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Structural Modification of Febrifugine. Some Methylenedioxy Analogs[1]

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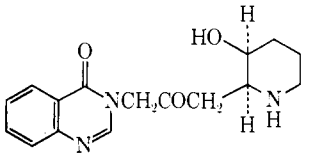
Some methylenedioxy analogs of febrifugine and related compounds have been synthesized. They were found to be active against *Plasmodium berghei*. Their toxicity in mice is much lower than that of febrifugine. The therapeutic indices of these compounds are comparable with those of the parent compound.

The emetic property[2-4] associated with febrifugine (I) has limited its potential usefulness as a chemotherapeutic agent against malaria.[5] Suitable structural modification of this compound may reduce its undesired toxic effect. Some synthetic work in this series has been described.[6-9] Side-chain modification of febrifugine had not been found fruitful;[6-10] on the other hand, mono- or disubstitution by certain groups on the quinazoline ring system, particularly at positions 5, 6, and 7, resulted in increased antimalarial activity and, in some cases, also increased the chemotherapeutic index.



I

The methylenedioxyphenyl group, an important moiety frequently found in natural products, has been reported to possess some interesting biological activities.[11-24] For example, higher antimalarial activity and lower toxicity are noted with 3-piperonylsydnones when compared with its analogous alkoxy derivatives.[25] Some psychotropic phenylisopropylamines are methylenedioxy derivatives.[26,27] The enhancement of biological activity is believed to be due to inhibition of *in vivo* drug metabolism through interference with biological oxidation of the effective agents by either inhibition of hydroxylation or hydride transfer.[20,28-33] This also explains the prolongation of hexobarbital-induced sleeping time in animals by methylenedioxyphenyl derivatives.[34] Based on this information, the preparation of the 5,6-, the 6,7-, and the 7,8-methylenedioxy derivatives of febrifugine and related compounds was undertaken.

The synthesis of the 6,7- and 7,8-methylenedioxy analogs Vb and Vd was carried out according to the following scheme (see Experimental Section).

Preparation of the 5,6-methylenedioxy analog Ve was carried out as follows. Nitration of 2,3-methylenedioxybenzaldehyde[35] (VI) gave a mixture of 2,3-methylenedioxy-6-nitrobenzaldehyde (VII) and the corresponding 5-nitro isomer VIII in a ratio of 2:1, as estimated by nmr. These isomers can be separated by fractional recrystallization from either Me_2O or MeOH. A more facile separation of the isomers in MeOH can be achieved in the next stage, wherein the aldehydes were oxidized to the corresponding acids (IX and X) by permanganate. 2,3-Methylenedioxy-6-nitrobenzoic acid (IX), which is much more soluble in MeOH than the corresponding 5-nitrobenzoic acid (X), was thus isolated and esterified to give XIa. Catalytic reduction of XIa

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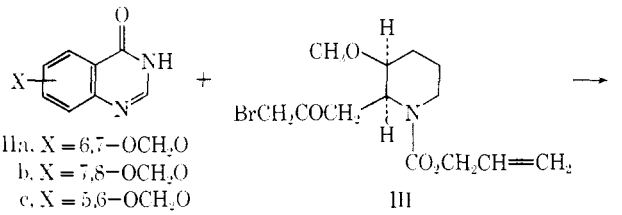
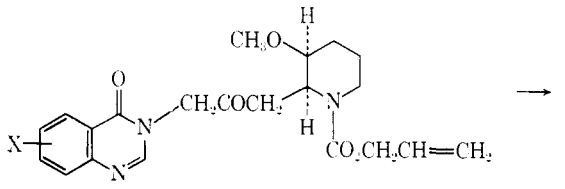
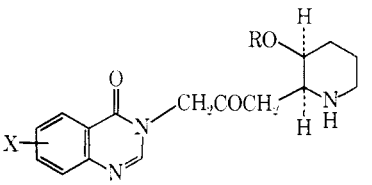


IIa, X = 6,7–OCH_2O
b, X = 7,8–OCH_2O
c, X = 5,6–OCH_2O

III

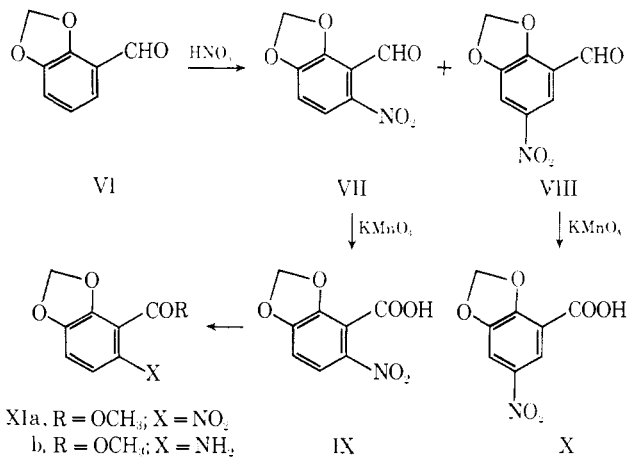


IVa, X = 6,7–OCH_2O
b, X = 7,8–OCH_2O
c, X = 5,6–OCH_2O



Va, X = 6,7–OCH_2O; R = CH_3
b, X = 6,7–OCH_2O; R = H
c, X = 7,8–OCH_2O; R = CH_3
d, X = 7,8–OCH_2O; R = H
e, X = 5,6–OCH_2O; R = CH_3

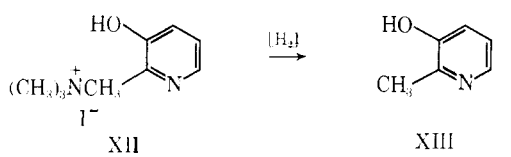
yielded methyl 2-amino-5,6-methylenedioxybenzoate (XIb). The latter was heated with $HCONH_2$ or a mixture of $HCONH_2$ and HCOOH to form the intermediate 5,6-methylenedioxy-4-quinazolone (IIc), albeit in low yield. The Me ether of 5,6-methylenedioxyfebrifugine (Ve) was prepared from IIc and III in the same fashion as described for the other two isomers.



VI VII VIII

XIa, R = OCH_3; X = NO_2
b, R = OCH_3; X = NH_2 IX X

The side-chain intermediate α-bromo ketone III was prepared by the method of Baker and McEvoy[6] except that one of its intermediates, 3-hydroxy-α-picoline (XIII), was obtained by hydrogenolysis of *N*-(3-



XII XIII

hydroxy-2-picolyl)trimethylammonium iodide (XII) rather than by the action of NH_4OH on 2-acetofuran at high temperature under pressure, as reported by these investigators.[6]

Table I
Test Results of Febrifugine and Febrifugine Analogs against *Plasmodium berghei* in Mice[a,b]

Compd	Sex	Dose (mg/kg)	Mean survival time (days) Treated	Control
I	M	0.63	6.9	6.1
	M	1.25	6.9	6.1
	M	2.50	9.1	6.1
	M	5.00	10.4	6.1
	M	10	12.4	6.1
	M	20	14.3	6.1
	F	0.63	6.8	6.2
	F	1.25	7.1	6.2
	F	2.50	8.3	6.2
	F	5.00	10.5	6.2
	F	10	12.3	6.2
	F	20	15.0	6.2
Va	M	10	6.8	6.2
	M	20	7.6	6.2
	M	40	7.8	6.2
	M	80	9.0	6.2
	M	160	10.6	6.2
	M	320	13.6	6.2
	F	40	7.4	6.2
	F	160	9.8	6.2
	F	640		6.2
Vb	F	5	7.4	6.1
	F	10	7.4	6.1
	F	20	10.6	6.1
	F	40	10.8	6.1
	F	80		6.1
Ve	F	10	6.4	6.1
	F	20	6.5	6.1
	F	40	6.6	6.1
	F	80	9.5	6.1
	F	160	10.9	6.1
	F	320	12.0	6.1
	F	640		6.1
Vd	F	10	6.4	6.1
	F	20	7.2	6.1
	F	40	10.0	6.1
	F	80	13.0	6.1
	F	160	15.0	6.1
	F	320	16.0	6.1
Ve	F	10	7.6	6.2
	F	20	7.9	6.2
	F	40	11.1	6.2
	F	80	12.0	6.2
	F	160	14.0	6.2
	F	320		6.2

[a] Test results were obtained by Dr. Leo Rane, University of Miami School of Medicine (Contract DA-49-193-MD-2218), and provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. [b] Mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical (subcutaneously in oil) at each dose level.

Test results of methylenedioxy analogs of febrifugine and the Me ethers against *P. berghei* are listed in Table I. For comparison, test results of febrifugine against the same system are also included. Toxic deaths[36] were observed at 10 mg/kg for febrifugine (I). On the other hand, no toxic deaths were encountered with doses of 320 mg/kg for Va, 40 mg/kg for Vb, 160 mg/kg for Ve, 20 mg/kg for Vd, and 80 mg/kg for Ve. The

(36) Deaths occurring on days 2–5 after infection are attributed to drug action and counted as "toxic deaths." Control animals do not die before day 6.

toxicity of the methylenedioxy compounds are indeed much lower than that of febrifugine but the therapeutic indices remained about the same. Because the activity pattern of the free alcohol and the Me ether in the other two isomer pairs are nearly identical, no further effort was made to cleave the Me ether Ve to yield 5,6-methylenedioxyfebrifugine.

Experimental Section

All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The uv absorption spectra were determined with a Beckman DK-2 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

6,7-Methylenedioxy-4-quinazolone (IIa).—A mixture of 9.75 g (0.05 mole) of methyl 2-amino-4,5-methylenedioxybenzoate[37] and 50 ml of $HCONH_2$ was heated at 100–110° for 1 hr and then at 190–195° for 0.5 hr. The precipitate, which formed on cooling, was collected by filtration and washed with MeOH to yield 6.3 g of crude product. The filtrate was diluted with 300 ml of H_2O whereupon additional 0.7 g of solid was obtained. The combined product was recrystallized from DMF to give 3.1 g (33%) of pure IIa as white crystals: mp 317–319° dec; λ_{max}^{EtOH} 236 (ε 48,000), 286 (48,000), 311 (5700), and 325 mμ (5400). *Anal.* ($C_9H_6N_2O_3$) C, H, N.

3-[2-Oxo-3-*cis*-(1-carboallyloxy-3-methoxy-2-piperidyl)propyl]-6,7-methylenedioxy-4-quinazolone (IVa).—This compound was prepared from 9.5 g (0.05 mole) of IIa and 0.05 mole of III by essentially the same procedure as described for the preparation of the corresponding febrifugine intermediate.[6] Recrystallization of the crude product (mp 147–153° dec) from EtOH gave 8.0 g (33%) of IVa·HCl as white solid, mp 154–156° dec. Absorption bands of spectra (uv, ir) were as expected. *Anal.* ($C_{22}H_{29}N_3O_7 \cdot HCl$) C, H, N, Cl^-.

3-[2-Oxo-3-*cis*-(3-methoxy-2-piperidyl)propyl]-6,7-methylenedioxy-4-quinazolone (Va)·2HCl.—The product was obtained in 80% yield by boiling 9 g (0.019 mole) of IVa with 100 ml of 6 *N* HCl as described for the corresponding febrifugine intermediate,[6] mp 225–227° dec. *Anal.* ($C_{18}H_{21}N_3O_5 \cdot 2HCl$) C, H, N, Cl^-.

3-[2-Oxo-3-*cis*-(3-hydroxy-2-piperidyl)propyl]-6,7-methylenedioxy-4-quinazolone (Vb)·2HCl.—A mixture of 6.3 g (0.0146 mole) of Va·2HCl was heated with 60 ml of 48% HBr at 135° for 20 min. The solution was evaporated to dryness under reduced pressure and evaporation was repeated after addition of 30 ml of EtOH. The residue was boiled briefly with 10 ml of EtOH saturated with dry HCl. The resulting solid was collected by filtration and recrystd from MeOH to give 4.3 g (70%) of white crystals, mp 228–231° dec. Absorption bands of spectra (uv, ir) were as expected. *Anal.* ($C_{17}H_{19}N_3O_5 \cdot 2HCl$) C, H, N, Cl^-.

7,8-Methylenedioxy-4-quinazolone (IIb).—A mixture of 5.85 g (0.03 mole) of methyl 2-amino-3,4-methylenedioxybenzoate[38] and 55 ml of $HCONH_2$ was heated, with stirring, at 130–140° for 1 hr, 140–170° for 1 hr and finally at 170–175° for 2 hr. Separation of some solids was noted at the end of this period. The reaction mixture was poured into 600 ml of H_2O. The resulting precipitate was collected by filtration, washed with H_2O, and dried in air to give 4.6 g (81%) of product, mp 325–330° dec. An analytical sample was prepared by recrystallization from DMF to yield off-white solid: mp 329–333° dec; λ_{max}^{EtOH} 251 (ε 38,000), 311 mμ (4200). *Anal.* ($C_9H_6N_2O_3$) C, H, N.

3-[2-Oxo-3-*cis*-(3-methoxy-2-piperidyl)propyl]-7,8-methylenedioxy-4-quinazolone (Vc)·HCl.—The condensation of IIb with III to yield IVb was carried out as described for its 6,7-isomer IVa. Hydrolysis of IVb with 6 *N* HCl gave 2.3 g of Vc as off-white solid, mp 185–195° dec, believed to be the unstable dihydrochloride. On further recrystallizations, the monohydrochloride was obtained as white crystals, mp 247–249° dec. *Anal.* ($C_{18}H_{21}N_3O_5 \cdot HCl$) C, H, N, Cl^-.

3-[2-Oxo-3-*cis*-(3-hydroxy-2-piperidyl)propyl]-7,8-methylenedioxy-4-quinazolone (Vd)·2HCl.—A mixture of 2 g of Vc·HCl and 20 ml of 48% HBr was heated at 130–140° for 20 min. It was evaporated to dryness under reduced pressure. The residue was treated with concentrated HCl and again was evaporated to dryness. The residue was twice recrystallized from EtOH to give 0.8 g (38%) of white crystals, mp 235–237°. *Anal.* ($C_{17}H_{19}N_3O_5 \cdot 2HCl$) C, H, N.

2,3-Methylenedioxy-6-nitrobenzaldehyde (VII) and 2,3-Methylenedioxy-5-nitrobenzaldehyde (VIII).—A mixture of 60.7 g (0.44 mole) of 2,3-dihydroxybenzaldehyde,[39,40] 92 g (0.53 mole) of CH_2Br_2, 62 g (0.45 mole) of anhyd K_2CO_3, and 4 g of CuO[41] was heated in 400 ml of DMF at 125–130° under N_2 for 2 hr. The solids were removed by filtration and were washed with MeOH. The combined filtrate was diluted with 1.3 l. of H_2O and extracted with a total of 1 l. of $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. On distillation *in vacuo*, 41.7 g (63%) of 2,3-methylenedioxybenzaldehyde (VI) was collected as yellow liquid, bp 68–70° (0.05 mm), lit.[35] mp 34°.

To 150 ml of concentrated HNO_3 was added, with stirring and cooling (ice bath), 16.5 g (0.11 mole) of VI in 10 min. Stirring was continued for another 10 min and the reaction mixture was poured into 700 ml of H_2O. The precipitated crude product was collected by filtration. It was recrystallized 3 times from Me_2CO to give 4.5 g (21%) of VII as yellow needles, mp 144–145°. Its nmr spectrum ($CDCl_3$) exhibits two singlets at τ 3.67 (2 H) and −0.42 (1 H), and two doublets centered at 2.97 and 2.10, respectively (1 H each; J = 9 cps). *Anal.* ($C_8H_5NO_5$) C, H, N.

From the mother liquor the other isomer VIII was isolated. It was purified by recrystallization (Me_2CO) to give yellow needles: mp 150–151°; nmr τ 3.58 (s 2 H); 2.10 (d 1 H, J = 2 cps), 1.58 (d, 1 H, J = 2 cps) and −0.27 (s, 1 H). *Anal.* ($C_8H_5NO_5$) C, H, N.

2,3-Methylenedioxy-6-nitrobenzoic Acid (IX) and 2,3-Methylenedioxy-5-nitrobenzoic Acid (X).—To a hot solution of 7.9 g (0.05 mole) of $KMnO_4$ in 200 ml of H_2O was added 5.85 g (0.03 mole) of VII in 150 ml of Me_2CO in 20 min. Me_2CO was then distilled on a H_2O bath. The residual aq suspension was heated on a steam bath for 20 min and filtered and the filter cake was thoroughly washed with H_2O. The combined filtrate was acidified with HCl to give 6.0 g (95%) of IX, mp 183–186°. It was purified by recrystallization from aq MeOH or Me_2CO–Skelly F as yellow crystals, mp 188–189°. *Anal.* ($C_8H_5NO_6$) C, H, N.

The 5-nitro isomer X was prepared in a similar manner. It could also be obtained by oxidation of the crude nitration products of 2,3-methylenedioxybenzaldehyde followed by trituration of the oxidation products with MeOH, wherein X is much less soluble than IX. X crystallized from MeOH as yellow needles, mp 204–206°. *Anal.* ($C_8H_5NO_6$) C, H, N.

Methyl 2,3-Methylenedioxy-6-nitrobenzoate (XIa).—A mixture of 10.6 g (0.05 mole) of IX and 20 ml of $SOCl_2$ was heated in 120 ml of $CHCl_3$ under reflux for 30 min. The clear solution was then evaporated to a syrup under reduced pressure. It was treated with 50 ml of MeOH and the mixture was allowed to stand at room temperature for 30 min before it was evaporated. The solid residue thus obtained was recrystallized from MeOH to give 9.02 g (80%) of XIa as yellow needles, mp 97–99°. *Anal.* ($C_9H_7NO_6$) C, H, N.

Methyl 2,3-Methylenedioxy-6-aminobenzoate (XIb).—A solution of 5.63 g (0.025 mole) of XIa in 120 ml of EtOH was shaken under H_2 in the presence of 10% Pd–C for 1 hr in a Parr hydrogenator. The catalyst was filtered and the solution evaporated to dryness to leave a yellow solid. Two recrystallizations from MeOH gave 3.41 g (70%) of XIb as yellow needles, mp 104–106°. *Anal.* ($C_9H_9NO_4$) C, H, N.

5,6-Methylenedioxy-4-quinazolone (IIc).—A mixture of 5.85 g (0.03 mole) of XIb, 10 ml of 90% HCO_2H, and 25 ml of $HCONH_2$ was heated, with stirring, at 125–135° for 1 hr, then at 130–185° for 1 hr, and finally for 3 hr at 185–190°. The mixture was poured into 400 ml of H_2O. The resulting precipitate was collected by filtration, washed with H_2O, and dried. The crude product was recrystallized from DMF–MeOH to give 0.34 g (6%) of pure IIc as off-white crystals, mp 279–281° dec. Repeated runs gave yields in this reaction ranging from 5 to 10%. *Anal.* ($C_9H_6N_2O_3$) C, H, N.

3-[2-Oxo-3-*cis*-(1-carboallyloxy-3-methoxy-2-piperidyl)-propyl]5,6-methylenedioxy-4-quinazolone (IVc).—This com-

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(41) M. Tomita and Y. Aoyagi, *Chem. Pharm. Bull. (Tokyo)*, **16**, 523 (1968).

pound was prepared from 3.8 g (0.02 mole) of IIe and 0.02 mole of III by essentially the same procedure as described for the preparation of IVa. Recrystallization from abs EtOH gave 3.65 g (38%) of IVe: mp 168–171°; λ_{max}^{EtOH} 226 (ε 29,000), 291 (7000), and 342 mμ (5300). *Anal.* ($C_{22}H_{26}ClN_3O_7$) C, H, N, Cl^-.

3-[2-Oxo-3-*cis*-(3-methoxy-2-piperidyl)propyl]-5,6-methylenedioxy-4-quinazolone (Ve).—A mixture of 2.40 g (0.005 mole) of IVe and 50 ml of 6 *N* HCl was boiled for 1 hr. The mixture was evaporated to dryness on a steam bath under reduced pressure. After addition of abs EtOH the residue was again evaporated to dryness. The solid product thus obtained was triturated with EtOH and filtered to give 2.0 g (95% yield) of white crystals, mp 207–210°. Further recrystallization with the addition of dry HCl yielded Ve as its dihydrochloride, mp 212–214° dec. Absorption bands of spectra (nmr, ir) were as expected. *Anal.* ($C_{18}H_{21}N_3O_5 \cdot 2HCl$) C, H, N, Cl^-. When no additional HCl was introduced during recrystallization, the final product was found to be a monohydrochloride. *Anal.* ($C_{18}H_{21}N_3O_5 \cdot HCl$) C, H, N, Cl^-.

3-Hydroxy-α-picoline (XIII).—To a solution of 106.4 g (0.17 mole) of 2-dimethylaminomethyl-3-hydroxypyridine[42] in 300 ml of Me_2CO was slowly added, with stirring, 99.4 g (0.7 mole) of MeI. The reaction mixture was cooled in an iced H_2O bath to keep the temperature of the reaction mixture below 30°. The quaternary ammonium salt XII started to precipitate in 1 hr. After the mixture was allowed to stand overnight at room temperature, the solid was collected by filtration to give 198 g of *N*-(3-hydroxy-2-picolyl)trimethylammonium iodide (XII) as white crystals, mp 150–160° dec. It was used for the following hydrogenation reaction without further purification.

A solution of 58.8 g (0.2 mole) of XII in 200 ml of 5% NaOH was hydrogenated in the presence of 0.6–0.7 g of 10% Pd–C. The absorption of 1 equiv of H_2 was completed within 5 hr. The catalyst was filtered and the filtrate was first made acidic with AcOH, then brought to pH 8–9 with NH_4OH. The solution was concentrated to a small volume. The resulting precipitate was collected by filtration, washed with H_2O, and dried in air. The average yield of more than 20 runs was 9.8 g (45%), mp 165–167°. Recrystallization from EtOAc gave 3-hydroxy-α-picoline as white crystals, mp 168.5–169.5°, lit. mp 163–165°,[42] 167–168°.[43] *Anal.* (C_6H_7NO) C, H, N.

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Structure and Anticoccidial Activity among Some 4-Hydroxyquinolinecarboxylates

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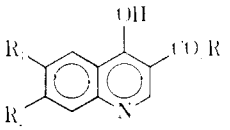
Structure requirements for anticoccidial activity have been elucidated for a series of 4-hydroxyquinoline-3-carboxylates.

Recent publications[1] have revealed that certain 6,7-disubstituted-4-hydroxy-3-quinolinecarboxylate esters are highly effective against a broad spectrum of coccidia. The most effective drugs in present use are **1**, **2**, and **3**, with **2** and **3** being the most potent.



1 (Buquinolate), R_1, R_2 = *i*-BuO; R_3 = Et

2 (Decoquinate), R_1 = $C_{10}H_{21}O$; R_2, R_3 = EtO

3 (Methylbenzoquate), R_1 = *n*-Bu; R_2 = $PhCH_2O$; R_3 = Me

Certain structure–activity relationships are apparent from published results.

(1) **R_1 = R_2 = Alkoxy.**—Maximum activity is obtained at about C_4 with rapid fall-off beyond. Branched-chain aliphatics are more effective than straight-chain.

(2) **R_1, R_2 = Alkoxy ($R_1 \neq R_2$).**—Nonidentical aliphatic ether groups in general confer higher anticoccidial potency. Activity seems to peak where R_1 is (C_8-C_{14})-O and R_2 is lower alkoxy.

(3) **R_1 = Alkyl; R_2 = Benzyloxy.**—High activity results for R_1 = Bu. Potency drops off where $R_1 < C_4H_9$.

(4) **Substitution in the 6 and 7 positions** seems to be essential for superior activity.

Our longtime interest in this class of compounds originated in connection with another problem. Applications of a lead developed in another series[2] gave ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate (cyproquinidate), an active coccidiostat.[3] The high biological activity of this substance prompted a comprehensive study to include compounds of types **4–7**.

The preparation of **4** and **5** was carried out in a conventional manner as shown in Scheme I.

Compounds of type **6** were prepared from *m*-acyloxyacetanilide (Scheme II) and **7** resulted by application of the same synthetic sequence to the *p*-acyloxyacetanilide.

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