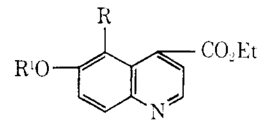
TABLE I

XANTHOQUININIC ACID DERIVATIVES



Compd	R	R′	HCl, salt mp, °C	Formula	Analysis
1	H	H	186–187[a]	$C_{12}H_{11}NO_3$	C, H, N
2	H	H	198–200	$C_{12}H_{12}ClNO_3$	C, H, N
3	Morpholinomethyl	H	153–155	$C_{17}H_{22}Cl_2N_2O_4 \cdot H_2O$	C, H, Cl, N, O
4	Diethylaminomethyl	H	130–132	$C_{17}H_{24}Cl_2N_2O_3 \cdot H_2O$	C, H, Cl, N, O
5	Piperidinomethyl	H	161–163	$C_{18}H_{24}Cl_2N_2O_3 \cdot H_2O$	C, H, Cl, N, O[b]
6	H	2-Diethylaminoethyl	170–171.5	$C_{18}H_{26}Cl_2N_2O_3$	C, H, Cl, N
7	H	2-Dimethylaminoethyl	202–203	$C_{16}H_{22}Cl_2N_2O_3 \cdot H_2O$	C, H, N[c]
8	H	2-Morpholinoethyl	202.5–203.5	$C_{18}H_{24}Cl_2N_2O_4$	C, H, N
9	H	2-Piperidinoethyl	181–183	$C_{19}H_{26}Cl_2N_2O_3$	C, H, N
10	H	3-Diethylaminopropyl	172–175	$C_{19}H_{28}Cl_2N_2O_3$	C, H, N
11	H	2-Diethylaminopropyl	160–162	$C_{19}H_{28}Cl_2N_2O_3$	C, H, N
12	H	2-Dimethylaminopropyl	174–176	$C_{17}H_{24}Cl_2N_2O_3$	C, H, N
13	Br	H	226–228[d]	$C_{12}H_{11}Br_2NO_3$	C, H, Br, N
14	Br	H	190–191[a]	$C_{12}H_{10}BrNO_3$	C, H, Br, N

[a] Free base. [b] Weight loss *in vacuo*, 2 hr at 100° < 1%. Loss at 140°, 4.6%. Calcd for loss of H_2O, 4.4%. [c] Weight loss after 2 hr *in vacuo* at 100° < 1%. Loss at 140°, 4.8%. Calcd for loss of H_2O, 4.75%. [d] HBr salt.

piously with H_2O. There was obtained 82 g, 79% of product, mp 183–185°. On recrystn from EtOH–H_2O, the material had mp 186–187° (lit. mp 185.5°).[3] The HCl salt of the ester was formed by bubbling dry HCl through a soln of the ester in EtOH that had been dild with Et_2O just to cloudiness and then cleared with a few drops of EtOH. It had mp 198–200° dec and was unchanged on recrystn from EtOH–Et_2O.

5-Morpholinomethyl-6-hydroxyquinoline-4-carboxylic Acid, Et Ester·2HCl (3). Experiment 1.—Xanthoquininic acid, Et ester (4.3 g, 0.02 mole) was dissolved in the minim of EtOH at room temp, 1.7 g of 40% formaldehyde soln and 2 g of morpholine were added, and the mixt was refluxed for 1 hr. The reaction mixt was evapd to dryness, the residue dissolved in abs EtOH, and an excess of alc HCl added. Addn of Et_2O to the soln gave a yellow cryst ppt, mp 153–155°. On recrystn of the material from EtOH–Et_2O, the mp spread rose to 151–157°. It was found finally that it was necessary to add a few drops of alc HCl to the recrystn solvents to narrow the mp range, mp 153–155°. The material was dried at 100° to yield 6 g (73%).

6-(2-Diethylaminoethoxy)quinoline-4-carboxylic Acid, Et Ester·2HCl (6).—Freshly cut Na (0.47 g, 0.02 g-atom) was dissolved in abs EtOH. To this soln was added 4.3 g, 0.02 mole, of Et xanthoquininate dissolved in the minim of abs EtOH. With stirring 2.7 g, 0.02 mole, of freshly distd 2-diethylaminoethyl chloride was added dropwise. The mixt was refluxed for 4 hr, cooled, and filtered to remove pptd NaCl. The EtOH was evapd and the residual oil dissolved in Et_2O. The Et_2O soln was extd repeatedly with aq 10% HCl. The aq soln of the dihydrochloride was made basic with 10% NaOH and extd 3 times with 50 ml of Et_2O. The Et_2O soln was dried (Na_2SO_4) and filtered, and the Et_2O stripped. The residual oil was dissolved in abs EtOH and an excess of alc HCl was added. The addn of Et_2O pptd the title compd, which was filtered and dried at 100°. There was obtained 6.3 g, 81% of product with mp 163–169°. Two recrystns from *i*-PrOH–Et_2O, to which 2 drops of alc HCl were added yielded anal. material, mp 170–171.5°.

5-Bromo-6-hydroxyquinoline-4-carboxylic Acid, Et Ester·HBr (13).—Ethyl xanthoquininate (5 g, 0.023 mole) was dissolved in glac AcOH and a soln of Br_2 in glac AcOH was added dropwise with stirring at room temp until the color of Br_2 persisted. The title comp pptd from the AcOH, was filtered off, washed with H_2O, and dried at 100°. There was obtained 7.4 g (85%) of compd, mp 215–220°. After 2 recrystns from EtOAc, the anal. material had mp 226–228° dec.

5-Bromo-6-hydroxyquinoline-4-carboxylic Acid, Et Ester (14).—During one attempt at the purification of **13**, 0.5 g of this material was suspended in 100 ml of H_2O, boiled for 20 min, and filtered hot. The residue, after drying at 100° had mp 185–190°. After 2 recrystns from EtOAc, it had mp 190–191°. This material gave no test for Br^-.

Potential Psychotomimetics. Bromomethoxyamphetamines

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In the study of psychotomimetic amphetamines, 2,5-dimethoxy-4-methylamphetamine (DOM) is the most potent compound yet discovered (50–150 times mescaline).[2] At least part of its potency is related to the nature of the para substituent. In light of Knoll's[3] studies on the psychotomimetic effects of *p*-bromomethamphetamine and its cross-tolerance to LSD, the synthesis and evaluation of bromomethoxyamphetamines appeared to be a logical extension. Br has a comparable size, but different electronic character than Me. Kang and Green[4] have recently demonstrated a correlation between the electronic character of the ring and hallucinogenic potency of methoxylated amphetamines. The substitution of Br into various ring positions of methoxylated amphetamines allows for several electronic arrangements.

Chemistry.—The general synthetic route involved preparation of the appropriately substituted benzaldehydes, condensation with $EtNO_2$, and reduction to the bromomethoxyamphetamines. Tables I and II summarize the compounds which have been prepared.

Attention is called to the report by Pandya and coworkers[5] concerning the bromination of *m*-hydroxybenzaldehyde. The product of this reaction is claimed to be 3-hydroxy-4-bromobenzaldehyde; however, the

(1) NDEA Title IV fellow, 1969–present.

(2) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).

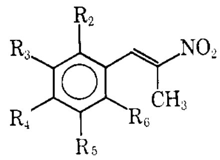
(3) J. Knoll in "Amphetamines and Related Compounds," E. Costa and S. Garattini, Ed., Raven Press, New York, N. Y., 1970, p 761.

(4) S. Kang and J. P. Green, *Nature (London)*, **226**, 645 (1970).

(5) K. C. Pandya, R. B. K. Pandya, and R. N. Singh, *J. Indian Chem. Soc.*, **29**, 363 (1952).

TABLE I

SUBSTITUTED 1-PHENYL-2-NITROPROPENES

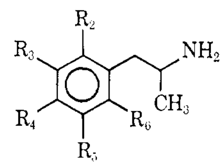


R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula[a]
Br	H	H	OCH_3	H	73–74.5	61.8	$C_{10}H_{10}BrNO_3$
H	Br	OCH_3	H	H	73–74	45	$C_{10}H_{10}BrNO_3$
H	OCH_3	Br	H	H	73–74.5	36.8	$C_{10}H_{10}BrNO_3$
Br	H	OCH_3	OCH_3	H	105–106	59.4	$C_{11}H_{12}BrNO_4$
H	OCH_3	Br	OCH_3	H	121–121.5	46.8	$C_{11}H_{12}BrNO_4$
OCH_3	H	Br	OCH_3	H	113.5–115	57	$C_{11}H_{12}BrNO_4$

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

TABLE II

BROMOMETHOXYAMPHETAMINE HYDROCHLORIDES



Compd	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula[a]
1	Br	H	H	OCH_3	H	151.5–153	20	$C_{10}H_{14}BrNO \cdot HCl$
2	H	Br	OCH_3	H	H	210–213	28.8	$C_{10}H_{14}BrNO \cdot HCl$
3	H	OCH_3	Br	H	H	161.5–163	32	$C_{10}H_{14}BrNO \cdot HCl$
4	Br	H	OCH_3	OCH_3	H	214–215.5	42	$C_{11}H_{16}BrNO \cdot HCl$
5	H	OCH_3	Br	OCH_3	H	221–222	36.8	$C_{11}H_{16}BrNO \cdot HCl$
6	OCH_3	H	Br	OCH_3	H	198–199	29.5	$C_{11}H_{16}BrNO \cdot HCl$

[a] See Table I, footnote *a*.

product which we isolated proved to be 2-bromo-5-hydroxybenzaldehyde. This assignment was verified by nmr spectroscopy and chemical conversion by O-methylation and permanganate oxidation to 2-bromo-5-methoxybenzoic acid. The physical properties of this material agreed with the literature values.[6]

The LAH reduction of 1-(bromomethoxyphenyl)-2-nitropropenes was complicated by the extreme ease of debromination. Low temperatures and equimolar amounts of reagents prevented debromination, but resulted in poor yields of the bromomethoxyamphetamines.

Biological Results.—The compounds were tested for an effect on a conditioned avoidance response in male rats. The detailed procedure has been reported previously.[7] The effects were compared with those produced by mescaline, 3,4-dimethoxyamphetamine, DOM, and the CNS-stimulant dextroamphetamine. This assay gives an indication whether a compound possesses stimulant action or one more like that of mescaline, 3,4-DMA, and DOM. Table III summarizes the biological data. All compounds which exhibited an effect similar to mescaline-type compounds have the *p*-Br substituent.[8] The data on the 2-bromo-5-methoxy analog (**3**) must be considered tentative, since 2,5-dimethoxyamphetamine which does not have a para substituent is active in humans but inactive in rats.[9]

(6) P. H. Beyer, *Recl. Trav. Chim. Pays-Bas*, **40**, 621 (1921).

(7) C. F. Barfknecht, J. M. Miles, and J. L. Leseney, *J. Pharm. Sci.*, **59**, 1842 (1970).

(8) During the revision of this manuscript, Dr. A. T. Shulgin informed us that 4-bromo-2,5-dimethoxyamphetamine has a potency in humans greater than DOM and an effect similar to 3,4-methylenedioxyamphetamine; *Pharmacology*, in press.

(9) J. R. Smythies, *Neurosci. Res. Program Bull.*, **8**, 79 (1970).

A correlation has been demonstrated between the degree of fluorescence and the psychotomimetic potency for methoxylated amphetamines; no such relationship seems to exist for this series.[10] For example, **2** and **6** have nearly the same degree of fluorescence, but differ widely in their biological effects. A detailed study of the pharmacology is in progress.

Experimental Section[11]

Bromomethoxybenzaldehydes.—All substituted benzaldehydes have been reported previously with the exception of 2,5-dimethoxy-4-bromobenzaldehyde and 3,5-dimethoxy-4-bromobenzaldehyde, whose syntheses are described below.

3,5-Dimethoxy-4-bromobenzaldehyde.—3,5-Dihydroxy-4-bromobenzoic acid (K & K Laboratories, Inc.) was di-O-methylated with Me_2SO_4 in the usual manner: yield 78% (EtOH-H_2O); mp 248–250° (lit.[12] 249–50°). The acid chloride was obtained by reaction with $SOCl_2$. The crude product (mp 124–128°) was used in the next step without further purification. The aldehyde was obtained by reduction of the acid chloride by $LiAlH(O\text{-}tert\text{-}Bu)_3$ as described by Ho, *et al.*[13] The crude aldehyde was recrystd from MeOH-H_2O; yield 52%; mp 112–114°. *Anal.* ($C_9H_9BrO_3$) C, H.

TABLE III

BIOLOGICAL RESULTS

Compd	Threshold[a] dose, mg/kg	Action
1	25	Inactive
2	9	CNS stimulation; onset of amphetamine-type toxicity at 18 mg/kg
3	7.5	Mescaline-like
4	25	Inactive
5	<10	Mescaline-like with some deaths at 10; inactive at 5 mg/kg
6	<2.5	Mescaline-like; effect much more profound than that caused by 2.5 mg/kg of DOM

[a] Dose at which action was observed; any compd which does not show a mescaline-like effect at 25 mg/kg (the "effective" dose of mescaline) is considered inactive. The threshold dose of 3,4-dimethoxyamphetamine·HCl and DOM·HCl are 12.5 and 2.5, resp.

(10) F. Antun, J. R. Smythies, F. Benington, R. D. Morin, C. F. Barfknecht, and D. E. Nichols, *Experientia*, in press.

(11) Melting points were taken on a Hoover Uni-Melt apparatus and are corrected. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra for all compounds were obtained on a Varian Associates T-60 and are consistent with the assigned structures.

(12) H. Erdtman and B. Leopold, *Acta Chem. Scand.*, **2**, 34 (1948).

(13) B. T. Ho, W. M. McIssac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert, Jr., and M. B. Noel, *J. Med. Chem.*, **13**, 26 (1970).

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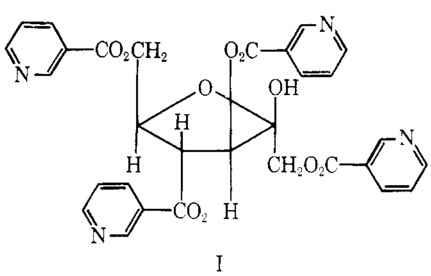
Nicotinic acid and various nicotinates have been shown to possess both coronary and peripheral vasodilating activity.[2,3] One such compound, 1,3,4,6-tetranicotinoylfructofuranose (I), is used clinically in Europe as a peripheral vasodilator.[4]



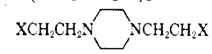
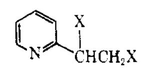
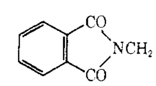
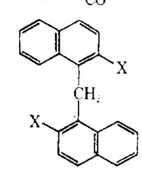
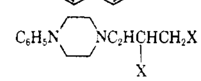
I

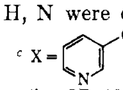
This paper describes the synthesis and pharmacological properties of a number of new mono- and polynicotinates. A wide variety of polyhydroxy compounds was selected for esterification, so that the resulting esters would differ in physicochemical properties such as solubility and rate of hydrolysis. Two 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	$4\text{-}ClC_6H_5$	92	C–B	$C_{21}H_{17}ClN_2O_5$
V	β-Naphthyl	120	C–B	$C_{25}H_{20}N_2O_5$
VI	$4\text{-}CH_3C_6H_5$	83	C–B	$C_{22}H_{20}N_2O_5$
VII	$3,4\text{-}Cl_2C_6H_4$	78	C–B	$C_{21}H_{16}Cl_2N_2O_5$
VIII	$4\text{-}OCH_3C_6H_4$	59–61	C–D	$C_{22}H_{20}N_2O_6$
IX	$3,4\text{-}(CH_3)_2C_6H_3$	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	$4\text{-}C_6H_5C_6H_4$	149	A–B	$C_{18}H_{13}NO_2$
XVI	$4\text{-}COOCH_3C_6H_4$	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).