Some Hypocholesteremic 2,3-Diphenylacrylonitriles[1]

G. M. K. HUGHES, P. F. MOORE, AND R. B. STEBBINS

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut

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The diethylaminoethyl ethers of 4-stilbenol, stilbesterol, hexestrol, and estradiol have been shown to be hypocholesteremic by inhibiting the reduction of desmosterol to cholesterol. Extensive series of dialkylaminoalkoxy derivatives of stilbene, 2,3-diphenylacrylonitrile, and 2,3-diphenyl-2-pentenenitrile have been made and their hypocholesteremic activity has been determined; members of the last class with *trans* stereochemistry are particularly potent agents.

Structure–Activity.—The chemical modification of estrogens to produce compounds that maintain the hypocholesteremic activity of estrogens, but lack feminizing properties, has been the goal of a number of workers. A particularly interesting discovery was that triparanol (**1**),[2] which is superficially structurally related to the triphenylethylene estrogens, is not only not estrogenic but is hypocholesteremic[3] by a mechanism not shown by estrogens,[4a] that of inhibiting the reduction of desmosterol to cholesterol.[5] Furthermore, since the desmosterol thus produced does not counterbalance the diminished production of cholesterol, there is a net lowering of sterol. It was thus of interest to determine the structural features responsible for this activity and to seek other compounds exhibiting this property.

Triparanol differs from the recognized class of estrogenic triphenylethylenes by the inclusion of a diethylaminoethoxy substituent and by being hydrated at the central bond. It seemed most likely that the basic ether function was responsible for conferring the new biochemical activity, and consistent with this was our demonstration that neither the phenol **2** nor the methyl ether **3** corresponding to triparanol was significantly active (Table I). Hypocholesteremic activity

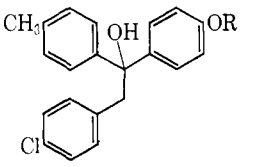
TABLE I

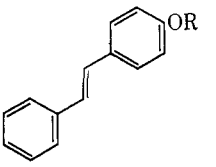
Compound no.	Dose, mg./kg./day	Route	Hypocholesteremic activity[a]
1	40	Oral	56
2	40	Oral	0
3	70	Subcutaneous	13
4	70	Subcutaneous	50
5	70	Subcutaneous	57

[a] See text.

was determined in groups of six Charles River rats weighing initially 140–150 g., by administration of the test compound for 6 days and then assaying their *apparent* plasma cholesterol by application of the Liebermann–Burchard color reaction.[6]

Hypocholesteremic activity was found in the two simpler compounds **4** and **5**. It had been confirmed in these laboratories[4b] that livers of rats treated with triparanol had a normal total sterol concentration, but that part of the cholesterol had been replaced by desmosterol, and that, in contrast, rats treated with high doses of estrogens had an elevated sterol concentration, but that the sterol was essentially pure cholesterol. Examination of the livers of animals treated with **4** and **5** showed that **4** induced estrogen-like changes, while **5** induced the formation of desmosterol.





1, R = $CH_2CH_2NEt_2$
2, R = H
3, R = CH_3

4, R = H
5, R = $CH_2CH_2NEt_2$

Schmähl[7] has reported that **4** is estrogenic. Here, then, was a case of a phenolic estrogen becoming an inhibitor of cholesterol biosynthesis on etherification with a diethylaminoethyl group. That this might be a more general phenomenon was demonstrated by the preparation of the diethylaminoethyl ethers of estradiol (**6**), stilbestrol (**7**), and hexestrol (**8**), all of which were hypocholesteremic (Table II) by inhibiting the reduction of desmosterol. Our sample of **6** was about 1/5000 as estrogenic as estradiol[8]; this could be a true value or represent estradiol as an impurity to the extent of one part in five thousand. Recently, the hypocholesteremic activity of the hexestrol bisether **8** in man has been reported[9] and its mode of action confirmed.[10] That the dialkylaminoethoxy group confers the property of inhibiting the reduction of desmosterol not only on phenolic estrogens, as we have shown, but also when present in at least one androgen is reported for 3β-(2-diethylaminoethoxy)androst-5-en-17-one[10] and its dimethyl analog.[11]

Following the finding of activity in 4-diethylaminoethoxystilbene (**5**), a series of basic ethers of stilbenol were prepared, but none appeared to be more active

(1) Presented at the 143rd National Meeting of the American Chemical Society in Atlantic City, N. J., Sept. 9–14, 1962.

(2) F. P. Palopoli, *Progr. Cardiovascular Diseases*, **2**, 489 (1960).

(3) T. R. Blohm, T. Karyia, M. W. Laughlin, and F. P. Palopoli, *Federation Proc.*, **18**, 369 (1959).

(4) (a) S. K. Figdor and R. Pinson, of these laboratories, private communication; (b) S. K. Figdor, E. C. Schreiber, R. B. Stebbins, P. F. Moore, and R. Pinson, *J. Med. Chem.*, **7**, 508 (1964).

(5) J. Avigan, D. Steinberg, M. J. Thompson, and E. Mosettig, *Progr. Cardiovascular Diseases*, **2**, 525 (1960).

(6) J. J. Carr and I. J. Drekter, *Clin. Chem.*, **2**, 353 (1956).

(7) D. Schmähl, *Arzneimittel-Forsch.*, **7**, 211 (1957).

(8) The authors thank Dr. J. G. Llaurado, of these laboratories, for this determination, using the method of E. B. Astwood, *Endocrinology*, **23**, 25 (1938).

(9) G. Annoni and A. Longaretti, *Med. Welt*, 1945 (1961).

(10) W. A. Phillips and J. Avigan, *Proc. Soc. Exptl. Biol. Med.*, **112**, 233 (1963).

(11) S. Gordon, E. W. Cantrall, W. P. Cekleniak, H. J. Albers, R. Littell, and S. Bernstein, *Biochem. Biophys. Res. Commun.*, **6**, 359 (1961).

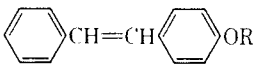
TABLE II

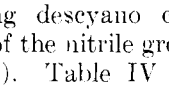
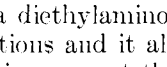
DIETHYLAMINOETHYL ETHERS OF ESTROGENS

Compd. no.	Formula	M.p., °C.	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found	Cryst. solvent[a]	Activity[b]
6[c]	$C_{24}H_{38}ClNO_2$	224–226	70.98	70.50	9.77	9.42	3.31	3.22	B-I	40
7[d]	$C_{30}H_{48}Cl_2N_2O_2$	239.5–241.5[e]	66.77	66.37	8.97	8.81	5.20	5.16	A	42
8[f]	$C_{30}H_{50}Cl_2N_2O_2$	227–230[e]	66.52	66.25	9.31	9.48	5.17	4.81	B	20

[a] See Experimental. [b] Reported for 40 mg./kg., oral. [c] Estradiol 3-diethylaminoethyl ether, kindly supplied by Mr. R. Berg of these laboratories. [d] 2,2′′′-[(Diethylvinylene)bis(*p*-phenyleneoxy)]bistriethylamine bishydrochloride, prepared by alkylation of stilbestrol using procedure A; D. A. Peak and T. I. Watkins [*J. Chem. Soc.*, 3292 (1951)] give m.p. 236°. [e] 2,2′′′-[1,2-Diethylethylenebis(*p*-phenyleneoxy)]bistriethylamine bishydrochloride; D. A. Peak and T. I. Watkins (see *d*) give m.p. 222°.

TABLE III



Compd.[a] no.	R	Formula	M.p., °C.	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found	Activity[b]
5	$-(CH_2)_2N(C_2H_5)_2$[c]	$C_{20}H_{26}ClNO$	210–212[d]	73.28	72.00	7.89	7.92	10.69[e]	10.44[e]	57[f,g]
9	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	$C_{20}H_{25}NO$	74–76	81.31	81.02	8.53	8.52	4.74	4.73	38[f]
10	$-(CH_2)_3N(CH_3)_2$[h]	$C_{19}H_{23}NO$	89	81.10	81.43	8.24	8.24	4.98	5.00	22[f]
11	$-(CH_2)_2N[CH(CH_3)_2]_2$	$C_{22}H_{29}NO$	78–79	81.69	82.07	9.04	9.26	4.33	4.38	+[i]
12		$C_{21}H_{25}NO$	74–76	82.04	81.97	8.20	8.29	4.56	4.61	+[i]
13		$C_{22}H_{28}N_2O$	91–92.5	78.53	78.62	8.39	8.51	8.33	8.94	0

[a] All compounds show λ_{max} 304 mμ (ε 2.90–3.07 × 10⁴) and 319 mμ (ε 2.88–302 × 10⁴). [b] Reported for 40 mg./kg., oral. [c] Hydrochloride. [d] M. D. Marinopoulo [*Ann. Pharm. Franc.*, **5**, 7(1947)] gives m.p. 214°. [e] Chlorine analysis. [f] At 70 mg./kg., s.c. [g] Activity at 40 mg./kg. *per os* is 28. [h] G. Cavallini and E. Massarani [*Farmaco* (Pavia), *Ed. Sci.*, **9**, 405 (1954); *Chem. Abstr.*, **49**, 12399 (1955)] have prepared these two compounds and reported their boiling points, and the melting point of the hydrochlorides. [i] Inhibits desmosterol reduction, but degree of activity could not be assessed; see text.

than **5** (Table III). The activities of **11** and **12** could not be assessed due to anomalous Liebermann–Burchard colors; however, examination of the livers of rats treated with the compounds in Table III showed that all of the compounds, except **13**, inhibited the reduction of desmosterol to cholesterol.[4] An extensive series of 2,3-diphenylacrylonitriles was prepared after it was found that 2-[*p*-(2-diethylaminoethoxy)phenyl]-3-phenylacrylonitrile (**14**) was more potent than the corresponding descyano compound (**5**), and that the position of the nitrile group was not critical (**15**, Tables I and IV). Table IV demonstrates again the superiority of a diethylaminoethoxy group over other basic ether functions and it also indicates that only attachment of this group at the 4-position is consistent with marked activity.

Table V lists the activities of a variety of additionally substituted diphenylacrylonitriles. Of the initial prototypes, **31** and **41**, having dimethylamino and methylthio substituents, respectively, showed enhanced potency, and systematic modification of these functions led to the most potent compound in this series, which contains the isopropylthio moiety (**43**). Compound **50** (Table VI), containing two diethylaminoethoxy functions also showed superior potency, but attempts to improve upon this by synthesizing other analogs with two basic ether functions led to considerable reduction activity except for **51**, a compound containing a piperazinyl moiety. This was a curious result in that this moiety was incompatible with activity in the stilbenol series (**13**), at least in the dose range used.

The final structural variation examined was the effect of an additional alkyl substituent on the stilbene bond, to give a series of 2,3-diphenyl-2-pentenenitriles (Table VII). Of the pairs of geometric isomers tested, the *trans* isomer was considerably more active than the *cis* isomer, and indeed our most potent compounds were in this series. Dose–response curves were established for four of these agents (**54**, **56**, **58**, and **61**) and the potencies were 0.9, 5.4, 3.6, and 6.8, respectively, relative to triparanol equal to 1 (to be published).

Chemistry.—Compounds **2** and **3** were prepared by the action of *p*-chlorobenzylmagnesium chloride on the appropriate benzophenone. The preparation of **2** from **3** was not attempted, since dehydration would undoubtedly occur during any process of demethylation.

The bisdiethylaminoethyl ethers of stilbestrol (**7**) and hexestrol (**8**) were prepared by alkylation of stilbestrol and hexestrol, respectively, with diethylaminoethyl chloride using sodium methoxide as base and toluene as reaction medium (procedure A) while procedure B uses potassium carbonate in acetone. As the work progressed it became apparent that procedure B is as effective as A and, in addition to being more convenient, causes less isomerization. Only in one case, during the preparation of **56**, was isomerization encountered using A.

The preparation of the amino ethers of 4-stilbenol, (**5**, **9–13**, Table III) was carried out using procedure A.

The derivatives of 2,3-diphenylacrylonitrile, (**14–53**, Tables IV, V, and VI) were all prepared by condensation of either a diethylaminoethoxybenzaldehyde with a phenylacetonitrile or of a diethylaminoethoxyphenylacetonitrile with a benzaldehyde. The preparation of *p*-(2-diethylaminoethoxy)phenylacetonitrile required first the preparation of *p*-hydroxyphenylacetonitrile. This has always been prepared by chemical reduction of *p*-nitrophenylacetonitrile followed by replacement of the amino group by hydroxyl *via* a diazotization reaction. Although catalytic reduction

was found to be more convenient and was used to provide samples of *p*-aminophenylacetonitrile, the demethylation of practical grade *p*-methoxyphenylacetonitrile by pyridine hydrochloride was found to be a superior method of preparing *p*-hydroxyphenylacetonitrile. Indeed, pyridine hydrochloride demethylation of phenolic methyl ethers was used extensively in this work because of the convenience and high yield. The relatively mild conditions employed by Buü-Hoi,[12] *et al.*, were very suitable provided relatively anhydrous reagent was used and this was readily achieved by distillation. The preparation of other benzaldehydes and phenylacetonitriles requires no comment beyond that which appears in the Experimental section.

The compounds in our most active series (Table VII), which are derivatives of 2,3-diphenyl-2-pentenenitrile, were prepared by a three-stage sequence beginning with a condensation of a phenylacetonitrile with a propiophenone, at least one of which bore a 4-methoxy group. Rorig[13] has described the use of either sodamide in toluene or xylene or sodium methoxide in methanol to effect this condensation and we routinely used the former conditions. The use of sodium hydride in dimethylformamide was equally acceptable,[14] but did not improve the yield. On a large scale (20 moles) the most convenient procedure employed sodium methoxide also in dimethylformamide.[14]

The yield of these condensations was never high (maximum 50%), and in the one case studied, the preparation of 2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile, the product was a 1:1 mixture of *cis* and *trans* isomers. Rorig[13] has described the isolation of the solid *trans* isomer of 2,3-diphenyl-2-pentenenitrile and of an oil which was largely the *cis* isomer. The stereochemistry was established by demonstrating that only the solid isomer could be cyclized to an indanone.

In the present work no attempt was made to separate the isomeric phenolic methyl ethers obtained from initial condensations, though fortuitously, pure *trans*-2-(*p*-chlorophenyl)-3-(*p*-methoxyphenyl)-2-pentenenitrile was isolated. Instead, the crude mixtures were demethylated with pyridine hydrochloride, and the isomeric phenols were isolated. In general, the *trans* isomer was obtained by crystallization of the mixed isomers and the *cis* isomer was isolated by chromatography on Florisil of the material obtained by the concentration of the mother liquors. This procedure was unnecessary in the case of *cis*- and *trans*-3-(*p*-hydroxyphenyl)-2-(*p*-chlorophenyl)-2-pentenenitrile, for the isomers were completely separated by crystallization of a mixture that had been partially purified so as to contain only the two required materials.

To obtain standards for quantitative chromatography, *cis*- and *trans*-3-(*p*-methoxyphenyl)-2-phenyl-2-pentenenitrile were prepared by methylation of the corresponding phenols. The properties of the *trans* isomer correspond to those reported by Rorig.[13]

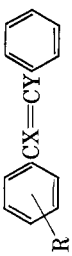
Our stereochemical assignments rest largely upon ultraviolet absorption data, *trans* being assigned to that

(12) Ng. Ph. Buü-Hoi, Ng. Hoo'n, and M. R. Khenissi, *J. Chem. Soc.*, 2307 (1951).

(13) K. Rorig, *J. Am. Chem. Soc.*, **73**, 1290 (1951).

(14) These improvements were effected by Mr. E. Bianco of these laboratories.

TABLE IV



Compd. no.	X	Y	R	Salt	Formula	M.p., °C	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Crystn. solvent[a]	λ_{max}	$\epsilon \times 10^{-4}$	Activity[b]
14	H	CN	4-$(C_2H_5)_2N(CH_2)_2O$—	HCl	$C_{21}H_{25}ClN_2O$	174–177	70.67	70.81	7.06	6.83	7.85	7.91	B	335	2.36	30[c]
15	CN	H	4-$(C_2H_5)_2N(CH_2)_2O$—	HCl	$C_{21}H_{25}ClN_2O$	187–188	70.67	70.84	7.06	7.30	7.85	7.78	A–C	330.5	2.44	33
16	H	CN	2-$(C_2H_5)_2N(CH_2)_2O$—	HCl	$C_{21}H_{25}ClN_2O$	126–128.5	70.67	70.62	7.06	7.10	7.85	7.12	A–G	338	1.38	7
17	H	CN	3-$(C_2H_5)_2N(CH_2)_2O$—	HCl	$C_{21}H_{25}ClN_2O$	184–186	70.67	70.42	7.06	7.03	7.85	7.65	B	313.5	2.03	0
18	CN	H	4-C_2H_5N(piperazine)$(CH_2)_2O$—	2HCl	$C_{27}H_{29}Cl_2N_3O$	271–273.5	63.74	63.28	6.29	6.41	9.71	9.44	A–D	330.5	2.27	18
19	H	CN	4-$C_5H_{10}N(CH_2)_2O$—	HCl	$C_{22}H_{25}ClN_2O$	203–205	71.62	71.47	6.83	7.13	7.59	7.42	B	335	3.04	0
20	H	CN	4-$(CH_3)_2NCH_2CH(CH_3)CH_2O$—	HCl	$C_{21}H_{25}ClN_2O$	155–158.5	70.67	70.93	7.06	7.06	7.85	7.79	F	336	2.87	5

[a] See Experimental. [b] Reported for 40 mg./kg., oral. [c] Activity at 18, 35, and 70 mg./kg. is 22, 37, and 67, respectively. The corresponding values for compound **5** are 12, 30, and 57, respectively.

TABLE V: $(C_2H_5)_2NCH_2CH_2O$–C$_6$H$_4$–CX=CY–C$_6$H$_4$–R

Compd. no.	X	Y	R	Salt	Formula	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Cryson. solvent[a]	λ_{max}	$\epsilon \times 10^{-4}$	Activity[b]
21	CN	H	4-CH_3	HCl	$C_{22}H_{27}ON_2Cl$	182.5–184	71.20	71.25	7.34	7.31	7.55	7.51	E	335	2.78	13
22	CN	H	4-CH $(CH_3)_2$	HCl	$C_{24}H_{31}ON_2Cl$	181–182	72.24	71.58	7.83	7.73	7.02	7.03	A–C	335	2.58	8
23	CN	H	4-CF_3	...	$C_{23}H_{25}ON_2F_3$	73–75	68.03	68.39	5.98	6.10	7.22	7.23	K	337	2.29	37
24	CN	H	4-CN	HCl	$C_{23}H_{24}ON_3Cl$	232.5–234.5	69.19	68.84	6.33	6.41	11.00	10.26	B	349	2.98	30
25	H	CN	4-F	HCl	$C_{21}H_{24}ON_2FCl$	204–206	67.28	67.23	6.45	6.56	7.47	7.28	A–C	337	2.84	13
26	H	CN	4-Cl	HCl	$C_{21}H_{26}ON_2Cl_2$	209–211	64.45	64.39	6.19	6.36	7.17	7.20	B	339.5	3.20	27
27	CN	H	2-Cl	HCl	$C_{21}H_{24}ON_2Cl_2$	175.3–176.8	64.45	64.51	6.19	6.19	7.17	7.34	A–C	328	1.99	22
28	CN	H	4-Cl	HCl	$C_{21}H_{24}ON_2Cl_2$	211–212	64.45	64.53	6.19	5.93	7.17	7.01	A–C	337	2.56	28
29	H	CN	4-NH_2	2HCl	$C_{21}H_{27}ON_3Cl_2$	267–270	61.76	61.58	6.67	6.34	10.30	10.18	A	365	2.42	22
30	H	CN	4-NHCOCH(=CHCOOH)	HCl	$C_{25}H_{18}O_4N_3Cl$	175–184	63.88	63.83	6.01	6.36	8.94	9.05	A–C	352	3.50	23
31	CN	H	4-$N(CH_3)_2$	2HCl	$C_{23}H_{31}ON_3Cl_2$	201.5–203.5	63.30	63.50	7.17	7.26	9.64	9.51	C	395	3.83	35
32	CN	H	4-$N(C_2H_5)_2$	HCl	$C_{25}H_{34}ON_3Cl$	188.5–191	70.15	71.00	8.01	7.80	9.82	9.82	C	*d*		33
33	CN	H	4-$NHCOCH_3$	...	$C_{23}H_{27}O_2N_3$	153–154	73.18	73.05	7.21	7.10	11.13	11.06	B	351	3.51	17
34	H	CN	4-$NHCONH_2$[c]	HCl	$C_{22}H_{27}O_2N_4Cl$	184–186.5	63.68	63.37	6.56	6.40	13.50	13.15	A–D	351	3.09	15
35	H	CN	4-$NHCOCH_2NEt_2$	2HCl	$C_{27}H_{38}O_2N_4Cl_2$	203–205	62.18	62.65	7.35	7.34	10.74	10.46	A–C	347.5	3.19	27
36	H	CN	4-NO_2	...	$C_{21}H_{23}N_3O_4$	109–111	69.02	68.82	6.34	6.45	11.50	11.23	A			55[f]
37	H	CN	4-CH_3O	Citrate	$C_{28}H_{34}N_2O_9$	127–130	61.98	61.25	6.32	6.42	5.16	4.94	F	344	2.55	22
38	CN	H	2-CH_3O	HCl	$C_{22}H_{27}ClN_2O_2$	146.5–147.5	68.28	68.17	7.03	7.03	7.24	7.21	C	345	1.94	20
39	CN	H	4-CH_3O	HCl	$C_{22}H_{27}ClN_2O_2$	177.5–178.5	68.28	68.47	7.03	7.12	7.24	7.05	E	346	3.06	15
40[d]	CN	H	4-$HOCH_2CH_2O$	HCl	$C_{23}H_{29}ClN_2O_4$	152–153	66.25	66.09	7.01	6.96	6.72	6.82	B	346	3.05	25
	CN	H	4-$HOCH_2CH_2O$	...	$C_{23}H_{28}N_2O_3$	87–88	72.50	72.60	7.42	7.33	7.36	7.58	H	346	2.98	
41	CN	H	4-CH_3S	HCl	$C_{22}H_{27}ClN_2OS$	207.5–209	65.56	65.82	6.75	6.84	6.95	7.05	A	360	3.36	42
42	CN	H	4-C_2H_5S	HCl	$C_{23}H_{29}ClN_2OS$	190–193	66.22	66.39	7.01	7.15	6.72	6.62	A	359	3.39	33
43	CN	H	4-$(CH_3)_2CH_2S$	HCl	$C_{24}H_{31}ClN_2OS$	171–173	66.88	66.64	7.25	7.36	6.50	5.96	C	356	3.27	50
	CN	H	4-$(CH_3)_2CH_2S$	...	$C_{24}H_{30}N_2OS$	68–69	73.04	73.23	7.67	7.73	7.10	7.23	A	355	3.02	
44	CN	H	4-$(CH_3)_2CHCH_2S$	HCl	$C_{25}H_{33}ClN_2OS$	165.5–167.5	67.46	67.63	7.48	7.11	6.30	6.29	A	360	3.45	42
45	CN	H	4-$CH_3(CH_2)_6S$	HCl	$C_{28}H_{39}ClN_2OS$	150–152	69.03	68.88	8.07	7.93	5.75	5.66	F	360	3.36	20
46	CN	H	4-$C_6H_{11}S$	...	$C_{27}H_{34}N_2OS$	76.5–79	73.61	73.90	7.89	7.22	6.45	6.28	K	358	3.35	17
47	CN	H	4-$C_6H_5CH_2S$	HCl	$C_{28}H_{31}ClN_2OS$	194.5–195.5	70.19	69.41	6.52	6.44	5.85	5.61	B	357.5	3.46	38

[a] See Experimental. [b] Reported for 40 mg./kg., oral. [c] Prepared by treating the free base of compound **29** with maleic anhydride in refluxing ether for 10 min. [d] λ_{max} 234 (1.03), 329 (1.63), and 405 mμ (0.45) in 0.01 *N* methanolic hydrochloric acid. [e] Prepared from *p*-ureidophenylacetonitrile, m.p. 171–173.5°, by the method of M. Rising [*J. Am. Chem. Soc.*, **42**, 131 (1920)], who gives m.p. 170.5°. [f] At 100 mg./kg., s.c. [g] *p*-2-Hydroxyethoxybenzaldehyde was prepared as described by J. Bernstein, H. L. Yale, M. Holsing, J. Martins, and W. A. Lott [*J. Am. Chem. Soc.*, **73**, 906 (1951)].

TABLE VI: R_1–C$_6$H$_4$–CH=C(CN)–C$_6$H$_4$–R_2

Compd. no.	R_1	R_2	Salt	Formula	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Cryson. solvent[a]	λ_{max}	$\epsilon \times 10^{-4}$	Activity[b]
48	2-$(C_2H_5)_2N(CH_2)_2O$	$O(CH_2)_2N(C_2H_5)_2$	2HCl	$C_{27}H_{39}Cl_2N_3O_2$	160.5–162	63.77	63.23	7.73	7.64	8.28	8.04	A–C	342.5	1.78	2
49	3-$(C_2H_5)_2N(CH_2)_2O$	$O(CH_2)_2N(C_2H_5)_2$	2HCl	$C_{27}H_{39}Cl_2N_3O_2$	137.5–138	63.77	63.16	7.73	7.75	8.27	8.01	A–C			0
50	4-$(C_2H_5)_2N(CH_2)_2O$	$O(CH_2)_2N(C_2H_5)_2$	2HCl	$C_{27}H_{39}Cl_2N_3O_2$	187–188.5	63.77	63.39	7.73	7.80	8.27	8.68	B	343.5	2.99	42
51	4-$(C_2H_5)_2N(CH_2)_2O$	$O(CH_2)_2$–piperazine–C_2H_5	3HCl	$C_{29}H_{43}Cl_3N_4O_2$	245–249	59.44	59.29	7.40	7.31	9.57	9.11	A	342.5	2.93	42
52	4-$(C_2H_5)_2N(CH_2)_2O$	$O(CH_2)_2N$–piperidine	2HCl	$C_{28}H_{39}Cl_2N_3O_2$	222.5–224.5	64.61	64.30	7.56	7.82	8.08	7.79	A–C	342.5	2.69	15
53	4-$(C_2H_5)_2N(CH_2)_2O$	$OCH_2CH(CH_3)CH_2N(CH_3)_2$	2HCl	$C_{27}H_{39}Cl_2N_3O_2$	188–191	63.77	64.16	7.73	7.93	8.27	8.22	A–C	343	2.75	13

[a] See Experimental. [b] Reported for 40 mg./kg., oral.

isomer of a pair having the greater extinction coefficient at the longest wave-length peak, even though *cis* isomer actually absorbs as a longer wave length in this area. This situation is also encountered in the case of α,α'-dialkylstilbenes.[15] The *trans* isomers also had the higher melting points; indeed, in one case partial thermal conversion of the lower melting *cis* isomer to the higher *trans* isomer was encountered [*cis*-2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile]. The *trans* isomer of any pair was also less soluble than the *cis* and more polar on paper and column chromatography.

During the course of the work the hydrolysis of some 2,3-diphenyl-2-pentenenitriles was investigated briefly. In addition to the normal hydrolysis of the nitrile group to the corresponding acid, there were obtained products corresponding to a reversal of the condensation by which the nitriles were synthesized. Thus, from the hydrolysis of a mixture of *cis*- and *trans*-2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile some 4-hydroxypropiophenone was obtained and the *trans* isomer of the corresponding diethylaminoethyl ether yielded some phenylacetic acid.

Experimental

Unless otherwise stated all activities in Tables II–VII are reported for 40 mg./kg. of agent, orally. Recrystallization solvents used were: A, methanol; B, ethanol; C, isopropanol; D, water; E, acetone; F, 2-butanone; G, ethyl acetate; H, ether; I, methylene chloride; J, chloroform; K, petroleum ether (b.p. 40–60°); L, hexane. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and ultraviolet absorption spectra were determined in ethanol.

1-(*p*-Chlorophenyl)-2-(*p*-hydroxyphenyl)-2-*p*-tolylethanol (2).—Treatment of the Grignard reagent from *p*-chlorobenzyl chloride (32.2 g.) in ether (75 ml.) with 4-hydroxy-4'-methylbenzophenone (10.6 g.) suspended in benzene (300 ml.), gave on working up a yellow oil which was dissolved in benzene (75 ml.). The slow addition of petroleum ether (b.p. 40–60°, 200 ml.) precipitated the crude product (10.18 g.) m.p. 128–130°, which was recrystallized twice from hexane–acetone (5:1) to give 5.32 g. of product, m.p. 127–128°. Chromatography on Florisil gave a total of 3.71 g. of homogeneous material on elution with methylene chloride. Recrystallization from hexane–acetone gave 2.53 g. of crystalline material, m.p. 153–154.5°.

Anal. Calcd. for $C_{21}H_{19}ClO_2$: C, 74.44; H, 5.66; Cl, 10.47. Found: C, 74.32; H, 5.64; Cl, 10.35.

1-(*p*-Chlorophenyl)-2-(*p*-methoxyphenyl)-2-*p*-tolylethanol (3).—4-Methoxy-4'-methylbenzophenone (10.04 g.) in benzene (25 ml.)–ether (25 ml.) was added to the Grignard reagent from *p*-chlorobenzyl chloride (6.44 g.) in ether. Conventional work-up gave 14.75 g. of a yellow oil that crystallized on standing, but which could not be successfully recrystallized. Concentration of a hexane solution gave 3.87 g. of a crystalline product, m.p. 88–91°. An analytical sample was recrystallized from aqueous ethanol and had m.p. 100–103.5°.

Anal. Calcd. for $C_{22}H_{21}ClO_2$: C, 74.88; H, 6.00; Cl, 10.05. Found: C, 75.52; H, 6.07; Cl, 1052.

General Preparation of Dialkylaminoalkyl Ethers of 4-Stilbenol. Alkylation Procedure A.—4-Stilbenol (0.05 mole) was added to a solution of sodium (0.05 g.-atom) in ethanol (25 ml.), and toluene (50 ml.) was added. After 30 min. a solution of the dialkylaminoalkyl chloride (liberated from 0.055 mole of its hydrochloride) in toluene (25 ml.) was added. After heating under reflux for 4 hr. half of the solvent was distilled, benzene (150 ml.) added, and the mixture extracted with 10% aqueous sodium hydroxide and washed with water. The residue obtained on removal of solvent was recrystallized from ethanol to obtain products with the physical constants shown in Table III. The hydrochloride of 4-diethylaminoethoxystilbene (**5**) was prepared by the addition of an ethyl acetate solution of hy-

TABLE VII

$(C_2H_5)_2NCH_2CH_2O$–C$_6$H$_4$–CX=CY–C$_6$H$_4$–R

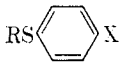
Compd. no.	X	Y	R	Stereochemistry[a]	Salt	Formula	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Crystn. solvent[b]	λ_{max}	$\epsilon \times 10^{-4}$	Activity[c]
54	C_2H_5	CN	H	T	HCl	$C_{23}H_{29}ClN_2O$	172–174	71.76	71.65	7.59	7.51	7.28	7.37	E	290.5	1.39	53
55	C_2H_5	CN	H	C	HCl	$C_{23}H_{29}ClN_2O$	123–126	71.76	71.64	7.59	7.62	7.28	7.34	F	300	1.17	8
56	C_2H_5	CN	Cl	T	HCl	$C_{23}H_{28}Cl_2N_2O$	222.5–224	65.87	65.60	6.74	6.80	6.69	6.76	A–G	294	1.47	73
57	C_2H_5	CN	Cl	C	Citrate	$C_{29}H_{35}ClN_2O_8$	130–132	60.57	60.70	6.14	6.26	4.87	4.84	E–L	305	1.23	28
58	C_2H_5	CN	F	T	HCl	$C_{23}H_{28}FN_2O$	174.5–176	68.55	68.89	7.00	7.09	6.95	7.08	E–L	292	1.38	78
59	CN	C_2H_5	H	T	HCl	$C_{21}H_{29}ClN_2O$	152–154	71.76	72.03	7.59	7.64	7.28	7.24	E–L	277	1.36	73
60	CN	C_2H_5	H	C	Citrate	$C_{29}H_{36}N_2O$	121–123	64.43	64.15	6.71	6.74	5.18	5.24	E	291	1.09	13
61	CN	C_2H_5	Cl	T	HCl	$C_{23}H_{27}ClN_2O$	141.5–143.5	65.87	65.24	6.74	6.90	6.69	6.44	E–L	284	1.43	75
62	CN	C_2H_5	Cl	C	Citrate	$C_{29}H_{35}ClN_2O$	133–135	60.57	60.40	6.14	6.23	4.87	4.87	E	298	1.34	23
63	CN	C_2H_5	$OCH_2CH_2N(C_2H_5)_2$	T	2HCl	$C_{29}H_{47}Cl_2N_3O_2$	203–205	64.91	64.28	8.09	8.06	7.84	7.87	A-F	292.5	1.48	2
64	CN	C_2H_5	$OCH_2CH_2N(C_2H_5)_2$	C	Citrate[d]	[e]									299.5	1.22[d]	0

[a] T = *trans*, C = *cis*. [b] See Experimental. [c] Reported for 40 mg./kg., oral. [d] The analytical data indicate $(C_{29}H_{41}N_3O_2)_2 \cdot (C_6H_8O_7)_3$. *Anal.* Calcd. for $C_{16}H_{106}N_6O_{25}$: C, 60.31; H, 7.07; N, 5.55. Found: C, 60.60; H, 7.34; N, 5.53. [e] Not obtained pure; a mixture, predominantly *cis*, was used.

(15) H. Suzuki, *Bull. Chem. Soc. Japan.*, **25**, 145 (1952).

TABLE VIII

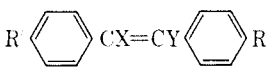
ALKYL PHENYL SULFIDES



R	X	B.p., °C. (mm.)	Formula	% C		% H		n_D (t °C.)
				Calcd.	Found	Calcd.	Found	
$(CH_3)_2CH$	H	90–91° (15)	$C_9H_{12}S$	71.00	70.89	7.95	7.99	1.5445[a] (24)
C_6H_{13}	H	152–158[b] (15)	$C_{12}H_{16}S$	74.94	74.49	8.39	8.46	1.5672[b] (24)
C_2H_5	Cl	107–108° (9)	C_8H_9ClS	55.62	55.72	5.25	5.32	1.5789[c] (26)
$(CH_3)_2CH$	Br	128–132[d] (12)	$C_9H_{11}BrS$	46.75	45.68	4.80	4.85	1.5825 (24)
$(CH_3)_2CHCH_2$	Cl	128–131 (10)	$C_{10}H_{13}ClS$	59.83	60.02	6.51	6.80	1.5548 (25)
$CH_3(CH_2)_6CH_2$	Cl	174–177 (10)	$C_{13}H_{19}ClS$	64.30	64.41	7.89	8.05	1.5395 (25)
C_6H_{13}	Br	189–191 (13)	$C_{12}H_{15}BrS$	53.13	53.54	5.58	5.87	1.5981 (24)
C_2H_5	CHO	151–153° (13)	$C_9H_{10}OS$	65.01	64.54	6.06	6.29	1.6290 (25.5)
$(CH_3)_2CH$	CHO	145–148° (12)	$C_{10}H_{12}OS$	66.67	65.94	6.67	7.33	1.5984 (24.5)
$(CH_3)_2CHCH_2$	CHO	163–166° (12.5)	$C_{11}H_{14}OS$	68.00	67.31	7.26	7.35	1.5879 (25)
$CH_3(CH_2)_6$	CHO	>220° (3)	$C_{14}H_{20}OS$	71.14	79.60	8.53	8.90	1.5605 (25)
C_6H_{13}	CHO	130–136 (0.5)	$C_{13}H_{18}OS$		[e]			1.6087 (24)

[a] H. Bochme and H.-J. Gran [*Ann. Chem.*, **577**, 68 (1952)] give b.p. 92–94° (16 mm.) and Ipatieff, *et al.*,[21] give b.p. 206–207.5°, $n^{20}D$ 1.5468. [b] R. W. Savile [*J. Chem. Soc.*, 2880 (1958)] reports b.p. 111° (0.1 mm.) and $n^{20}D$ 1.5680. [c] M. Kulka [*Can. J. Chem.*, **36**, 750 (1958)] prepared this by alkylation of *p*-chlorothiophenol with ethyl sulfate and reported b.p. 123° (18 mm.) and $n^{20}D$ 1.5800. [d] H. S. Holt and E. E. Reid [*J. Am. Chem. Soc.*, **46**, 2329 (1924)] prepared this from *p*-isopropylthioaniline and give b.p. 120° (11 mm.). [e] R. Fusco and R. Trave, [*Ann. Chim.* (Rome), **41**, 139 (1951)] prepared these compounds by alkylation of *p*-mercaptobenzaldehyde, itself obtained from *p*-aminobenzaldehyde, and record R, b.p. (15 mm.): C_2H_5, 151–153°; $(CH_3)_2CH_2$, 150–152°; $(CH_3)_2CHCH_2$, 164–165°. [f] Pot residue analyzed and used. [g] No satisfactory analysis obtained.

TABLE IX



X	Y	R'	R	Stereochemistry[a]	Formula	M.p., °C.	% C		% H		% N		Crysto. solvent[b]	λ_{max}	$\epsilon \times 10^{-3}$
							Calcd.	Found	Calcd.	Found	Calcd.	Found			
C_6H_5	CN	HO	H	T	$C_{17}H_{15}NO$	170–171[c]	81.90	81.95	6.06	6.11	5.62	5.58	E	297.5	1.30
C_6H_5	CN	CH_3O	H	T	$C_{18}H_{17}NO$	105.5–107[d]	82.10	82.27	6.51	6.43	5.32	5.38	C	292	1.34
C_6H_5	CN	HO	H	C	$C_{17}H_{15}NO$	127.5–128.5	81.90	81.25	6.06	6.16	5.62	5.56	H	307.5	1.17
C_6H_5	CN	CH_3O	H	C	$C_{18}H_{17}NO$	99–101	82.10	82.12	6.51	6.57	5.32	5.39	C	304	1.16
C_6H_5	CN	HO	Cl	T	$C_{17}H_{14}ClNO$	158.5–160.5	71.96	71.91	4.98	5.02	4.93	4.82	I	301	1.40
C_6H_5	CN	CH_3O	Cl	T	$C_{18}H_{16}ClNO$	121–124	72.60	71.98	5.41	5.37	4.70	4.76	H–K	296	1.42
C_6H_5	CN	HO	F	T	$C_{17}H_{14}FNO$	156.5–158	76.39	76.62	5.29	5.33	5.25	5.24	B–D	298	1.29
CN	C_6H_5	HO	H	T	$C_{17}H_{15}NO$	175–177	81.90	82.12	6.06	6.09	5.62	5.71	E–L	285	1.19
CN	C_6H_5	HO	H	C	$C_{17}H_{15}NO$	159–162	81.90	81.89	6.06	5.90	5.62	5.77	E–L	298	0.97
CN	C_6H_5	HO	Cl	T	$C_{17}H_{14}ClNO$	182–184.5	71.96	71.81	4.98	5.02	4.93	5.18	B–D	289	0.33
CN	C_6H_5	HO	Cl	C	$C_{17}H_{14}ClNO$	154.5–158	71.96	71.71	4.98	5.01	4.93	4.87	E–L	301	11.96

[a] T = *trans*, C = *cis*. [b] See Experimental; [c] Lit.[13] m.p. 172–173°. [d] Lit.[13] m.p. 104.5–105.5°.

drogen chloride to a solution of the base in the same solvent, and the salt was recrystallized from methanol.

4-[2-(4-Ethyl-1-piperazinyl)ethoxy]stilbene (13).—4-(2-Bromoethoxy)stilbene, m.p. 132.5–135° (lit.[16] 128°) (5.0 g.), 1-ethylpiperazine (9.14 g.), and sodium iodide (2.4 g.) were heated together in refluxing 2-butanone (50 ml.) for 7 hr. The solvent was removed, and the residue warmed with water. The insoluble material was collected (6.6 g.). Recrystallization from ethanol (charcoal) gave 2.50 g. of colorless crystals, m.p. 91–92.5°.

General Preparation of Dialkylaminoalkoxyphenylphenylacrylonitriles.—To equimolar parts (0.02 moles) of the appropriate phenylacetonitrile and benzaldehyde dissolved in refluxing methanol (30 ml.), sodium methoxide (0.02 mole) in methanol (10–20 ml.) was added. The majority of the solvent was removed after 10–20 min., the residue added to water, and the mixture acidified with 6 *N* hydrochloric acid. Insoluble hydrochlorides were filtered, and those compounds giving soluble hydrochlorides were isolated by solvent extraction after basification and their hydrochlorides made in ethyl acetate. The hydrochlorides were crystallized with the solvents indicated in the tables.

***p*-(2-Diethylaminoethoxy)phenylacetonitrile.**—*p*-Methoxyphenylacetonitrile (50 g., Eastman Kodak, practical grade) and freshly distilled pyridine hydrochloride (200 g.) were heated together under reflux for 1 hr.; the mixture was cooled to about 80° and added to ice-water (600 ml.). Concentrated hydrochloric acid (5 ml.) was added and the solution extracted with ether. The product was isolated by extraction into 10% sodium hydroxide solution followed by acidification and re-extraction into ether. After washing with water and drying by percolation through anhydrous sodium sulfate, the solvent was removed and the residue crystallized from benzene to give 31.8 g. (70%) of *p*-hydroxyphenylacetonitrile, m.p. 68–70° (lit.[15] m.p. 70°).

Alkylation of 75.2 g. of *p*-hydroxyphenylacetonitrile with diethylaminoethyl chloride was carried out by procedure A and the product isolated by extraction into hydrochloric acid. It was then basified and re-extracted into ether. The residue (99.5 g.) was distilled to give 85.1 g. (65%), b.p. 188–193° (6–6.5 mm.), $n^{25}D$ 1.5141.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.00; H, 8.55; N, 12.09.

Diethylaminoethoxybenzaldehydes.—Alkylation of salicylaldehyde (48.9 g.) with diethylaminoethyl chloride by procedure A gave 54.0 g. (61%) of *o*-(2-diethylaminoethoxy)benzaldehyde,[18] b.p. 141–147° (0.35–0.40 mm.), $n^{24}D$ 1.5248.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.17; H, 8.66; N, 5.87.

Alkylation with a 50% excess of alkylating agent of *m*-hydroxybenzaldehyde (50.0 g.) by procedure A gave in 61% yield *m*-(2-diethylaminoethoxy)benzaldehyde, b.p. 137–139° (0.13 mm.), $n^{25}D$ 1.5232.

(16) E. Massarani, G. Cavallini, D. Nardi, and W. Ferrari, *Farmaco* (Pavia), *Ed. Sci.*, **12**, 329 (1957).

(17) R. Pschorr, O. Wolfes, and W. Buckow, *Chem. Ber.*, **33**, 162 (1900).

(18) L. Katz, L. S. Karger, W. Schroeder, and M. S. Cohen, *J. Org. Chem.*, **18**, 1380 (1953), prepared this compound in 41% yield using potassium hydroxide as condensing agent; b.p. 118° (0.08 mm.).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.32; H, 8.62; N, 6.38.

p-(2-Diethylaminoethoxy)benzaldehyde was obtained from Aldrich Chemical Co., Inc.

***p*-(2-Bromoethoxy)phenylacetonitrile.**—A solution of sodium hydroxide (11.84 g.) in water (96 ml.) was added during 2 hr. to a solution of *p*-hydroxyphenylacetonitrile (40.0 g.) and ethylene bromide (111.2 g.) in ethanol (800 ml.) heated under reflux. Heating was continued a further hr., the ethanol removed *in vacuo*, water (400 ml.) added, followed by 20% sodium hydroxide solution (50 ml.), and the product extracted into ether. The combined ethereal extracts were washed with brine, dried with Na_2SO_4, and concentrated to yield crystalline *p*-(2-bromoethoxy)-phenylacetonitrile (22.5 g., 32%), m.p. 53–53.8°. Material from a previous run, recrystallized from ether–petroleum ether (b.p. 40–60°), was analyzed: m.p. 51–53.5°.

Anal. Calcd. for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.20; N, 5.84. Found: C, 50.20; H, 4.23; N, 6.08.

***p*-[2-(4-Ethyl-1-piperazinyl)ethoxy]phenylacetonitrile.**—The above halide (20.0 g.), 1-ethylpiperazine (47.7 g.), and sodium iodide (12.1 g.) were heated together in refluxing 2-butanone (250 ml.) for 7 hr. The solvent was removed *in vacuo* and the residue partitioned between water and ether. The combined ethereal extracts were washed with brine, dried with Na_2SO_4, the solvent was evaporated, and the residue triturated with petroleum ether (b.p. 40–60°) to give 15.0 g. (66%) of product, m.p. 33–34°. Crystallization from ether–petroleum ether (b.p. 40–60°) gave 10.0 g. of *p*-[2-(4-ethyl-1-piperazinyl)ethoxy]-phenylacetonitrile, m.p. 34–35°.

Anal. Calcd. for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.48; N, 15.37. Found: C, 70.11; H, 8.27; N, 15.64.

***p*-(2-Piperidinoethoxy)benzaldehyde.**—This compound was obtained from *p*-hydroxybenzaldehyde (12.2 g.) on alkylation with piperidinoethyl chloride (36.8 g., 100% excess) using procedure A in 58% yield (13.5 g.), b.p. 147–148° (0.05 mm.) [lit.[19] 150° (0.09 mm.)]; λ_{max}^{EtOH} 284 mμ (ε 17,600).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.96; H, 8.32; N, 6.01.

***p*-(3-Dimethylamino-2-methylpropoxy)benzaldehyde** was prepared analogously to the above ether in 94% yield, b.p. 120–121° (0.1 mm.); λ_{max}^{EtOH} 284 mμ (ε 18,000).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 69.95; H, 8.67; N, 6.32.

***p*-Trifluoromethylbenzaldehyde** was kindly supplied by Dr. C. E. Maxwell of these laboratories, b.p. 60–67° (13 mm.), $n^{29}D$ 1.4602 [lit.[20] 64.5° (13 mm.), $n^{20}D$ 1.4630].

***p*-Aminophenylacetonitrile** was supplied by Dr. R. K. Drinkard of these laboratories, who prepared it by catalytic reduction of *p*-nitrophenylacetonitrile.

***p*-Diethylaminoacetamidophenylacetonitrile.**—Chloroacetyl chloride (6.4 g.) was added dropwise at room temperature to a solution of triethylamine (5.7 g.) and *p*-aminophenylacetonitrile (7.5 g.) in chloroform (100 ml.). After 15 min. water was added which caused crystals (8.5 g.), m.p. 101–113°, to separate. Recrystallization from methanol (charcoal) gave 5.6 g. of *p*-chloroacetamidophenylacetonitrile as yellow-orange crystals, m.p. 123.5–126.5°.

p-Chloroacetoamidophenylacetonitrile (4.0 g.) was heated under reflux for 3 hr. with diethylamine (7.08 g.). The cooled reaction mixture was partitioned between methylene chloride and 2.5 *N* sodium hydroxide solution, and after washing with water the organic solvent was removed and the solid residue (4.30 g.), m.p. 76–80°, crystallized from aqueous methanol to give *p*-diethylaminoacetamidophenylacetonitrile (3.64 g.), m.p. 78.5–81°, as colorless feathery needles. A small portion on recrystallization had m.p. 79.5–81°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.24; H, 7.68; N, 17.15.

***p*-Alkylthiobenzaldehydes.**—*p*-Methylthiobenzaldehyde was kindly supplied by Dr. C. E. Maxwell of these laboratories who prepared it by the action of dimethylformamide on the Grignard reagent from *p*-bromothioanisole, the reagent being made by the entrainment method using ethyl bromide. The other aldehydes were prepared in similar fashion. The properties of the aldehydes and their precursors are shown in Table VIII.

Isopropyl- and cyclohexylthiobromobenzene were prepared by bromination of the corresponding alkyl phenyl sulfide, the latter being prepared by alkylation of thiophenol.[21]

p-Ethyl-, *p*-isobutyl-, and *p*-heptylthiochlorobenzene were prepared by alkylation of commercially available *p*-chlorothiophenol.

Diethylaminoethoxy-2,3-diphenyl-2-pentenenitriles.—The physical constants of the amino ethers are shown in Table VII; those of the intermediates used in their preparation are collected together in Table IX.

***cis*- and *trans*-2-Phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile.**—Sodamide (16.8 g.) was added to a solution of phenylacetonitrile (50.4 g.) in refluxing xylene (350 ml.). 4′-Methoxypropiophenone (71.0 g.) was then added dropwise and the heating under reflux continued for a further 30 min. after the addition. After cooling, the mixture was treated with water (300 ml.) and then glacial acetic acid (30 ml.). The layers were separated and the aqueous phase extracted with ether. The combined organic extracts were dried with Na_2SO_4, the solvent was removed, the residue treated with ether–petroleum ether (150 ml., 1:2), and the crystals were collected (56 g., 50%). Quantitative paper chromatography using the pure isomers obtained as below as standards established the product as a 1:1 mixture of the *cis* and *trans* isomers.

The mixed isomers (56 g.) were heated under reflux with freshly distilled pyridine hydrochloride (283 g.) for 1 hr., the mixture allowed to cool to about 100°, and water (500 ml.) added followed by 6 *N* hydrochloric acid (30 ml.). The precipitate (56 g.) was filtered, dried, dissolved in hot methylene chloride (300 ml.), and the solution cooled and evaporated under nitrogen until crystallization started. The *trans* isomer (11.5 g.), m.p. 167–171°, separated.

The *cis* isomer was obtained by chromatography on Florisil of second crop material from the isolation of the *trans* isomer using methylene chloride as eluting solvent. The *cis* isomer came off the column immediately behind the solvent front. Recrystallization from ether gave the product, m.p. 127.5–128.5°, λ_{max}^{EtOH} 307.5 mμ (ε 13,000), which resolidified and remelted at 150–153°. Infrared absorption and paper chromatography showed that this latter material consisted of a mixture of the isomers.

2-Phenyl-3-(*p*-hydroxyphenyl)-2-pentenoic Acid.—*cis*-2-Phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile (10.0 g.) was heated under reflux in isoamyl alcohol (100 ml.) with sodium hydroxide pellets (20.0 g.) for 21 hr. Dilution with water, acidification, and extraction into ether gave on evaporation a residual oil which on trituration with methylene chloride yielded the acid (5.40 g.), m.p. 222.5–225°. Two recrystallizations from acetone raised the m.p. to 224–226.5°, λ_{max}^{EtOH} 260 mμ (ε 11,800).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.85; H, 6.05.

Similar hydrolysis of the mixed isomers (20.0 g.) yielded the same acid (3.5 g.) on trituration with petroleum–ether, and chromatography on Florisil of the mother liquors gave, in addition to starting material, 4′-hydroxypropiophenone (1.52 g.), m.p. 148–149.5°, mixture m.p. with authentic sample, 146–149°.

Hydrolysis of *trans*-2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-2-pentenenitrile hydrochloride (5.0 g., see below) under the same conditions gave, in addition to unidentified material, phenylacetic acid (1.0 g.), m.p. 73–75°, m.m.p. 75–77.5°, in the ethereal extract.

***trans*-2-Phenyl-3-(*p*-methoxyphenyl)-2-pentenenitrile. Alkylation Procedure B.**—Methylation of *trans*-2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile with methyl iodide (2 moles) in refluxing acetone overnight in the presence of potassium carbonate (2.5 moles) gave the *trans*-methyl ether, which was recrystallized twice from isopropyl alcohol.

***cis*-2-Phenyl-3-(*p*-methoxyphenyl)-2-pentenenitrile.**—Methylation of *cis*-2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile as for the *trans* isomer gave the corresponding *cis*-methyl ether. Infrared absorption and paper chromatography further established the nonidentity of the two isomers, the *cis* isomer being the more polar in the isooctane–dimethylformamide system.

***trans*-3-[*p*-(2-Diethylaminoethoxy)phenyl]-2-phenyl-2-pentenenitrile (54).**—Alkylation of *trans*-3-(4-hydroxyphenyl)-2-phenyl-2-pentenenitrile with an excess of diethylaminoethyl chloride (procedure B) gave the amino ether as a yellow oil which was converted into its hydrochloride with hydrogen chlo-

(19) M. W. Goldberg and S. Teifel, U. S. Patent 2,774,766 (1956); *Chem. Abstr.*, **51**, 8139 (1957).

(20) R. Filler and H. Novar, *J. Org. Chem.*, **25**, 733 (1960).

(21) V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 2731 (1938).

ride in ethyl acetate. The hydrochloride was recrystallized from acetone.

cis-**3-[*p*-(2-Diethylaminoethoxy)phenyl]-2-phenyl-2-pentenenitrile (55).**—The only attempted preparation of this isomer by alkylation of the corresponding phenol was carried out using sodium methoxide as condensing agent at a time when it was not appreciated that this reagent caused partial isomerization. The pure isomer was obtained in poor yield by the direct condensation of 4-diethylaminoethoxypropiophenone with phenylacetonitrile. Alkylation (method A) of 4′-hydroxypropiophenone (60.0 g.) gave on distillation 66.7 g. of 4′-(2-diethylaminoethoxy)-propiophenone, b.p. 156° (0.5 mm.), n^{26}D 1.5220, λ_{max}^{EtOH} 271 mμ (ε 16,500).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.65; H, 9.51; N, 5.80.

The **dihydrogen citrate**, m.p. 99–100°, was crystallized from ethyl methyl ketone, λ_{max}^{EtOH} 267 mμ (ε 16,100).

Anal. Calcd. for $C_{29}H_{31}NO_8$: C, 57.13; H, 7.08; N, 3.17. Found: C, 56.99; H, 7.19; N, 3.20.

Condensation of 4′-(2-diethylaminoethoxy)propiophenone (25.0 g.) with phenylacetonitrile (11.7 g.) in xylene using sodamide (3.9 g.) in the usual way gave a crude product (32.9 g.) which was distilled. Two fractions, b.p. 162–183° and 183–190° (0.27 mm.), were combined (14.7 g.) and chromatographed on alumina. Elution with benzene gave the *cis* isomer (3.0 g.) isolated as its hydrochloride which was recrystallized from ethyl methyl ketone.

trans-**2-(*p*-Chlorophenyl)-3-(*p*-methoxyphenyl)-2-pentenenitrile.**—Trituration of the oil residue (92.0 g.) obtained from the condensation of equimolar quantities of 4-chlorophenylacetonitrile with 4-methoxypropiophenone on the 0.33*M* scale with ether–petroleum ether gave two crops (5.80 and 3.70 g.) of the pure *trans* isomer. An analytical sample was recrystallized from ether–petroleum ether.

Further concentration of the above mother liquors gave, in three crops, a total of 21.8 g. of mixed *cis* and *trans* isomers.

trans-**2-(*p*-Chlorophenyl)-3-(*p*-hydroxyphenyl)-2-pentenenitrile.**—Treatment of the above *trans*-methyl ether (8.5 g.) with freshly distilled pyridine hydrochloride (45.0 g.) under reflux for 1 hr. gave, on addition of water and extraction into ether, 7.6 g. of a mixture of isomeric phenols. The *trans* isomer (1.5 g.) crystallized preferentially from methylene chloride and an analytical sample was obtained on recrystallization from the same solvent.

cis- **and** *trans*-**2-(*p*-Chlorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-2-pentenenitrile (57 and 56).**—Alkylation of *trans*-2-(*p*-chlorophenyl)-3-(*p*-hydroxyphenyl)-2-pentenenitrile (5.68 g.) with dimethylaminoethyl chloride (from 7.40 g. of its hydrochloride) by procedure B gave, on working up, 7.3 g. of an orange viscous oil which was a mixture of the isomeric amino ethers. Chromatography on alumina gave the *cis* isomer (1.3 g.) on elution with 1:1 petroleum ether–benzene and the *trans* isomer (3.2 g.) on elution with benzene, both products being oils. The *cis* isomer was converted into a dihydrogen citrate which was recrystallized from acetone–hexane. The *trans* isomer was converted to its hydrochloride in ethyl acetate which was recrystallized from methanol–ethyl acetate.

trans-**2-(*p*-Fluorophenyl)-3-(*p*-hydroxyphenyl)-2-pentenenitrile.**—The oil (11.7 g.) obtained on condensation of *p*-fluorophenylacetonitrile and 4′-methoxypropiophenone on a 0.37 *M* scale was distilled and the fraction (56 g.), b.p. 160–275° (22 mm.), was demethylated with pyridine hydrochloride (280 g.). The product (52.7 g.), which was a dark oil, was crystallized from methylene chloride to give 14.0 g. of a mixture of the *trans*-2-(*p*-fluorophenyl)-3-(*p*-hydroxyphenyl)-2-pentenenitrile and an unidentified phenolic compound. Crystallization from dilute ethanol gave the *trans* isomer, m.p. 149–152° (5.5 g.), a portion of which was analyzed after recrystallization from the same solvent, m.p. 156.5–158°.

trans-**3-[*p*-(2-Diethylaminoethoxy)phenyl]-2-(*p*-fluorophenyl)-2-pentenenitrile (58).**—Alkylation of the above phenol (4.0 g.) with diethylaminoethyl chloride gave the amino ether as an oil which was converted to its hydrochloride which was recrystallized from acetone–hexane to give 2.01 g. of product.

trans-**2-(*p*-Hydroxyphenyl)-3-phenyl-2-pentenenitrile.**—Condensation of equimolar amounts of *p*-methoxyphenylacetonitrile and propiophenone on an 0.41 *M* scale in the presence of 1 equiv. of sodamide in xylene gave on working up 126 g. of a dark oil. A portion of this oil (71.0 g.) was heated under reflux with freshly distilled pyridine hydrochloride (400 g.) and on working up 46.0 g. of a solid was obtained which was percolated through Florisil in methylene chloride; the appropriate cuts were combined and rechromatographed to give a total of 35 g. of mixed isomers. Crystallization from acetone–hexane gave 9.60 g. of material, m.p. 169–172°, which on recrystallization gave the pure isomer (6.47 g.). An analytical sample was further recrystallized from acetone–hexane.

cis-**2-(*p*-Hydroxyphenyl)-3-phenyl-2-pentenenitrile.**—The second (11.5 g., m.p. 149–159°) and third (2.50 g., m.p. 145–147°) crops from the above crystallization were combined and chromatographed on Florisil and the material was eluted with 1:1 and 2:1 methylene chloride–benzene (10.66 g.), combined, and crystallized from acetone–hexane to give 8.26 g. of the *cis* isomer, m.p. 157–160°. An analytical sample was obtained after further recrystallization from acetone–hexane.

cis- **and** *trans*-**2-[*p*-(2-Diethylaminoethoxy)phenyl]-3-phenyl-2-pentenenitrile (60 and 59).**—The above phenols were alkylated by procedure B. From the *trans* isomer (5.0 g.), 5.86 g. of the hydrochloride of the product were obtained and from the *cis* isomer (3.0 g.), 2.30 g. of the amine dihydrogen citrate.

cis- **and** *trans*-**3-(*p*-Chlorophenyl)-2-(*p*-hydroxyphenyl)-2-pentenenitrile.**—The oily residue (96.4 g.) obtained on working up the condensation of equimolar quantities of *p*-methoxyphenylacetonitrile and 4′-chloropropiophenone on an 0.34 *M* scale was distilled, and the fraction (42.0 g., b.p. 262–280° (22 mm.), was demethylated with pyridine hydrochloride (210 g.). The product (35.5 g.) was partially purified by chromatography on Florisil in methylene chloride containing increasing proportions of methanol. Material eluting with up to 2% methanol in methylene chloride (15.3 g.) was rechromatographed and material eluting with benzene–methylene chloride (3:1) and methylene chloride was crystallized from ether–petroleum ether to give 3.0 g. of *trans*-3-(*p*-chlorophenyl)-2-(*p*-hydroxyphenyl)-2-pentenenitrile, m.p. 173–183°. A portion was recrystallized twice from aqueous methanol for analysis, m.p. 182–184.5°.

The mother liquor from the initial crystallization was concentrated to yield 6.1 g. of *cis*-3-(*p*-chlorophenyl)-2-(*p*-hydroxyphenyl)-2-pentenenitrile in which no *trans* isomer could be detected by paper chromatography. Recrystallization from acetone–hexane (60 ml., 1:5) gave 3.0 g. of pure *cis* isomer, m.p. 154.5–158°.

cis- **and** *trans*-**3-(*p*-Chlorophenyl)-2-[*p*-(2-diethylaminoethoxy)phenyl]-2-pentenenitrile (62 and 61).**—Both isomers were obtained by alkylation of the appropriate phenol with diethylaminoethyl chloride by procedure B. The *trans* isomer gave a crystalline hydrochloride, and the *cis* isomer, from which a crystalline hydrochloride could not be obtained, was converted to its citrate.

cis- **and** *trans*-**2,3-Bis,*p*-(2-diethylaminoethoxy)phenyl]-2-pentenenitrile (64 and 63).**—The oily product obtained after condensation of *p*-methoxyphenylacetonitrile and *p*-methoxypropiophenone under the influence of sodamide in toluene[13] was freed of unchanged starting materials by distillation (0.2 mm.). The residue (35.5 g.) was partially purified by percolation through Florisil in benzene to give 14.7 g. of an oil which was demethylated with pyridine hydrochloride. The crude product was triturated with ether to give a solid which was not sufficiently soluble in any suitable solvent for chromatographic separation of the isomers of Florisil. A product (8.0 g.) containing only two components, presumed to be the required *cis* and *trans* isomers of 2,3-bis(*p*-hydroxyphenyl)-2-pentenenitrile was obtained, however, by percolation through Florisil in benzene–methanol (2:1). This mixture of bisphenols (8.0 g.) was alkylated with diethylaminoethyl chloride using procedure A and the product (11.0 g.) was chromatographed on alumina. Material eluting with benzene gave a crystalline citrate, but paper chromatography in the isooctane–dimethylformamide system showed that this product, though predominantly the *cis* isomer, contained some of the *trans* isomer. The *trans* isomer was eluted with methylene chloride containing 0.25–5% of methanol, and was isolated as its bishydrochloride.