one (75), 12.2 g of hydroxylamine·HCl, 97.6 ml of 10% NaOH, and 290 ml of EtOH was refluxed for 15 min. The reaction mixt was poured into 1.25 l. of water to yield 5.05 g (100%) of 84.

U. Reduction of the *p*-Nitrobenzylidenedioxy Group to the *p*-Aminobenzylidenedioxy Group.[27] 14α,17α-Aminobenzylidenedioxypregn-4-ene-3,20-dione (29). A mixt of 31.5 g of 14α,17α-*p*-nitrobenzylidenedioxypregn-4-ene-3,20-dione (28), 1.2 l. of PhH, and 300 g of Fe (activated with HCl) was refluxed and ten 6-ml portions of water were added in the course of 5 hr. The mixt was stirred for another 2 hr and filtered. The filtrate was washed with water and evapd *in vacuo*. The oily residue (32 g) was crystd from 80 ml of PhH to yield 19.5 g (66%) of 29.

V. Acylation of the *p*-Aminobenzylidenedioxy Group. 14α,17α-[*p*-(*N*-Chloroacetylamino)benzylidenedioxy]pregn-4-ene-3,20-dione (30). To a soln of 3 g of 14α,17α-*p*-aminobenzylidenedioxypregn-4-ene-3,20-dione (29) in 27 ml of 1,2-dichloroethane and 1.5 ml of ethyldiisopropylamine a mixt of 0.85 ml of chloroacetyl chloride and 2.5 ml of 1,2-dichloroethane was added dropwise at 0°. After 45 min, the reaction mixt was dild with 1,2-dichloroethane, washed with NaOH soln, H_2SO_4 soln, and water, and evapd *in vacuo*. The residue was chromatographed on silica gel with PhH-Me_2O, 9:1. By evapn of the appropriate fractions and crystn from Et_2O 2.55 g (72.7%) of 30 was obtained. In a similar way the *N*-bromoacetyl compound (31) was prepd with bromoacetyl chloride.

W. Hydrolysis of 3'-Methoxycarbonylpropylidenedioxy Group. 14α,17α-(3'-Carboxypropylidenedioxy)pregn-4-ene-3,20-dione (17). A mixt of 1 g of 14α,17α-(3'-methoxycarbonylpropylidenedioxy)-pregn-4-ene-3,20-dione (16), 8 ml of EtOH, and 2 ml of 10% NaOH was refluxed for 0.5 hr. The mixt was cooled, dild with water, and acidified to pH 2 with HCl. The cryst product was filtered and recrystd several times from MeOH–water and once from $CHCl_3$–heptane to yield 0.20 g (20.7%) of 17.

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5-Hydroxy-3-piperidylidenemethane Derivatives as Spasmolytics

Mitsutaka Kawazu,* Takeshi Kanno, Seiichi Saito, and Hajime Tamaki

Research Laboratories, Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan. *Received January 5, 1972*

N-Methyl-3-piperidylidenedithienylmethane methobromide (VIII) was found to be as potent a spasmolytic agent as atropine. In order to search for active compounds with lessened anticholinergic side effects (dryness of mouth, mydriasis), some 5-hydroxy, acyloxy, and methoxy derivatives of VIII were synthesized. (The results of the comparative studies *in vitro* on those compounds are discussed.) As a result of the *in vivo* test, *N*-methyl-5-methoxy-3-piperidylidenedithienylmethane methobromide (VIIIb) proved to be an excellent spasmolytic and its side effects were considerably weaker than those of the parent compound (VIII).

Although a number of anticholinergic agents have been synthesized, the continued use of atropine in spite of its unpleasant side effects seems to indicate that the available synthetic drugs are not entirely satisfactory. One of the drawbacks is undoubtedly due to their poor absorbability from the intestinal tract, a characteristic of quaternary ammonium compounds. In order to obtain a sufficient response by oral administration relatively high doses are required, whereas an adequate potency is obtained at low doses by injection. The problem of the poor absorption may have

been solved in the case of some tropan esters. However, the other major drawback, namely the anticholinergic side effects such as dryness of mouth and mydriasis, hardly could be eliminated while their spasmolytic activity was nearly equivalent to that of atropine.[1]

Although it appears extremely difficult to remove both drawbacks simultaneously and perhaps impossible to completely eliminate the side effects without any loss of activity, we may still be able to find drugs with an improved therapeutic index by structural modification.

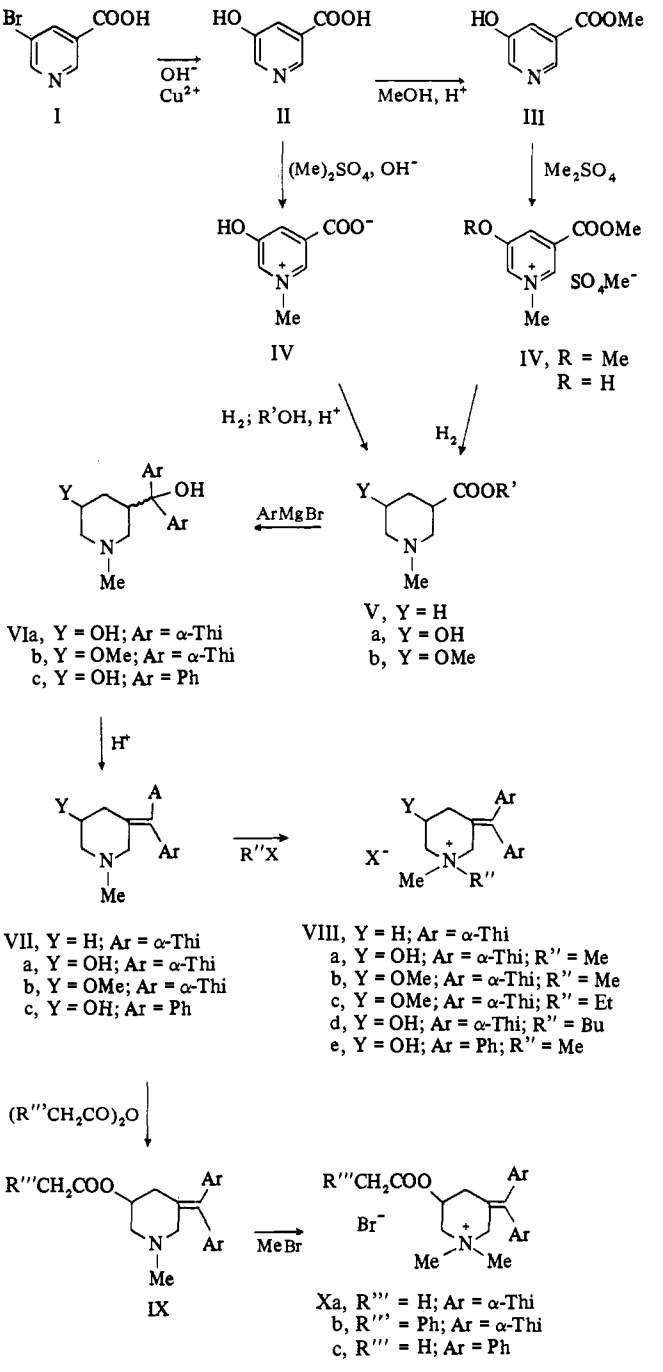
Cannon[2] summarized some of the basic structural requirements for high anticholinergic activity. In piperidine derivatives, for example, there should be at least one planar ring not larger than phenyl or thienyl, a hydroxy group or a double bond on a quaternary carbon which is located at an optimal distance from the basic nitrogen, and an alkyl group smaller than isopropyl on the cationic head. On the basis of this empirical rule, *N*-methyl-3-piperidylidenedithienylmethane (VII), known to be an effective antitussive,[3] was chosen as a candidate for our studies. The methobromide of this compound (VIII) showed a significant spasmolytic activity, which was equal to or greater than that of atropine, as had been expected. However, the decrease in the degree of the side effects was not sufficient.

Although many anticholinergic agents bearing a hydroxy group have been synthesized and evaluated biologically, the effect of introduction of a hydroxy function on the cholinolytic activity is unpredictable. For instance, the cholinolytic activities of the α-diphenylpropylamine series are increased[4] by introduction of a hydroxy group on the α position, while the reverse is true in the case of the 4-diphenylpiperidylidenemethane series reported by Grisar, *et al.*[5]

Synthesis of the 5-hydroxy-3-piperidylidenemethane derivatives was of interest in this respect because some desirable change in the anticholinergic side effects might result from the introduction of the hydroxy function.

Chemical Aspects. Synthesis of 5-hydroxy-3-piperidylidenediarylmethane derivatives was carried out as shown in Scheme I. 5-Hydroxynicotinic acid (II) has been synthesized from 5-bromonicotinic acid (I) *via* 5-aminonicotinic acid by Graf,[6] and also from 4,4-diethoxy-2-formylglutamate by Mangoni.[7] We tried to obtain II directly from I because both methods appeared to be somewhat cumbersome for a large-scale synthesis. After several fruitless trials, II could be obtained in an excellent yield by refluxing I in NaOH solution in the presence of $CuSO_4$ and Cu powder. Selection of the reaction conditions suitable for the synthesis of each nipecotinate (V) was unexpectedly complicated. Addition of Me_2SO_4 into the dilute NaOH solution of II at room temperature gave a betaine (IV′) in a good yield. Hydrogenation of IV′ in 10% NaOH solution with Raney Ni afforded 5-hydroxynipecotinic acid. Esterification of this acid with EtOH and HCl gave Va. Treatment of methyl 5-hydroxynicotinate (III) with Me_2SO_4 in the presence of anhydrous K_2CO_3 in C_6H_6–MeOH (4:1) afforded crude IV as a viscous oil which was directly hydrogenated without purification to give Vb. On the other hand, Va was the major product when the solvent was MeOH or the reaction temperature was below 5° in the methylation step, indicating that the methylation was incomplete. Elimination of the hydroxy and the methoxy groups occurred in all cases, affording methyl *N*-methylnipecotinate when PtO_2 was used as a catalyst for the reduction. The carbinols, VIa, VIb, and VIc, were synthesized by a procedure similar to that of Sugimoto, *et al.*[8] Compds VIa and VIb did not show

Scheme I



a sharp melting point, so that they appeared to be a mixture of stereoisomers. In fact, two isomers could be separated using Al_2O_3 column chromatography in the case of VIb. Since dehydration of both isomers with dilute hydrochloric acid gave the identical product (VIIb), the other compounds (VIa and VIc) were dehydrated directly without purification. Although attempts to crystallize the acylates (IX) were unsuccessful, they were chromatographically pure and, hence, were allowed to react with MeBr. Table I shows the yields and the physical constants of the new compounds.

Pharmacological Results and Discussion. The introduction of a 5-hydroxy or 5-methoxy group to the piperidine ring of the free base series (VII) resulted in a remarkable reduction in the anticholinergic activity. The activities of VIIa and VIIb were approximately 0.05 the activity of the parent compound VII. On the other hand, little pharmaco-

Table I. Physical Data

Compd	Ar	Y	R''	Mp, °C	Yield, %	Recrystn solvent	Formula
VIa	α-Thi	OH		160-165	76	C_6H_6-(*i*-Pr)$_2$O	$C_{15}H_{19}NO_2S_2$
VIb 1	α-Thi	OMe		130-132[a]	88	C_6H_6	$C_{16}H_{21}NO_2S_2$
VIb 2				142-144[a]		Et_2O-C_6H_6	
VIc	Ph	OH		196-198	89	C_6H_6	$C_{19}H_{23}NO_2$
VIIa	α-Thi	OH		76-77	89	Et_2O	$C_{15}H_{17}NOS_2$
VIIb	α-Thi	OMe		70-71	95	Et_2O	$C_{16}H_{19}NOS_2$
VIIc	Ph	OH		127-128	90	Et_2O	$C_{19}H_{21}NO_2$
VIII	α-Thi	H	Me	225-226	92		$C_{16}H_{20}NS_2Br$
VIIIa	α-Thi	OH	Me	260-262	67	MeOH-Et_2O	$C_{16}H_{20}NOS_2Br$
VIIIb	α-Thi	OMe	Me	197-200[b]	88	EtOH-Et_2O	$C_{17}H_{22}NOS_2Br$
VIIIc	α-Thi	OMe	Et	201-202	73	MeOH-(*i*-Pr)$_2$O	$C_{18}H_{24}NOS_2I$
VIIId	α-Thi	OH	Bu	194-197	82	MeOH-Me_2CO	$C_{19}H_{26}NOS_2Br$
VIIIe	Ph	OH	Me	262-264	89	MeOH-Me_2CO-Et_2O	$C_{20}H_{24}NOBr$
Xa	α-Thi	OAc	Me	205-207	85	Me_2CO-Et_2O	$C_{18}H_{22}NO_2S_2Br$
Xb	α-Thi	$OCOCH_2Ph$	Me	132-134	80	Me_2CO-Et_2O	$C_{24}H_{26}NO_2S_2Br$
Xc	Ph	OAc	Me	176-178	87	Me_2CO-Et_2O	$C_{22}H_{26}NO_2Br$

[a] Stereoisomers. [b] Monohydrate mp 190-192°.

Table II. Pharmacological Data

Compd	Relative act.				LD_{50}, mg/g (mice, ip)
	Anti-Ach act.	Sialoschesis	Mydriasis	Inhibition of gastric hypermotility[c]	
VII	50.0[a]	0	15	–	
VIIa	3.2	0	0	–	
VIIb	2.2	0	0	–	
VIII	77.0	60[b]	85[b]	+++	88
VIIIa	66.7	60	86	+++	65
VIIIb	62.7	20	53	+++	97.2 (713)[d]
VIIIc	2.8	0	14	a	
VIIId	2.0	a	a	a	
VIIIe	3.3	20	19	a	
Xa	6.7	40	25	a	
Xb	6.3	0	12	a	
Xc	6.0	20	6	a	
Atropine	100.0	100	100	++	

[a] Relative potencies of antiacetylcholine activity were calculated by the following equation. Ratio = [(anti-log of pA_2 value of each test compound)/(anti-log of pA_2 value of atropine)] × 100. [b] Refer to the method in the Experimental Section. [c] 20 μg of each test compound was administered (iv): –, no effect; ++, moderate inhibition; +++, complete inhibition; a, not tested. [d] Value in parenthesis is oral LD_{50}.

dynamic change was observed in the series of the quaternary compounds VIIIa and VIIIb. These results indicate that the hydroxy or the methoxy group may be tolerated by the acetylcholine receptor when the binding of the compound to the receptor site is adequately strong. Replacement of the methyl group at the cationic head with an alkyl group larger than ethyl (VIIIc and VIIId) led to a considerable reduction of all the pharmacological activities. The potencies of acylates Xa and Xb were considerably weaker than that of VIIIa. According to the studies by Schueler,[9] 3-acetoxy-*N*-methylpiperidine methoiodide possesses a weak muscarinic effect; therefore the diminished cholinolytic activities of Xa and Xb are not surprising. In this respect it was unexpected that the anticholinergic activity of the acetate of the diphenyl derivative (Xc) was rather increased compared to that of the hydroxy derivative (VIIIe). Although further work in detail is necessary to explain these opposite effects of the same substituent, these data suggest that the mode of binding of the acyl derivatives to the receptor may be somewhat different from that of the hydroxy derivatives.

Lands[4] found that the cholinolytic activity of the α-diphenyl-α-hydroxypropylamine series was slightly increased when one of the phenyl groups had been replaced by a cyclohexyl group and was decreased to one-half when it was replaced by an isopropyl group. The aryl group could contribute to the formation of the drug-receptor complex conceivably by means of charge-transfer, hydrophobic, and van der Waals forces. The total energy in hydrophobic bonding and van der Waals forces of a phenyl group has been known to be about 8.6 kcal/mole, and this value is twice as large as the energy in the hydrophobic bonding of a propyl group[10] and equivalent to that of a hexyl group.

Therefore, in these cases, the role of a phenyl ring in the binding is considered to be hydrophobic bond formation, thus suggesting the existence of a hydrophobic region in the receptor.

Although the situation in our rigid compounds should be different from that in conformationally mobile α-diphenylpropylamines, it may be stated that if one of the aromatic rings may contribute to the binding by means of charge transfer, the activity of the acyl derivatives Xa, Xb, and Xc should not be the same because the vertical ionization potential of thiophene is smaller than that of benzene.[11] In fact, the potency in the Ach activity of VIIIa is 20 times greater than that of VIIIe. However, the potencies of those acyl derivatives Xa, Xb, and Xc were almost equal. One of the possible explanations for this result is that both aromatic rings of these compounds may slip out from the region of charge transfer, probably due to a tight binding of the acyl group to the esteratic site of the receptor, thus binding themselves hydrophobically to an extra site of the

receptor. Since the energy in the hydrophobic bonding of a phenyl group and that of a thienyl group may be considered approximately equal, it may be reasonable that the acyl derivatives have similar activities. Shaw[12] reported that *N*-methyl-3-acetoxypiperidine was found to be a moderately good substrate for Ach-esterase, a finding which would partially support our explanation. Only compound VIIIb showed weak sialoschetic and mydriatic activities without any loss of its antispasmodic activity. Evaluations for the clinical use of this compound as an orally active spasmolytic are under way. Although the potency of VIIIb by oral administration has not been proved as yet, the drawback of poor absorbability in oral therapy is expected to be less significant because the ratio of the oral/ip LD_{50} values (approximately 7) is not as great. The differences in the side-effect activities of the acylates prompted us to further investigate some other alkyl ethers. The results of these studies will be published in a forthcoming paper.

Experimental Section

Melting points were determined on a Yamato capillary mp apparatus Model Mp-1 and were uncorrected. Ir spectra were recorded using Hitachi 215 ir spectrophotometer and Nujol suspensions unless otherwise indicated. Nmr spectra were obtained on a J.E.O.L (J.N.M.) MH-60 spectrometer using $CDCl_3$ as solvent (Me_4Si). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

5-Hydroxynicotinic acid (II). A mixture of 5-bromonicotinic acid (50 g), $CuSO_4 \cdot 5H_2O$ (15 g), and Cu powder (2 g) in 10% NaOH (400 ml) was stirred and refluxed for 20 hr. After cooling, the dark solution was treated with H_2S to remove copper ions. The filtrate was decolorized with Norite and adjusted to pH 3–4 with concd HCl, and the acid precipitated was collected, washed with H_2O, and dried to give (30 g, 87%) mp 292–298° dec, recrystalized from MeOH, mp 298–299° dec (lit[6] mp 299°).

Methyl *N*-Methylnipecotinate (V), Y = H, from IV'. Ten g of IV', dissolved in a mixture of H_2O (20 ml) and MeOH (20 ml), was hydrogenated in the presence of PtO_2 (100 mg) at room temperature. After filtration of the catalyst, the filtrate was evaporated to dryness. The residue was esterified with satd HCl–MeOH. The ester was purified by distillation to give an oil (4.2 g, 40%): bp 100° (4 mm). The ir and nmr spectra were identical with those of an authentic sample.

Methyl *N*-Methyl-5-hydroxynipecotinate (Va), R' = Me. Me_2SO_4 (31.6 g) was added dropwise to a suspension of III (38.2 g) in MeOH (100 ml) and stirred at room temperature overnight. The solvent was evaporated off, and the residue was hydrogenated in a mixture of MeOH (120 ml) and concd NH_4OH (18 ml) with Raney Ni (32 ml) in an autoclave at 100 atm, 90°. The product was purified by distillation to give Va (18.17 g, 42%): bp 106–108° (4 mm); ir (liq) 3400, 1735, 1470, 1440, 1260, 1190, 1150 cm^{-1}; nmr ($CDCl_3$) 6.04 (m, 1 H, $<^{OH}_{H}$), 6.32 (s, 3 H, $-CO_2Me$), 6.52 (s, 1 H, D_2O-exchangeable OH), 7.73 (s, 3 H, N-Me).

Ethyl *N*-Methyl-5-hydroxynipecotinate (Va), R' = Et. Me_2SO_4 (33.2 g) was added dropwise to a solution of II (11 g) in 10% NaOH (100 ml) with cooling and was stirred for 3 hr. The solution was washed with ether, and the H_2O layer was adjusted to pH 4 with concd H_2SO_4. The precipitated salt was filtered to give IV' (8.94 g, 71%): recrystallized from MeOH, mp 264–265° dec; ir 3400, 3050, 1600 cm^{-1}; nmr (CF_3COOH) 1.25 (br, 1 H), 1.54 (br, 2 H), 5.52 (s, 3 H). *Anal.* ($C_7H_7NO_3 \cdot H_2O$) C, H, N. This salt (6.0 g) was hydrogenated in a mixture of 10% NaOH (20 ml) and MeOH (400 ml) in the presence of Raney Ni at room temperature for 4 hr, neutralized with concd H_2SO_4, and evaporated to dryness. The residue was esterified in satd HCl–EtOH in the usual manner. After removal of the solvent, the residue was neutralized to give an oil (4.1 g, 92%): ir (liq) 3360, 1724, 1255, 1185, 1160 cm^{-1}; nmr ($CDCl_3$) 5.59 (br, s, 1 H, -OH), 5.80 (g, 2 H, J = 7 Hz, $-CH_2CH_3$) 6.30 (m, 1 H, $<^{OH}_{H}$), 7.72 (s, 3 H, N-Me), 8.75 (t, 3 H, J = 7 Hz, $-CH_2CH_3$).

Methyl *N*-Methyl-5-methoxynipecotinate (Vb), R' = Me. III (460 g) and K_2CO_3 (621 g) were suspended in C_6H_6–MeOH (4 : 1, 5 L). Me_2SO_4 (1124 g) was added dropwise at room temperature under bubbling N_2 from the bottom. The mixture was stirred at room temperature for 12 hr. The inorganic precipitate was filtered off and washed with C_6H_6–MeOH (1 : 1). The filtrates were combined and evaporated. The residue was hydrogenated in MeOH (1.6 L) in the presence of Raney Ni (200 ml) and NEt_3 (20 ml) in an autoclave at 100 atm for 20 hr with heating at 70°. The mixture was filtered, extracted with Et_2O, and adjusted to pH 11 with K_2CO_3, and the extract was dried and evaporated. The residue was purified by distillation giving an oil (450 g, 80%): bp 80–81° (0.5 mm); ir (liq) 1725, 1460, 1435, 1250, 1185, 1165, 1100 cm^{-1}; nmr ($CDCl_3$) 6.35 (s, 3 H, $-CO_2Me$), 6.45 (s, 3 H -OMe), 7.70 (s, 3 H, N-Me).

N-Methyl-(5-methoxy-3-piperidyl)dithienylmethanol (VIb). The Grignard reagent was prepared from Mg (51 g) and α-bromothiophene (343 g) in abs THF (500 ml). The solution of Vb (157 g) in abs THF (300 ml) was added dropwise with cooling and was stirred at room temperature overnight. H_2O (200 ml) was added dropwise with cooling, and 10% HCl was added to decompose the Mg salts. After basifying with K_2CO_3, the solution was extracted with $CHCl_3$, and the extract was dried, evaporated, and crystallized from Et_2O to give 240 g (88%), mp 137–143°, of VIb including the two stereoisomers; 3 g of this mixture was chromatographed on Al_2O_3. The minor part was eluted with C_6H_6 to give 0.6 g (20%): recrystallized from C_6H_6, mp 130–132° (VIb-1). *Anal.* ($C_{16}H_{21}NO_2S_2$) C, H, N. The main part was eluted with C_6H_6–$CHCl_3$ to give 2.35 g (80%): recrystallized from C_6H_6–Et_2O, mp 142–144° (VIb-2). *Anal.* ($C_{16}H_{21}NO_2S_2$) C, H, N.

General Procedure. Grignard Reaction of *N*-Methylnipecotinate Derivatives. The Grignard reagents were prepared from 2 g-atoms of Mg and α-bromthiophene or brombenzene in abs THF. The solution of *N*-methylnipecotinates (V) (1 mole) in abs THF was added dropwise below 5° and stirred overnight at room temperature. The reaction mixture was treated with NH_4Cl-saturated H_2O and extracted with $CHCl_3$, and the extract was dried, evaporated, and crystallized by triturating with Et_2O.

Dehydration of the Carbinols. The solution of the carbinols (VI) in 10% HCl (about 3-fold vol) was heated at 70–80° for 2 hr (5 hr was required in the case of VIc). The reaction mixture was basified with 40% NaOH solution, extracted with C_6H_6, dried, and evaporated. The residue was crystallized from Et_2O or C_6H_6–hexane.

Acylation of the 3-Piperidylidenemethanes. Compds VII were heated with an excess of the acid anhydrides in the presence of pyridine at 80° for 1 hr, poured into 10% Na_2CO_3 solution, extracted with C_6H_6, washed with H_2O, dried, and evaporated to give oily IX.

Quaternary Salts VIII, X. The tertiary bases were treated with an excess of alkyl halide in acetone at room temperature. After 5 hr, the crystalline product was collected and recrystallized from EtOH, Et_2O, or Me_2CO. (In the case of BuBr, the product was obtained under reflux for 2 days.)

Pharmacological Methods. Anticholinergic Activity. Anticholinergic activity was measured kymographically on the isolated guinea pig ileum by estimating inhibition of the isotonic contraction induced by methacholine in the presence of the test compounds. The relative potencies as expressed in per cent of the activity of atropine were calculated from the pA_2 values (*cf.* pA_2 of VIIIb, 8.38; pA_2 of atropine, 8.57).

Antisialogog Activity. Groups of 5 male albino mice, weighing about 20 g, were used. Ten mg/kg of the test compounds was administered intraperitoneally. The inhibitory effect of the compounds was estimated from the number of mice which did not show any salivation within 20 min after the administration of pilocarpine (10 mg/kg, sc) and expressed as the number of nonsalivating animals in per cent of the total number of animals tested.

Mydriatic Activity. Three mg/kg of each test compound was administered intraperitoneally. Groups of 5 male albino mice were employed. The pupil diameter was measured at 5 min after the administration of the compound. The potencies are expressed as the measured diameter in percentage of the maximally dilated diameter.

Inhibitory Activity against Gastric Hypermotility. Male albino rats were used. Gastric hypermotility induced by bethanechol infusion was recorded with a transducer connected to a rubber balloon fixed in the pyloric region; 20 μg/kg of the test compounds was administered intravenously.

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Antimalarials. 3. 2,6-Bis(aryl)-4-pyridinemethanols with Trifluoromethyl Substituents†

A. Markovac,* M. P. LaMontagne, P. Blumbergs, A. B. Ash, and C. L. Stevens

Ash Stevens Inc., Detroit, Michigan 48202. *Received January 21, 1972*

A series of 21 α-alkylaminomethyl-2,6-bis(aryl)-4-pyridinemethanols, where aryl is substituted phenyl bearing a CF_3 substituent on one or both phenyl rings, were synthesized from the corresponding 2,6-bis(aryl)isonicotinic acids. Among the 21 compounds, 19 were curative against *Plasmodium berghei* in mice at a dosage of 160 mg/kg; 11 of these were curative at 40 mg/kg, 3 were curative at 20 mg/kg, and 2 were active at 10 mg/kg.

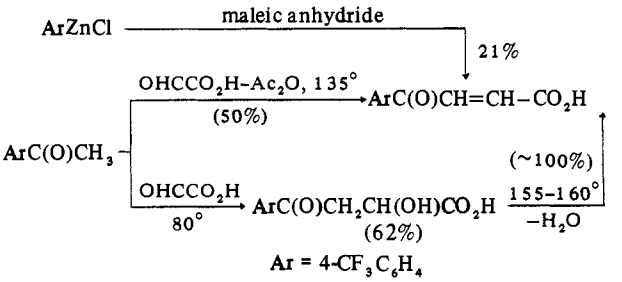
In the preceding paper[1] in this series, we reported the antimalarial activity against *Plasmodium berghei* in mice‡ for 29 α-alkylaminomethyl-2,6-bis(aryl)-4-pyridinemethanols bearing Cl, Br, F, and OCH_3 substituents on the aryl (phenyl) rings. As this earlier work was in progress, other laboratories investigating the related 4-quinolinemethanols[3] and the 9-phenanthrenemethanols[4] observed increased antimalarial efficacy when one or more of the halo substituents were replaced with a CF_3 group. Accordingly, our work was directed to analogs containing a CF_3 group in one or both phenyl rings, the results of which are reported herein.

Chemistry. Candidate antimalarials bearing a CF_3 group on both phenyl rings, or on one ring combined with one or two halo substituents on the other phenyl ring, were prepared by methods described earlier.[1] The six required intermediate isonicotinic acids listed in Table I were prepared by the Zecher–Krohnke ring-closure method.[5] For the important isonicotinic acid Ia, the 4-$CF_3C_6H_4$ group is required in both Zecher–Krohnke intermediates. The pyridinium bromide salt was prepared from 4-$CF_3C_6H_4C(O)CH_3$ in a conventional way and the acrylic acid was prepared in 3 ways as shown by Scheme I.

4-$CF_3C_6H_4C(O)CH{=}CHCO_2H$ was prepared in low (20%) yield by condensing 4-$CF_3C_6H_4ZnCl$ with maleic anhydride.[6] In an improved method, 4-$CF_3C_6H_4C(O)CH_3$ was condensed at 135° with 1 mole of glyoxylic acid in Ac_2O with a little Et_3N as catalyst to yield the acrylic acid in 50% yield. Temperature control, however, was critical to avoid tar formation. In larger scale work, the condensation was performed neat at 80° to form 2-hydroxy-3-(4-trifluoromethylbenzoyl)propionic acid which was isolated and dehydrated neat at 155–160° (1–2 mm).

The intermediates for the meta isomer Ib were prepared from the corresponding 3-substituted intermediates. The 4

Scheme I

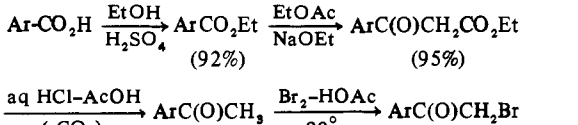


Ar = 4-$CF_3C_6H_4$

unsym isonicotinic acids Ic, Id, Ie, and If were prepared from 4-(and 3-)trifluoromethylphenacylpyridinium bromides and the required 4-bromo, 4-chloro-, and 3,4-dichlorobenzoylacrylic acids.[1]

The amino alcohol side chain was introduced by the method of Lutz and coworkers.[7] The sequence was carried through without purification of intermediates, although it is preferable to purify at the bromomethyl ketone stage and 4 examples are listed in Table II. In the case of IIa, the diazo ketone (89% from Ia) was isolated and characterized. For larger scale work, an alternative route to the bromomethyl ketones was sought which did not utilize CH_2N_2. The method selected and developed for IIa used the Claisen condensation[8] as the key step in the sequence.

Compound Ia was converted to the ethyl ester (92%) which was treated with EtOAc and NaOEt[8] to yield the ethyl 4-pyridinoylacetate (95%). Hydrolysis–decarboxylation using a concd aqueous HCl–AcOH (1 : 1, v/v) system gave the 4-pyridyl methyl ketone in high yield (95–97%). The dropwise addition of Br_2 (1.1 equiv) in AcOH to the methyl ketone in AcOH at 90° gave bromomethyl ketone IIa (80%) with minimum over- or underbromination.



Ar = 2,6-bis(4-$CF_3C_6H_4$)-4-pyridyl-

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‡The antimalarial tests were performed by Dr. Leo Rane of the University of Miami.[2] See footnote *a*, Table IV. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.