($\lambda_{max}^{CHCl_3}$ 255 (shoulder; 4.10); 287 (3.98); 323 (shoulder; 3.32); 342 (shoulder; 2.50); 373 (1.53); 381 mμ (1.75)) and the dark-orange-colored 2,4,6-trinitrofluorenone derivative, from benzene, m.p. 175–176°.

Anal. Calcd. for $C_{33}H_{20}FN_3O_7$: C, 67.3; H, 3.4; F, 3.2. Found: C, 67.1; H, 3.6; F, 2.9.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

Derivatives of *cis*- and *trans*-3-Stilbazoles

FRANK H. CLARKE, GERALDINE A. FELOCK, GLADYS B. SILVERMAN, AND CLARA M. WATNICK

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cis- and *trans*-3-Stilbazole derivatives each containing a carboxy, carboxamido or cyano group in the alpha or beta position were prepared. Stereochemical assignments were made on the basis of their ultraviolet spectra and confirmed by chemical transformations.

In our search for new medicinal agents we have prepared a number of *cis*- and *trans*-3-stilbazole derivatives each containing a carboxy, carboxamido, or cyano group in the alpha or beta position.[1] The stereochemistry of stilbazole derivatives has been studied in only a few instances[2–4] and although the synthesis of *trans*-3-stilbazole (VII) was described by Beard and Katritzky[5] while this work was in progress, no attention has been given to the stereochemistry of derivatives of 3-stilbazole. Thus, the configuration of the precursor of VII, α-carboxy-3-stilbazole[5–7] (V) has not been discussed and a number of β-cyano-3-stilbazoles have been described[8,9] without mention of their stereochemistry.

On the other hand, the geometrical isomers of stilbene derivatives have been carefully studied[10] and it has been found possible to make structural assignments on the basis of their ultraviolet spectra[10–12] even when only one of a pair of geometrical isomers is available.[13,14] Most stilbene derivatives exhibit two *major* absorption bands in their ultraviolet spectra. The band at the lower wave length is the more intense for *cis*-stilbenes and that at the higher wave length is more intense for the *trans* isomers.[12,14] This useful observation is valid in the stilbene series even when the double bond is substituted with a cyano, carboxy, or carboxamido group[12] and has now been found to apply for the corresponding stilbazole derivatives (see Table II.)

The Perkin condensation of sodium phenylacetate with benzaldehyde is known to give the more stable *cis*-α-carboxystilbene.[15] Therefore, it is not surprising that when 3-pyridinealdehyde was condensed with sodium phenylacetate in the presence of acetic anhydride the product was shown by its ultraviolet spectrum to be *cis*-β-carboxy-3-stilbazole[16] (I). Similarly, the α-carboxy-3-stilbazole V formed under the conditions described by Beard and Katritzky[5] was found to have the *cis* configuration. These stereochemical assignments made on the basis of ultraviolet spectra were confirmed by chemical transformations. Thus the decarboxylation of I using copper chromite in quinoline solution[17] gave the new *cis*-3-stilbazole (II) which was readily isomerized to the *trans* isomer (VII) with iodine in nitrobenzene.[17] Furthermore, I was converted *via* the acid chloride to the corresponding *cis*-β-carboxamido-3-stilbazole (III) which, upon dehydration with *p*-toluene-

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(1) In order to facilitate discussion of their stereochemistry and interconversions, these compounds are named as derivatives of *cis*- and *trans*-3-stilbazole following the precedent of Codington and Mosettig.[12] Thus compound I is named *cis*-β-carboxy-3-stilbazole although in *Chemical Abstracts* the name *trans*-α-phenyl-3-pyridineacrylic acid would probably be used.

(2) N. Sperber, D. Papa, and M. Sherlock, *J. Am. Chem. Soc.*, **78**, 4489 (1956).

(3) L. Horwitz, *J. Org. Chem.*, **21**, 1039 (1956).

(4) T. Katsumoto, *Bull. Chem. Soc. Japan*, **33**, 242 (1960).

(5) J. A. T. Beard and A. R. Katritzky, *Rec. trav. chim.*, **78**, 592 (1959).

(6) A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 150 (1958).

(7) M. Hartmann and W. Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

(8) J. Klosa, *Arch. Pharm.*, **289**, 177 (1956).

(9) R. N. Castle and W. S. Seese, *J. Org. Chem.*, **20**, 987 (1955).

(10) L. Crombie, *Quart. Revs.*, **6**, 101 (1952).

(11) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold Ltd., London, 2nd Edition, 1957, p. 269.

(12) J. F. Codington and E. Mosettig, *J. Org. Chem.*, **17**, 1027, 1035 (1952).

(13) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

(14) K. Rorig, *J. Am. Chem. Soc.*, **75**, 5381 (1953).

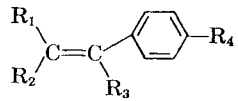
(15) An explanation of the stereochemistry of condensation reactions of benzaldehyde has been discussed by H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959).

(16) This compound was originally prepared in 1948 in the laboratories of Schering Corporation by D. Papa and A. Strauss.

(17) Method of D. F. DeTar and Y. W. Chu, *J. Am. Chem. Soc.*, **77**, 4410 (1955).

TABLE I

SUBSTITUTED STILBAZOLES



No.	R_1[a]	R_2[a]	R_3	R_4	Recrystallizing Solvent	M.P.,[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
cis													
I	3Py	H	COOH	H	Ethanol	197–200	$C_{14}H_{11}NO_2$	74.65	74.65	4.92	4.84	6.22	6·28
II	3Py	H	H	H	Acetone	148–150[c]	$C_{13}H_{11}N\cdot HCl$	71.70	71.35	5.56	5.48	6.44	6.38
III	3Py	H	$CONH_2$	H	Benzene	147–149	$C_{14}H_{12}N_2O$	74.99	75.16	5.38	5.23	12.49	12.62
IV	3Py	H	CN	H	Benzene–petroleum ether	64–66	$C_{14}H_{10}N_2$	81.53	81.73	4.89	4.90	13.58	13.75
V	3Py	COOH	H	H	Ethanol	235–238[d]							
VI	3Py	$CONH_2$	H	H	Acetone	195–196	$C_{14}H_{12}N_2O$	74.99	74.55	5.38	5.08	12.49	12.30
trans													
VI	H	3Py	H	H	Cyclohexane	77–79[e]							
VIII	H	3Py	CN	H	Ethanol	92–93[f]							
IX	CN	3Py	H	H	Acetone-cyclohexane	107–109	$C_{14}H_{10}N_2$	81.53	81.87	4.89	4.97	13.58	13.60
X	H	3Py	CN	Cl	Ethanol	140–141[g]							
XI	H	3Py	CN	OCH_3	Benzene–petroleum ether	112–114	$C_{15}H_{12}N_2O$	76.25	76.29	5.12	5.21	11.86	12.04
XII	H	3Py	CN	NO_2	Methanol	156–157	$C_{14}H_9N_3O_2$	66.92	66.94	3.61	3.41	16.73	16.90
XIII	H	3Py	CN	NH_2	Ethanol	169–171	$C_{14}H_{11}N_3$	75.97	76.12	5.01	5.31	18.99	18.88
XIV	H	3Py	CN	$NHCOCH_3$	50% Acetic acid	223–224	$C_{16}H_{13}N_3O$	72.98	73.23	4.98	4.88	15.96	16.17
XV	H	3Py	CN	$N(CH_3)_2$	2-Propanol	122–124	$C_{16}H_{15}N_3$	77.08	77.20	6.06	6.30	16.86	17.00
XVI	H	2Py	CN	$N(CH_3)_2$	Benzene–petroleum ether	136–138	$C_{16}H_{15}N_3$	77.08	76.83	6.06	6.08	16.86	17.19
XVII	H	4Py	CN	$N(CH_3)_2$	Benzene–petroleum ether	154–157	$C_{16}H_{15}N_3$	77.08	76.98	6.06	5.97	16.86	17.34
XVIII	CN	3Py	H	$N(CH_3)_2$	Benzene–petroleum ether	139–141	$C_{16}H_{15}N_3$	77.08	76.77	6.06	6.27	16.86	17.15
XIX	H	3Py	$CONH_2$	H	Acetone-pentane[h]	129–130	$C_{14}H_{12}N_2O$	74.99	74.96	5.38	5.43	12.49	12.16
XX	$CONH_2$	3Py	H	H	Acetone-ether	151–152	$C_{14}H_{12}N_2O$	74.99	75.22	5.38	5.14	12.49	12.60
XXI	H	3Py	$CONH_2$	Cl	Acetone-cyclohexane	155–159	$C_{14}H_{11}ClN_2O$	64.99	64.87	4.26	4.06	10.83	10.85
XXII	H	3Py	$CONH_2$	$N(CH_3)_2$	85% Methanol	201–203	$C_{16}H_{17}N_3O$	71.88	71.95	6.41	6.32	15.72	15.66
XXIII	H	4Py	$CONH_2$	H	Acetone	178–180	$C_{14}H_{12}N_2O$	74.97	74.92	5.39	5.50	12.49	12.48

[a] Py = Pyridyl. [b] Melting points are corrected. [c] Hydrochloride salt. [d] Lit.[5] m.p. 235–236°. [e] Lit.[5] m.p. 72–73°. [f] Lit. m.p.[8,9] 82–89°, 92°. [g] Lit.[9] m.p. 138–139°. [h] See Experimental for crystal modification.

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA[a] OF SUBSTITUTED STILBAZOLES[b]

No.	Methanol[c]	Dilute Acid[c]
cis		
I	258 (11.5) 283 (10.6)	252 (13.1) 290 (7.4)
II[d]	220 (17.5) 275 (12.2)	248 (12.2) 283 (10.1)
III	260 (12.8) 280s (11.5)	250 (13.1) 285s (8.5)
IV	240s (10.6) 291 (11.5)	247 (13.3) 286 (9.1)
V	218s (13.6) 279 (15.3)	281 (14.7)
VI	276 (15.5)	220s (14.1) 279 (13.8)
trans		
VII[e]	223 (12.5) 302 (24.8)	238 (8.9) 300 (22.3)
VIII	224 (9.4) 311 (21.4)	242 (7.4) 314 (12.8)
IX	224 (10.8) 310 (23.2)	224 (10.0) 315 (21.7)
X[f]	230 (11.0) 314 (23.9)	225 (9.6) 317 (18.6)
XI	243 (11.0) 333 (20.4)	252 (12.5) 342 (16.1)
XII	220 (12.3) 323 (27.7)	242s (8.1) 317 (26.3)
XIII	255 (14.0) 371 (18.9)	238 (9.8) 309 (18.5)
XIV	246 (16.0) 334 (25.0)	242 (11.6) 316 (16.2)
XV[g]	262 (16.4) 393 (22.4)	220 (9.6) 300 (19.0)
XVI	261 (15.6) 400 (23.7)	265 (7.9) 314 (14.2)
XVII	261 (17.1) 412 (21.9)	226 (8.8) 315 (20.5)
XVIII[h]	253 (12.3) 385 (28.4)	223 (7.8) 304 (18.6)
XIX	222 (11.5) 290 (20.1)	243 (9.9) 292 (15.3)
XX	220s (12.0) 288 (21.6)	245 (10.0) 294 (17.6)
XXI	223 (12.0) 293 (23.0)	247 (11.4) 300 (18.4)
XXII	255 (12.5) 356 (23.2)	246 (12.0) 289 (18.4)
XXIII	223 (12.0) 293 (21.8)	230 (9.6) 324 (19.7)

[a] λ_{max} in mμ (10^{-3} ϵ); *s* = Shoulder. [b] Compounds I to VI are substituted *cis*-stilbazoles and have intense absorption below 220 mμ; the remainder are substituted *trans*-stilbazoles: See Table I for structures. [c] Solutions in methanol and 0.1*N* hydrochloric acid contain approximately 3 mg. of compound in 100 ml. of solvent. [d] Hydrochloride; methanol replaced by 0.1*N* sodium hydroxide in 95% methanol; also 220s (14.6) in dilute acid. [e] Also 290 (24.8) in methanol and 246 (8.7) in dilute acid. [f] Also 243 (11.0) in dilute acid. [g] Also 235 (8.6) in dilute acid. [h] Also 328s (6.4) in methanol.

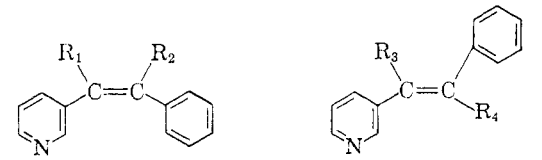
sulfonyl chloride and pyridine[18] gave *cis*-β-cyano-3-stilbazole (IV). By the same procedures *cis*-α-carboxy-3-stilbazole (V) was converted mostly to *cis*-(with some *trans*-)3-stilbazole[19] (II) and to *cis*-α-carboxamido-3-stilbazole (VI).

In contrast to the Perkin condensation which gives α-carboxystilbene of *cis* configuration, the base catalyzed condensation of benzaldehyde and phenylacetonitrile forms α-cyanostilbene of *trans* configuration. Similarly, when 3-pyridinealdehyde was condensed with phenylacetonitrile in the presence of a strong base, *trans*-β-cyano-3-stilbazole (VIII) was formed, while benzaldehyde and 3-pyridylacetonitrile gave *trans*-α-cyano-3-stilbazole (IX). These nitriles were hydrolyzed with aqueous sulfuric acid to the corresponding *trans*-β- (and α-)-carboxamido-3-stilbazoles (XIX and XX), respectively. Attempts to prepare *trans*-β-carboxy-3-stilbazole by further hydrolysis of the *trans* nitrile

(18) Method of C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).

(19) Beard and Katritzky[5] obtained a low yield of *trans*-3-stilbazole by the decarboxylation of *cis*-α-carboxy-3-stilbazole (V) under different conditions.

Figure 1



I. R_1 = H; R_2 = COOH
II. R_1 = R_2 = H
III. R_1 = H; R_2 = $CONH_2$
IV. R_1 = H; R_2 = CN
V. R_1 = COOH; R_2 = H
VI. R_1 = $CONH_2$; R_2 = H

VII. R_3 = R_4 = H
VIII. R_3 = H; R_4 = CN
XIX. R_3 = H; R_4 = $CONH_2$

VIII led to isomerization and only the *cis* acid, I, was isolated.

A number of alpha and beta substituted 3-stilbazoles with groups in the para position of the benzene ring were prepared by analogous reactions as were a few 2- and 4-stilbazole derivatives. The stereochemical assignments of all of the compounds described in this paper are summarized in Table I.

The ultraviolet absorption maxima of the compounds listed in Table I are recorded in Table II for methanol and acid solutions. In addition to the features described above it may be noted that in acid solution the spectra of most of the *trans*-stilbazoles have an intense "stilbene" band[20] with a maximum absorption near 300 mμ.

The infrared spectrum of *cis*-3-stilbazole is readily distinguished from that of the *trans* isomer (see Experimental). Important features of the latter spectrum have already been described.[21]

EXPERIMENTAL

An example of each procedure is given in detail and closely related compounds were prepared analogously with the exceptions noted. Yields are based on products with melting points less than 3° lower than those of analytical samples. Melting points of analytical samples, analyses and recrystallizing solvents are given in Table I.

cis-β-Carboxy-3-stilbazole (I). A mixture of 15.8 g. (0.10 mole) of sodium phenylacetate, 10.7 g. (0.10 mole) of 3-pyridinealdehyde, and 80 ml. of acetic anhydride was stirred under reflux for 2 hr. The mixture was cooled, diluted with one-half its volume of water, warmed to obtain a clear solution, and then cooled again and the product collected; yield, 12.5 g. (55%).

cis-α-Carboxy-3-stilbazole (V) was prepared by the method of Beard and Katritzky.[5]

cis-3-Stilbazole (II). *cis*-β-Carboxy-3-stilbazole (I) (15.0g.) was added portionwise over a 15 min. interval to a stirred suspension of 1.5 g. of copper chromite in 35 ml. of freshly distilled quinoline,[17] the temperature being maintained at 230° throughout the addition and for 30 min. thereafter. The reaction mixture was cooled, filtered and distilled *in vacuo*, first to remove quinoline (b.p. 61–63°/0.2 mm.), and finally to give the product as a yellow oil, b.p. 103–104°/0.3 mm., n^{25} 1.620; yield, 10.3 g. (85%).

The infrared spectrum of *cis*-3-stilbazole in carbon disulfide solution was characterized by the following bands

(20) W. H. Laarhoven, R. J. F. Nivard, and E. Havinga, *Rec. trav. chim.*, **79**, 1153 (1960).

(21) A. R. Katritzky, A. J. Boulton, and D. J. Short, *J. Chem. Soc.*, 1519 (1960). The distinctive features of the infrared spectra of *cis*- and *trans*-2-stilbazole have also been described.[4]

between 10 and 14 μ: 10.42 (m-s), 10.52 (m-s), 10.84 (sh), 10.92 (m-s), 11.55 (m-s), 12.85 (s), and 13.14 (m-s), μ.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.07, H, 6.02; N, 7.65.

The product obtained by the decarboxylation of *cis*-α-carboxy-3-stilbazole (V) using the same procedure was shown by its infrared and ultraviolet spectra to be mostly *cis*-3-stilbazole, together with a small proportion of the *trans* isomer.

trans-3-Stilbazole (VII). A solution of 9.3 g. of *cis*-3-stilbazole (II) in 50 ml. of nitrobenzene to which a few crystals of iodine had been added[17] was refluxed for 20 min. The solution was then cooled, diluted with ether, and extracted with dilute hydrochloric acid. The aqueous solution was washed with ether, then made alkaline with ammonia, and extracted with ether. The ether extracts were treated with decolorizing charcoal, dried over anhydrous sodium sulfate, filtered, and the solvent removed. The residual oil solidified and the solid product was triturated with cyclohexane and collected; yield, 8.0 g. (86%).

In contrast to that of the *cis* isomer the infrared spectrum of *trans*-3-stilbazole in carbon disulfide solution possessed only four maxima of medium to strong intensity between 10 and 14 μ: 10.22 (m-s), 10.44 (vs), 12.63 (vs), and 13.46 (vs) μ.

cis-β-Carboxamido-3-stilbazole (III). A mixture of 10.0 g. of *cis*-β-carboxy-3-stilbazole (I) and 30 ml. of thionyl chloride was refluxed for 1.5 hr. and the excess of thionyl chloride was distilled *in vacuo*—the last traces being removed by adding benzene and removing it *in vacuo* twice in succession. The residual solid was triturated with anhydrous ether, collected, and added portionwise to 100 ml. of anhydrous liquid ammonia. After the excess of ammonia had evaporated, the solid residue was extracted with hot acetone. The extract was filtered, concentrated, and cooled to give the product as colorless crystals; yield, 8.5 g. (85%).

The same procedure was used for the preparation of *cis* α-carboxamido-3-stilbazole (VI).

cis-β-Cyano-3-stilbazole (IV) *p*-Toluenesulfonyl chloride (5.2 g.) (0.027 mole) was added to a stirred suspension of 6.0 g. (0.027 mole) of *cis*-β-carboxamido-3-stilbazole (III) in 5.0 g. (0.061 mole) of pyridine.[18] After one hour at room temperature a clear solution resulted and an emulsion formed after an additional hour. The reaction mixture was diluted with ether and the solution washed several times with 10% sodium hydroxide and once with water, dried over anhydrous sodium sulfate, and evaporated. The addition of petroleum ether to the residual oil gave a solid which could not be recrystallized. The solid was dissolved in water and the solution made strongly alkaline with sodium hydroxide, whereupon the product separated as colorless crystals; yield, 4.0 g. (72%).

trans-β-Cyano-3-stilbazole (VIII). A solution of 2.68 g. (0.025 mole) of 3-pyridinealdehyde and 2.93 g. (0.025 mole) of phenylacetonitrile in 20 ml. of absolute ethanol was warmed to 50° and 1.5 ml. of a solution of sodium ethoxide in absolute ethanol (3.0 g. sodium in 30 ml. absolute ethanol) added. The reaction mixture was allowed to stand without heating for one hour, and was then cooled and 4.0 g. of the product collected. Additional product (1.0 g.) was obtained by adding water to the mother liquor; total yield, 5.0 g. (98%).

Compounds X to XVIII inclusive were prepared in a similar manner. In most cases the reaction mixture was kept at 40–50° for 5 min., cooled and the product was collected immediately. In one instance (compound XIII) the reaction mixture was concentrated on the steam bath to one-third its volume after standing for 1 hr. at room temperature. In each case the melting point of the product when first collected was very close to that of the analytical sample. Yields varied from 70% to 100%.

trans-β-Carboxamido-3-stilbazole (XIX). *trans*-β-Cyano-3-stilbazole (VIII) (52.0 g.) was dissolved in 560 ml. of 85% (v./v.) aqueous sulfuric acid and the mixture was heated and stirred on the steam bath for 2 hr. The solution was then cooled and poured cautiously into a mixture of 1.5 l. of 50% aqueous sodium hydroxide solution and 5 l. of crushed ice. The gummy precipitate which formed became solid upon standing and was collected, suspended in water, and again collected. The crude product was recrystallized from a mixture of 2-propanol and 2-propyl acetate to give 36.8 g. (65%) of colorless crystals, m.p. 134–137°. The product was further recrystallized from 2-propanol and 2-propyl acetate for analysis; m.p. 136–137°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.39; H, 5.65; N, 12.17.

On the other hand, a crystal modification of the same compound (m.p. 129–130°) was obtained from acetone-pentane solution (see Table I for analysis). Although the infrared spectra of Nujol mulls of the crystal modifications were clearly different, the spectra of their chloroform solutions were identical, as were their ultraviolet absorption spectra in methanol and in dilute acid solutions.

Compounds XX, XXI, and XXIII were prepared similarly in yields of 18%, 39%, and 54% respectively. In the case of compound XX the crude product failed to solidify and the gum was extracted with methylene chloride and the oil obtained upon removal of solvent was triturated with ether to give solid material for recrystallization. Compound XXII was obtained in 95% yield using 50% (v./v.) aqueous sulfuric acid.

In an experiment using more vigorous conditions, a solution of 2.0 g. of *trans*-β-cyano-3-stilbazole (VIII) in 20 ml. of 60% sulfuric acid was heated and stirred at 100° for 3 hr., allowed to stand overnight at room temperature, treated with an excess of 50% sodium hydroxide solution (cooling), and finally made acidic with acetic acid. *cis*-β-Carboxy-3-stilbazole (I) (1.0 g., m.p. 145–170°) was obtained, which after two recrystallizations from 70% ethanol had a melting point of 195–199°, undepressed upon admixture with an authentic sample.

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BLOOMFIELD, N. J.