8-Methoxy-2-(trifluoromethyl)quinoline (38, Scheme V). The reductive dehalogenation of compound 37 was based upon a procedure used for the hydrogenolysis of 3-halo-6,8-dimethoxyisoquinolines.[9] Compound 37 (13 g, 0.049 mol) and 2 g of 10% palladium-on-carbon catalyst were mixed in a hydrogenation bottle. Ethanolic potassium hydroxide (1 *N*, 130 ml) was added to the reaction mixture and it was shaken in a low-pressure Parr hydrogenator at room temperature until the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration and the filtrate was concentrated on a rotary evaporator to give a yellow oil. The oil was dissolved in 40 ml of acetone and then poured into 2500 ml of ice–water. The solution was stirred overnight. The solid that formed was collected by filtration and purified by recrystallization from ethanol–water, 8 g, 71% yield, mp 90–92°, $C_{11}H_8F_3NO$.

2-(Trifluoromethyl)-8-hydroxyquinoline (39, Scheme V). Compound **38** (9 g, 0.039 mol) was refluxed in 90 ml of 48% hydrobromic acid for 6 hr. The reaction mixture was then poured into 1500 ml of ice–water and stirred overnight. The colorless solid that formed (6 g, 71% yield) was collected and recrystallized from ethanol–water, mp 48–49°.

5-Methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (40) and 7-Methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (41, Scheme V). *m*-Anisidine (20 g, 0.16 mol) was added slowly to 150 ml of polyphosphoric acid. The resulting mixture was heated to 80°. Ethyl trifluoroacetoacetate (31.9 g, 0.170 mol) was then added to the mixture in small portions with vigorous stirring over a period of 20 min. After 2.5 hr at 100°, the flask was cooled and its contents were poured into 2500 ml of ice–water. The resulting mixture was stirred overnight. The precipitate that formed was collected by filtration, dried, and recrystallized from absolute ethanol to give 27 g of an isomeric mixture, mp 200–213°. The components of the mixture were separated by dry-column chromatography using a 2 × 24 in. column filled with 250 g of Woelm silica gel. The column was eluted with chloroform. The first fractions (3 × 500 ml) were collected and evaporated *in vacuo* to afford pure **40** (12.3 g, 31% yield), mp 131–132°. The column was next eluted with a 50:50 mixture of chloroform and absolute ethanol (4 × 400 ml). After the removal of solvent, these fractions afforded 17.2 g (43.5% yield) of 41, mp 255–256°, $C_{11}H_8F_3NO_2$.

4-Chloro-5-methoxy-2-(trifluoromethyl)quinoline (42, Scheme V). Phosphorus pentachloride (5.49 g, 0.026 mol) and phosphorus oxychloride (12.3 g, 0.080 mol) were alternately added to compound **40** (6 g, 0.025 mol) in small portions over a period of 20 min. The reaction mixture was processed as described for compound 37 to give 5.8 g (91% yield) of the desired product, **42**, mp 92–94°, $C_{11}H_7ClF_3NO$.

5-Methoxy-2-(trifluoromethyl)quinoline (43, Scheme V). The reductive dehalogenation of compound **42** was carried out as described for compound **38**. The resulting solid was recrystallized from ethanol to give 2.5 g (52% yield) of product, mp 60–61°, $C_{11}H_8F_3NO$.

2-(Trifluoromethyl)-5-hydroxyquinoline (44, Scheme V). Compound **43** (15 g, 0.066 mol) and 150 ml of 48% hydrobromic acid were treated as described for compound 39. The solid thus obtained was recrystallized from ethanol–water to give 12 g (85% yield) of product, **44**, mp 198–201°, $C_{10}H_6F_3NO$.

3-Substituted 3,4-Dihydro-5-(trifluoromethyl)-2*H*-1,3-oxazino[5,6-*c*]quinolines 45–47 (Table VI). These compounds were prepared from the corresponding substituted 4-hydroxyquinolines 36 and 41 using the general procedure described for the preparation of 2,3-dihydro-5-phenyl-2-piperonyl-1*H*-1,3-oxazino[6,5-*c*]quinoline (6).

3-Substituted 3,4-Dihydro-9-(trifluoromethyl)-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines 51–57 (Table VII). These compounds were synthesized by the following general procedure described in detail for the preparation of 3-benzyl-3,4-dihydro-9-(trifluoromethyl)-2*H*-pyrido[3,2-*h*]-1,3-benzoxazine **(51)**. Benzylamine (0.506 g, 0.004 mol), paraformaldehyde (0.282 g, 0.009 mol), and 60 ml of 50% benzene–ethanol were heated for 2 hr under reflux. To this was slowly added a solution of compound 39 (1 g, 0.004 mol) in 20 ml of absolute ethanol. The resulting mixture was heated under reflux for 9 hr. It was then cooled and evaporated *in vacuo* to afford a yellow oil. The oil was treated with decolorizing carbon and recrystallized from absolute ethanol.

3- and 8-Substituted 3,4-Dihydro-2*H*-pyrido[2,3-*h*]-1,3-benzoxazines 58–61 (Table VIII). These compounds were synthesized by the following general procedure described in detail for the preparation of 3-(*p*-chlorobenzyl)-3,4-dihydro-8-(trifluoromethyl)-2*H*-pyrido[2,3-*h*]-1,3-benzoxazine **(59)**. Paraformaldehyde (0.28 g, 0.009 mol), *p*-chlorobenzylamine (0.66 g, 0.004 mol), and 40 ml of 50% ethanol–benzene were heated under reflux for 2 hr. Compound 44 (1 g, 0.004 mol) was added to the mixture and it was heated under reflux for an additional 26 hr. The solvent was removed *in vacuo* and the viscous material which remained was crystallized from ethanol to yield compound **59**.

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3,4-Dihydroisocarbostyril and 1,2,3,4-Tetrahydroisoquinoline Derivatives of Ephedrine

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3,4-Dihydroisocarbostyril and 1,2,3,4-tetrahydroisoquinoline derivatives of ephedrine were synthesized and screened for central nervous system activity in the mouse. Some of these compounds prevented reserpine ptosis, potentiated *d*-amphetamine toxicity, prolonged hexobarbital sleep time, and/or prevented hydrochloric acid writhing in mice.

Many heterocyclic derivatives of ephedrine and norephedrine have been synthesized and tested for biological activity. For example, morpholine, 2-oxazoline, oxazolidine, di- and tetrahydro-1,3,4-oxadiazines, 2-thiazoline, thiazolidine, dihydro-1,3,4-thiadiazine, tetrahydro-*as*-triazine, and imidazolidine derivatives have been reported.[1] Many of these compounds possess interesting biological activity.[1] For this

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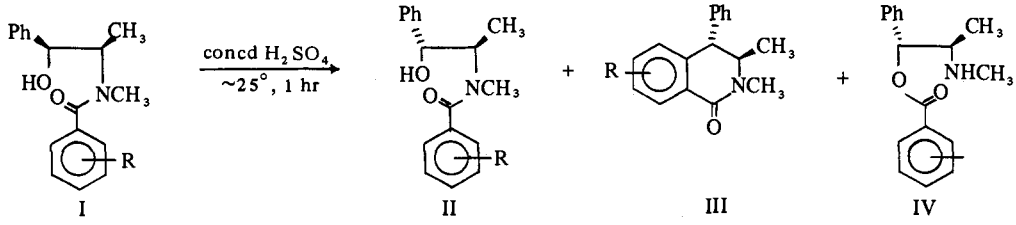


	I	II	III	IV
a, *p*-$(CH_3)_3C$		70	20	10
b, *m*-CH_3		65	30	5
c, *m*-NO_2		75	0	25
d, *o*-CH_3		100	0	0

reason we wish to report the synthesis of two new heterocyclic derivatives of ephedrine, namely, 3,4-dihydroisocarbostyrils and 1,2,3,4-tetrahydroisoquinolines.

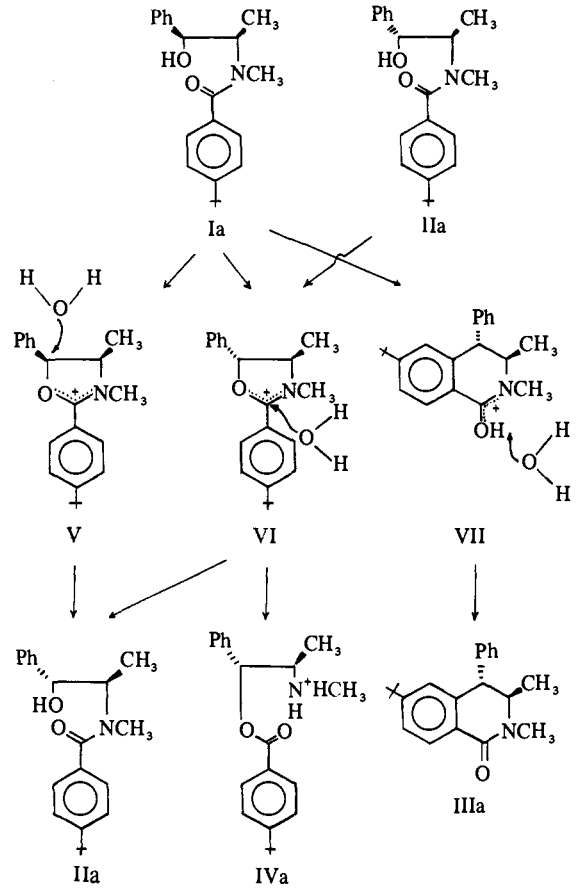
Brucker, *et al.*,[2] and Welsh[3] have reported acid-catalyzed N → O acyl migrations in *N*-acyl derivatives of ephedrine and ψ-ephedrine. We have found that concentrated H_2SO_4 besides promoting N → O acyl migration also cyclodehydrates. For example, treatment of *N*-(*p-tert*-butylbenzoyl)-(−)-ephedrine (Ia) with concentrated H_2SO_4 at ambient temperature for 1 hr caused a quantitative conversion to a 70:20:10 mixture of *N*-(*p-tert*-butylbenzoyl)-(+)-ψ-ephedrine (IIa), *trans*-(+)-*6-tert*-butyl-3,4-dihydro-2,3-dimethyl-4-phenylisocarbostyril (IIIa), and *O*-(*p-tert*-butylbenzoyl)-(−)-ψ-ephedrine sulfate (IVa).

We studied the affect of configuration of the ephedrine amide (erythro *vs.* threo), the position (ortho, meta, or para) and nature of substitution on the benzamido moiety, and reaction conditions on the product composition. Treatment of *N*-(*p-tert*-butylbenzoyl)-(+)-ψ-ephedrine (II) with concentrated H_2SO_4 at ambient temperature for 1 hr produced a 27:10:55 mixture of II, III, and IV and eight parts benzoic acid.

In regard to the influence of substituents on the benzamide group on the course of the reaction, we found that an electron-donating group (CH_3) in the meta position promotes cyclodehydration, whereas an electron-withdrawing group (NO_2) inhibits cyclodehydration. An ortho substituent inhibits both cyclodehydration and N → O acyl migration and results in 100% inversion of configuration of the hydroxyl-bearing carbon atom (erythro → threo).

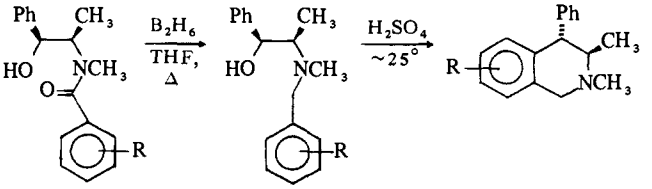
Regarding the affect of reaction conditions, we found that increasing the time of contact between compound Ia and H_2SO_4 from 1 to 24 hr gave a similar product composition (76:7:8), except for a reduction in isocarbostyril. This reduction in isocarbostyril (from 20 to 7%) was accompanied by the formation of 9% *p-tert*-butylbenzoic acid. Raising the reaction temperature to 80° (2-hr contact) increased the formation of *p-tert*-butylbenzoic acid to 15% and the *O*-ester to 45% and gave no isocarbostyril. Other acidic reagents, such as PPA, HBr in HOAc, fuming H_2SO_4, and BF_3, all failed to cyclodehydrate amide I to isocarbostyril. Thus, concentrated H_2SO_4 at room temperature for 1 hr gave the highest yield of isocarbostyril product and that best yield was only 30%.

These results indicate that dissolution of the erythro hydroxy amide Ia results initially in two competing reactions: (1) hydroxyl oxygen attacking carbonyl carbon to give a *cis*-oxazolidinium intermediate V, and (2) dissociation of protonated hydroxyl to give a benzyl carbonium ion. The benzyl carbonium ion undergoes attack by carbonyl oxygen to give a *trans*-oxazolidinium intermediate VI and attack by the phenyl moiety to give an isocarbostyril intermediate VII. When the H_2SO_4 solution is poured onto crushed ice, the three cationic intermediates V, VI, and VII are attacked by H_2O. The *cis*-oxazolidinium V is attacked exclusively at C-5 to give the threo hydroxy amide IIa. The *trans*-oxazolidinium VI is attacked at C-2 and opens to give threo hydroxy amide IIa and threo amino ester IVa. The *trans*-oxazolidinium VI is not attacked at C-5 as evidenced by the fact that no erythro hydroxy amide is isolated. The isocarbostyril intermediate VII loses a proton to give the isocarbostyril IIIa.



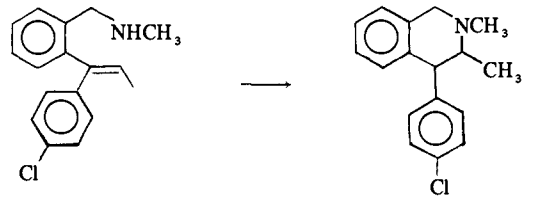
Dissolution of the threo hydroxy amide IIa in H_2SO_4 gives a different distribution of products because no *cis*-oxazolidinium intermediate V is formed and the rate of formation of the *trans*-oxazolidinium VI is much faster because of the favorable trans disposition of phenyl and methyl in the threo hydroxy amide IIa. Thus five times more amino ester IVa and one-half as much isocarbostyril IIIa are formed from the threo hydroxy amide than from the erythro hydroxy amide Ia.

Because all reactions that compete with cyclohydration involve the carbonyl group, it was reduced with B_2H_6 in refluxing THF. The resulting *N*-benzylephedrines were cyclodehydrated in high yield by 1-hr contact with H_2SO_4 to 1,2,3,4-tetrahydroisoquinolines.

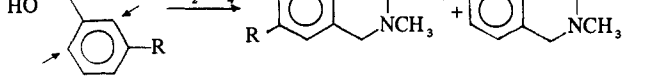


R = H, 2-CH_3, 3-CH_3, 3-Cl, 2,4-Cl_2, 4-*tert*-Bu, 4-NO_2

This is a very efficient 1,2,3,4-tetrahydroisoquinoline synthesis that gives 3,4-disubstituted tetrahydroisoquinolines that do not have activating moieties (OCH_3) in the 6,7 positions. Heretofore, this type of tetrahydroisoquinoline was very difficult to prepare. The well-known and much used methods, such as Pictet-Spengler,[4] Bischler-Napiralski,[5] Pomeranz-Fritsch,[6] Bobbitt,[7] and Hasner,[8] which all involve electrophilic substitution on phenyl, either will not work at all or will give only very low yields of this type of di- or tetrahydroisoquinoline. Recently, Freter, Dubois, and Thomas reported[9] a method of synthesis of 3,4-disubstituted tetrahydroisoquinolines not having activating (CH_3O) moieties in the 6,7 positions. Rather than ring closure *via* electrophilic substitution on phenyl, the ring is formed by amine addition to a double bond. The only disadvantages to this method are the synthetic effort needed to prepare the amino olefin, and the product is a mixture of cis ($J_{H_3-H_4}$ = 4.4 Hz) and trans ($J_{H_3-H_4}$ = 6.0-8.0 Hz) isomers.



A comparison of the concentrated H_2SO_4 cyclodehydration of *N*-(substituted benzyl)ephedrines and *N*-(substituted benzoyl)ephedrines revealed that in the case of the *N*-(substituted benzyl)ephedrines the cyclodehydration proceeded in high yield regardless of the nature or position of the substituent on the benzyl moiety, for example, *p*-O_2N and *o*-CH_3 whereas, in the case of *N*-(substituted benzoyl)ephedrines, these types (electron withdrawing or ortho) of substituents prevented cyclization (Table I). When *N*-(meta-substituted benzyl)ephedrines were cyclodehydrated, a mixture of the 5- and 7-substituted tetrahydroisoquinolines was obtained. A mixture of two different tetrahydroisoquinolines was obtained because cyclization occurred at both of the two different ortho positions. The product composition was determined (where R = Cl or CH_3) both by glc and nmr (the 3-CH_3's have different chemical shifts). The isomers were separated (where R = CH_3) by column chromatography. The isomers were differentiated by means of the magnitude of the H_3-H_4 coupling. The H_3-H_4 coupling of the 5-Cl and 5-CH_3 substituted compounds is 3.8 Hz, whereas the 7-Cl and 7-CH_3 is 8.5 Hz. The magnitude of the H_3-H_4 coupling is less for the 5-substituted compounds because steric interaction between the 5 substituent and the 4-Ph compresses the H_3-H_4 dihederal angle.



The products resulting from H_2SO_4 treatment of *N*-(substituted benzoyl and benzyl)ephedrines were all designated as trans (threo) isomers based on pmr analysis and because the sulfuric acid treatment of both erythro and threo hydroxy amides gave the same three products.

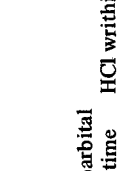
Both the isocarbostyrils and the thioisocarbostyril exhibited small H_3-H_4 coupling (1.3-1.6 Hz). Undoubtedly, this is because of ring flattening by the C=O and C=S. $LiAlH_4$ reduction of an isocarbostyril gave the same tetrahydroisoquinoline as was obtained by sulfuric acid cyclization of the appropriate *N*-benzylephedrine. The thioisocarbostyril was prepared by P_2S_5 treatment of the isocarbostyril.

Table I. Benzyl- and Benzoylephedrines

$C_6H_5CHCH(CH_3)N(CH_3)R$
OR_1

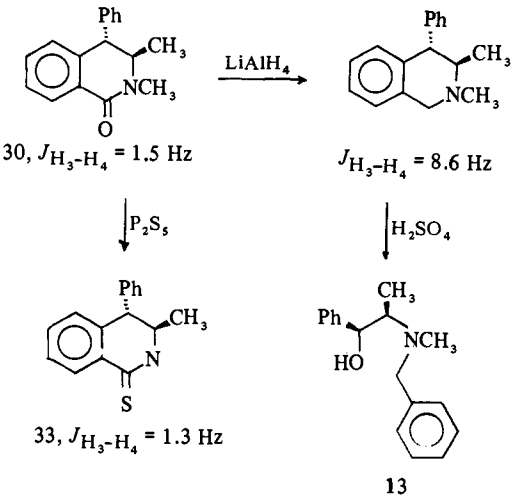
No.	R	R_1	Isomer	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
1	4-$(CH_3)_3CC_6H_4CO$	H	Erythro-(−)	186-188	88	*i*-PrOH	$C_{21}H_{27}NO_2$	C, H, N
2	H	4-$(CH_3)_3CC_6H_4CO$	Threo-(−)	230-233	10	MeOH-Et_2O	$C_{21}H_{27}NO_2 \cdot 0.5H_2SO_4$	C, H
3	4-$(CH_3)_3CC_6H_4CO$	H	Threo-(+)	139-141	81	*i*-PrOH	$C_{21}H_{27}NO_2$	C, H, N
4	4-$(CH_3)_3CC_6H_4CO$	H	Erythro-(+)	186-187	90	*i*-PrOH	$C_{21}H_{27}NO_2$	C, H, N
5	3,4,5-$(CH_3O)_3C_6H_2CO$	H	Erythro-(+)	144-146	92	*i*-PrOH-Et_2O	$C_{19}H_{23}NO_5$	C, H, N
6	3-$CH_3C_6H_4CO$	H	Erythro-(−)	100-103	70	*i*-PrOH-Et_2O	$C_{18}H_{21}NO_2$	C, H, N
7	4-$(CH_3)_3CC_6H_4CO$	H	Threo-(−)	138-140	68	*i*-PrOH-Et_2O	$C_{21}H_{27}NO_2$	C, H, N
8	H	4-$(CH_3)_3CC_6H_4CO$	Threo-(+)	203-205	10	*i*-PrOH	$C_{21}H_{27}NO_2 \cdot HCl$	C, H, N
9	H	4-$(CH_3)_3CC_6H_4CO$	Threo-(+)	228-231	11	*i*-PrOH	$C_{21}H_{27}NO_2 \cdot 0.5H_2SO_4$	C, H
10	C_6H_5CO	H	Threo	135-136	92	*i*-PrOH-Et_2O	$C_{17}H_{19}NO_2$	C, H, N
11	H	C_6H_5CO	Threo	192-194	12	*i*-PrOH	$C_{17}H_{19}NO_2 \cdot 0.5H_2SO_4$	C, H
12	H	C_6H_5CO	Threo	215-217	14	*i*-PrOH-MeOH	$C_{17}H_{19}NO_2 \cdot HCl$	C, H, N
13	$C_6H_5CH_2$	H	Erythro	144-147	87	*i*-PrOH-Et_2O	$C_{17}H_{21}NO \cdot HCl$	C, H, N
14	3-$CH_3C_6H_4CH_2$	H	Erythro	182-184	60	*i*-PrOH	$C_{18}H_{23}NO \cdot HCl$	C, H, N
15	3-$CH_3C_6H_4CO$	H	Threo	147-148	30	*i*-PrOH	$C_{18}H_{21}NO_2$	C, H, N
16	2-C_4H_3SCO	H	Erythro	78-80	84	*i*-PrOH-Et_2O	$C_{15}H_{17}NO_2S$	C, H, N
17	2-C_4H_3SCO	H	Threo	111-113	82	EtOH-Et_2O	$C_{15}H_{17}NO_2S$	C, H, N
18	2-$CH_3C_6H_4CO$	H	Threo	161-163	94	*i*-PrOH	$C_{18}H_{21}NO_2$	C, H, N
19	2-$CH_3C_6H_4CH_2$	H	Erythro	186-188	70	*i*-PrOH-Et_2O	$C_{18}H_{23}NO \cdot HCl$	C, H, N
20	3-ClC_6H_4CO	H	Erythro	91-93	90	Et_2O-hexane	$C_{17}H_{18}ClNO_2$	C, H, N
21	3-$ClC_6H_4CH_2$	H	Erythro	204-205	80	MeOH-Et_2O	$C_{17}H_{20}ClNO \cdot HCl$	C, H, N
22	4-$O_2NC_6H_4CO$	H	Erythro	188-190	75	*i*-PrOH	$C_{17}H_{18}N_2O_4$	C, H, N
23	4-$O_2NC_6H_4CH_2$	H	Erythro	223-225	68	MeOH-Et_2O	$C_{17}H_{20}N_2O_3 \cdot HCl$	C, H, N
24	2,4-$Cl_2C_6H_3CO$	H	Erythro	139-141	84	MeOH-Et O	$C_{17}H_{17}Cl_2NO_2$	C, H, N
25	2,4-$Cl_2C_6H_3CH_2$	H	Erythro	196-198	93	EtOH-Et_2O	$C_{17}H_{19}Cl_2NO \cdot HCl$	C, H, N

Table II. 3,4-Dihydroisocarbostyrils and 1,2,3,4-Tetrahydroisoquinolines



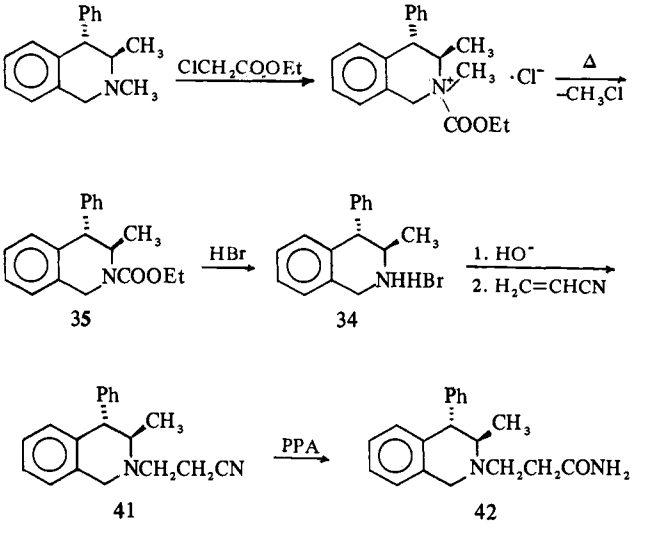
No.	R	R_1	R_2	Mp or bp (mm), °C	Yield, %	Recrystn solvent	Formula	Analyses	Mouse LD_{50}, mg/kg ip	Screening dose, mg/kg ip	Reserpine ptosis	Potentiate d-amphetamine toxicity	Hexobarbital sleep time	HCl writhing
26	CH_3	6-$(CH_3)_3C$	O	208–209	20	*i*-PrOH	$C_{21}H_{25}NO$	C, H, N	316	95	0/10	1/10	53/39	0/4
27	CH_3	6-$(CH_3)_3C$	H_2	89–91	71	MeOH	$C_{21}H_{27}N$	C, H, N	825	250	2/10	0/10	79/39	1/4
28	$COOC_2H_5$	6-$(CH_3)_3C$	H_2	93–95	94	*i*-PrOH–H_2O	$C_{23}H_{29}NO_2$	C, H, N	159	48	0/10	0/10	51/44	0/4
29	CH_3	6-$(CH_3)_3C$	O	206–208	19	*i*-PrOH	$C_{21}H_{25}NO$	C, H, N	825	250	1/10	2/10	61/53	0/10
30	CH_3	H	O	148–150	18	*i*-PrOH	$C_{17}H_{17}NO$	C, H, N	681	204	0/10	0/10	45/37	0/4
31	CH_3	7-CH_3	O	138–140	27	*i*-PrOH	$C_{18}H_{19}NO$	C, H, N	825	250	3/10	1/10	51/44	0/4
32	CH_3	8-CH_3	H_2	94–95	73	*i*-PrOH	$C_{18}H_{21}N$	C, H, N	46	14.1	12 (8–18)	3/10	129/38	4/4
33	CH_3	H	S	138–139	87	$CHCl_3$–Et_2O	$C_{17}H_{17}NS$	C, H, N	562	170	0/10	0/10	148/37	0/4
34	H	H	H_2	219–221	60	*i*-PrOH–Et_2O	$C_{16}H_{17}N \cdot HBr$	C, H, N	68	20	1/10	12 (8–18)	102/44	1/4
35	$COOC_2H_5$	H	H_2	158–159 (0.4)	63		$C_{19}H_{21}NO_2$	C, H, N	562	168	2/10	17 (10–33)	58/38	0/4
36	CH_3	6-Cl	H_2	228–230	78	*i*-PrOH–Et_2O	$C_{17}H_{18}ClN \cdot HCl$	C, H, N	147	36	14 (8–26)	0/10	44/38	0/4
37	CH_3	6,8-Cl_2	H_2	258–260	80	MeOH–Et_2O	$C_{17}H_{17}Cl_2N \cdot HCl$	C, H, N	121	35.4	27 (19–36)	1/10	139/53	1/4
38	CH_3	6-NO_2	H_2	233–235 dec	79	EtOH	$C_{17}H_{18}N_2O_2 \cdot HBr$	C, H, N	147	36	1/10	0/10	43/37	0/4
39	CH_3	6-NH_2	H_2	106–107	76	EtOH	$C_{17}H_{20}N_2$	C, H, N	121	35.4	0/10	0/10	57/38	4/4
40	CH_3	6-CH_3CONH	H_2	156–158	79	EtOH	$C_{19}H_{22}N_2O$	C, H, N	147	36	1/10	2/10	39/37	0/4
41	CH_2CH_2CN	H	H_2	132–133	91	EtOH	$C_{19}H_{20}N_2$	C, H, N	147	36	0/10	0/10	43/38	0/4
42	$CH_2CH_2CONH_2$	H	H_2	102–103	70	EtOH	$C_{19}H_{22}N_2O$	C, H, N	121	35.4	2/10	1/10	61/38	1/4
43	Imipramine								95	53	35 (26–47)	50 (30–83)	95/27	4/4

2,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was N-demethylated by pyrolysis of the carbethoxy quaternary derivative followed by removal of the carbethoxy group *via* strong acid hydrolysis. 3-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was allowed to react with acrylonitrile to give a 91% yield of 2-(β-cyanoethyl)-3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline. The cyano group was hydrolyzed to an amido group with PPA.



Pharmacology. The isocarbostyrils and tetrahydroisoquinolines listed in Table II were evaluated for CNS activity in the mouse using the resperine ptosis, potentiation of amphetamine toxicity, hexobarbital sleep time, and HCl writhing tests. The results are listed in Table II. The test methods are described in the Experimental Section. Compounds **32**, **36**, and **37** were active in the reserpine ptosis test and compare favorably with imipramine which in our hands had ED_{50} = 35 mg/kg.

Compounds **34** and **35** were active in the potentiation of



d-amphetamine toxicity test. Five compounds (**27**, **32**, **33**, **34**, and **37**) prolonged hexobarbital sleep time more than twofold. Of these five compounds active in the hexobarbital sleep time test, compounds **27** and **32** reinduced sleep in hexobarbital treated mice suggesting a CNS rather than a metabolic mechanism of action.

Compounds **32** and **39** were active in the HCl writhing test.

In summary, this series of 3,4-dihydroisocarbostyrils and 1,2,3,4-tetrahydroisoquinolines shows some CNS activity

which is manifested in potentiating the effect of hexobarbital and *d*-amphetamine in mice and antagonizing the effect of reserpine and HCl. In these four tests, compound 32 shows the best activity profile and behaved similarly to the antidepressants imipramine and amitriptyline.

Experimental Section‡

Preparation of *N*-Benzoylephedrines Listed in Table I. To a stirred mixture of 0.1 mol of *l*-ephedrine, 0.2 mol of Et_3N, and 300 ml of CH_2Cl_2 was added, over a 30-min period, a solution of 0.1 mol of the substituted benzoyl chloride in 100 ml of methylene chloride. The mixture was stirred and heated at reflux temperature for 18 hr. The cooled mixture was diluted with 500 ml of $CHCl_3$, washed (H_2O, HCl, $NaHCO_3$), dried ($MgSO_4$), and evaporated *in vacuo*. The residual solid was recrystallized from appropriate solvents.

H_2SO_4 Treatment of *N*-Benzoylephedrines. To 50 ml of concentrated H_2SO_4 stirred in a beaker was added, portionwise, 15 g of N-substituted benzoylephedrine. The mixture was stirred at ambient temperature for 1 hr, poured onto 500 g of crushed ice, and extracted thoroughly with $CHCl_3$. The washed ($NaHCO_3$, H_2O) and dried ($MgSO_4$) $CHCl_3$ extract was evaporated *in vacuo*. The residual oil was dissolved in anhydrous Et_2O and treated with ethereal HCl to precipitate the *O*-(substituted benzoyl)-ψ-ephedrine hydrochlorides listed in Table I (these have a threo configuration). The ether filtrate was washed ($NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on 300 g of alumina (Baker 0537) using benzene as eluent. The first material eluted was the trans-substituted 2,3-dimethyl-4-phenyl-3,4-dihydroisocarbostyril (Table II), and this was followed by N-substituted benzoyl-ψ-ephedrine (Table I).

Preparation of *N*-Benzylephedrines Listed in Table I. To 100 ml of 1.0 *M* B_2H_6 in THF stirred and cooled to 5° was added, over 1 hr, a solution of 0.1 mol of *N*-benzoylephedrine in 400 ml of THF. The mixture was stirred and heated at the reflux temperature for 18 hr, cooled, treated with 50 ml of THF–H_2O (1:1) and then 50 ml of HCl–H_2O (1:1), concentrated *in vacuo*, basified with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was dissolved in anhydrous Et_2O and treated with ethereal HCl until precipitation of the hydrochloride was completed. The hydrochloride was purified by recrystallization.

Preparation of 1,2,3,4-Tetrahydroisoquinolines Listed in Table II. To 100 ml of concentrated H_2SO_4 stirred at ambient temperature was added, portionwise, 0.1 mol of the *N*-benzylephedrine hydrochloride. After 1 hr of stirring, the mixture was poured onto 600 g of crushed ice, basified (Na_2CO_3), and extracted with $CHCl_3$. The washed (brine) and dried ($MgSO_4$) $CHCl_3$ extract was evaporated *in vacuo*. The residue was purified by recrystallization or, in some cases, was converted to hydrochloride or hydrobromide (Table II).

trans-2,3-Dimethyl-4-phenyl-3,4-dihydrothioisocarbostyril (33). To a solution of 4 g of *trans*-2,3-dimethyl-4-phenyl-3,4-dihydroisocarbostyril in 100 ml of $CHCl_3$ was added, portionwise, 5 g of P_2S_5. The mixture was stirred and heated at reflux temperature for 18 hr. The cooled mixture was basified with a cold 20% NaOH solution and then stirred for 1 hr. The $CHCl_3$ layer was separated, washed (H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized with $CHCl_3$–Et_2O.

$LiAlH_4$ Reduction of *trans*-2,3-Dimethyl-4-phenyl-3,4-dihydroisocarbostyril. To a stirred mixture of 4.0 g of $LiAlH_4$ and 100 ml of THF was added, dropwise, a solution of 5.0 g of *trans*-2,3-dimethyl-4-phenyl-3,4-dihydroisocarbostyril in 150 ml of dry THF. The mixture was stirred and heated at the reflux temperature for 18 hr. The cooled mixture was treated with 5 ml of H_2O, 5 ml of 10% NaOH, and 5 ml of H_2O and suction filtered, and the filtrate was evaporated *in vacuo*. The oily residue was dissolved in dry ether and treated with ethereal HCl. The hydrochloride (4.3 g, 87%) was purified by recrystallization from *i*-PrOH–Et_2O, mp 206–207°. *Anal.* C, H, N.

Ethyl 3-Methyl-4-phenyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (35). A stirred mixture of 74 g (0.31 mol) of 2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline and 250 ml of anhydrous benzene was treated, dropwise, with a solution of 34 g (0.31 mol) of ethyl chloroformate in 100 ml of anhydrous benzene. The mixture was stirred and heated at reflux temperature for 18 hr and evaporated *in vacuo*, and the oil residue was distilled under reduced pressure.

3-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (34). A mixture of 65 g (0.22 mol) of ethyl 3-methyl-4-phenyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate and 100 ml of 38% HBr in HOAc was heated at reflux temperature for 18 hr and cooled, and the crystalline solid was removed by suction filtration, washed with ether, and recrystallized.

3-Methyl-4-phenyl-3,4-dihydro-2(1*H*)-isoquinolinepropionitrile (41). A mixture of 32 g (0.14 mol) of 3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, 18 g (0.30 mol) of acrylonitrile, and 200 ml of EtOH was heated at the reflux temperature for 18 hr and cooled, and the crystalline solid was suction filtered, washed with Et_2O, and recrystallized.

3-Methyl-4-phenyl-3,4-dihydro-2(1*H*)-isoquinolinepropionamide (42). A mixture of 2.2 g of 3-methyl-4-phenyl-3,4-dihydro-2(1*H*)-isoquinolinepropionitrile and 25 g of PPA was triturated and heated on a steam bath for 2 hr, cooled, mixed with 300 g of crushed ice, basified (Na_2CO_3), and extracted with $CHCl_3$. The washed (H_2O) and dried ($MgSO_4$) $CHCl_3$ solution was evaporated *in vacuo*. The residue was recrystallized from an appropriate solvent.

6-Amino-2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (39). A solution of 6.0 g of 2,3-dimethyl-4-phenyl-6-nitro-1,2,3,4-tetrahydroisoquinoline in 75 ml of MeOH was hydrogenated at ambient temperature on Raney nickel catalyst in the Paar apparatus. The pressure dropped from 43 to 37 lb/in.^{2} in 2 hr. Crystalline product was recrystallized from EtOH.

6-Acetamido-2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (40). A mixture of 5.0 g (0.19 mol) of 6-amino-2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline and 25 ml of Ac_2O was heated at the reflux temperature for 5 hr, cooled, poured onto 300 g of crushed ice, basified with Na_2CO_3, and extracted with $CHCl_3$. The washed (H_2O) and dried ($MgSO_4$) $CHCl_3$ solution was evaporated *in vacuo* and the gummy residue rubbed with ether–petroleum ether (bp 30–60°).

Pharmacology. Acute Toxicity in Mice. Adult male mice, in groups of four, were given the test compound, ip, using at least three dose levels and observed for 24 hr. LD_{50} values were calculated by the method of Litchfield and Wilcoxon.[10]

Antagonism to Reserpine-Induced Ptosis in Mice. Adult male mice were given test compound ip (this screening dose was *ca.* 0.3 LD_{50}) 30 min prior to a reserpine (5 mg/kg ip) challenge. Observation for ptosis was made 45 min after reserpine. Results are given as the ratio of the number of mice protected to number of mice tested. When 6/10 or more mice were protected at this screening dose, additional tests were made to determine the ED_{50} (method of Litchfield and Wilcoxon). In these cases, the ED_{50} values and their 95% confidence limits are listed instead of the protection ratios.

Potentiation of Amphetamine Toxicity in Aggregated Mice. Adult male mice, in groups of ten, were given test compound ip (0.3 LD_{50}), saline control, or amphetamine (5 mg/kg, "positive" control. All animals were dosed with amphetamine (5 mg/kg) 30 min later and aggregated by placement in cubic wire-mesh cages 16 cm on a side. They were then kept in a walk-in incubator (30°, for both noise and temperature control) for 5 hr at which time the dead were counted. If three or more were dead in the saline control group or six or less in the "positive" amphetamine control group, the entire experiment was discounted arbitrarily. Results are given as a ratio of number of mice dead to number of mice in the group. When 6/10 or more mice were found dead at the screening dose, additional tests were made to determine the ED_{50}. In these cases, the ED_{50} values and their 95% confidence limits are listed instead of the lethality ratios.

Hexobarbital Sleep Time Test. Adult male mice were injected ip with the test compound 30 min prior to the ip injection of 100 mg/kg of hexobarbital. The time in minutes between injection of the hexobarbital and the regain of the righting reflex was taken as the duration of the sleeping time. The results are expressed as a ratio of the treated group over the control group. Reinduction of sleep was determined by ip injection of the compound just as the mice were regaining the righting reflex.

Hydrochloric Acid Writhing Test. Adult male mice weighing 18–22 g were used in this test. Writhing was induced by the ip injection of 10 ml/kg of a 0.1% HCl solution. The compound to be tested was administered ip 30 min prior to the HCl solution. The results are expressed as a ratio of the number of animals not writhing to the number of animals tested.

‡Melting points were determined in open capillary tubes using the Thomas-Hoover Uni-Melt and are uncorrected. Nmr spectra were obtained using a Varian A-60 spectrometer on 10% $CDCl_3$ solutions with TMS as internal standard. Ir spectra were obtained using a Perkin-Elmer 337 grating spectrophotometer. The elemental analyses were done by Midwest Microlabs, Indianapolis, Ind. Where analyses are indicated by only symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

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Antiparasitic Nitroimidazoles. 3. Synthesis of 2-(4-Carboxystyryl)-5-nitro-1-vinylimidazole and Related Compounds

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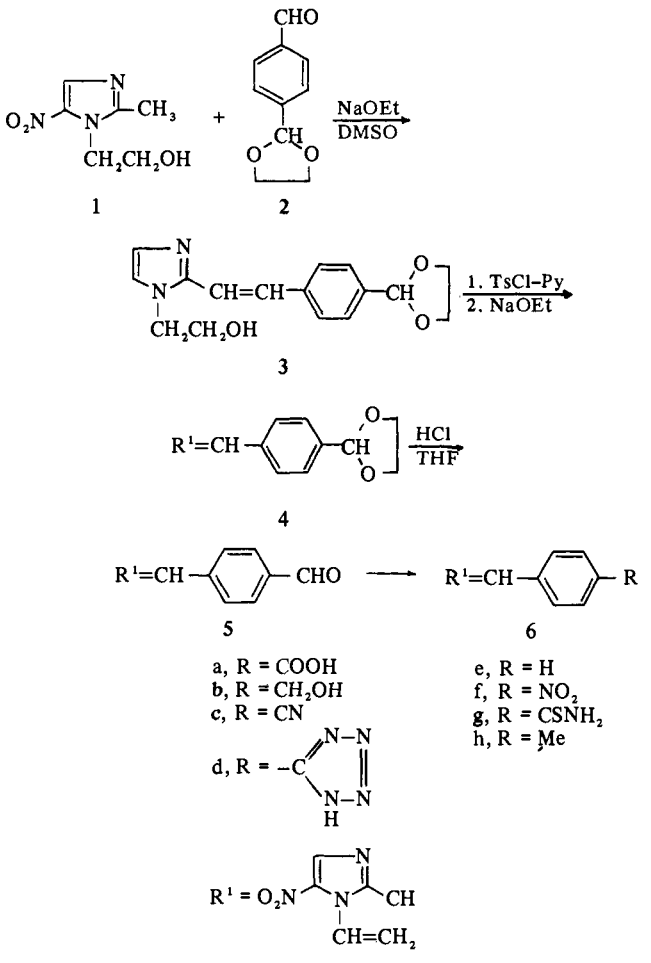
The synthesis of 6 (R = COOH), one of its metabolities (R = $CONHCH_2COOH$), and 31 related compounds is described. The compounds were examined for antiparasitic activity against *Trichomonas vaginalis* and *Entamoeba histolytica in vitro* and *in vivo* and against various *Trypanosoma* species *in vivo*. The compounds were also tested against *Schistosoma mansoni* in mice and hamsters. Comparisons are made with standard drugs.

The need for new classes of drugs effective against the African trypanosomiases has been stressed in specialist publications during the last few years.[1,2] In part I[3] of this series of papers, we described the antiprotozoal activity of a series of 2-styryl-5-nitroimidazoles emphasizing in particular their antitrypanosomal properties. A related paper† discusses the metabolism, in various species, of several of these styrylimidiazoles and describes the isolation and identification of a metabolite, 2-(4-carboxystyryl)-5-nitro-1-vinylimidazole (**6a**). This compound, its β-glucuronide, and its glycine conjugate were isolated from the urine of mice, rats, rabbits, hamsters, and dogs† after oral or parenteral dosing of 2-(4-methylstyryl)-5-nitro-1-vinylimidazole[3] (**6h**). In this paper we describe the synthesis and antiparastic activity of **6a** and various related compounds. As we were uncertain as to whether the acid **6a** or the alcohol **6b** were active metabolites (*cf.* lucanthone-hycanthone),[4] a synthesis was devised which was capable of yielding either compound (Scheme I).

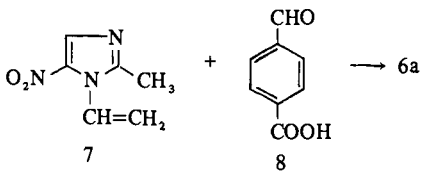
Scheme I



Although **2** was readily prepared, purification by distillation under reduced pressure was not possible due to concomitant disproportion into terephthaldehyde and its bisethylene acetal. However, the base-catalyzed condensation of **2** with metronidazole **1** gave the styrylimidazole **3** which was converted to the *N*-vinyl compound as shown in Scheme I.

Acetal **4** underwent acid-catalyzed cleavage to the aldehyde **5** which on oxidation[5] gave a high yield of the acid **6a** while reduction with $NaBH_4$ gave the alcohol **6b**.

Compound **6a** could also be prepared by direct condensation of **7**[3] with 4-carboxybenzaldehyde (**8**) in the presence of base, but the reaction was capricious due to the instability of **6a** under the strongly basic conditions.[6]



Condensation of **1** with **8** (Scheme II) gave **9** which was readily converted to the chloride **10** on treatment with the DMF-$SOCl_2$ complex[7] followed by hydrolysis. Dehydrohalogenation of **10** with a variety of bases gave **6a** in poor yield.

†D. M. Morton and J. N. Green, unpublished results.