calc'd for $C_{15}H_{12}ClNO$: C, 69.9; H, 4.7.

Found: C, 69.6; H, 5.0.

SUPPLEMENTARY COMPOUNDS

cis-Stilbene (λ_{max} 283, 222 mμ; log ε 4.09, 4.40) was prepared by illumination of *trans*-stilbene (10) (λ_{max} 295, 228 mμ; log ε 4.49, 4.27).

cis-α-Carboxystilbene was prepared by condensation of potassium phenylacetate with benzaldehyde in acetic anhydride at 100°, as described for the chloro analog IV; m.p. 172–

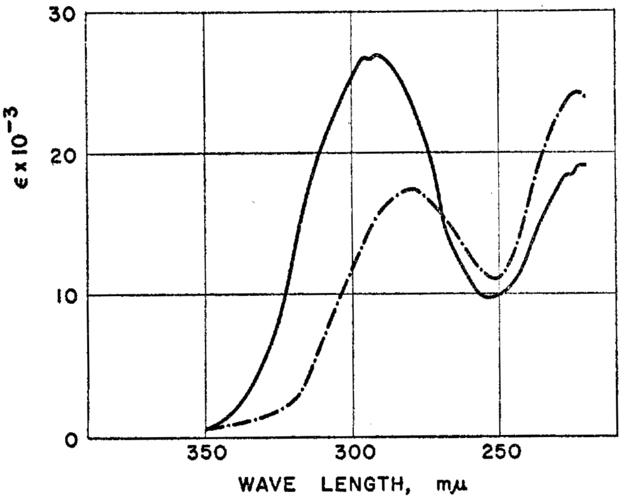

FIGURE 3. ULTRAVIOLET SPECTRA OF THE CARBOXAMIDOSTILBENES. ———— *trans-α*-Carboxamido-4-chlorostilbene; —·— *cis-α*-Carboxamido-4-chlorostilbene

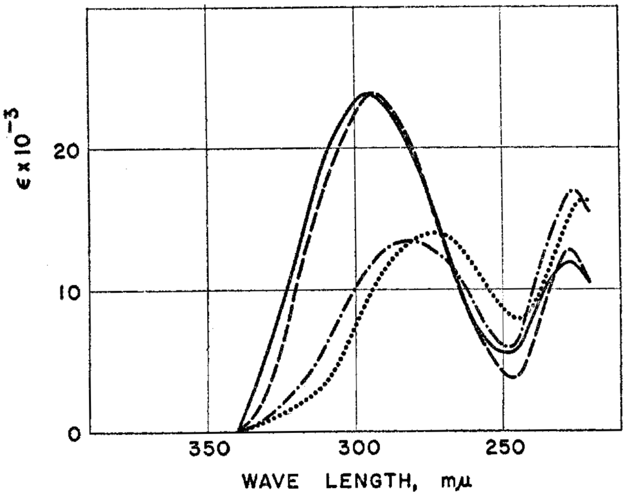

FIGURE 4. ULTRAVIOLET SPECTRA OF THE CARBOXYSTILBENES. ———— *trans-α*-Carboxy-4-chlorostilbene; — — — *trans-α*-Carboxystilbene; —·— *cis-α*-Carboxy-4-chlorostilbene; ······ *cis-α*-Carboxystilbene

174° (11); λ_{max} 274, 220 mμ, (log ε 4.15, 4.21). The *methyl ester* melted at 75–75.5° (11, 12); λ_{max} 284 mμ, (log ε 4.20).

trans-α-Carboxystilbene (6, 11, 12), was prepared by illumination of *cis-α*-carbomethoxystilbene, and subsequent hydrolysis of the resulting oily *trans-α*-carbomethoxystilbene: 6.0 g. of the *cis*-ester in 200 ml. of benzene was illuminated for 18 hours in the manner described for the ethyl ester of IV. By triturating the residue left on evaporation of the benzene with petroleum ether at room temperature, and finally at −50° a fairly complete separation of the stereoisomeric esters was achieved. By saponification of the oily component (2.7 g.) with aqueous-ethanolic sodium hydroxide solution and subsequent acidification a crude acid of m.p. 115–128° was obtained. By fractional crystallization from petroleum ether some *cis* acid (0.45 g., m.p. 166–169°) was separated. The mother liquors finally yielded a *trans* acid melting at 135–137°; λ_{max} 294, 228 mμ, (log ε 4.38, 4.11). The oily *methyl ester* was prepared with diazomethane and could not be induced to crystallize, λ_{max} 284 mμ, (log ε 4.33).

cis-α-Carboxamidostilbene was prepared according to Stoermer and Voht (6) *via* the acid chloride; m.p. 127–128°, yield, 67%.

cis-α-Cyanostilbene.[6] *(a). By dehydration of the above amide in xylene with phosphorus pentoxide,* as described for the corresponding chloro analog. The crude oil which solidified readily on cooling below 0°, was distilled (90–100° at 0.05 mm.) twice. The main fraction was a colorless oil; m.p. 15–20°, n_D^{20} 1.6347. λ_{max} 295, 224 mμ, (log ε 4.22, 4.36). *(b). By illumination of the trans cyanide* (see below). The cyanide (10 g.) (m.p. 85–86°) in 60 ml. of dry benzene was illuminated for 52 hours. The oil obtained after evaporation of the benzene was treated with a benzene-petroleum ether mixture, whereby about 0.15 g. of a compound melting at 225–227° (not further investigated), and about 1.5 g. of starting material were obtained. By fractional distillation *in vacuo* three fractions were obtained melting approximately at 12–18°, n_D^{20} between 1.6370 and 1.6425.

trans-α-Cyanostilbene was prepared according to Meyer and Frost (13), from phenyl cyanide and benzaldehyde; m.p. 85–86°. It was also obtained by adding two drops of bromine to a solution of 0.8 g. of the *cis*-cyanide (from the dehydration of the amide) in 15 ml. of carbon tetrachloride and allowing the mixture to stand for 20 hours. On evaporation under reduced pressure a red-colored oil remained which gave, on trituration with ethanol and crystallization, 0.2 g. of material melting at 85–86°, λ_{max} 312, 227 mμ, (log ε 4.41, 4.27).

SUMMARY

Two attempts to synthesize stilbene amino alcohols of type X, carrying a chlorine in position 4 and the alkamine chain in α, failed. *cis*-4-Chlorostilbene-α-carbonyl chloride (II) did not yield the desired diazoketone, but reacted with two moles of diazomethane forming a pyrazoline derivative (I). *cis*-α-Cyano-4-chlorostilbene (V) and methylmagnesium iodide did not lead to the expected ketimine but gave the *trans* form (VIII) of the starting material.

The steric relation of the 4-chlorostilbene-α-acids and cyanides, and their chlorine-free analogs was established by comparing the U.V. spectra of the appropriate derivatives.

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[6] This cyanide was designated as the *allo* form by Stoermer and Voht (ref. 6, page 42) who obtained it by illumination of the stereoisomeric form of m.p. 86°.