2,5-Dimethoxy-4-bromobenzaldehyde.—2,5-Dimethoxybenzaldehyde (66.5 g, 0.4 mole) was dissolved in 300 ml of CH_2Cl_2. Anhyd $SnCl_4$ (115 g, 0.44 mole) was added, followed by 64 g of Br_2 over a 1-hr period. The resulting soln was refluxed for 2 hr and stirred overnight at room temp. The orange suspension was poured over 500 g of ice, and the layers were sepd. The CH_2Cl_2 layer was washed with 10% $NaHCO_3$ and H_2O and dried (Na_2SO_4). After filtration the solvent was removed *in vacuo*, and the solid residue recrystd from MeOH-H_2O to yield 64 g (66%) of the aldehyde, mp 132-3°. *Anal.* ($C_9H_9BrO_3$) C, H.

The structure was confirmed by oxidation with MnO_4^- to 2,5-dimethoxy-4-brombenzoic acid, mp 170° (lit.[14] mp 170°).

Substituted-1-phenyl-2-nitropropenes.—The substituted benzaldehydes were refluxed with $EtNO_2$ and NH_4OAc in AcOH as described by Gairaud and Lappin.[15]

Bromomethoxyamphetamine Hydrochlorides.—All amphetamines were prepared from the corresponding 1-phenyl-2-nitropropenes by LAH reduction.[16]

(14) A. Luttringhaus and H. Gralheer, *Justus Liebigs Ann. Chem.*, **550**, 67 (1941).
(15) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).
(16) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 581.

Nicotinic Acid Esters as Coronary Vasodilators[1]

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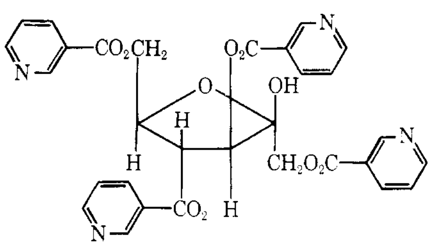
Nicotinic acid and various nicotinates have been shown to possess both coronary and peripheral vasodilating activity.[2,3] One such compound, 1,3,4,6-tetranicotinoylfructofuranose (I), is used clinically in Europe as a peripheral vasodilator.[4]



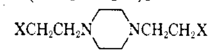
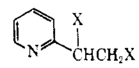
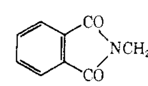
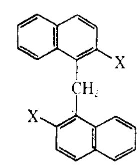
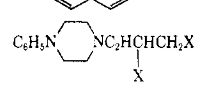
I

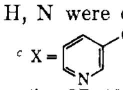
This paper describes the synthesis and pharmacological properties of a number of new mono- and polynicotinates. A wide variety of polyhydroxy compounds was selected for esterification, so that the resulting esters would differ in physicochemical properties such as solubility and rate of hydrolysis. Two of the OH compounds, XIII and XX, used in esterification possess coronary vasodilating activity.

Pharmacology.—In the present study, compounds which caused a 20% increase in coronary sinus blood pO_2 for at least 10 min with minimal effect on blood pressure and heart rate qualified for further testing.

One of the members (IX) of the series of aromatic ethers of polyhydroxy alcohols (II–IX), caused an appreciable rise in pO_2 with very little undesirable effect on heart rate or blood pressure. The effect, however, was highly variable and testing was discontinued. Compound VIII caused a considerable rise in pO_2, but there was excessive increase in blood pressure and heart rate. Of the other compounds listed in Table I, XII and XX were the most promising, but were found to have too short a duration of action. Compound XIV was effective, but too variable to warrant further study.

Table I[a,b]

Compound No.	R	Mp, °C	Recrystn[d] solvent	Formula
	$ROCH_2C(X)HCH_2X$[c]			
II	C_6H_5	88–89	A–B	$C_{21}H_{18}N_2O_5$
III	α(Naphthyl)	92	A–B	$C_{25}H_{20}N_2O_5$
IV	4-ClC_6H_5	92	C–B	$C_{21}H_{17}ClN_2O_5$
V	β-Naphthyl	120	C–B	$C_{25}H_{20}N_2O_5$
VI	4-$CH_3C_6H_5$	83	C–B	$C_{22}H_{20}N_2O_5$
VII	3,4-$Cl_2C_6H_4$	78	C–B	$C_{21}H_{16}Cl_2N_2O_5$
VIII	4-$OCH_3C_6H_4$	59–61	C–D	$C_{22}H_{20}N_2O_6$
IX	3,4-$(CH_3)_2C_6H_3$	76–80	A–B	$C_{23}H_{22}N_2O_5$
	$RN(CH_2CH_2X)_2$			
X	CH_3	56	A	$C_{17}H_{19}N_3O_4$
XI	C_6H_5	70	C–B	$C_{22}H_{21}N_3O_4$
XII	$O(CH_2CH_2X)_2$	63	C–B	$C_{16}H_{16}N_2O_5$
XIII		121	C–B	$C_{20}H_{24}N_4O_4$
XIV		82	A	$C_{19}H_{15}N_3O_4$
	RX			
XV	4-$C_6H_5C_6H_4$	149	A–B	$C_{18}H_{13}NO_2$
XVI	4-$COOCH_3C_6H_4$	103	A	$C_{15}H_{13}NO_4$
XVII	$CH_3N(CH_2)_2$ with $CH_2C_6H_5$	152	C	$C_{16}H_{18}N_2O_2$
XVIII		121	C–B	$C_{16}H_{12}N_2O_4$
XIX		163	E	$C_{33}H_{22}N_2O_4$
XX		68	A–C	$C_{25}H_{26}N_4O_4$

[a] Yields, 21–86%. [b] *Anal.* C, H, N, O or C, H, N were obtained and were in agreement with calcd values. [c] X = 
[d] Recrystn from A, Et_2O; B, $CHCl_3$; C, petr ether (bp 37–48°); D, C_6H_6; E, could not be crystd. Microanal. of crude product.

Experimental Section[5]

All of the polyhydroxy compounds used in esterification were either commercially available or were synthesized according to known procedures. The nicotinates were synthesized by the action of nicotinoyl chloride·HCl on the corresponding alcoholic compounds in the presence of pyridine by the general procedure of Pongratz and Zirm.[6]

General Method of Synthesis of II–XX.—The appropriate alcohol (0.05 mole) was added to a cold mixture of nicotinoyl

(1) Previous papers in this series: (a) D. S. Bariana, *J. Med. Chem.*, **12**, 927 (1969); (b) D. S. Bariana, *ibid.*, **13**, 544 (1970).
(2) H. A. Oelkers, *Arzneim.-Forsch.*, **12**, 1416 (1965).
(3) Z. J. Vajdelek and M. Protiva, *Chem. Listy*, **45**, 448 (1951); *Chem. Abstr.*, **47**, 8067 (1953).
(4) F. Bonati and H. Tiepolo, *Gazz. Med. Ital.*, **121**, 113 (1962).

(5) All melting points were taken with the Thomas-Hoover capillary melting point apparatus. Microanalysis were performed at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Ill. Ir spectra were recorded on a Beckman IR-8 infrared spectrophotometer.
(6) A. Pongratz and K. L. Zirm, *Monatsh. Chem.*, **88**, 330 (1957).

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).

Acknowledgments.—The author wishes to express his appreciation to Dr. T. Darby, Mr. L. Wiemeler, and Mr. C. Shannon of the Pharmacology Department of Abbott Laboratories, North Chicago, Ill., for pharmacological investigations and permission to use their data.

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 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

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.

(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).