HCl. The product (0.17 g, 60%) was recryst'd from *i*-PrOH, mp 300–304° dec. *Anal.* ($C_7H_{14}N_5O_2Cl$) C, H, N, Cl.

6-Chloro-9-(ethoxymethyl)purine.—To a suspension of 3.85 g (25.0 mmoles) of 6-chloropurine in 75 ml of DMF contg 8.0 ml (55.0 mmoles) of Et_3N was added 2.50 g (27.5 mmoles) of chloromethyl ethyl ether. After stirring the reaction mixt for 36 hr at 55–60°, it was cooled in ice and filtered. The filtrate was concd *in vacuo* to give a syrup which was chromatographed on 150.0 g of silica gel (200 mesh, column 3.0 cm i.d.) with a solvent of $CHCl_3$–MeOH (9.5:1) to give the crude product; yield, 3.12 g (56.3%), mp 72–75°. The analytical product was obtained by recrystg the crude material from Et_2O; yield, 2.26 g (40.8%); mp 79–81°. *Anal.* ($C_8H_9ClN_4O$) C, H, Cl, N.

9-Ethoxymethyladenine.—A soln of 0.64 g (3.0 mmoles) of 6-chloro-9-(ethoxymethyl)purine in 35.0 ml of 25% MeOH–NH_3 was heated at 60–70° for 18 hr in a bomb. The reaction mixt was evapd to dryness and the residue was extd with hot Me_2CO (2 × 15 ml). The Me_2CO ext was evapd *in vacuo* to give the crude product; yield 0.53 g (91.4%); mp 184–188°. One recrystn from Me_2CO and one from MeOH gave the pure product; yield, 0.49 g (84.5%); mp 190–192° (188° softens). *Anal.* ($C_8H_{11}N_5O$) C, H, N.

Reagents and Assay Procedures.—Adenosine deaminase (Type I, calf intestinal mucosa) was purchased from the Sigma Chemical Co. The enzyme experiments were performed at pH 7.6 in 0.05 *M* phosphate buffer at 25°. The K_m was determined by the procedure of Lineweaver and Burk.[6] The assay for the study of reversible inhibitors has previously been described[2a] and is a modification of the procedure of Kaplan[7] based on the work of Kalckar.[8]

(6) H. Lineweaver and D. Burk, *J. Amer. Chem. Soc.*, **56**, 658 (1934).
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Xanthoquininic Acid Derivatives

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Some 4-aminoquinolines have a high activity in the treatment of bronchial asthma[1a–c] and malaria, as well as having antiarrhythmic[2a–c] properties. Compound I, R = CH_3, X = 2, has antiasthmatic, antihistaminic, and antiarrhythmic activity but no antimalarial activity, whereas I, X = CCCC(C), R = C_2H_5, and chloroquine have good antimalarial activity. The latter also has antiasthmatic and antiarrhythmic activity. Thus as part of an earlier study we were interested in the modification of the quinoline nucleus to produce compds of type IIc and IId.

The starting point in our synthesis was quininic acid (IIa) which was demethylated to xanthoquininic acid IIb[3] and converted into its Et ester. This phenol was then subjected to the Mannich reaction to produce the 5-substituted derivs of type IIc. The 6-dialkyaminoalkoxy derivs IId were prepared from the Na salt of the phenol with the appropriate dialkylaminoalkyl halides.

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(2) (a) D. M. Aviado, private communication, 1968. (b) M. A. Silver and D. M. Aviado, *Exp. Parasitol.*, **24**, 152 (1969). (c) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).
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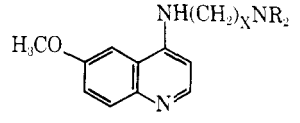
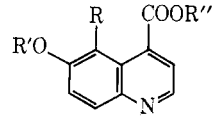
During this work we treated 6-hydroxyquinoline-4-carboxylic acid Et ester with Br in AcOH. This readily



I

a, R = R″ = H; R′ = CH_3
b, R = R′ = H



II

c, R = secondary amino CH_2; R′ = H; R″ = C_2H_5
d, R = H; R′ = dialkylaminoalkyl; R″ = C_2H_5

introduced one Br atom and the product pptd out as the bromide·HBr. When boiled in H_2O this compd lost HBr and gave the free base. Introduction of the Br atom at the 5 position was confirmed by the pmr spectrum which exhibited two AB quartets in the aromatic region with $J_{2,3}$ = 4.3 Hz and $J_{7,8}$ = 9.2 Hz consistent with other quinoline derivatives.[4]

All compds prepared are listed in Table I. When evaluated for antiarrhythmic,[2a–c] antimalarial,[5] and antiasthmatic[1a–c] activity none of the compds showed any appreciable activity.

Experimental Section

Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points of hydrates were taken on a Fisher-Johns block, those of nonhydrates in a Thomas-Hoover capillary type apparatus. Melting points are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

6-Hydroxyquinoline-4-carboxylic Acid, Xanthoquininic Acid.—Quininic acid (6-methoxyquinoline-4-carboxylic acid, mp 275–278°, 101.6 g, 0.5 mole) was refluxed in 300 ml of HI, sp gr 1.7, for 12 hr. The reflux mixt was concd to 0.5 its vol, dild several times its vol with H_2O, made alk with 10% NaOH, treated with Norit A, and filtered. With stirring and cooling, the filtrate was made slightly acid with AcOH. Crystn started and was completed on standing in the refrigerator overnight. The pale yellow material was filtered, resuspended in H_2O, boiled for a few min, and filtered hot. The microcryst residue (88 g, 93%) was nearly colorless, mp 339–342° dec (lit. mp 320° dec.)[3] On recrystn from DMF–H_2O, or redissolving in alk and repptg with AcOH, a colorless product was obtained which decompd at 340–342°. If placed in the oil bath at 300° decompn points as high as 347–348° were obtained. *Anal.* Calcd for $C_{10}H_7NO_3$: C, H, N.

6-Hydroxyquinoline-4-carboxylic Acid, Et Ester.—Xanthoquinic acid (94.5 g, 0.4 mole) was placed in a 1-l. flask, and a mixt of 450 ml of abs EtOH and 50 ml of concd H_2SO_4 was added. The whole was refluxed for 8 hr, most of the EtOH was removed at the aspirator, and the viscous dark red-brown mixt was poured with stirring into 1 l. of ice H_2O. With cooling and stirring, the mixt was neturalized with 20% NaOH and placed in the refrigerator overnight. The pale yellow ppt was filtered and washed co-

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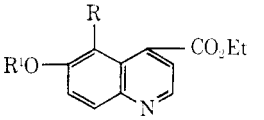
TABLE I
XANTHOQUININIC ACID DERIVATIVES



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

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