Fluorine-Containing Amino Acids and Their Derivatives. 4.[1] Synthesis and Antibacterial Activity of *Threo* and *Erythro* 1-Fluorodehydroxylated Chloramphenicol Analogues

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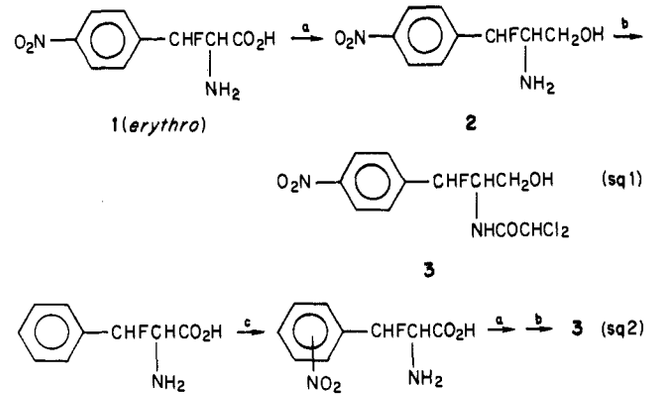
Both *threo* and *erythro* 1-fluorodehydroxylated chloramphenicol analogues were synthesized and tested for antimicrobial activity. None showed antibacterial or antifungal activity, clearly demonstrating that substitution of the secondary hydroxyl group with fluorine abolishes the antibacterial activity of the parent compound, chloramphenicol. This finding sharply contrasts with that of previous workers, in which fluorination of the 3-hydroxyl group enhanced antibacterial activity against many chloramphenicol-resistant strains.

In our previous paper, we reported on the stereoselective synthesis and the unusual conformational features of both *erythro* and *threo* diastereomers of 3-fluorophenylalanine. We now report the conversion of these diastereomers into novel 1-fluorodehydroxylated analogues of the well-known antibiotic, chloramphenicol, and discuss their antibacterial activities.

Substitution of the hydroxyl group of biologically active substances by an isoelectronic function, fluorine, can lead to more potent analogues.[2] Thus, our principal concern in this study was to see how the antibacterial activity of chloramphenicol is affected by this substitution, as it may lead to a better understanding of the structure–activity relationship and/or the mechanism of inactivation by plasmid-mediated acetylation. In general, the propanediol moiety of chloramphenicol and, especially, the stereochemical configuration of the substituents on the asymmetric carbon atoms 1 and 2 have been considered essential for antibacterial activity.[3] Surprisingly, however, the 3-fluorodehydroxylated analogue, recently reported by Nagabushan et al. during the course of our study[4] on fluoroamino acids and their derivative, showed enhanced antibacterial activity, particularly against chloramphenicol-resistant strains.[5] This novel example proved that biological activity is not lost by substitution of the 3-hydroxyl group by fluorine. Therefore, we were prompted to examine the effect of fluorine substitution of the secondary hydroxyl group on the antibacterial activity of chloramphenicol. We herein describe findings on substitution of the secondary alcohol which sharply contrast with previous findings on substitution of the primary alcohol.

Scheme I. Synthesis of *erythro* 1-Fluorodehydroxylated Chloramphenicol (Unnatural Type)[a]



[a] (a) (i) B_2H_6/THF, (ii) HCl. (b) $(Cl_2CHCO)_2O$-Et_3N/MeOH. (c) (i) CF_3SO_3H or HBF_4, (ii) $NO_2^+BF_4^-$/CH_3CN.

Chemistry. The synthetic schemes for both the *erythro* (unnatural type) and the *threo* (natural type) 1-fluorodehydroxylated chloramphenicol are summarized in Schemes I and II, respectively. To obtain the desired *erythro* compound, *erythro*-3-fluoro-*p*-nitrophenylalanine (1) was reduced with diborane to the amino alcohol **2**, without defluorination.[6] After many unsuccessful attempts, which resulted in defluorination, dichloroacetylation of **2**, using a large excess of dichloroacetic anhydride in methanol, gave the desired product, *erythro*-2-(dichloroacetamido)-3-fluoro-3-(*p*-nitrophenyl)propanol, in approximately 30% yield. The structure of this compound was unambiguously confirmed on the basis of its spectral data (see Experimental Section). We also examined the nitration of **4**, as shown by sequence 2, because of the relatively low yield in the reductive amination reaction leading to **1**. Nitration of **4**, which involved protection of the amino group by a very strong acid, such as trifluoromethanesulfonic acid or tetrafluorohydroboric acid, and treatment of the resulting salt with nitronium tetrafluoroborate[7] in acetonitrile gave a mixture of ortho-, meta-, and para-nitrated products in 55% yield. Unfortunately, the isomer ratio of the mixture was 1:2:1. As nitration of unsubstituted phenylalanine is known to exclusively produce the para-nitrated product,[8] our results

(1) (a) Part 3: Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T.; Misaki, S. *J. Org. Chem.* **1984**, *49*, 1163 and our papers cited therein. (b) Tsushima, T.; Kawada, K.; Tsuji, T.; Misaki, S. *Ibid.* **1982**, *47*, 1107.

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(4) Reference 1 and see also: (a) Tsushima, T.; Sato, T.; Tsuji, T. *Tetrahedron Lett.* **1980**, *21*, 3591. (b) Tsushima, T.; Nishikawa, J.; Sato, T.; Tanida, H.; Tori, K.; Tsuji, T.; Misaki, S.; Suefuji, M. *Ibid.* **1980**, *21*, 3593.

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(6) Anhoury, M. L.; Arickx, M.; Crooy, P.; Neys, R. D.; Eliaers, J. *J. Chem. Soc., Perkin Trans 1* **1974**, 191.

(7) Kuhn, S. J.; Olah, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4564.

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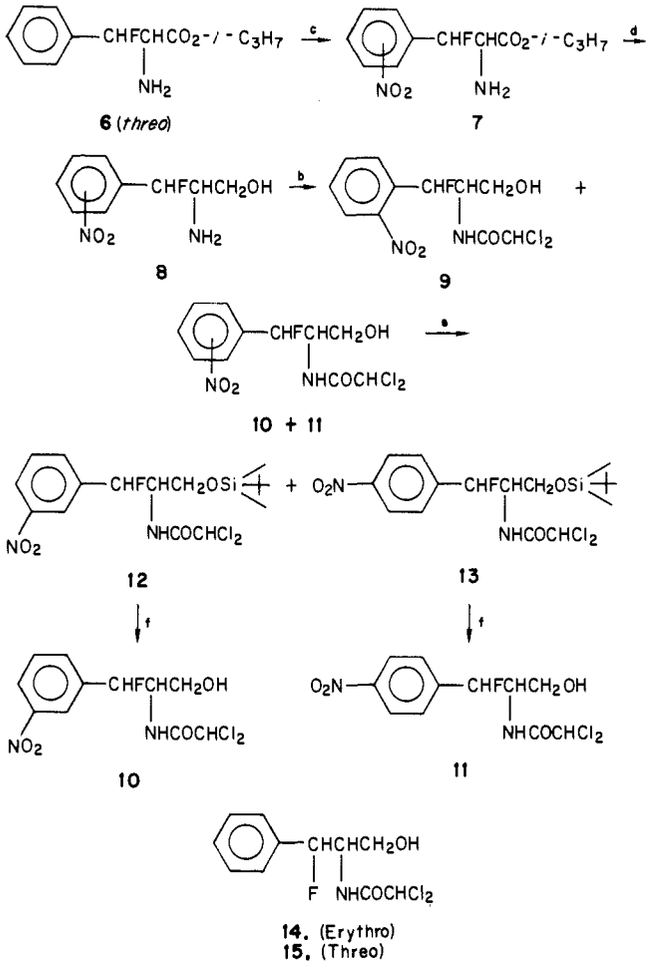
Table I. Antifungal and Antibacterial Activities of 1-Fluorodehydroxychloramphenicol Analogues (MIC, μg/mL)

compd	C.a.[a]	A.f.[a]	T.a.[a]	S.a.[b]	S.p.[b]	E.c.[b]	K.p.[b]	P.a.[b]
3	>100	>100	>100	>100	>100	>100	>100	>100
9	>100	>100	>100	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100	>100	50	>100
14	>100	>100	>100	>100	>100	>100	>100	>100
15	>100	>100	>100	>100	>100	>100	>100	>100
ref.	>100	>100	>100	12.5	12.5	3.1	0.8	25.0

[a] Fungi: C.a. = *Candida albicans*; A.f. = *Aspergillus fumigatus*; T.a. = *Trichophyton asteroides*. [b] Bacteria: S.a. = *Staphylococcus aureus*; S.p. = *Streptococcus pyogenes*; E.c. = *Escherichia coli*; K.p. = *Klebsiella pneumoniae*; P.a. = Pseudomonas *aeruginosa*.

Scheme II. Synthesis of *threo* 1-Fluorodehydroxylated Chloramphenicol (Natural Type)[a]



[a] (a-c) See Scheme I. (d) $Ca(BH_4)_2$/EtOH. (e) *t*-$BuMe_2SiCl$-DMAP/CH_2Cl_2. (f) Bu_4NF/THF.

clearly showed that introduction of fluorine at the benzylic position drastically changed the preferred orientation from ortho-para to meta. The final product (**3**) of this procedure was identical with the sample obtained in sequence 1. In view of the tedious separation process of the nitro isomers at the final stage, we favor sequence 1 despite its low yield in the prior reductive amination step.

In synthesizing the natural type derivative, *threo*-2-(dichloroacetamido)-3-fluoro-3-(*p*-nitrophenyl)propanol (**11**) and its isomers (**9** and **10**), the only available starting material was *threo*-3-fluorophenylalanine isopropyl ester (**6**), which was prepared by the method of Wade et al.[9] Preparation of the *p*-nitro derivative using their method[9] was abandoned because of the failure of the aziridine ring

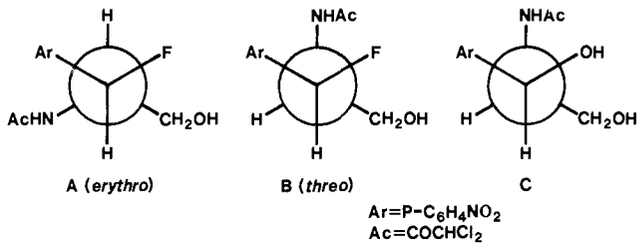


Figure 1. Staggered conformations of chloramphenicol derivatives.

opening step. Compound **6** was converted to a mixture of nitro isomers, **7**, which was reduced with calcium borohydride[10] in ethanol to give the desired amino alcohol **8** in very high yield, without defluorination. The mixture of amino alcohols thus obtained was converted to the mixture of dichloroacetyl derivatives **9**–**11** as described earlier. Only the ortho isomer could be isolated and characterized at this stage (see Experimental Section). Chromatographic separation of the other isomers (**10** and **11**) was unsuccessful, even with use of HPLC techniques, and required conversion to the dimethyl-*tert*-butylsilylated derivatives **12** and **13** to block the highly polar hydroxyl group. Only then could the two isomers be easily separated by usual silica gel column chromatography and desilylated back to the desired products (**10** and **11**) with tetra-*n*-butylammonium fluoride (see Experimental Section). We also prepared the *erythro* and the *threo* derivatives **14** and **15** by almost the same method as that for the nitro compounds for antibacterial activity screening.

The NMR spectroscopic measurement of the *erythro* isomer **3** showed a vicinal H–H coupling constant of 7.0 Hz and a F–H coupling constant of 13 Hz at the C_1 and C_2 carbons, which suggests that this isomer preferably takes a different rotational conformation from that of the parent chloramphenicol, as shown by the structure A in Figure 1.[11] The *threo* isomer **11**, on the other hand, showed a much smaller H–H coupling constant of 2.5 Hz and a much larger F–H coupling constant of 25 Hz, suggesting that this isomer preferably takes the same conformation as that of chloramphenicol (see structures B and C in Figure 1).[11]

Biological Results and Discussion

In vitro antimicrobial and antifungal activities of both the *erythro*-type (**3** and **14**) and the *threo*-type compounds

(8) Bergel, F.; Stock, J. A. *J. Chem. Soc.* **1954**, 2409.
(9) (a) Wade, T. N.; Gaymard, F.; Guej, R. *Tetrahedron Lett.* **1979**, 2681. (b) Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328.
(10) (a) Kollonitsch, J.; Fuchs, O.; Gábor, V.; *Nature (London)* **1954**, *173*, 125. (b) *Ibid.* **1955**, *175*, 346.
(11) Comparison of the observed coupling constants with those which we had previously observed for *threo*- and *erythro*-3-fluorophenylalanines in an NMR spectroscopic study[1a] of their rotational conformations clearly showed that the *erythro* isomer mainly exists in the conformation which has the trans H–H and the gauche F–H alignment and the *threo* isomer is present mainly in the conformation which has the gauche H–H and the trans F–H alignment.[4] Previously, the conformation of chloramphenicol has been determined to be C as shown in Figure 1.[3c-d]

(9, 10, 11, and 15) are summarized in Table I.[12] None showed antibacterial activity or antifungal activity against these microorganisms. The only minor exception was the natural-type chloramphenicol analogue 11, which exhibited very weak activity against *Klebsiella pneumoniae*. However, comparison of the antimicrobial activity of this compound with that of chloramphenicol clearly shows that substitution of the secondary hydroxyl group with fluorine abolishes the high antimicrobial activity of the parent compound. As previous workers have found that fluorine substitution of the primary alcohol enhances biological activity, the present study offers the sharply contrasting conclusion that replacement of the secondary hydroxyl group by a fluorine in the D-*threo* configuration results in loss of biological activity.

Experimental Section

General Procedures. Unless otherwise stated, the uncorrected melting points were determined with a Yanagimoto hot-stage apparatus. ^1H and ^{19}F NMR were taken on Varian T60 and EM-360 spectrometers for solutions in $CDCl_3$ containing 1% Me_4Si and 3% C_6F_6 as internal standards, respectively, and IR spectra were recorded on a Hitachi 215 grating spectrometer for solutions in $CHCl_3$. Mass spectra were obtained with a Hitachi RMU-6 spectrometer. Elution chromatography was carried out on a Merck Lobar silica gel column (type B) using ethyl acetate–benzene (1:2 or 1:1) as an eluant.

***erythro*-2-Amino-3-fluoro-3-(*p*-nitrophenyl)-1-propanol Hydrochloride (2).** This compound was prepared by diborane reduction of 1 by using essentially the same method as that reported by Crooy et al. No significant defluorination was observed. The crude product which showed ^1H NMR (D_2O) signals at δ (Me_4Si) 4.00–4.30 (m, 3 H, CH_2OH and $CH(NH_3^+)$), 6.57 (dd, 1 H, CHF, J_{HF} = 44 Hz, J_{HH} = 4 Hz), 8.07 and 8.78 (AB q, 4 H, aromatic J = 9.0 Hz) was immediately subjected, without purification, to dichloroacetylation in the next step.

***erythro*-2-(Dichloroacetamido)-3-fluoro-3-(*p*-nitrophenyl)-1-propanol (3).** The crude product 2 (236 mg) was suspended in methanol (4 mL) and cooled to −40 °C. To this suspension was added triethylamine (1.71 mL), followed by dropwise addition of dichloroacetic anhydride (1.44 mL, 10 equimolar) over 13 min. The temperature was gradually raised to reach 0 °C during 3 h. The reaction mixture was then poured into cold dilute aqueous hydrochloric acid and extracted with ethyl acetate. The organic extract was washed twice, in sequence, with cold dilute aqueous hydrochloric acid, cold dilute aqueous sodium bicarbonate, and cold water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded an oily crude product (153 mg). Column chromatography of this product, followed by recrystallization from *i*-PrOH, afforded a pure crystalline product 3 (84 mg) in 23.2% overall yield from the starting material 1. This was characterized as follows: mp 168–168.5 °C; IR ($CHCl_3$) 3400 (NH), 1700 (C=O), 1610 (arom), 1525 and 1350 (NO_2), 1140, 1100 cm^{-1}; ^1H NMR (CD_3OD) δ 3.60–3.87 (m, 2 H, CH_2OH), 3.97–4.63 (m, 1 H, $CH(NH_2)$), 5.67 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 7 Hz), 6.12 (s, 1 H, $CHCl_2$), 7.60 and 8.20 (AB q, 4 H, arom J = 9.0 Hz); ^{19}F NMR (CD_3OD) δ (int C_6F_6) −22.21 (J = 46, 13 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 309, 307, and 305 (M^+ − F), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.84. Found: C, 40.76; H, 3.36; N, 8.51; F, 5.89.

Nitration of *erythro*-3-Fluorophenylalanine (4). First, compound 4 (1.08 g) was converted to the trifluoromethanesulfonic acid salt (1.81 g) by treatment with trifluoromethanesulfonic acid (0.82 g) in water. To the well-stirred suspension of this salt (1.48 g) in CH_3CN (8 mL) was added nitronium tetrafluoroborate (740 mg, 1.5 mol equiv) at room temperature and the mixture was kept overnight until completion of the reaction. The reaction mixture was then poured into cold water and the resulting aqueous solution was treated with ion-exchange resin (AG 50W-X8, 30 mL) with 1 N aqueous ammonia as eluant. Collection of the ninhydrin-positive fractions and evaporation of water under reduced pressure at below 30 °C afforded a crude mixture of nitration products. The approximate ratio of ortho-, meta-, and para-nitrated isomers was determined to be 1:2:1 by NMR spectroscopic measurement of the crude product. The crude mixture was subjected, without purification, to reduction and dichloroacetylation as described above. The final reaction mixture was separated by silica gel column chromatography to afford the desired product of sequence 2, which was found to be identical with compound 3 of sequence 1 by comparison of the spectroscopic data.

Nitration of *threo*-3-Fluorophenylalanine Isopropyl Ester (6). As mentioned above, the starting material 6 was first converted to the pure trifluoromethanesulfonic acid salt in 87% yield by treatment with the acid in ethyl acetate, followed by recrystallization from hexane–ethyl acetate. Next, the salt (1.58 g) was suspended with acetonitrile (7 mL) and treated with nitronium tetrafluoroborate (540 mg, 1.14 equiv) at room temperature overnight as done with the *erythro* derivative 1. The crude product (1.03 g) showed an approximate nitration yield of 55% by NMR measurement: ^1H NMR ($CDCl_3$) δ 1.00–1.43 (m, 6 H, $CHMe_2$), 3.50–4.23 (m, 1 H, $CHNH_2$), 4.73–5.30 (m, 1 H, $CHMe_2$), 5.30–6.37 (m, 1 H, CHF), 6.87–8.30 (m, 4 H, arom H).

***threo*-2-Amino-3-fluoro-3-(nitrophenyl)-1-propanol (8).** To ethanol (23 mL) maintained at −40 °C were added sodium borohydride (576 mg) and then calcium chloride (846 mg) with vigorous stirring. Then the temperature was gradually raised to reach −20 °C during 1 h. To this solution was added the ethanol solution of the crude free nitro ester 7 (1.03 g/17 mL) and the solution was kept at this temperature for 4 h. The reaction mixture was then poured into cold water and extracted with ethyl acetate. The organic extract was washed twice with water, dried over anhydrous magnesium sulfate, and condensed under reduced pressure, leaving an oily residue in an estimated yield of reduction higher than 90%. This crude amino alcohol showed no loss of fluorine on NMR spectroscopic measurement and was used without purification for the subsequent acylation reaction: ^1H NMR (CD_3OD) δ 3.43–4.22 (m, 2 H, CH_2 and $CH(NH_2)$, 5.22–6.15 (m, 1 H, CHF), 7.23–8.38 (m, 4 H, arom).

***threo*-2-(Dichloroacetamido)-3-fluoro-3-(*o*-nitrophenyl)-1-propanol (9).** Treatment of crude product 8 (646 mg) with dichloroacetic anhydride as for 3 produced a mixture of o-9, *m*-10, and *p*-11 isomer (553 mg). After silica gel column chromatography (Merck Lobar Column, type B), ortho isomer 9 was isolated from this mixture but not the meta and para isomers. A pure sample of 9 (49 mg) was obtained after recrystallization from ether and characterized as follows: mp 135–137 °C; IR ($CHCl_3$) 3420 (NH), 1700 (C=O), 1530 and 1350 (NO_2), 1140, 1100 cm^{-1}; ^1H NMR (CD_3OD) δ 3.64–4.07 (m, 2 H, CH_2), 4.10–4.60 (m, 1 H, CHN), 6.13 (s, 1 H, $CHCl_2$), 6.55 (dd, 1 H, CHF, J_{HF} = 47 Hz, J_{HH} = 1.5 Hz), 7.30–7.87 (m, 3 H, arom), 8.22 (m, 1 H, arom); ^{19}F NMR (CD_3OD) δ −33.17 (J = 47, 29 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 311, 309, and 307 (M^+ − OH), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.84. Found: C, 40.70; H, 3.47; N, 8.63; F, 6.06. The mixture consisting of meta and para isomers 10 and 11 was converted to the dimethyl-*tert*-butylsilyl enol ether derivatives 12 and 13 for chromatographic separation as follows.

***threo*-2-(Dichloroacetamido)-3-fluoro-3-(*m*- and *p*-nitrophenyl)-1-propanol (10 and 11).** This mixture (66 mg) was suspended in dichloromethane (2.3 mL) and treated with dimethyl-*tert*-butylsilyl chloride (156 mg, 5 equiv) in the presence of triethylamine (199 μL, 7 equiv) and (dimethylamino)pyridine (25 mg, 1 equiv) at room temperature overnight. The reaction mixture was washed successively with cold water, saturated aqueous ammonium chloride, and cold water and then dried over magnesium sulfate. Evaporation of the solvent yielded an oily crude mixture of silyl ether derivatives 12 and 13. The mixture was separated by usual silica gel column chromatography (Merck Lobar column, type B) to afford pure samples of 12 (44 mg) and 13 (33 mg), which were confirmed by NMR spectroscopic measurement as meta isomer 12 and para isomer 13, respectively. For

(12) For experimental details, see our previous paper: Totani, T.; Aono, K.; Yamamoto, K.; Tawara, K. *J. Med. Chem.* **1981**, *24*, 1492.

meta isomer 12: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H, Me_2-t-BuSi), 0.92 (s, 9 H, t-Bu), 3.57–3.87 (m, 2 H, CH_2), 3.93–4.80 (m, 1 H, CHN), 5.83 (s, 1 H, $CHCl_2$), 5.92 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 4 Hz), 6.63–7.00 (1 H, NH), 7.47–7.80 (m, 2 H, arom), 8.07–8.33 (m, 2 H, arom). For para isomer 13: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H, Me_2-t-BuSi), 0.92 (s, 9 H, t-Bu), 3.57–3.87 (m, 2 H, CH_2), 3.93–4.80 (m, 1 H, CHN), 5.83 (s, 1 H, $CHCl_2$), 5.92 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 4 Hz), 6.63–7.00 (1 H, NH), 7.55 and 8.24 (AB q, 4 H, arom, J_{HH} = 9.0 Hz). Next, each separated compound was desilylated back to the desired products 10 and 11 by treatment with tetraethylammonium fluoride in THF and recrystallized from i-PrOH–hexane to afford pure samples of 10 (29 mg) and 11 (19 mg), which were characterized as follows. For the meta isomer 10: mp 144–145 °C; IR ($CHCl_3$) 3405 (NH), 1700 (C=O), 1600 (arom), 1540 and 1350 (NO_2), 1140, 1100 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.50–4.28 (m, 2 H, CH_2), 4.40–4.70 (m, 1 H, CHN), 6.00 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 2.5 Hz), 6.13 (s, 1 H, $CHCl_2$), 7.43–8.40 (m, 4 H, arom); ^{19}F NMR (CD_3OD) δ −35.15 (J = 46, 28 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 309, 307, and 307 (M^+ − F), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.84. Found: C, 40.77; H, 3.48; N, 8.58; F, 5.53. For the para isomer 11: mp 139–140 °C; IR ($CHCl_3$) 3400 (NH), 1700 (C=O), 1600 (arom), 1520 and 1350 (NO_2), 1100 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.50–4.28 (m, 2 H, CH_2), 4.40–4.70 (m, 1 H, CHN), 6.00 (dd, 1 H, CHF, J_{HF} = 46 Hz, J_{HH} = 2.5 Hz), 6.13 (s, 1 H, $CHCl_2$), 7.57 and 8.17 (AB q, 4 H, arom, J = 9.0 Hz); ^{19}F NMR (CD_3OD) δ −35.42 (J = 46 Hz, 25 Hz); mass spectrum, m/z 329, 327, and 325 (M^+ + H), 309, 307, and 305 (M^+ − F), 297, 295, and 293 (M^+ − CH_2OH), 241 (M^+ − $CHCl_2$), 174, 172, and 170 (M^+ − $C_6H_4NO_2CHF$), 60 (C_2H_6NO). Anal. Calcd for $C_{11}H_{11}O_4N_2Cl_2F$: C, 40.63; H, 3.41; N, 8.62; F, 5.82. Found: C, 40.75; H, 3.48; N, 8.42; F, 5.70.

Antimicrobial Activity. All fungal and bacterial strains used in this experiment were prepared as reported in our earlier paper.[12] Minimum inhibitory concentrations (MICs) were also determined as reported earlier.

Registry No. DL-1, 80817-88-5; (±)-**2**, 93863-23-1; (±)-**3**, 93863-24-2; DL-4, 79617-87-1; DL-4·CF_3SO_3H, 93863-25-3; DL-o-NO_2-4, 93863-26-4; DL-m-NO_2-4, 93863-27-5; DL-p-NO_2-4, 80817-88-5; DL-**6**, 79617-86-0; DL-**6**·CF_3SO_3H, 93894-94-1; DL-o-NO_2-**7**, 93863-28-6; DL-m-NO_2-**7**, 93863-29-7; DL-p-NO_2-**7**, 93863-30-0; (±)-o-NO_2-**8**, 93863-31-1; (±)-m-NO_2-**8**, 93863-32-2; (±)-p-NO_2-**8**, 93863-33-3; (±)-**9**, 93863-34-4; (±)-**10**, 93863-35-5; (±)-**11**, 93863-36-6; (±)-**12**, 93863-37-7; (±)-**13**, 93863-38-8; (±)-14, 93863-39-9; (±)-**15**, 93863-40-2; $(Cl_2CHC(O))_2O$, 4124-30-5.

3,4-Diphenyl-1*H*-pyrazole-1-propanamine Antidepressants

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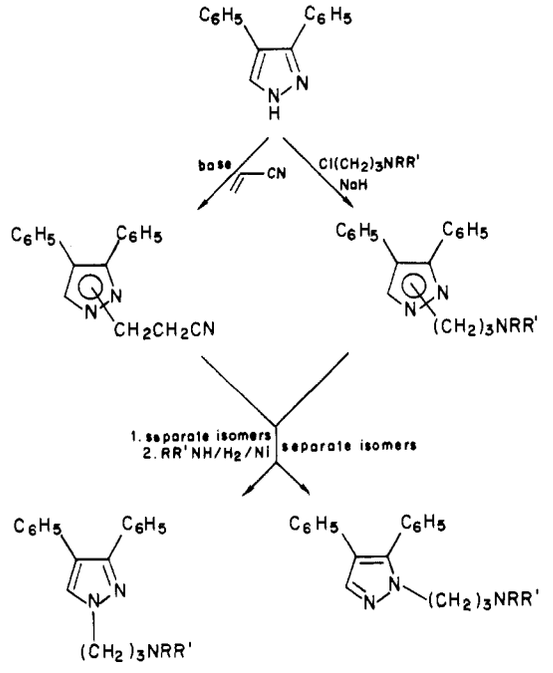
A small series of compounds is described in which a narrow SAR has identified *N,N*-dimethyl-3,4-diphenyl-1*H*-pyrazole-1-propanamine, **3**, as a potential antidepressant with reduced side effects. The isomeric *N,N*-dimethyl-4,5-diphenyl-1*H*-pyrazole-1-propanamine was completely inactive in the primary antidepressant screens. Compounds were synthesized by Michael addition of acrylonitrile to diphenylpyrazole followed by reductive alkylation of the resultant diphenylpyrazolepropionitriles. Compound **3** was equipotent with imipramine in standard antidepressant assays in animals but showed no significant anticholinergic action and did not antagonize the antihypertensive effects of clonidine and guanethidine.

Following on the heels of two decades of intensive research on tricyclic structures as antidepressants, more recent work has brought forth a myriad of compounds of diverse nature. Recent publications describe these "second generation" antidepressants and summarize a vast body of chemistry dedicated to them.[1,2] Major objectives in this new work are drugs with more rapid onset of action and a reduced number and intensity of side effects. Principally, the major targeted adverse effects are sedation and anticholinergic actions which are often encountered in the clinic and which limit outpatient acceptance.

We herein report on a small group of 3,4-diphenylpyrazoles, patterned after the classical tricyclics, whose pharmacological and toxicological profiles in animals suggest they will possess antidepressant activities with marked reductions in side-effect liability. In particular, **3**, fezolamine, was as potent as imipramine in several animal models of depression but, unlike the latter, did not exhibit anticholinergic effects nor induce CNS depression or sedation at oral dosage levels significantly above those required for antidepressant-indicating efficacy in the same animals. Further, **3** was shown to have a significantly reduced potential for producing antihistamine-like and cardiovascular effects as compared to the tricyclics and, unlike imipramine, did not interfere with the antihypertensive effects of guanethidine or clonidine.

Scheme I



Chemistry. The compounds of Table I were prepared

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