TABLE II[a,b]

Compound No.	Dosage, mg/kg	pO_2 Change, %	pO_2 Duration, min	Blood pressure Change, mm Hg	Blood pressure Duration, min	Heart rate Change, %	Heart rate Duration, min
II	10	19	5	14	25	−9	25
VI	10	11	16	17	5	−11	15
VIII	10	70	9	42	15	−47	15
IX	10	100	20	7	12	4	3
XI	10	33	12	15	10	23	20
XII	10	31	8	0	0	0	0
XIII	5	13	3	14	15	−8	15
XIV	10	37	17	12	7	−7	2
XV	10	9	2	8	15	0	0
XVIII	10	11	7	0	0	−7	10
XX	2	59	1	−30	20	21	20

[a] The compounds were injected in the jugular vein of anesthetized dogs at 2–10 mg/k. The change in O_2 tension of the coronary sinus blood (pO_2), heart rate, and blood pressure were recorded by a procedure described in H. G. Schoepke, T. D. Darby, and H. D. Brondyk, *Pharmacologist*, **8**, 204 (1966). A compound possessing useful vasodilating activity should cause no increase in pO_2 for extended periods with minimal effects on heart rate and blood pressure. Von P. Heistracher, O. Kraupp, and G. Spring, *Arzneim-Forsch.*, **14**, 1098 (1964). [b] The compounds which were prepared but not listed in Table II were either ineffective in raising the pO_2 or had adverse effects on blood pressure and heart rate.

chloride·HCl (0.12 mole), pyridine (0.24 mole), and 150 ml of $CHCl_3$. The reaction mixture was stirred and refluxed gently in a steam bath for 1.5 hr. The reaction mixt was cooled and added to ice-H_2O mixt. The $CHCl_3$ layer was washed successively with 0.5 *N* NaOH soln and cold H_2O. The $CHCl_3$ layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was treated with Et_2O and crystallized (see Table I).

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Resolution of DL-α-Methylphenylalanine

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In a pioneering resolution[1] L-(−)-*N*-acetyl-α-methylphenylalanine was obtained in a low yield and in a state difficult to purify. Since in most mammalian physiology the derived L-amino acid is likely to be the active antipode and since the interpretation of test results is easier if one isomer is essentially free of the other a more efficient separation seemed highly desirable.

From an ethanolic solution of DL-*N*-acetyl-α-methylphenylalanine, a cinchonidine salt of the L-(−) enantiomorph precipitated. One crystallization was sufficient to free the salt from traces of the D-(+) isomer. Quinine, brucine, strychnine, and D-(+)-phenethylamine formed no solid salt or gave salts of racemic starting material. Cinchonine formed an insoluble salt of the D-(+) enantiomorph. This is not surprising since cinchonidine and cinchonine are mirror images at the most basic portion of these molecules although overall they are diastereomers. The cinchonidine salt was decomposed and the *N*-Ac group hydrolyzed with HCl to yield L-(−)-α-methylphenylalanine·HCl. This process yields about half of the total L-(−)-amino acid as the HCl salt essentially free of D-(+) enantiomorph. The free amino acid was obtained by treatment with an ion-exchange resin. By reason of greater water solubility the HCl salt is generally preferred over the free amino acid.

The mother liquors from the cinchonidine salt enriched in D-(+)-*N*-acetyl-α-methylphenylalanine were decomposed and the cinchonine salt prepared. At this stage L-lysine and L-arginine salts afforded no useful purification. The cinchonine salt was processed as above to obtain the corresponding D-(+) antipode. In principle the resolution could be started with either cinchonidine or cinchonine salt but in practice the cinchonidine salt was obtained in higher yield and led directly to the desired L enantiomorph. Purity of the enantiomorphs was verified by phase solubility analysis.

Ord spectra were obtained on the L-(−) HCl salt and on the L-(−)- and D-(+)-amino acids. These data are listed in Table I along with those for the D-(+)-HCl salt

TABLE I

OPTICAL ROTATORY DISPERSION

λ, mμ	L-(−)-AA·HCl φ,[a] degrees	D-(+)-AA·HCl φ,[b] degrees	L-(−)-AA φ,[a] degrees	D-(+)-AA φ,[a] degrees
400	0	−8.4	−10	+10
350	+15	−22.9	0	0
300	+60	−68.8	+40	−40
250	+320		+300	−300
220	+4000		+3100	−2800
C[c]	0.102	0.257	0.033	0.101

[a] The values of φ, the molecular rotation at 25°, are ±10% or ±20° whichever is larger. Spectra were obtained in 1 *M* HCl. [b] At 18.5° in 3 *M* HCl. [c] The concn is listed in per cent soln.

obtained by Terashima, *et al.*[1] The agreement is satisfactory considering the variation in temperature and concentration. With each sample the first extremum of a Cotton effect was reached at 220 mμ. Superimposed fine structure, due to optically active Ph absorption bands, is present in each spectrum between 245 and 270 mμ. Pharmacological testing[2] of the individual

(1) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **14**, 1138 (1966).

(2) M. L. Torchiana, C. C. Porter, C. A. Stone, and H. M. Hanson, *Biochem. Pharmacol.*, **19**, 1601 (1970).

enantiomorphs shows that all the heart-depleting catecholamine activity resides in the L-(−) isomer. L-(−)-α-Methylphenylalanine is a tyrosine hydroxylase inhibitor and its pattern of biochemical and pharmacological behavior falls between those of L-(−)-α-methyl-*p*-tyrosine, a pure tyrosine hydroxylase inhibitor, and DL-α-methyl-*m*-tyrosine whose effects are related to its rapid metabolism to metaraminol.

This resolution makes available L-(−)-α-methylphenylalanine for study of metabolic inhibition and metabolic pathways. It has already been useful in an elegant chiral study.[3] The D-(+) enantiomorph may find use in antibiotic peptides where substitution can be made for D-(+)-phenylalanine.

Experimental Section[4]

DL-*N*-Acetyl-α-methylphenylalanine.—With recrystn from 58% EtOH the title compound, mp 199–201° (lit. mp 196–197°,[1] 195–197°,[5] 203–204°[6]), was obtained in two crops from DL-α-methylphenylalanine (95.0%) by Schotten–Bauman acylation: $pH_{1/2}$ 4.6 (50% MeOH). *Anal.* ($C_{12}H_{15}NO_3$) C, H, N, Eq. wt.

L-(−)-*N*-Acetyl-α-methylphenylalanine, Cinchonidine Salt.—To a soln of 234 g (1.058 moles) of *N*-acylamino acid in 438 ml of abs EtOH was added a soln of 312 g (1.058 moles) of cinchonidine in 438 ml of abs EtOH. The mixt was cooled to room temp, dild with Et_2O (1930 ml), seeded with crystals from a probe experiment, and allowed to stand overnight at 25°. The ppt was washed with three 75-ml portions of 3:1 Et_2O–EtOH. The yield of salt amounted to 222.5 g (82.3%), mp 207–210°. Recrystn from EtOH–Et_2O as before yielded 163.0 g (59.7%), mp 215–216°; $[\alpha]_{578}^{23}$ −49.2 ± 1.0° (*c* 1, abs EtOH) suitable for further processing. The analytical material was crystd to constant values: mp 218–219° dec; $[\alpha]_{578}^{23}$ −47.0 ± 1.0° (*c* 1, abs EtOH); uv max (MeOH) 225, 285, 302, and 315 mμ (log ε 4.57, 3.71, 3.59, and 3.50); ir spectrum consistent. *Anal.* ($C_{31}H_{37}N_3O_4$) C, H, N.

L-(−)-*N*-Acetyl-α-methylphenylalanine.—To 1750 ml of H_2O and 131 ml of 2.5 *N* HCl was added 163.0 g (0.316 mole) of the above cinchonidine salt and the mixt was stirred at 0–5° for 1 hr. An additional 172-ml portion of 2.5 *N* HCl was added and the stirring was continued at 0–5° for 1 hr. The mixt was then filtered and the ppt was washed with three 75-ml portions of cold H_2O. The yield of product amounted to 64.4 g (92.2%): mp 203–205°; $[\alpha]_{578}^{24}$ −42.1 ± 1.0° (*c* 1, abs EtOH). The anal. material was recrystd from Me_2CO: mp 206–207° (lit.[1] mp 196.5–200.5°); uv max (MeOH) 252, 257.5, 263, and sh 247.5 mμ (log ε 2.17, 2.24, 2.09, and 2.00); ir spectrum consistent. Further crystn did not change the melting point or rotation. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N, equiv wt.

L-(−)-α-Methylphenylalanine·HCl.—To 536 ml of 6 *N* HCl was added 64.4 g (0.291 mole) of the acetylamino acid. After 6 hr at reflux the mixt was cooled to 25° spontaneously then at 15° for 30 min. The mixt was filtered and the ppt was washed with three 25-ml portions of 2 *N* HCl at 0–5°. The yield of L-(−)-α-methylphenylalanine·HCl amounted to 55.1 g (88.0%): mp 217–219°; $[\alpha]_{578}^{23}$ −2.1 ± 0.5°; $pH_{1/2}$ 2.6 (H_2O); Cu salt complex $[\alpha]_{546}^{25}$ +142° (*c* 0.2, $CuSO_4$ soln);[7] uv max (MeOH) 252, 258, 263, and sh 247.5 mμ (log ε 2.24, 2.30, 2.19, and 2.11); ir spectrum consistent. *Anal.* ($C_{10}H_{13}NO_2$·HCl) C, H, Cl, N, equiv wt.

L-(−)-α-Methylphenylalanine.—The amino acid·HCl was dissolved in H_2O and passed over a column of resin, IR-120 (H_3^+O cycle). The column was eluted with H_2O to neutrality and following that with 500 ml of 1 *N* NH_4OH. Concn of the ammoniacal eluate yielded a crude product: mp 290–291° dec. The crude amino acid was dissolved in 178 ml of refluxing MeOH and upon concn to about 100 ml crystn began. The mixt was allowed to cool spontaneously and stand overnight at 25°, chilled to 5°, and filtered and the ppt was washed with MeOH: yield, 1.85 g (41.5%); mp 306.5° dec; purity by phase solubility 98.5 ± 0.5%; (abs EtOH) $[\alpha]_{578}^{23}$ −2.5° (*c* 1, 1 *N* HCl); uv max (MeOH) 237, 252.5, 258, 264, and sh 247 (log ε 2.02, 2.23, 2.30, 264, and 2.13); Cu salt complex $[\alpha]_{546}^{23}$ +182.5° (*c* 0.2, $CuSO_4$ soln). This material proved difficult to dehydrate and showed a tendency to rehydrate. Anal. was obtained on a sample showing 2.3% loss on drying (100°, 1 mm) corrected to the anhyd basis. *Anal.* ($C_{10}H_{13}NO_2$) C, H, N.

Another sample with a purity by phase solubility of 97.4 ± 0.5% (abs EtOH) showed $[\alpha]_{578}^{24}$ −22.8° (*c* 1, H_2O).

Enriched D-(+)-*N*-Acetyl-α-methylphenylalanine.—From the mother liquors of the L-(−) enantiomorph, cinchonidine salt by the method previously described for the L-(−) isomer, 27.55 g (89.4%) of enriched D-(+)-*N*-acetyl-α-methylphenylalanine was obtained, mp 193–195°.

D(+)-*N*-Acetyl-α-methylphenylalanine Cinchonine Salt Monohydrate.—Equimolar amts (0.020 mole) of enriched D-(+)-*N*-acetyl-α-methylphenylalanine and cinchonine were dissolved in 40 ml of warm EtOH. The mixture was cooled to 25°, seeded with crystals from a probe experiment, and allowed to stand for 64 hr. After cooling the mixt to 0°, the ppt was sepd by filtration, washed, and dried at 25°. The pure salt monohydrate amounted to 3.25 g (25.4% based on the D-(+) content of enriched starting material): mp 116–118°; $[\alpha]_{578}^{27}$ +88.7° (*c* 2, abs EtOH). The salt was recrystd from abs EtOH in 46.2% yield with no change in rotation or melting point; uv max (MeOH) 226, 285, 303, and 316 mμ (log ε 4.54, 3.68, 3.56, and 3.49); ir spectrum consistent. *Anal.* ($C_{31}H_{37}N_3O_4 \cdot H_2O$) C, H; N: calcd, 7.87; found, 7.40.

D-(+)-*N*-Acetyl-α-methylphenylalanine.—By a method analogous to that described for the L-(−) isomer 0.42 g (84.3%) of D-(+)-*N*-acetyl-α-methylphenylalanine was obtained: mp 204–207°; $[\alpha]_{578}^{26}$ +42.7° (*c* 1, abs EtOH). The material was recryst from 33% EtOH to yield an anal. sample: 0.30 g (52.8%); mp 206–207° (lit.[1] mp 200.5–202.5°); $[\alpha]_{578}^{24}$ +44.0° (*c* 1, abs EtOH); uv max (MeOH) 247, 252.5, 258, and 263 mμ (log ε 2.03, 2.19, 2.26, and 6.03); ir consistent; $pH_{1/2}$ 4.95 (50% MeOH). *Anal.* ($C_{12}H_{15}NO_3$) C, H, N, equiv wt.

D-(+)-α-Methylphenylalanine·HCl.—By the method described for the L-(−) isomer 10.0 g (100%) of D-(+)-α-methylphenylalanine·HCl was obtained: mp 217–219°. The anal. material, 0.245 g (49.0%), was obtained by recrystn from Me_2CO–hexane: mp 214–215° (lit.[1] mp 210–214.5° dec); $[\alpha]_{578}^{22}$ +2.1° (*c* 1.2, 1 *N* HCl); uv max (MeOH) 252.5, 258, and 264 mμ (log ε 2.14, 2.21, and 2.10); ir spectrum (Nujol) similar to but differs from that of the L-(−) enantiomorph due to a polymorphic crystalline form. *Anal.* ($C_{10}H_{13}NO_2$·HCl) C, H, Cl, N.

D-(+)-α-Methylphenylalanine.—By the method described for the L-(−) isomer 7.4 g (94.8%) of D-(+)-α-methylphenylalanine was obtained: mp 307–308° dec. This material was recrystd as was the L-(−) enantiomorph to yield 3.55 g (48.0%) of product: mp 315° dec; purity by phase solubility 99.1 ± 0.9%, (abs EtOH), $[\alpha]_{578}^{23}$ +20.6° (*c* 1, H_2O); uv max (MeOH) 247, 252, 258, and 264 mμ (log ε 1.99, 2.15, 2.25, and 2.12); ir spectrum identical with that of L-(+) isomer, ord data in Table I. *Anal.* ($C_{10}H_{13}NO_2$) C, H, N.

DL-α-Methylphenylalanine·HCl.—Equimolar amts (0.88 g, 0.00408 mole) of D-(+)- and L-(−)-α-methylphenylalanine were dissolved in 15 ml of concd HCl and crystd. The yield of rac material was 0.75 g (42.6%): mp 241–244° (lit.[1] mp 241–243°), rac at all wavelengths; uv max (MeOH) 252.5, 258, 264, sh 243, sh 248, and sh 267.5 mμ (log ε 2.15, 2.28, 2.18, 1.88, 2.02, 1.82); ir spectrum identical with that obtained by Stein, *et al.*[8]

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Boos and associates for microanalytical data, to Messrs. A. B. White and R. W. Walker for phase solubility analysis and infrared spectra, respectively, and to Drs. C. C. Porter and J. J. Wittick for pharmacological testing and optical rotatory measurements, respectively.

New Compounds

Some Substituted γ,γ-Pentamethyleneparaconamides

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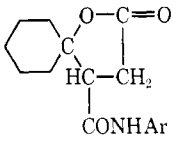
In connection with our interest in pharmacological properties of paraconamide derivatives, we have synthesized some derivatives of γ,γ-pentamethyleneparaconamide. However, none of the compounds described here (Table I) was active when screened for insecticide, fungicide, and herbicide activity. The methods of preparation are adaptations of known procedures.

TABLE I

N-ARYLPARACONAMIDE



No.	Ar	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
1	C_6H_5	195–197	MeOH–H_2O	87.6	$C_{16}H_{19}NO_3$
2	2-ClC_6H_4	118–120	EtOH–H_2O	79.6	$C_{16}H_{18}ClNO_3$
3	4-ClC_6H_4	207–210	MeOH	74.5	$C_{16}H_{18}ClNO_3$
4	α-$C_{10}H_7$	210–211	MeOH	92.9	$C_{20}H_{21}NO_3$
5	β-$C_{10}H_7$	175–176	EtOH	91.6	$C_{20}H_{21}NO_3$

[a] All compds were analyzed for C, H, N.

Experimental Section[1]

γ,γ-Pentamethyleneparaconyl Chloride.—A mixture of 9.9 g (0.05 mole) of γ,γ-pentamethyleneparaconic acid[2] and 10 ml of $SOCl_2$ was refluxed for 6 hr. Excess $SOCl_2$ was removed under diminished pressure, then PhH was added and evapd to dryness. Recrystn of the residue from hexane gave 10.1 g (93.5%) of product, mp 86–87°. *Anal.* ($C_{10}H_{13}ClO_3$) C, H.

General Procedure for Compounds Listed in Table I.—To a soln of the appropriate amine in 10–40 ml of PhH was added a soln of 0.05 mole of acid chloride in 90 ml of PhH at room temp and stirred for an additional hr. The sepd cryst were collected, washed with H_2O, and recrystd to give the pure paraconamides listed in Table I.

(1) All melting points are uncorrected. Microanalyses were performed by Miss Teruko Nisi. The analytical results obtained for the indicated elements are within ±0.3% of the theoretical values.

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Synthesis of 2,3,6-Trimethoxy-β-phenethylamine

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In a recent paper, Matsuhiro and Furst[1] have questioned the identity of 2,3,6-trimethoxy-β-phenethylamine, which was first reported by Merchant and Mountwalla[2] and later by us.[3] The present paper concerns an unequivocal synthesis of this amine which had not previously been reported by us in our investigation of the deamination of polymethoxy-β-phenethylamines by liver monamine oxidase.[3,4]

Experimental Section

2,3,6-Trimethoxyphenylacetonitrile.—A slurry of 100 g (0.47 mole) of 2,3,6-trimethoxybenzoic acid, mp 148–149° (reported,[5] 148–149°), obtained in 61% yield from 1,2,4-trimethoxybenzene by the procedure of Gilman and Thirtle,[5] in 1 l. of dry C_6H_6 was added gradually to a stirred mixt of 38 g (1 mole) of LAH in 1 l. of anhyd Et_2O. The mixt was stirred and heated under reflux for 4 hr, cooled, and decompd with H_2O and dil H_2SO_4. The Et_2O–C_6H_6 layer was sepd, washed with H_2O, dil Na_2CO_3, and H_2O, dried ($MgSO_4$), and filtered. The filtrate was treated with 5 ml of pyridine and 75 ml of $SOCl_2$ was added slowly. The mixt was stirred at room temp for 2 hr and poured into ice–H_2O; the org layer was sepd, washed (H_2O, dil Na_2CO_3, H_2O), dried ($MgSO_4$), and filtered and the solvents were evapd. The residual oily crude chloride was dissolved in 700 ml of Me_2CO and stirred for 28 hr with a soln of KCN in 300 ml of H_2O. The Me_2CO was evapd, and the residue was extd with Et_2O; this ext was washed (H_2O) and dried ($MgSO_4$), the Et_2O was evapd, and the residue distd; bp 128–133° (0.25 mm); yield, 24 g (25%). *Anal.* ($C_{11}H_{13}NO_3$) C, H, N.

2,3,6-Trimethoxy-β-phenethylamine.—A soln of 16 g (0.077 mole) of 2,3,6-trimethoxyphenylacetonitrile in 60 ml of MeOH contg 8.3 g of NH_3 and 10 ml of Raney Ni catalyst slurry were placed in a 300-ml stirring autoclave, which was sealed and pressured to 105 kg/cm² with H_2. The mixt was stirred and heated at 125° for 2 hr and filtered, the MeOH was evapd, and the residue was distd; bp 110–115° (0.4 mm); yield, 13.9 g (86%). A soln of the free base in Et_2O treated with dry HCl gave the HCl salt, mp 122–123° (reported[1] 134–135°), after one crystn from EtOH–EtOAc–Et_2O. After 2 more recrystns from *i*-PrOH–EtOAc (1:3), the HCl salt melted at 131–132° (Fisher block). The tlc (on silica gel (Chroma-Plate 7 G), developed with 1-Bu-

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