Table I. Pharmacology of N-Substituted Phenylmorphans

Compound	Analgesic activity[a]		PDC[b]	Antagonistic activity[b]
	ED_{50} (hot plate)	ED_{50} (Nilsen)		
1·HCl	1.5 (2.4–2.9)		Intermediate	No
8·HCl	0.4 (0.28–0.45)		High	No
5·HBr	14.5 (10.5–20.1)	14.1 (9.3–21.5)	No	0.01[c,d]
6·HBr	6.8 (5.2–8.8)	21.5 (15.4–30.3)	No	Slight[e]
7·HBr	11.2 (7.9–15.7)	7.5 (3.7–15.3)	No	0.01[c,f]
12·HBr	4.9 (3.8–6.3)	7.7 (5.6–10.4)	No	0.01[c,d]
13·HBr	9.9 (7.7–12.8)	5.5 (4.2–7.4)	No	No[g]
14·HBr	16.9 (11.8–24.1)	5.3 (3.4–8.3)	No	0.01[c,h]
Nalorphine hydrochloride	36.3 (27.1–48.7)	4.8 (2.7–8.5)	No	1.0
Pentazocine hydrochloride	12.3 (9.3–16.3)	4.7 (2.9–5.1)	No	0.02[c]
Morphine sulfate	1.2 (0.9–1.3)	0.8 (0.6–1.2)	High[i]	No

[a]Subcutaneous administration, mg/kg: T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, and E. L. May, *J. Pharm. Sci.*, **61**, 86 (1972); N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965). [b]Data from the Department of Pharmacology, University of Michigan, personal communication from H. H. Swain, J. Woods, and J. E. Villarreal; for methodology, see ref 8. [c]Relative value; nalorphine = 1. [d]Somewhat longer acting than nalorphine. [e]Only a hint of antagonistic activity at 4 and 8 mg/kg; 16 mg/kg induced convulsions. [f]Short acting. [g]No apparent effect at 4, 8, and 18 mg/kg. [h]Same duration of action as nalorphine. [i]Stabilizing dose 3.0 mg/kg compared with 1.6 mg/kg for **8**.

DMF were stirred together at 80° for 6 hr and evaporated to dryness *in vacuo*. The residue was treated with $CHCl_3$ and H_2O. Drying (Na_2SO_4) and evaporation of the $CHCl_3$ layer gave an oil which was evaporatively distilled [bp 180–200° (0.4 mm)] giving 0.44 g (62%) of a viscous oil which was treated with HBr–AcOH. Recrystallization of the resultant HBr salt of **5** from EtOH gave 0.5 g of pure needles, mp 205.5–207°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N, Br.

The (+) isomer **12**, similarly prepared from **11**, was converted to the HBr salt with HBr–MeOH: mp (from EtOH) 236.5–238.5°; $[\alpha]^{20}D$ +7.55°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N.

(±)-2-Allyl-5-*m*-hydroxyphenylmorphan (6) Hydrobromide. Allyl bromide (0.45 g), 0.7 g of **4**, 0.9 g of K_2CO_3, and 25 ml of DMF were stirred together at 80–90° for 6.5 hr and evaporated to dryness *in vacuo*. The residue was treated with $CHCl_3$ and H_2O. Drying (Na_2SO_4) and evaporation of the $CHCl_3$ gave a brown oil (0.8 g) which was treated with HBr–AcOH. The resultant hydrobromide crystallized from EtOH in prisms (0.6 g, 55%), mp 222–223°. *Anal.* ($C_{17}H_{24}BrNO$) C, H, N, Br.

(+) isomer 13 was similarly obtained from **11** as the HBr salt in 72% yield: mp 176–178°; $[\alpha]^{20}D$ +10.6°. *Anal.* ($C_{17}H_{24}BrNO$) C, H, N.

(±)-2-Cyclopropylmethyl-5-*m*-hydroxyphenylmorphan (7) Hydrobromide. To a stirred suspension of 0.25 g of **4**, 3 ml of Et_3N, and 10 ml of CH_2Cl_2 was added (cooling) 0.36 g of cyclopropylcarbonyl chloride in 2 ml of CH_2Cl_2. The resulting clear solution was refluxed overnight, washed with 10% HCl and then H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue (0.4 g of *N,O*-dicarbonyl compound, ν_{CO} 1745, 1630 cm^{-1}) was reduced with 0.5 g of $LiAlH_4$ in refluxing THF (20 ml) for 20 hr to give 0.2 g of an oily base (after the usual work-up) which was converted to the hydrobromide (HBr–AcOH). Recrystallization from EtOH gave 0.2 g (54%) of pure **7**·HBr, mp 220–222°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N, Br.

(+) isomer 14 was prepared from **11** in a similar manner: yield of hydrobromide 62%; mp 226–226.5°; $[\alpha]^{20}D$ +117.8°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N.

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Alkaloids in Mammalian Tissues. 4. Synthesis of (+)- and (−)-Salsoline and Isosalsoline[1]

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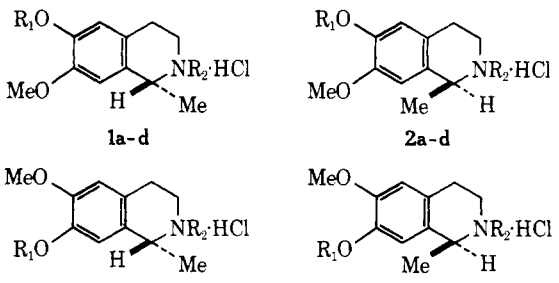
Based on the concept that alkaloids may not be exclusively plant products but may be formed in the mammalian system by Pictet–Spengler condensation of amino acids and biogenic amines with carbonyl substrates (for leading references, see ref 1), we have prepared a number of optically active substituted tetrahydroisoquinolines derived from L-dopa[2] and dopamine.[3] Recently, definite support for this speculation was provided by the detection of 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolinol) and 6,7-dihydroxy-1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaveroline) in the urine of Parkinsonian patients on L-dopa treatment.[4] While the stereochemistry of these alkaloids has yet to be established, their occurrence indicates the possibility that minor metabolites of L-dopa or dopamine, such as their two mono-*O*-methyl ethers, might also undergo similar transformations. In this connection, we now report the synthesis, characterization, and preliminary pharmacology of the enantiomeric salsolines **1b** and **2b**, the isosalsolines **3b** and **4b**, and the related *N*-methyl derivatives **1d–4d**.

Chemistry. The alkaloid (+)-salsoline (**1b**) and its antipode **2b**, previously obtained in poor yield by Pictet–Spengler condensation of 3-hydroxy-4-methoxyphenethyl-

† This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.

amine with CH_3CHO followed by resolution with *d*-tartaric acid,[5] as well as the heretofore unknown monophenolic isomers **3b** and **4b** were readily synthesized by acid-catalyzed O-debenzylation of the corresponding optically active benzyloxy precursors **1a–4a,** prepared from the known racemates[6] by facile resolution with dibenzoyl-*d*-tartaric acid. Reductive condensation of **1a–4a** with CH_2O and $NaBH_4$ followed by O-debenzylation of the intermediates **1c–4c** afforded the isomeric *N*-methyl derivatives **1d–4d.** Alternatively and in contrast to its reported racemization,[7] treatment of **1b** with CH_2O and HCO_2H also yielded the optically active tertiary amine **1d.** The absolute configuration of **1d** and **3d,** assigned by comparison of their nmr, ORD, and CD spectra with those of **1b** and **2b** of known stereochemistry,[8] was confirmed by their conversion with CH_2N_2 into (+)-carnegine which possesses the *R* configuration.[8]



a, $R_1 = C_7H_7$; $R_2 = H$
b, $R_1 = R_2 = H$
c, $R_1 = C_7H_7$; $R_2 = Me$
d, $R_1 = H$; $R_2 = Me$

Pharmacology. Acute toxicity studies in mice of the enantiomeric salsolines and isosalsolines **1b–4b** and their *N*-methyl derivatives **1d–4d** (Table I) were performed including observations of behavioral effects.[9] The intravenous LD_{50}'s were all in the range 24–63 mg/kg with the exception of the salsolines **1b** and **2b** which were less toxic. In general, the compounds were 10–20 times less toxic by the oral route than by the intravenous route. The primary behavioral effects were tremors, convulsions, and decreased motor activity.

The above compounds showed no anti-Parkinson activity in the reserpine-reversal test in mice[10] and were devoid of antihypertensive activity in spontaneously hypertensive rats.[11]

Experimental Section ‡

(1*R*)-6-Benzyloxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Dibenzoyl-*d*-tartrate (1a·dbdt) and Hydrochloride (1a). A mixture of 38 g (0.13 mol) of (±)-6-benzyloxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline[6] and 50 g (0.13 mol) of dibenzoyl-*d*-tartaric acid was dissolved in 500 ml of CH_3CN. The solution was stored at room temperature for 18 hr; the crystals (50 g) were collected and recrystallized from 1 l. of CH_3OH to give 39 g (89% based on 0.065 mol) of **1a**·dbdt: mp 180–181°; $[\alpha]_D$ −59.4°. *Anal.* ($C_{18}H_{21}NO_2 \cdot C_{18}H_{14}O_8$) C, H, N.

‡All melting points (corrected) were taken in open capillary tubes with a Thomas-Hoover melting apparatus. The ultraviolet spectra were measured in *i*-PrOH with a Cary recording spectrophotometer Model 14M. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model HA-100 spectrophotometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 at 25° using a 1% solution in MeOH. Rotatory dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Analyses are indicated only by symbols of the elements; analytical results obtained for the elements were within ±0.35% of the theoretical values. Water of crystallization in compounds **2b**·HCl and **4b**·HCl was determined with the Karl Fischer reagent.

Table I. Acute Toxicity (LD_{50}, mg/kg)

Compd	iv	po
1b	140	>1000
1d	24	450
2b	245	>1000
2d	45	625
3b	45	500
3d	28	350
4b	63	500
4d	49	500

An aqueous solution of 37.8 g (0.056 mol) of **1a**·dbdt was rendered alkaline with 10% NaOH and extracted with EtOAc; the extract was evaporated and the residue was dissolved in ethanolic HCl, evaporated, and crystallized from EtOH to give 17.6 g (85%) of **1a:** mp 210–211°; $[\alpha]_D$ +18.8°; nmr δ 1.60 (d, 2, *J* = 7 Hz, CH_3), 2.70, 3.50 (m, 4, CH_2CH_2), 3.76 (s, 3, CH_3O), 4.45 (m, 1, CHN), 5.06 (s, 2, $PhCH_2O$), 6.85 (s, 2, aromatics), 7.37 (s, 5, Ph), 9.50 (br, 3, OH + $^+NH_2$); uv_{max} 206 nm (ε 57,000), 230 (9700, sh), 282 (4030), 286 (4050); ORD (*c* 0.30, MeOH) $[\phi]_{700}$ +39°, $[\phi]_{589}$ +53°, $[\phi]_{405}$ +91°, $[\phi]_{292}$ −1450° (tr), $[\phi]_{280}$ 0°, $[\phi]_{267}$ +860° (pk), $[\phi]_{254}$ 0°, $[\phi]_{240}$ −3230° (tr), $[\phi]_{233}$ 0°, $[\phi]_{213}$ +15,050° (pk); CD (*c* 0.009 *M*, MeOH), $[\theta]_{302}$ 0, $[\theta]_{282}$ −1740, $[\theta]_{254}$ −320, $[\theta]_{234}$ −9680, $[\theta]_{215}$ −6020. *Anal.* ($C_{18}H_{21}NO_2 \cdot HCl$) C, H, N.

(1*R*)-(+)-6-Hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(+)-Salsoline Hydrochloride] (1b). A mixture of 6.7 g (0.021 mol) of **1a** in 60 ml of 12 *N* HCl and 60 ml of C_6H_6 was vigorously stirred under a N_2 atmosphere for 17 hr and 60 ml of H_2O was added. The crystals that formed were collected and dried to give 3.8 g (79%) of **1b:** mp 174–175°; $[\alpha]_D$ +31.0° [lit.[5] mp 171–172°; $[\alpha]_D$ +40.1° (H_2O)]; nmr δ 1.59 (d, 3, *J* = 7 Hz, CH_3), 2.88, 3,28 (m, 4, CH_2CH_2), 3.77 (s, 3, CH_3O), 4.38 (m, 1, CHN), 6.61, 6.78 (s, 2, aromatics), 9.10, 9.45, 9.95 (br, 3, OH + $^+NH_2$); uv_{max} 204 nm (ε 39,400), 227 (5900), 284 (3540), 286 (3530); ORD (*c* 0.23, MeOH) $[\phi]_{700}$ +52°, $[\phi]_{589}$ +75°, $[\phi]_{400}$ +142°, $[\phi]_{368}$ +148°, $[\phi]_{350}$ +140°, $[\phi]_{314}$ 0°, $[\phi]_{293}$ −1100° (tr), $[\phi]_{283}$ 0°, $[\phi]_{266}$ +1300° (pk), $[\phi]_{247}$ 0°, $[\phi]_{240}$ −1100° (tr), $[\phi]_{235}$ 0°, $[\phi]_{205}$ +30,000° (pk), $[\phi]_{197}$ 0°; CD (*c* 0.01 *M*, MeOH) $[\theta]_{303}$ 0, $[\theta]_{288}$ −1620, $[\theta]_{286}$ −1500, $[\theta]_{282}$ −1740, $[\theta]_{252}$ −220, $[\theta]_{231}$ −5800, $[\theta]_{220}$ −4400, $[\theta]_{214}$ −7000, $[\theta]_{206}$ 0, $[\theta]_{201}$ +19,000. *Anal.* ($C_{11}H_{15}NO_2 \cdot HCl$) C, H, N.

(1*R*)-(−)-6-Benzyloxy-1,2-dimethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1c). An aqueous solution containing 8.3 g (0.025 mol) of **1a** was rendered alkaline with NH_4OH and extracted with EtOAc. The extract was evaporated, the residue (7 g) was dissolved in a mixture of 10 ml (0.9 mol) of 37% CH_2O and 100 ml of MeOH and stored at room temperature for 17 hr, and 5 g of $NaBH_4$ was added over 15 min while maintaining the temperature between 15 and 20°. After stirring the reaction mixture for 1 hr, the volatiles were evaporated; the residue was dissolved in H_2O and extracted with EtOAc. The extract was acidified with ethanolic HCl, the solution evaporated to dryness, and the residue crystallized from EtOH to give 6.2 g (75%) of **1c:** mp 152–154°; $[\alpha]_D$ −4.0°; nmr δ 1.51, 1.68 (2 d, 3, *J* = 7 Hz, CH_3), 2.71, 2.80 (2 d, 3, CH_3N), 2.70–3.50 (m, 4, CH_2CH_2), 3.76 (s, 3, CH_3O), 4.43 (m, 1, CHN), 5.05 (s, 2, CH_2O), 6.82, 6.87 (s, 2, aromatics), 7.37 (s, 5, Ph), 11.50 (br, 1, ^+NH); uv_{max} 225 nm (ε 63,000), 230 (10,600, sh), 282 (3900), 286 (3930); ORD (*c* 0.33, MeOH) $[\phi]_{700}$ −7°, $[\phi]_{589}$ −16°, $[\phi]_{336}$ −320° (inf), $[\phi]_{292}$ −2000° (tr), $[\phi]_{279}$ 0°, $[\phi]_{273}$ +650°, $[\phi]_{261}$ 0°, $[\phi]_{241}$ −6500° (tr), $[\phi]_{232}$ 0°, $[\phi]_{227}$ +6000° (sh), $[\phi]_{213}$ +12,500° (pk); CD (*c* 0.01 *M*, MeOH) $[\theta]_{299}$ 0, $[\theta]_{284}$ +2280, $[\theta]_{254}$ −520, $[\theta]_{233}$ −12,600, $[\theta]_{207}$ 0. *Anal.* ($C_{19}H_{23}NO_2 \cdot HCl$) C, H, N.

(1*R*)-(−)-1,2-Dimethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(−)-*N*-Methylsalsoline Hydrochloride] (1d). In a manner similar to the procedure given for **1b,** 4 g (0.012 mol) of **1c** was debenzylated to give 2.7 g (93%) of **1d:** mp 250–252° (from EtOH); $[\alpha]_D$ −3.8°, $[\alpha]_{365}$ −27.0°; nmr δ 1.50, 1.66 (2 d, 3, CH_3), 2.69, 2.79 (2 d, 3, CH_3N), 2.80–3.70 (m, 4, CH_2CH_2), 3.77 (s, 3, CH_3O), 4.42 (m, 1, CHN), 6.67, 6.75 (2 s, 2, aromatics), 8.90, 11.47 (br, 2, OH + ^+NH); uv_{max} (45,000), 226 (6600), 287 (3800); ORD (*c* 0.24, MeOH) $[\phi]_{700}$ +3.5°, $[\phi]_{600}$ 0°, $[\phi]_{589}$ −2°, $[\phi]_{294}$ −2200° (tr), $[\phi]_{280}$ 0°, $[\phi]_{270}$ +750° (pk), $[\phi]_{257}$ 0°, $[\phi]_{237}$ −5000° (tr), $[\phi]_{232}$ 0°, $[\phi]_{220}$ +5500° (sh), $[\phi]_{210}$ +15,000° (pk); CD (*c* 0.01 *M*, MeOH) $[\theta]_{302}$ 0, $[\theta]_{283}$ −3000, $[\theta]_{252}$ −400, $[\theta]_{230}$ −9500, $[\theta]_{215}$ −3500, $[\theta]_{210}$ −6500, $[\theta]_{206}$ 0. *Anal.* ($C_{12}H_{17}NO_2 \cdot HCl$) C, H, N.

Alternatively, a mixture of 0.91 g (0.044 mol) of the free base of

1b, 1 ml of 37% CH_2O, and 1 ml of 90% HCO_2H was heated at 95° for 2 hr; 50 ml of saturated K_2CO_3 solution was added and extracted with ethyl acetate. The extract was acidified with ethanolic HCl and evaporated to dryness and the residue crystallized from ethanol to give 0.55 g (51%) of **1d**, mp 250–252°, identical with **1d** obtained from **1c**.

(1*S*)-(−)-6-Benzyloxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2a). The combined mother liquors of **1a**·dbdt were evaporated, the residue was dissolved in H_2O, and the solution was rendered alkaline with 10% NaOH and extracted with EtOAc. The extract was acidified with ethanolic HCl, the mixture evaporated to dryness, and the residue crystallized from EtOH to give 12.6 g (61% based on 0.065 mol) of **2a**: mp 210–211°; $[\alpha]_D$ −18.0°; identical in nmr and uv with **1a**; ORD and CD mirror images of **1a**. *Anal.* ($C_{18}H_{21}NO_2$·HCl) C, H, N.

(1*S*)-(−)-6-Hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*S*)-(−)-Salsoline Hydrochloride] (2b). In a manner similar to the procedure given for **1b**, 6.0 g (0.019 mol) of **2a** was debenzylated to afford 3.2 g (73%) of **2b**: mp 174–175°; $[\alpha]_D$ −31.5° [lit.[5] mp 171–173°; $[\alpha]_D$ −39.2° (H_2O)]; identical in nmr and uv with **1b**; ORD and CD mirror images of **1b**. *Anal.* ($C_{11}H_{15}NO_2$·HCl·0.25H_2O) C, H, N.

(1*S*)-(+)-6-Benzyloxy-1,2-dimethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2c). N-Methylation of 9.9 g (0.031 mol) of **2a**, according to the procedure described for **1c**, afforded 7.6 g (74%) of **2c**: mp 148–150°; $[\alpha]_D$ +4.0°; identical in nmr and uv with **1c**; ORD and CD mirror images of **1c**. *Anal.* ($C_{19}H_{23}NO_2$·HCl) C, H, N.

(1*S*)-(+)-1,2-Dimethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*S*)-(+)-*N*-Methylsalsoline Hydrochloride)] (2d). In a manner similar to the procedure given for **1b**, 4.0 g (0.012 mol) of **2c** was debenzylated to afford, after crystallization from EtOH, 2.7 g (93%) of **2d**: mp 250–251°; $[\alpha]_D$ +3.2°, $[\alpha]_{365}$ +27.0°; identical in nmr and uv with **1d**; ORD and CD mirror images of **1d**. *Anal.* ($C_{12}H_{17}NO_2$·HCl) C, H, N.

(1*R*)-7-Benzyloxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Dibenzoyl-*d*-tartrate (3a·dbdt) and Hydrochloride (3a). A solution of 41.1 g (0.138 mol) of (±)-7-benzyloxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline[6] and 55.5 g (0.145 mol) of dibenzoyl-*d*-tartaric acid in 450 ml of CH_3CN was refrigerated overnight. The crystals which formed (37.7 g) were recrystallized from 600 ml of *i*-PrOH to give 30 g (62% based on 0.069 mol) of **3a**·dbdt: mp 163–165°; $[\alpha]_D$ −54.3°. *Anal.* ($C_{18}H_{21}NO_2$·$C_{18}H_{14}O_8$) C, H, N.

In a manner similar to the procedure given for **1a**, the above dibenzoyl tartrate was converted into 12.4 g (56%) of **3a**: mp 220–221°; $[\alpha]^{25}_D$ +24.7°; nmr δ 1.56 (d, 3, J = 7 Hz, CH_3), 2.96, 3.27 (m, 4, CH_2CH_2), 3.76 (s, 3, CH_3O), 4.39 (m, 1, CHN), 6.77, 6.93, (2 s, 2, aromatics), 7.40 (m, 5, Ph), 9.82 (br, 2, $^+NH_2$); uv_{max} 230 nm (ε 8700, sh), 281 (3780), 285 (3790); ORD (*c* 0.48, MeOH) $[\phi]_{700}$ +56°, $[\phi]_{589}$ +76°, $[\phi]_{380}$ +164°, $[\phi]_{262}$ +167°, $[\phi]_{330}$ −1130° (pk), $[\phi]_{312}$ 0°, $[\phi]_{293}$ −1330° (tr), $[\phi]_{284}$ 0°, $[\phi]_{265}$ +1420° (pk), $[\phi]_{244}$ 0°, $[\phi]_{241}$ −330° (tr), $[\phi]_{240}$ 0°, $[\phi]_{229}$ +4170° (pk), $[\phi]_{222}$ +2080°, $[\phi]_{210}$ +22,500° (pk); CD (*c* 0.015 M, MeOH) $[\theta]_{305}$ 0, $[\theta]_{281}$ −1970, $[\theta]_{255}$ −167, $[\theta]_{233}$ −4670, $[\theta]_{255}$ −1670, $[\theta]_{215}$ −7000, $[\theta]_{208}$ 0, $[\theta]_{204}$ +25,000. *Anal.* ($C_{18}H_{21}NO_2$·HCl) C, H, N.

(1*R*)-(+)-7-Hydroxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(+)-Isosalsoline Hydrochloride] (3b). Acid-catalyzed debenzylation of 5.7 g (0.0178 mol) of **3a** by the procedure given for **1b** afforded 4.0 g (98%) of **3b**: mp 241–242°; $[\alpha]_D$ +24.7°; nmr δ 1.54 (s, 3, J = 7 Hz, CH_3), 2.94, 3.30 (m, 4, CH_2CH_2), 3.77 (s, 3, CH_3O), 4.39 (m, 1, CHN) 6.66, 6.70 (2 s, 2, aromatics); uv_{max} 204 nm (ε 42,200), 227 (7700, sh), 286 (3600); ORD (*c* 0.23, MeOH) $[\phi]_{700}$ +39°, $[\phi]_{589}$ +54°, $[\phi]_{400}$ +101°, $[\phi]_{375}$ +105°, $[\phi]_{350}$ +98°, $[\phi]_{317}$ 0°, $[\phi]_{292}$ −950° (tr), $[\phi]_{282}$ 0°, $[\phi]_{265}$ +1300° (pk), $[\phi]_{238}$ 0°, $[\phi]_{227}$ +2250° (pk), $[\phi]_{207}$ 0°; CD (*c* 0.01 *M*, MeOH) $[\theta]_{304}$ 0, $[\theta]_{285}$ −1600, $[\theta]_{252}$ −120, $[\theta]_{207}$ −20,000, $[\theta]_{202}$ 0. *Anal.* ($C_{11}H_{15}NO_2$·HCl) C, H, N.

(1*R*)-(+)-7-Benzyloxy-1,2-dimethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3c). In a manner similar to the procedure described for **1c**, 8.8 g (0.028 mol) of **3a** was converted into 7.9 g (86%) of **3c**: mp 188–189°; $[\alpha]_D$ +0.5°, $[\alpha]_{365}$ −27.5°; nmr δ 1.48, 1.64 (2 s, 3, J = 7 Hz, CH_3), 2.70, 2.85 (2 d, 3, J = 5 Hz, CH_3N), 2.80, 3.50 (m, 4, CH_2CH_2), 3.77 (s, 3, CH_3O), 4.41 (m, 1, CHN), 5.05 (s, 2, CH_2O), 6.82, 6.91, 6.94 (3 s, 3, aromatics), 7.42 (m, 5, Ph); uv_{max} 205 nm (ε 56,250), 230 (9500, sh), 282 (3640), 286 (3770); ORD (*c* 0.36, MeOH) $[\phi]_{700}$ +6.0°, $[\phi]_{589}$ +5.1°, $[\phi]_{510}$ 0°, $[\phi]_{292}$ −1855 (tr), $[\phi]_{280}$ 0°, $[\phi]_{270}$ +835° (pk), $[\phi]_{265}$ 0°, $[\phi]_{241}$ −3250° (tr), $[\phi]_{233}$ 0°, $[\phi]_{227}$ +5330° (pk), $[\phi]_{220}$ +4640° (tr), $[\phi]_{212}$ +6960° (pk); CD (*c* 0.01 *M*, MeOH) $[\theta]_{298}$ 0, $[\theta]_{283}$ −2410, $[\theta]_{253}$ 0, $[\theta]_{232}$ −7880, $[\theta]_{223}$ −2780, $[\theta]_{212}$ −7880. *Anal.* ($C_{19}H_{23}NO_2$·HCl) C, H, N.

(1*R*)-(−)-1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(−)-*N*-Methylisosalsoline Hydrochloride] (3d). Debenzylation of 4.0 g (0.012 mol) of **3c** according to the procedure described for **1b** afforded 2.5 g (85%) of **3d**: mp 200–202°; $[\alpha]_D$ −1.4°; $[\alpha]_{365}$ − 42.6°; nmr δ 1.46, 1.60 (2 d, 3, J = 7 Hz, CH_3), 2.68, 2.80 (2 d, 3, J = 5 Hz, CH_3N), 2.80–3.50 (m, 4, CH_2CH_2), 3.78 (s, 3, CH_3O), 4.41 (m, 1, CHN), 6.65, 6.73 (2 s, 2, aromatics), 9.00 (br, 1, OH); uv_{max} 203 nm (ε 50,300), 226 (7500), 285 (3900); ORD (*c* 0.24, MeOH) $[\phi]_{700}$ 0°, $[\phi]_{589}$ −6.5°, $[\phi]_{294}$ −1750° (tr), $[\phi]_{281}$ 0°, $[\phi]_{272}$ +1000° (pk), $[\phi]_{265}$ +900° (sh), $[\phi]_{251}$ 0°, $[\phi]_{235}$ −4000° (tr), $[\phi]_{231}$ 0°, $[\phi]_{225}$ 4500° (pk), $[\phi]_{210}$ 0°; CD (*c* 0.01 *M*, MeOH) $[\theta]_{308}$ 0, $[\theta]_{292}$ −1720, $[\theta]_{284}$ −2000, $[\theta]_{251}$ −240, $[\theta]_{232}$ −7000, $[\theta]_{218}$ 0, $[\theta]_{207}$ −20,000, $[\theta]_{200}$ 0. *Anal.* ($C_{12}H_{17}NO_2$·HCl) C, H, N.

(1*S*)(−)-7-Benzyloxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4a). The combined mother liquors of **3a**·dbdt were evaporated, the residue was dissolved in H_2O, and the solution was rendered alkaline with 10% NaOH and extracted with CH_2Cl_2. The extract was acidified with ethanolic HCl, the mixture evaporated, and the residue crystallized twice from EtOH to give 14.0 g (64% based on 0.069 mol) of **4a**: mp 220–221°; $[\alpha]_D$ −24.0°; identical in nmr and uv with **3a**; ORD and CD mirror images of **3a**. *Anal.* ($C_{18}H_{21}NO_2$·HCl) C, H, N.

(1*S*)-(−)-7-Hydroxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*S*)-(−)-Isosalsoline Hydrochloride] (4b). In a manner similar to the procedure given for **1b**, 8.0 g (0.025 mol) of **4a** was debenzylated to afford 4.9 g (85%) of **4b**: mp 241–242°; $[\alpha]_D$ −26.0°; identical in nmr and uv with **3b**. *Anal.* ($C_{11}H_{15}NO_2$·HCl·0.25H_2O) C, H, N.

(1*S*)-(−)-7-Benzyloxy-1,2-dimethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4c). N-Methylation of 8.8 g (0.028 mol) of **4a**, according to the procedure described for **1c**, gave 7.7 g (84%) of **4c**: mp 190–191°; $[\alpha]_D$ −0.5°, $[\alpha]_{365}$ −27.5°; identical in nmr and uv with **3c**; ORD and CD mirror images of **3c**. *Anal.* ($C_{19}H_{23}NO_2$·HCl) C, H, N.

(1*S*)-(+)-1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*S*)-(+)-*N*-Methylisosalsoline Hydrochloride] (4d). In a manner similar to the procedure given for **1b**, 4.0 g (0.012 mol) of **4c** was debenzylated to afford 2.5 g (85%) of **4d**: mp 200–202°; $[\alpha]_D$ +1.6°; $[\alpha]_{365}$ +40.0°; identical in nmr and uv with **3d**; ORD and CD mirror images of **3d**. *Anal.* ($C_{12}H_{17}NO_2$·HCl) C, H, N.

Conversion of (*R*)-(−)-*N*-Methylsalsoline Hydrochloride (1d) and (*R*)-(−)-*N*-Methylisosalsoline Hydrochloride (3d) into (*R*)-(+)-Carnegine. To a solution of 1.0 g (4.1 mmol) of **1d** in 60 ml of MeOH was added an excess of CH_2N_2 in Et_2O. The mixture was stored at 4° for 4 hr and then at 25° overnight. The resulting solution was evaporated at 40° in a stream of N_2; the residue was suspended in dilute $NaHCO_3$ and extracted with EtOAc. The extract was evaporated to leave 700 mg (77%) of an oil, identical in $[\alpha]_D$ and nmr with authentic (*R*)-(+)-carnegine.[12]

In a similar manner, 500 mg (2.05 mmol) of **3d** was converted to afford 300 mg (66%) of (*R*)-(+)-carnegine.

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Synthesis and Antibacterial Activity of Some Substituted 4-Quinolone-3-carboxylic Acids

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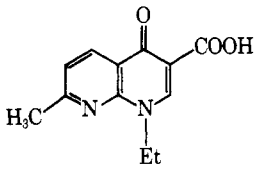
The activity of nalidixic[1,2] (1) and oxolinic[3,4] (2) acids against gram-negative pathogens in refractory urinary tract infections[5] suggested the synthesis and study of related compounds. Although a number of substituted *N*-alkyl-4-quinolone-3-carboxylic acids have been prepared and claimed to have antibacterial activity,[6] only few 8-substituted representatives have been studied thus far. The present note deals with this type (**3a–h**) and with *N*-ethylbenzo[*h*]-4-quinolone-3-carboxylic acid (**4**). In an attempt to improve upon the considerable antibacterial activity of the latter, we also synthesized 6- and 7-methoxybenzo[*h*]-4-quinolone-3-carboxylic acid (**5** and **6**), since it seemed possible that methoxy groups so placed might simulate the methylenedioxy ring of oxolinic acid.



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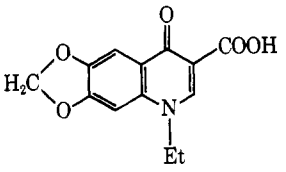

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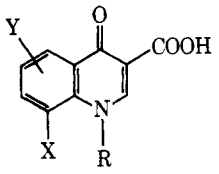
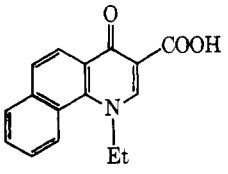


	R	X	Y
3a	H	MeO	H
b	Et	MeO	H
c	Et	EtO	H
d	H	Cl	5-Me
e	H	Cl	H
f	Et	Cl	H
g	Et	Cl	6-Cl
h	Me	Me	H



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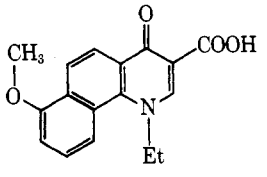

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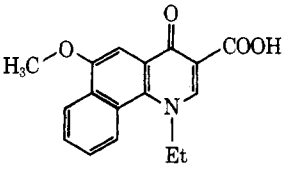

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The acids were obtained by modifications of the Gould-Jacobs synthesis. The required alkylanilines were prepared by reductive alkylation of the corresponding anilines with Raney nickel catalyst. The methoxynaphthylethylamines were obtained by reduction of the acetamido compounds with sodium bis(2-methoxyethoxy)aluminum hydride ("Red-Al," Aldrich). Condensations of the secondary amines with diethyl ethoxymethylenemalonate (EMME) require higher temperatures and longer times than those of primary amines[7,8] (Table I). Cyclization to the acids was effected by P_2O_5 in nitrobenzene;[7] polyphosphoric acid[8] was used to cyclize less reactive malonates (Table II).

† This note is dedicated to Dr. Alfred Burger, with whom I had the pleasure to be associated some years ago and whose continued friendship I consider a privilege.

Table I. Arylethylamines (ArNHEt) and Their Reaction with EMME

Ar	Bp or mp, °C	Yield, %	Condensation with EMME: Time, hr	Condensation with EMME: Temp, °C
2-MeO-C_6H_4	111–115 (9 mm)[a]	54	0.3	160
2-EtO-C_6H_4	114–117 (10 mm)[b]	48	0.3	160
2-Cl-C_6H_4	98–100 (10 mm)[c]	68	18	100
2,4-$(Cl)_2$-C_6H_3[d]	96–97 (1 mm)	55	18	100
5-MeO-$C_{10}H_7$-α	70–72[e]	25	18	100
4-MeO-$C_{10}H_7$-α[f]	71–72.5	26	18	100

[a]Lit. 117° (31 mm): M. Förster, *J. Prakt. Chem.*, [2] **21**, 341 (1880). [b]Lit. 234–236° (751 mm): E. Diepolder, *Ber.*, **31**, 495 (1898). [c]Lit. 219° (726 mm): C. M. Suter and F. B. Dains, *J. Amer. Chem. Soc.*, **50**, 2733 (1928). [d]*Anal.* ($C_8H_9NCl_2$) N. [e]Lit.[12] 74.5–75°. [f]*Anal.* ($C_{13}H_{15}NO$) C, H, N.

Table II. Physical Properties and Preliminary Screening of 4-Quinolone-3-carboxylic Acids

No.	Method	Yield, % (based on amine)	Mp, °C[a]	MIC, μg/ml: *P. vulgaris*	MIC, μg/ml: *S. aureus*
3a	A	62	282–283[b]	>100	>100
3b	A	51	255–258[c,d]	100	>100
3c	A	58	199–202[e]	>100	>100
3d	*f*	76	290–292[g]	>100	>100
3e	A	83	239–242[c,h]	>100	>100
3f	A, B	16, 43	161–163[i]	50	>100
3g	B	12	207–208.5[j]	25	>100
3h	A	85	259–261[k]	>100	>100
4	A	76	242–243[k]	6.3	50
5	B	19	257.5–258.5[l]	12.5	25
6	B	74	249–251[m]	*n*	
1	Nalidixic acid			6.3	>100
2	Oxolinic acid[o]			0.39	3.13–12.5

[a]Recrystallized from EtOH unless otherwise noted. [b]Lit. 280° dec: W. M. Lauer, R. T. Arnold, B. Tiffany, and J. Tinker, *J. Amer. Chem. Soc.*, **68**, 1268 (1946). [c]Recrystallized from MeCN. [d]Lit.[8] 261–262.5°. [e]Lit.[8] 199–200°. [f]Method of R. G. Gould and W. A. Jacobs, *J. Amer. Chem. Soc.*, **61**, 2890 (1939). [g]Lit. 285–286° dec: B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, **15**, 230 (1972). [h]Lit. 248–250° dec: D. S. Tarbell, *J. Amer. Chem. Soc.*, **68**, 1277 (1946). [i]*Anal.* ($C_{12}H_{10}NO_3Cl$) C, H, N. [j]*Anal.* ($C_{12}H_9NO_3Cl_2$) C, H, N, Cl. [k]Reference 7. [l]*Anal.* ($C_{17}H_{13}NO_4$) C, H, N. [m]*Anal.* ($C_{17}H_{13}NO_4$) C, H, N. [n]Too insoluble to test adequately by the method used. [o]Data from ref 4a.

The compounds were first screened against *Proteus vulgaris* and *Staphylococcus aureus*. The most promising acids were then tested against representatives of genera present in urinary tract infections. Determination of the minimal inhibitory concentration (MIC) was made by visual examination of a twofold dilution series.

Results and Discussion

The only compounds with significant antibacterial activity were acids **3f**, **3g**, **4**, and **5** (Table II). Their mini-