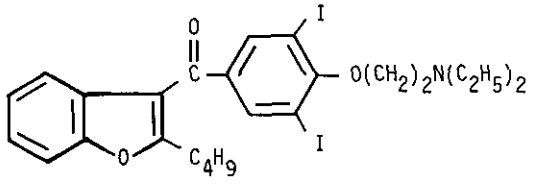
SYNTHESES OF 2-ALKYL-3-(4-DIALKYLAMINOALKOXY-BENZOYL)-THIENO(3,2-c)PYRIDINES

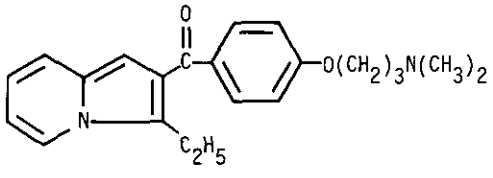
Daniel Fréhel*, Robert Boigegrain and Jean-Pierre Maffrand
Ligne Hémobiologie, Sanofi-Recherche
195, route d'Espagne, 31036 Toulouse (France)

Abstract - This paper deals with the syntheses of thieno(3,2-c)pyridinic isosteres 4 of two potent anti-anginal and/or antiarrythmic agents : amiodarone 1 and butoprozin 2. The corresponding tetrahydrogenated analogs are also synthesized.

The grafting on various heterocycles (indole[1], benzo(b)furan[2], benzo(b)thiophene[3], indolizine[4]) of the pharmacophoric 4-dialkylaminoalkoxy-benzoyl group gives compounds with remarkable anti-anginal and/or anti-arrythmic[5] activities such as amiodarone[6] 1 and butoprozin[6] 2.

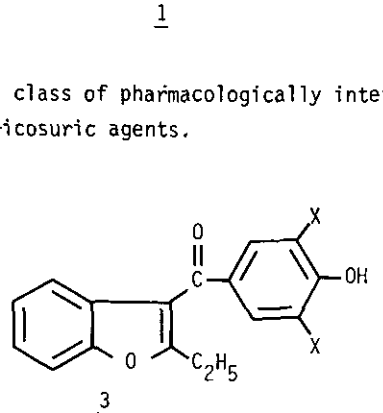


1



2

In this class of pharmacologically interesting products, we can add the phenols 3 which are potent uricosuric agents.

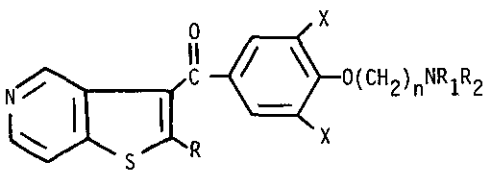


3

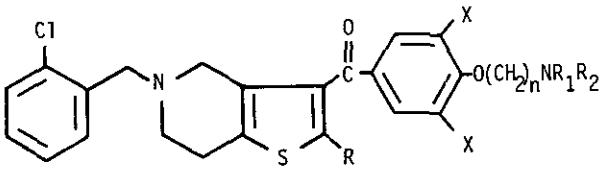
X = Br : benzbromarone[6]
X = I : benziodarone[6]

Furthermore, the platelet antiaggregating and antithrombotic[7] activities of ticlopidine[8] 6 lead us to synthesize various thieno(3,2-c)pyridines.

This paper deals with the synthesis of compounds 4 and tetrahydrogenated analogs 5, which we can consider as thieno(3,2-c)pyridinic isosteres of amiodarone and butoprozin.



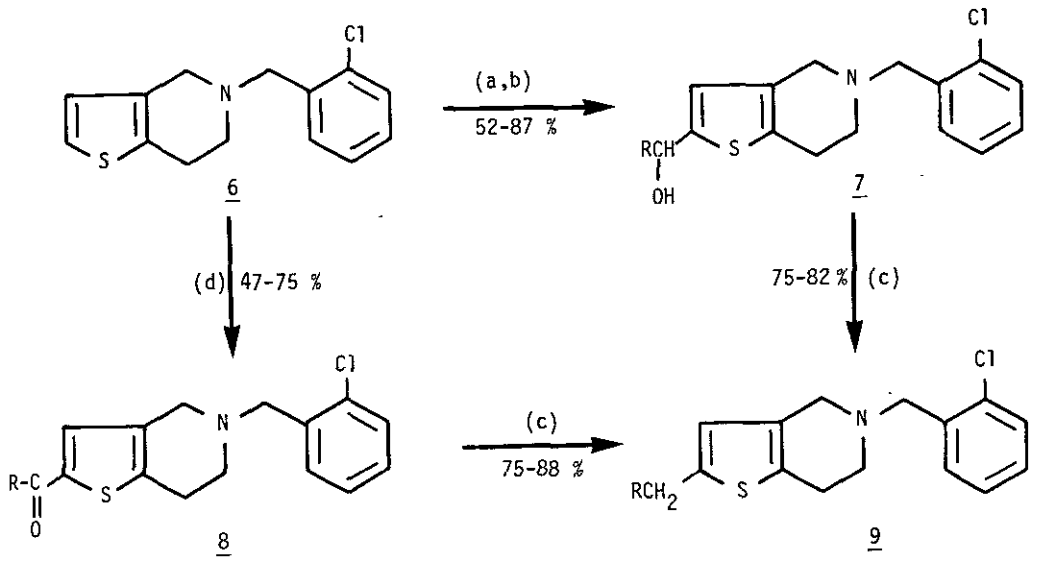
4



5

Two access ways are used to graft a saturated linear aliphatic chain in position 2 on the ticlopidine skeleton (Scheme 1).

Scheme 1



6 7 8 9

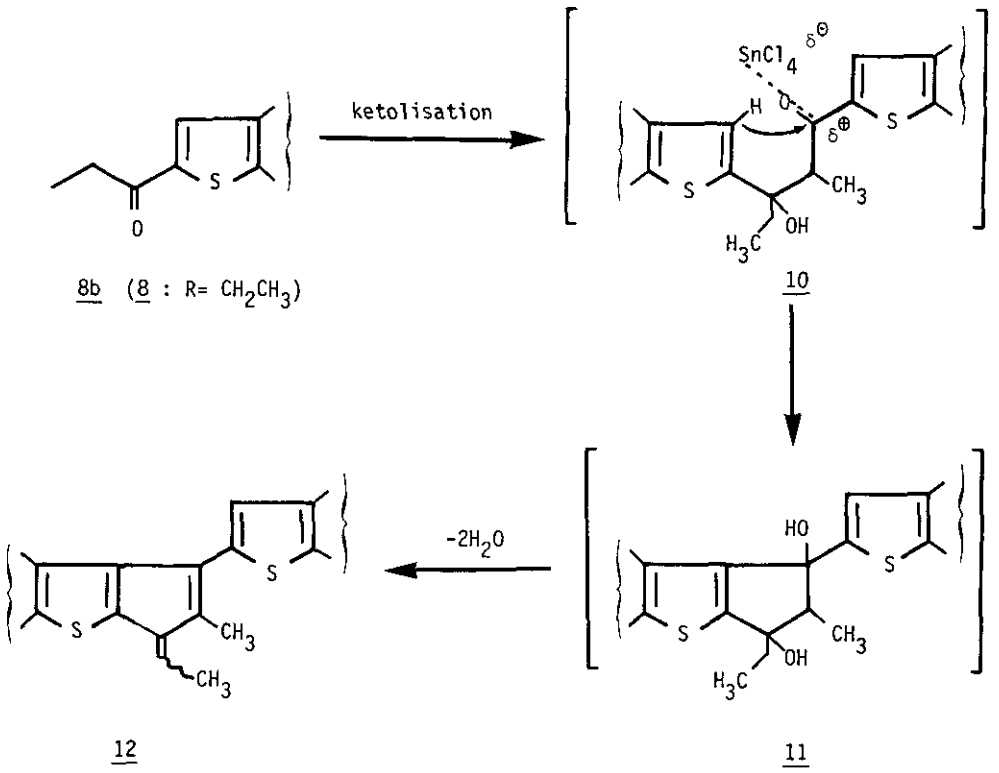
(a) : BuLi (1.3 eq.), HMPT (2 eq.), tetrahydrofuran, -10°C then 0°C, 1h.
(b) : RCHO (3 eq.) , tetrahydrofuran, -40°C then r.t., overnight.
(c) : $NaBH_4$ (2 eq.), CF_3COOH (15 eq.), dichloromethane, 0°C then r.t., 3h.
(d) : RCOCl (1.3 eq.), $SnCl_4$ (3.5 eq.), 1,2-dichloroethane, r.t., overnight.

The first access way consists in condensing the organolithium reagent, prepared from selective lithiation of ticlopidine 6 in position 2, with aliphatic aldehydes to get the secondary alcohols 7. Hydrogenolysis of alcohol function according to Gribble procedure [9] gives C-alkylated thienopyridines 9.

The second access way involves acylation of ticlopidine 6 with aliphatic acid halides according to Friedel-Crafts reaction, using stannic chloride[10] as a Lewis catalyst. Obtained ketones 8 are completely reduced in thienopyridines 9 according to another Gribble procedure[11].

A secondary reaction rendered evidence during acylation of ticlopidine 6 with propionyl chloride. Indeed, ketolisation of thienopyridine 8b (8 : R= CH_2CH_3) gives hydroxy-ketone 10. Complexing of the carbonyl function by stannic chloride (a Lewis catalyst) within the reaction medium, occurs as is proposed in scheme 2. It allows intramolecular electrophilic cyclisation into a dicarbinol compound 11, double dehydration of which gives a dimeric compound 12 (yield : 40 %).

Scheme 2



8b (8 : R= CH_2CH_3)

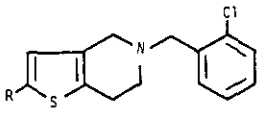
10

11

12

Table I summarizes the physicochemical characteristics of the new C_2-alkylated tetrahydrothieno(3,2-c)pyridines.

TABLE I



Compound (3)	R	Salt	mp (°C) (solvent)	Yield (%)	60 MHz ^{1}H NMR (solvent) ;δ (ppm) , J(Hz) s : singlet; bs: broad singlet ; t : triplet q : quartet ; m multiplet.
7a	$CH(OH)CH_3$	-	oil	87	$CDCl_3$: 1.37(d,J=6,3H,CH_3) , 2.70(bs,4H,NCH_2CH_2) ; 3.43(bs,2H, NCH_2-thienyl) ; 3.70(s,2H,NCH_2Ar) ; 4.80(q,1H,$CHOHCH_3$) , 6.40(s,1H,thiophen) , 6.93-7.27(m,4H,arom.).
7b	$CH(OH)CH_2CH_3$	-	oil	52	$CDCl_3$: 0.80-1.93(m,7H,$(CH_2)_2CH_3$) , 2.80(bs,4H,NCH_2CH_2) ; 3.53(bs, 2H,NCH_2-thienyl) ;3.80(s,2H,NCH_2Ar) ; 4.73(t,J=7,1H, $CHOHCH_2$) ; 6.50(s,1H,thiophen) ; 7.06-7.60(m,4H,arom.).
8a	$COCH_3$	oxalate	152 (iPrOH-AcOEt)	55	$CDCl_3$: 2.43(s,3H,$COCH_3$) , 2.87(bs,4H,NCH_2CH_2) ; 3.60(bs,2H, NCH_2-thienyl) ; 3.80(s,2H,NCH_2Ar) ; 7.06-7.60(m,5H,thiophen and arom.).
8b	$COCH_2CH_3$	maleate	120 (iPrOH-iPr_2O)	47	$CDCl_3$: 1.17(t,J=7,3H,CH_2CH_3) , 2.80(q,J=7,2H,CH_2CH_3) ; 2.87(bs, 4H,NCH_2CH_2) ; 3.60(bs,2H,NCH_2-thienyl) ; 3.80(s,2H,NCH_2Ar), 7.00-7.57(m,5H,thiophen and arom.).
8c	$CO(CH_2)_2CH_3$	maleate	188 (MeOH)	75	$CDCl_3$: 0.76-1.13(m,3H,CH_2CH_3) ; 1.33-2.00(m,2H,CH_2CH_3) ; 2.47-3.00 (m,6H,$COCH_2$ and NCH_2CH_2) ; 3.47(bs,2H,NCH_2-thienyl) ; 3.57 (s,2H,NCH_2Ar) ; 7.01-7.17(m,5H, thiophen and arom.).
8d	$CO(CH_2)_5CH_3$	maleate	110 (EtOH-Et_2O)	73	$CDCl_3$: 0.73-1.93(m,11H,$(CH_2)_4CH_3$) ; 2.57-3.00(m,6H,$COCH_2$ and NCH_2CH_2) ; 3.57(bs,2H,NCH_2-thienyl) ; 3.80(s,2H,NCH_2Ar) ; 7.00-7.57(m,4H,arom.).
9a	C_2H_5	hydrochloride	140 (H_2O)	82(1)	$CDCl_3$: 1.23(t,J=7,3H,CH_2CH_3) ; 2.73(q,J=7,2H,CH_2CH_3) ; 2.80(bs, 4H,NCH_2CH_2) ; 3.50(bs,2H,NCH_2-thienyl) ; 3.73(s,2H,NCH_2Ar); 6.33(s,1H,thiophen) ; 7.00-7.67(m,4H,arom.).
9b	$n\text{-}C_4H_9$	hydrochloride	195 (MeOH)	75(2)	$CDCl_3$: 0.73-1.73(m,9H,$(CH_2)_3CH_3$) ; 2.40-2.93(m,4H,NCH_2CH_2) ; 3.47(bs,2H,NCH_2-thienyl) ; 3.73(s,2H,NCH_2Ar) , 6.33(s,1H, thiophen) ; 7.00-7.67(m,4H,arom.).
9c	$n\text{-}C_7H_{15}$	hydrochloride	150 (iPrOH-iPr_2O)	88(2)	$CDCl_3$: 0.67-1.93(m,15H,$(CH_2)_6CH_3$) ; 2.60-3.00(m,4H,NCH_2CH_2) 3.60 bs,2H,NCH_2-thienyl) ; 3.87(s,2H,NCH_2Ar) ;6.43(s,1H, thiophen) , 6.96-7.57(m,4H,arom.).

(1) From secondary alcohol ; (2) From ketone ; (3) Satisfactory elementary analyses for the synthesized compounds are obtained.

The second part of this paper deals with grafting in position 3 the pharmacophoric 4-dialkylaminoalkoxy-benzoyl groups on already synthesized C_2-alkylated tetrahydrothieno(3,2-c)pyridines 9. Acylation, according to Friedel-Crafts reaction, of tetrahydrothieno(3,2-c)pyridines 9, with 4-methoxybenzoyl chloride gives compounds 13 (Scheme 3).

N-debenzylation of tetrahydrothieno(3,2-c)pyridines 13, using intermediate trichloroethyl carbamates 15 gives, after reduction with zinc in an acetic acid medium, tetrahydrothieno(3,2-c) pyridines 16. Direct oxidation of 16 in thieno(3,2-c)pyridines 14, especially with potassium ferricyanide in an alkaline medium[12] , were unsuccessful. Careful oxidation, with N-chlorosuccinimide in an alkaline medium[13], of tetrahydrothieno(3,2-c)pyridine 16b (16 : R= n-C_4H_9) gives dihydrothieno(3,2-c)pyridine 17, but this one could not be aromatized, with 10 % Pd/C in refluxed ethanol[14], in thieno(3,2-c)pyridine 14b (14 : R= n-C_4H_9). However,careful oxidation, with N-bromosuccinimide in chloroform[15], of tetrahydrothieno(3,2-c)pyridines 13 gives dihydro(3,2-c) pyridinium bromides 18 which could be aromatized, with 10 % Pd/C in refluxed ethanol, in thieno(3,2-c)pyridinium bromides 19. Those can be ultimately dequaternized, using 1,4-diazabicyclo[2.2.2] octane[16] in dimethylformamide, to give thieno(3,2-c)pyridines 14. Finally, we found that thieno(3,2-c)pyridines 14 could be directly obtained using pyrolysis of tetrahydrothieno(3,2-c)pyridines 13 in diphenyloxide in presence of 10 % Pd/C.

Table II and III summarize the physical characteristics of the new 2,3-disubstituted thieno(3,2-c) pyridines.

Using 48 % hydrobromic acid in an acetic acid medium[17], demethylation of thieno(3,2-c)pyridines 14 gives phenols 20 (Schema 4).

Two synthetic pathways allow to graft the dialkylaminoalkyl chain on the phenolic function, which is first transformed in phenolate :

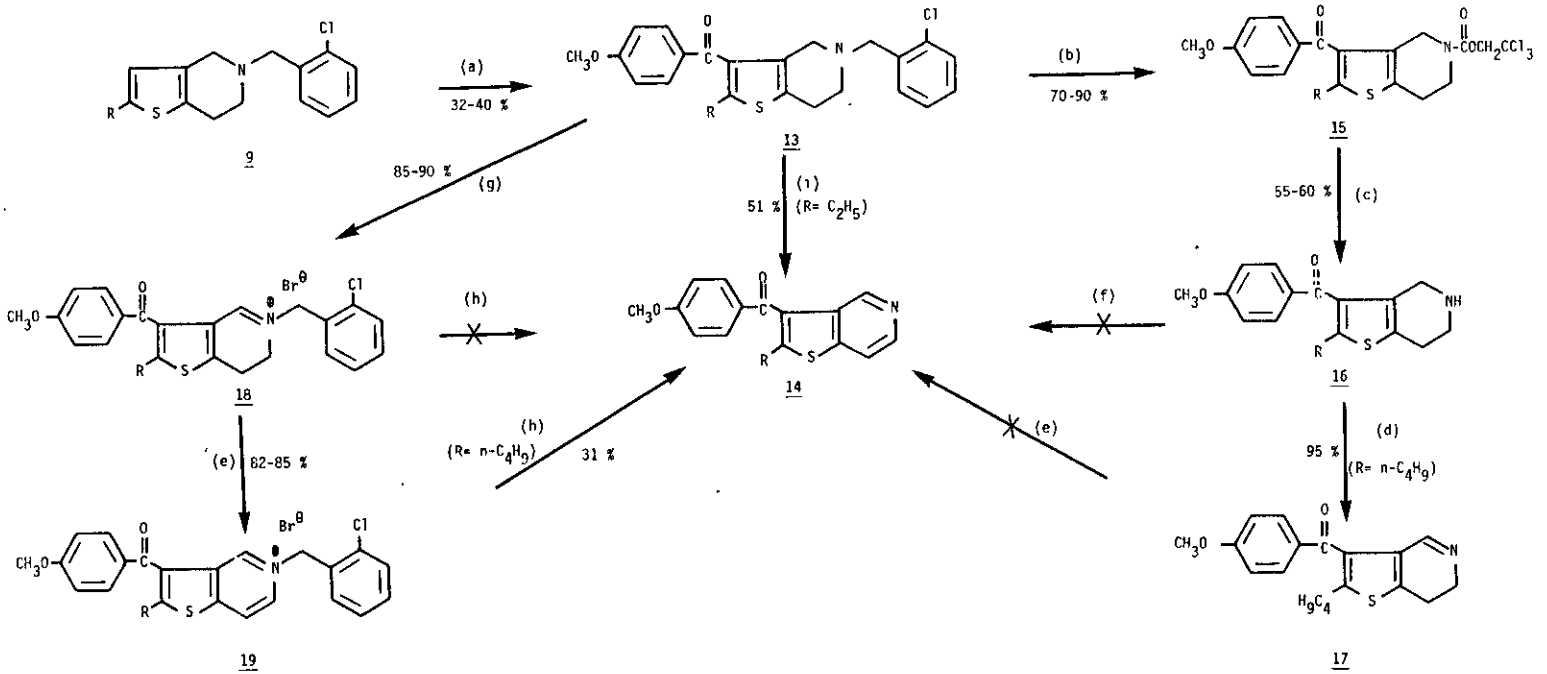
- direct alkylation of phenates with N-chloroalkyl N,N-dialkylamines[18], easy to access, giving thieno(3,2-c)pyridines 22 (4 : X = H).
- alkylation of phenates with 1,2-dichloroethane or 1,3-dichloropropane[18] , giving O-chloroalkyl thieno(3,2-c)pyridines 21 (X = Cl) : those condense with secondary amines to give thieno(3,2-c)pyridines 22 (4 : X : H).

It is noticeable that alkylation of phenates with mixed dihalides, such as 1-bromo-3-chloropropane, gives a mixture of O-chloroalkyl and O-bromoalkyl thieno(3,2-c)pyridines 21 (X = Cl) and 21 (X = Br). The yield of secondary amine condensation with thieno(3,2-c)pyridines 21 is not improved by addition of sodium or lithium iodide in reaction medium .

Phenols 20 may be transformed in phenates by refluxing in methanol with sodium acetate. Those are converted in dibromophenols 23 , using bromine in an acetic acid medium[18]. Grafting of the dialkylaminoalkyl chain on the phenolic function of these dibromophenols is obtained by either directly alkylating dibromophenols 23 with N-chloroalkyl N,N-dialkylamines or using intermediate chloroalkylated thieno(3,2-c)pyridines 24. Thus, thieno(3,2-c)pyridines 25 (4: X = Br) are obtained (Scheme 4 ; Table IV).

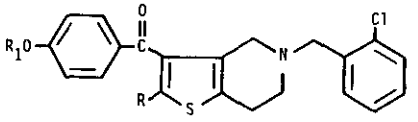
Scheme 5 deals with the synthesis of 4,5,6,7-tetrahydro-thieno(3,2-c)pyridines 27 (5: X = H, n=2), structural analogs of thieno(3,2-c)pyridines 21 (4: X = H, n=2).

Scheme 3



(a) : $(4\text{-}OCH_3)C_6H_4COCl$ (1.3 eq.) , $SnCl_4$(3.4 eq.) , 1,2-dichloroethane, r.t., 20 h.
(b) : Cl_3CCH_2OCOCl(1.3 eq.) , toluene, reflux, 5 h.
(c) : Zn powder (2 3 eq.), acetic acid, 50°C, 5h.
(d) : N-chlorosuccimide (1.5 eq.), diethyl oxide, r.t., 2h.; then 1.1 N ethanolic KOH (1 eq), diethyl oxide, r.t., 3h.
(e) : 10 % Pd/C (0.6 eq.), ethanol, reflux, overnight.
(f) : $K_3Fe(CN)_6$ (4 eq.), KOH(2.2 eq.), water-dioxane, r.t., overnight.
(g) : N-bromosuccimide (1.1 eq.), chloroform, r.t., 3h.
(h) : 1,4-diazabicyclo(2.2.2)octane (2 eq.), dimethylformamide, 120°C, 6 h.
(i) : 10 % Pd/C (0.8 eq.), diphenyloxide, 260°C, 0.5 h.

Table II



Compound (2)	R_1	R	Salt	mp.(°C) Solvent	Yield (%)	60MHz H^1NMR(solvent) ; δ(ppm) ; J(Hz) s: singlet; bs: broad singlet; d: doublet; t: triplet; m: multiplet
13a	CH_3	C_2H_5		80 (iPrOH)	32	$CDCl_3$: 1.13(t,J=7,3H,$CH_2\underline{CH_3}$); 2.63(q,J=7,2H,$\underline{CH_2}CH_3$); 2.83(bs,4H,$NCH_2\underline{CH_2}$); 3.43(bs,2H,$NC\underline{H_2}$-thienyl); 3.70(s,2H,$NC\underline{H_2}Ar$); 3.83(s,3H,$O\underline{CH_3}$); 6.87 and 7.73(2d,J=8,4H,$Ar\underline{O}CH_3$); 7.00-7.57(m,4H,arom.).
13b	CH_3	n-C_4H_9	hydrochloride	180 (EtOH-iPrOH)	42	$CDCl_3$: 0.60-1.80(m,7H,$(\underline{CH_2})_2\underline{CH_3}$); 2.60(t,J=7,2H,$\underline{CH_2}(CH_2)_2CH_3$); 2.80(bs,4H,$NCH_2\underline{CH_2}$); 3.40(bs,2H,N-$\underline{CH_2}$-thienyl); 3.67(s,2H,$NC\underline{H_2}Ar$); 3.83(s,3H,$O\underline{CH_3}$); 6.87 and 7.73(2d,J=8,4H,$Ar\underline{O}CH_3$); 7.00-7.53(m,4H,arom.).
26a	H	C_2H_5	hydrochloride	240 (EtOH-MeOH)	40	DMSO-d_6:1.07(t,J=7,3H,$CH_2\underline{CH_3}$); 2.57(q,J=7,2H,$\underline{CH_2}CH_3$); 2.80(bs,4H,$NCH_2\underline{CH_2}$); 3.33(bs,2H,$NC\underline{H_2}$-thienyl); 3.67(s,2H,$NC\underline{H_2}Ar$); 6.80 and 7.53(2d,J=8, 4H,$Ar\underline{O}H$); 7.00 and 7.47(m,4H,arom.).
26b	H	n-C_4H_9	hydrochloride	202 (CH_3CN)	22	$CDCl_3$: 0.60-1.60(m,7H,$CH_2(\underline{CH_2})_2\underline{CH_3}$); 2.47(t,J=7,2H,$\underline{CH_2}(CH_2)_2CH_3$); 2.93(bs, 4H,$NCH_2\underline{CH_2}$); 3.57(bs,2H,$NC\underline{H_2}$-thienyl); 3.83(s,2H,$NC\underline{H_2}Ar$); 6.50 and 7.50(2d,J=8,4H,$Ar\underline{O}H$); 7.00-7.47(m,4H,arom.).
27a	$(CH_2)_2N(CH_3)_2$	C_2H_5	dioxalate	134 (iPrOH)	36	$CDCl_3$: 1.17(t,J=7,3H,$CH_2\underline{CH_3}$); 2.57(q,J=7,2H,$\underline{CH_2}CH_3$); 2.80(s,6H,$N(\underline{CH_3})_2$); 3.00-3.73(m,8H,$N\underline{CH_2}\underline{CH_2}$,$O\underline{CH_2}\underline{CH_2}N$ and $NC\underline{H_2}$-thienyl); 3.80(s,2H, $NC\underline{H_2}Ar$); 4.40(t,J=7,2H,$O\underline{CH_2}CH_2$); 7.00 and 7.67(2d,J=9,4H,$\underline{Ar}O$-); 7.13-7.57(m,4H,arom.).
27b	$(CH_2)_2N(C_2H_5)_2$	C_2H_5	dioxalate	128 (CH_3CN-iPrOH)	51	$CDCl_3$: 0.90-1.33(m,9H,$CH_2\underline{CH_3}$ and $N(CH_2\underline{CH_3})_2$); 2.40-3.00(m,12H,$\underline{CH_2}CH_3$, $OCH_2\underline{CH_2}N(\underline{CH_2}CH_3)_2$ and $NC\underline{H_2}CH_2$); 3.43(bs,2H,$NC\underline{H_2}$-thienyl); 3.67(s, 2H,$NC\underline{H_2}Ar$); 4.13(t,J=7,2H,$O\underline{CH_2}CH_2$); 6.90 and 7.80(2d,J=9,4H,$\underline{Ar}O$-); 7.00-7.50(m,4H,arom.).
27c	$(CH_2)_2N(nC_4H_9)_2$	C_2H_5	dioxalate	137 (ETOH)	31	CF_3COOH(1) : 0.60-1.83(m,13H,$CH_2(\underline{CH_2})_2\underline{CH_3}$ and $N(CH_2\underline{CH_3})$; 2.67(t,J=7,2H, $\underline{CH_2}CH_3$); 3.13-4.07(m,12H,$NC\underline{H_2}\underline{CH_2}$ and $O\underline{CH_2}\underline{CH_2}N(\underline{CH_2}CH_3)_2$); 4.50(bs, 2H,$NC\underline{H_2}$-thienyl); 4.67(s,2H,$NC\underline{H_2}Ar$) ; 7.07 and 7.83(2d,J=9,4H, $\underline{Ar}O$-); 7.50(bs,4H,arom.).

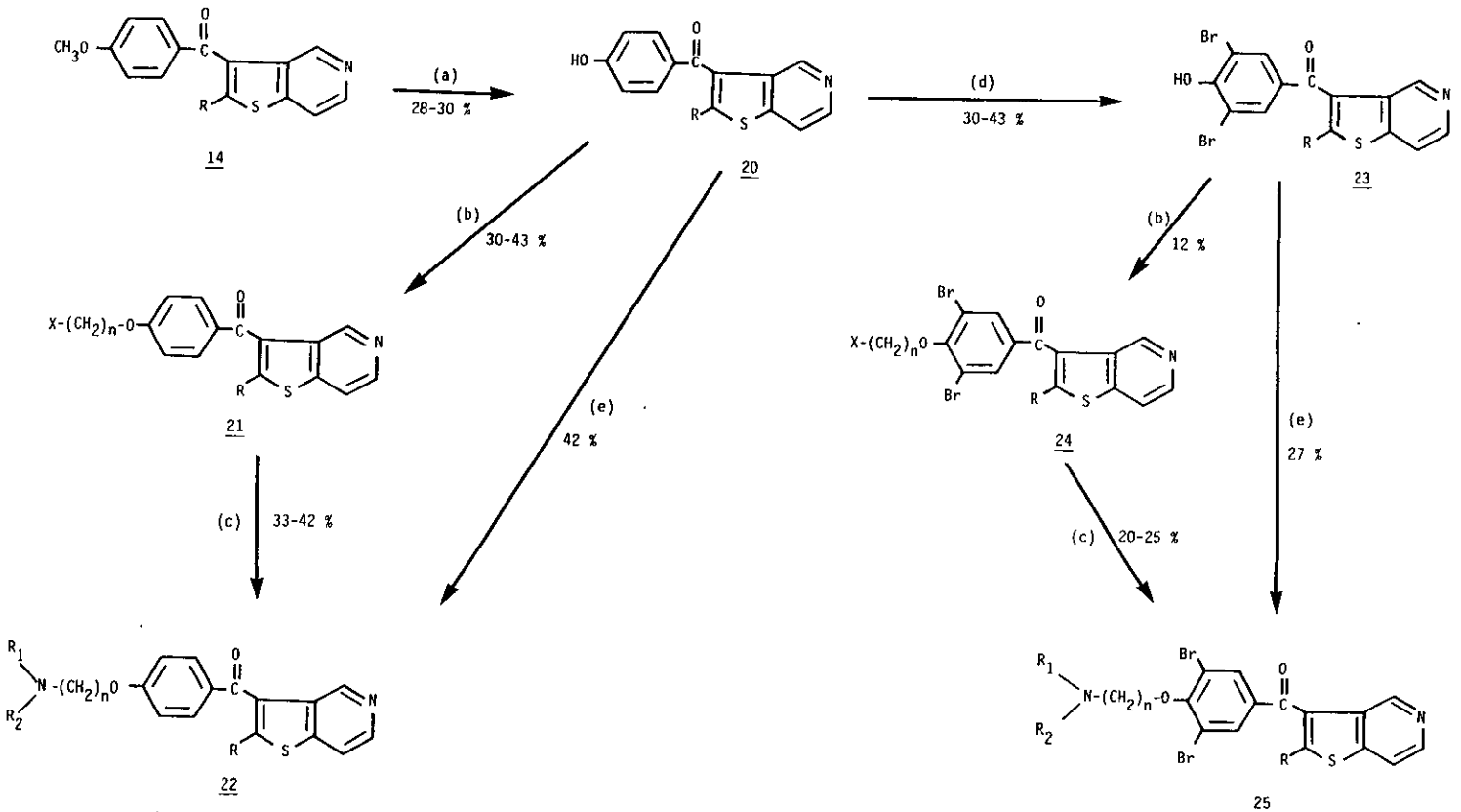
(1): H^1NMR spectrum of dioxalate (2) . satisfactory elementary analyses for the synthesized compounds are obtained.

Table III

Compounds (3)	m.p.(°C) Solvent	Yield (%)	60 MHz H^1NMR (solvent) , δ(ppm), J(Hz) bs: broad singlet; s:singlet; d: doublet; t: triplet; q: quartet; m: multiplet
15 (R = C_2H_5)	70 (iPr_2O)	90	$CDCl_3$: 1.13(t,J=7,3H,$CH_2\underline{CH_3}$); 2.63(q,J=7,2H,$\underline{CH_2}CH_3$); 2.77-3.07(m,2H,$NCH_2\underline{CH_2}$); 3.67-4.00(m,2H,$NCH_2\underline{CH_2}$); 3.83(s,3H,OCH_3); 4.40(bs,2H,NCH_2-thienyl); 4,67(s,2H,OCH_2CCl_3); 6.87-7.73(2d,J=8,4H,$ArOCH_3$).
15 (R = n-C_4H_9)	96 (pentane)	88	$CDCl_3$: 0.60-1.80(m,7H,$(CH_2)_2CH_3$); 2.43-3.00(m,4H,$CH_2(CH_2)_2CH_3$ and NCH_2CH_2); 3.67-4.00(m,2H,NCH_2CH_2); 3.83(s,3H,OCH_3); 4.40(bs,2H,NCH_2-thienyl); 4.67(s,OCH_2CCl_3); 6.90 and 7.73(2d,J=8,4H,$ArOCH_3$).
16 (R = C_2H_5)	128 (1) (*iPrOH-EtOH*)	60	$CDCl_3$: 1.13(t,J=7,3H,CH_2CH_3); 2.40-3.33(m,6H,CH_2CH_3 and NCH_2CH_2); 3.67(bs,2H,NCH_2-thienyl); 3.83(s, 3H,OCH_3); *6.83 and 7.80(2d,J=8,4H,$ArOCH_3$).*
16 (R = n-C_4H_9)	114 (1) (iPrOH-EtOH)	55	$CDCl_3$: 0.58-1.56(m,7H,$(CH_2)_2CH_3$); 2.33-3.27(m,6H,CH_2CH_3 and NCH_2CH_2); 3.63(bs,2H,NCH_2-thienyl); 3.80(s, 3H,OCH_3); 6.87 and 7.73(2d, J=8,4H,$ArOCH_3$).
17	*oil*	95	CF_3COOD : 0.67-2.00(m,7H,$(CH_2)_2CH_3$); 2.57-3.00(m,2H,$CH_2(CH_2)_2CH_3$); 3.27-3.73(m,2H,NCH_2CH_2); 3.87-4.50(m,2H,NCH_2CH_2); 3.90(s,3H,OCH_3); 7.07 and 7.83(2d,J=8,4H,$ArOCH_3$); 8.67(s,1H,N-CH=).
18 (R = C_2H_5)	(2)	90	CF_3COOD : 1.27(t,J=7,3H,CH_2CH_3); 2.83(q,J=7,2H,CH_2CH_3); 3 33-3.80(m,2H,NCH_2CH_2);3.93-4.47(m,2H,NCH_2CH_2); 4.00(s,3H,OCH_3); 5.23(s,2H,NCH_2Ar); 7.07 and 7.83(2d,J=8,4H,$ArOCH_3$); 7.27-7.67(m,4H,arom.); 8 50(s,1H,NCH=).
18 (R = n-C_4H_9)	(2)	90	CF_3COOD : 0.70-2.00(m,7H,$(CH_2)_2CH_3$); 2.60-3.13(m,2H,$CH_2(CH_2)_2CH_3$); 3.33-3.73(m,2H,NCH_2CH_2); 3.93-4.40(m, 2H,NCH_2CH_2); 4.00(s,3H,OCH_3); 5.17(s,2H,NCH_2Ar); 7.07 and 7.87(2d,J=8,4H,$ArOCH_3$); 7.30-7.84 (m,4H,arom.); 8.47(s,1H,NCH=);
19 (R = C_2H_5)	(2)	85	CF_3COOD : 1.17-160(m,3H,CH_2CH_3); 2.60-3.17(m,2H,CH_2CH_3) 4.00(s,3H,OCH_3); 5.90(s,2H,NCH_2Ar); 7.03 and 7.83(2d,J=8,4H,$ArOCH_3$); 7.32-7.84(m,4H,arom.); 8.50(s,2H,NCH=); 9.00(S,1H,NCH=CH).
19 (R = n-C_4H_9)	(2)	82	CF_3COOD : 0.77-2.07(m,7H,$(CH_2)_2CH_3$); 2.83-3.27(m,2H,$CH_2(CH_2)_2CH_3$); 4.00(s,3H,OCH_3); 6.00(s,2H,NCH_2Ar); 7.07 and 7.83(2d,J=8,4H,$ArOCH_3$); *7.73-7.83(m,4H,arom.); 8.57(s,2H,NCH=); 9.00(s,1H,NCH=CH).*

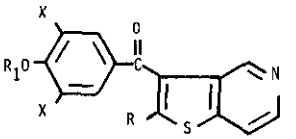
(1) : hydrochloride. (2) : used without purification in the next step . (3) · satisfactory elementary analyses for the synthesized compounds are obtained.

Scheme 4



(a) : aq.48% HBr/acetic acid (2.5/1), 80°C, 4 h.
(b) : N NaOH(1 eq.), r.t., 1 h ; then $Cl(CH_2)_nCl$ (5 eq.), dimethylformamide, r.t., 48 h.
(c) : R_1R_2NH(4 eq.), dimethylformamide, 100°C, 18 h.
(d) : $CH_3COONa.H_2O$ (2.1 eq.), methanol, reflux, 2 h ; then Br_2 (2.2 eq.), acetic acid, r.t., 2h.
(e) : K_2CO_3 (3 eq.), water-dichloroethane, reflux, 1 h. ; then $Cl(CH_2)_nNR_1R_2.HCl$ (1.2 eq.), water-dichloroethane, reflux, 4 h.

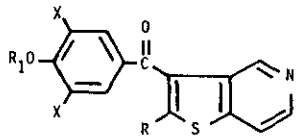
Table IV



Compound (1)	X	R_1	R	Salt	m.p.(°C) solvent	Yield (%)	60 MHz H^1NMR (solvent); δ (ppm); J(Hz) s : singlet; d: doublet; t: triplet; q: quartet; m: multiplet
14a	H	CH_3	C_2H_5	hydrochloride	165 (iPrOH)	51	$CDCl_3$: 1.30(t,J=7,3H,$CH_2\underline{CH_3}$); 2.90(q,J=7,2H,$\underline{CH_2}CH_3$); 3.83(s,3H,$O\underline{CH_3}$)6.70-8.83 (m,7H,arom.).
14b	H	CH_3	n-C_4H_9	-	oil	31	$CDCl_3$: 0.67-1.93(m,9H,$C_4\underline{H_9}$); 3.83(s,3H,$O\underline{CH_3}$); 6.80-8.00(m,5H,$\underline{Ar}OCH_3$ and NCH=$\underline{CH}$), 8.33 (d,J=6,1H,NC$\underline{H}$=CH); 8.60(s,1H,N=$\underline{CH}$).
20a	H	H	C_2H_5	hydrochloride	188 (*EtOH*)	28	DMSO-d_6: 1.27(t,J=7,3H,$CH_2\underline{CH_3}$); 2.87(q,J=7,2H,$\underline{CH_2}CH_3$); 7.00 and 7.83(2d,J=9,4H,$\underline{Ar}$OH). 8.07(d,J=6,1H,NCH=$\underline{CH}$); 8.47(d,J=6,1H,NC$\underline{H}$=CH); 8.73(s,1H,N=$\underline{CH}$).
20b	H	H	n-C_4H_9	hydrochloride	181 (iPrOH)	30	DMSO-d_6: 0.60-2.00(m,7H,$(\underline{CH_2})_2\underline{CH_3}$); 2.57-3.00(m,2H,$\underline{CH_2}(CH_2)_2CH_3$); 6.80 and 7.60(2d,J=9, 4H,$\underline{Ar}$OH); 7.93(d,J=6,1H,NCH=$\underline{CH}$); 8.33(d,J=6,1H,NC$\underline{H}$=CH); 8.56(s,1H,N=$\underline{CH}$).
21a	H	$(CH_2)_3Br$	C_2H_5	-	oil	30	DMSO-d_6: 1.23(t,J=7,3H,$CH_2\underline{CH_3}$); 2.00-2.57(m,2H,$O\underline{CH_2}\underline{CH_2}CH_2Br$); 2.83(q,J=7,2H,$\underline{CH_2}CH_3$); 3.16-4.00(m,2H,$OCH_2\underline{CH_2}\underline{CH_2}Br$); 4.20(t,J=6,2H,$O\underline{CH_2}(CH_2)_2Br$); 7.07 and 7.73 (2d,J=9,4H,$\underline{Ar}$O-); 8.03(d,J=6,1H,NCH=$\underline{CH}$); 8.40(d,J=6,1H,NC$\underline{H}$=CH); 8.60(s,1H,N=$\underline{CH}$).
21b	H	$(CH_2)_3Cl$	C_2H_5	-	oil	43	DMSO-d_6: 1.20(t,J=7,3H,$CH_2\underline{CH_3}$); 2.00-2.47(m,2H,$O\underline{CH_2}\underline{CH_2}CH_2Cl$); 2.83(q,J=7,2H,$\underline{CH_2}CH_3$); 3.57-4.00(m,2H,$OCH_2\underline{CH_2}\underline{CH_2}Cl$);4.20(t,J=6,2H,$O\underline{CH_2}CH_2CH_2Cl$); 7.07 and 7.77(2d, J=9,4H,$\underline{Ar}$O-); 8.00(d,J=6,1H,NCH=$\underline{CH}$); 8.40(d,J=6,1H,NC$\underline{H}$=CH); 8.67(s,1H,N=$\underline{CH}$).
22a(2)	H	$(CH_2)_2N(C_2H_5)_2$	C_2H_5	dioxalate	132 (EtOH)	42	$CDCl_3$: 1.07(t,J=7,3H,$CH_2\underline{CH_3}$); 1.17(t,J=7,6H,$N(CH_2\underline{CH_3})_2$); 2.33-3.13(m,8H,$\underline{CH_2}CH_3$, $N(\underline{CH_2}CH_3)_2$ and $NCH_2\underline{CH_2}O$); 4.07(t,J=6,2H,$O\underline{CH_2}CH_2$); 6.83 and 7.80(2d,J=9,4H, $\underline{Ar}$O-); 7.93(d,J=6,1H,NCH=$\underline{CH}$); 8.33(d,J=6,1H,NC$\underline{H}$=CH); 8.67(s,1H,N=$\underline{CH}$).
22b(3)	H	$(CH_2)_3N(CH_3)_2$	C_2H_5	dioxalate	112 (EtOH)	33	$CDCl_3$: 1.17(t,J=7,3H,$CH_2\underline{CH_3}$); 2.20(s,6H,$N(\underline{CH_3})_2$); 1.73-2.60(m,4H,$OCH_2\underline{CH_2}\underline{CH_2}N<$ and $>N\underline{CH_2}$-); 2.87(q,J=7,2H,$\underline{CH_2}CH_3$); 4.07(t,J=6,2H,$O\underline{CH_2}$-); 6.87 and 7.63(2d, J=9,4H,$\underline{Ar}$O-); 7.90(d,J=6,1H,NCH=$\underline{CH}$); 8.33(d,J=6,1H,NC$\underline{H}$=CH); 8.67(s,1H,N=$\underline{CH}$).
22c(3)	H	$(CH_2)_3N(nC_4H_9)_2$	C_2H_5	dioxalate	68 (EtOH)	42	DMSO-d_6: 0.67-2.67(m,27H,$CH_2\underline{CH_3}$ and $OCH_2\underline{CH_2}\underline{CH_2}N(n\text{-}C_4\underline{H_9})_2$); 2.80(q,J=7,2H,$\underline{CH_2}CH_3$); 4.07(t,J=6,2H,$O\underline{CH_2}$-); 6.93 and 7.67(2d,J=9,4H,$\underline{Ar}$O-); 7.90(d,J=6,1H,NCH=$\underline{CH}$); 8.33(d,J=6,1H,NC$\underline{H}$=CH); 8.57(s,1H,N=$\underline{CH}$).

(1) satisfactory elementary analysis for the synthesized compounds are obtained ; (2) direct alkylation ; (3) two-steps alkylation (cf. scheme 4)

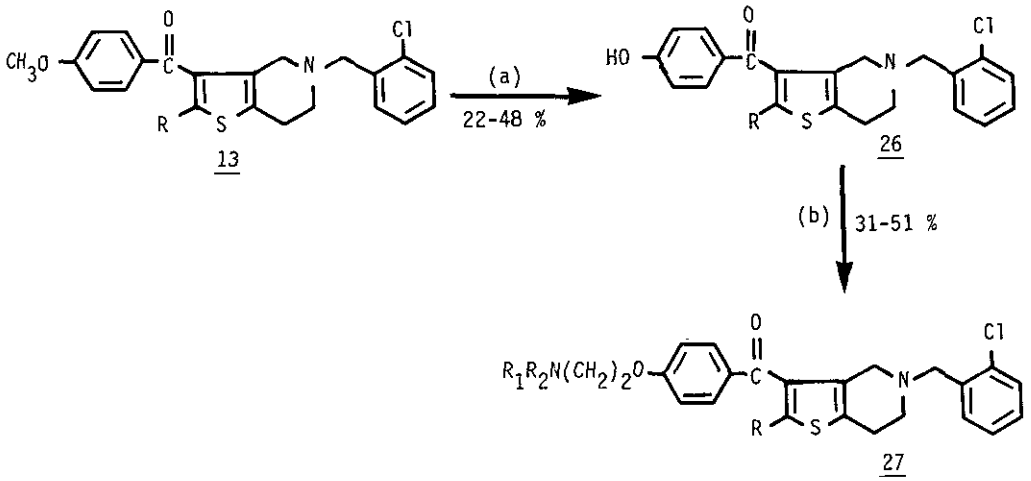
Table IV (suite)



Compound (1)	X	R_1	R	Salt	m.p. (°C) solvent	Yield (%)	60 MHz H^1NMR (solvent); δ(ppm); J(Hz) s : singlet; d : doublet; t: triplet; q: quartet; m: multiplet
23a	Br	H	C_2H_5	hydrochloride	216 (EtOH-MeOH)	30	DMSO-d_6 : 1.23(t,J=7,3H,$CH_2\underline{CH_3}$); 2.87(q,J=7,2H,$\underline{CH_2}CH_3$); 7.90(s,2H,ArO); 8.20(d,J=6,1H, NCH=CH); 8.50(d,J=6,1H,NCH=CH); 8.80(s,1H,N=CH).
23b	Br	H	C_4H_9	hydrochloride	198 (iPrOH-EtOH)	43	$CDCl_3$: 0.80-2.00(m,7H,$CH_2(\underline{CH_2})_2\underline{CH_3}$); 2.90(t,J=7,2H,$\underline{CH_2}(CH_2)_2CH_3$); 7.67(d,J=6,1H; NCH=CH); 7.83(s,2H,ArO-); 8.33(d,J=6,1H,NCH=CH); 8.67(s,1H,N=CH).
24a	Br	$(CH_2)_3Cl$	C_2H_5	-	oil	12	DMSO-d_6 : 1.27(t,J=7,3H,$CH_2\underline{CH_3}$); 2.23(t,J=6,2H,$OCH_2\underline{CH_2}CH_2Cl$); 2.83(t,J=7,2H,$\underline{CH_2}CH_3$); 3.83(t,J=6,2H,$OCH_2CH_2\underline{CH_2}Cl$); 4.33(t,J=6,2H,$\underline{OCH_2}CH_2CH_2Cl$); 7.93(s,2H,ArO-); 8.00(d,J=6,1H,NCH=CH); 8.33(d,J=6,1H,NCH=CH), 8.67(s,1H,N=CH).
25a(2)	Br	$(CH_2)_2N(C_2H_5)_2$	C_2H_5	dioxalate	130 (iPrOH)	27	$CDCl_3$: 1.07(t,J=7,3H,$CH_2\underline{CH_3}$); 1.20(t,J=7,6H,$N(CH_2\underline{CH_3})_2$); 2.40-3.13(m,10H,$\underline{CH_2}CH_3$ and $OCH_2(\underline{CH_2})_2N(\underline{CH_2}CH_3)_2$); 4.13(t,J=6,2H,$\underline{OCH_2}CH_2CH_2N\lesssim$); 7.67(d,J=6,2H, NCH=CH); 7.90(s,2H,ArO-); 8.37(d,J=6,1H,NCH=CH); 8.67(s,1H,N=CH).
25b(3)	Br	$(CH_2)_3N(CH_3)_2$	C_2H_5	dioxalate	120 (iPrOH)	20	$CDCl_3$: 1.27(t,J=7,3H,$CH_2\underline{CH_3}$); 1.93-3.67(m,6H,$\underline{CH_2}CH_3$ and $OCH_2(\underline{CH_2})_2N\lesssim$); 2.50(s,6H, $N(\underline{CH_3})_2$); 4.33(t,J=6,2H,$\underline{OCH_2}CH_2CH_2N\lesssim$); 7.73(d,J=6,1H,NCH=CH); 7.90(s, 2H,ArO-); 8.39(d,J=6,1H,NCH=CH); 8.71(s,1H,N=CH).
25c(3)	Br	$(CH_2)_3N(nC_4H_9)_2$	C_2H_5	-	oil	25	$CDCl_3$: 0.73-1.83(m,19H,$CH_2\underline{CH_3}$and $OCH_2\underline{CH_2}CH_2N(CH_2)_2(\underline{CH_2})_2(\underline{CH_3})_2$);2.57-3.13(m,8H,$\underline{CH_2}CH_3$ & $-\underline{CH_2}N(\underline{CH_2}(CH_2)_2CH_3)_2$); 4.20(t,J=6,2H,$OCH_2$-); 7.70(d,J=6,1H,NCH=CH);7.92(s, 2H,ArO-); 8.37(d,J=6,1H,NCH=CH); 8.70(s,1H,N=CH).

(1) Satisfactory elementary analysis for the synthesized compounds are obtained;(2) direct alkylation ; (3) two-steps alkylation (cf. scheme 4)

Scheme 5



(a) : aq. 48 % HBr/acetic acid (3/1), 80°C, 4h.

(b) : K_2CO_3 (3 eq.), water-dichloromethane, reflux, 1 h. ; then $R_1R_2N(CH_2)_2Cl$. HCl (1.2 eq.) , water-dichloromethane, reflux, 4 h.

Dimethylation of 4,5,6,7-tetrahydro-thieno(3,2-c)pyridines 13 gives phenols 26. Grafting of the dialkylaminoethyl chain on the phenolic function of compounds 26, using direct alkylation with N-(2-chloroethyl- N,N-dialkylamines, according to the previous synthetic pathway , gives 4,5,6,7-tetrahydro thieno(3,2-c)pyridines 27 (5 : X = H, n=2).

Table IV summarizes the physicochemical characteristics of the new 2,3-disubstituted 4,5,6,7-tetrahydro-thieno(3,2-c)pyridines.

All thienopyridines grafted with the pharmacophoric 4-dialkylaminoalkoxy-benzoyl groups are submitted to pharmacological screening.

ACKNOWLEDGEMENTS : Alain Cabrol, Marguerite Miquel, Michel Roc and Andrée Saint-Blancat rendered skilful technical assistance.

REFERENCE AND NOTES

1. H. Inon, H. de Vogelaer, M. Descamps, J. Bauthier, M. Colot, R. Charlier, Eur.J.Med.Chem.,1977,12,483.

2. French Patent 1,339,389 ; Chem.Abst.,1964,60,2892g.
Belg. Patent 766 392 ; Chem.Abst.,1972,76,140493g.

3. N. Claeys, C. Goldenberg, R. Wanderstrick, E. Deray, M. Descamps, G. Delaunois, J. Bauthier and R. Charlier, Chim.Ther.,1972,7,377.

4. G. Rosseels, M. Peiven, H. Inion, E. Deray, M. Prost, M. Descamps, J. Bauthier, J. Richard, C. Tornay, M. Colot and M. de Claviere, Eur.J.Med.Chem.,1982,17,581.

5. R. Charlier, G. Deltour, A. Baudine and F. Chaillet, Arzneim.Forsch.,1968,18,1408.

6. Aminodarone trademark : Cordarone® ; Benzbromarone trademark : Desuric® ;Benziodarone trademark : Amplivix® ;Butoprozine : clinical studies.

7. Pharmacological review on ticlopidine : E. Panak, J.P. Maffrand, C. Picard-Fraire, E. Vallée, J. Blanchard and R. Roncucci, Haemostasis,1983,13(S1),1-52.

8. M. Podesta, D. Aubert and J.C. Ferrand, Eur.J.Med.Chem.,1974,9,487.
J.J. Thebault, C.E. Blatrix, J.F. Blanchard and E.A. Panak, Clin.Pharmacol.Ther.,1975,18,485.

9. G.W. Gribble, R.M. Leese and B.E. Evans, Synthesis, 1977,172.

10. F. Clemence, O. Le Martret, R. Fournex, G.Plassard and M. Dagnaud,Eur.J.Med.Chem.,1974,9,390.

11. G.W. Gribble, W.J. Kelly and S.E. Emery, Synthesis,1978,763.

12. S. Gronowitz and E. Sandberg, Arkiv Kemi,1970,32,217

13. K. Sakane, Bull.Chem.Soc.Japan, 1974,47,1297.

14. M. Descamps and F. Binon, Bull.Soc.Chem.Belges,1962,71,579.

15. (a) R. Filler,Chem.Revs.,1963,63,21.
(b) E. Eckhart, Magy.Kem.Foly.,1964,70,296 ; Chem.Abst.,1964,61,13344d.

16. T.L. Ho, Synthesis,1972,12,702.

17. L. Long and A. Burger, J.Org.Chem.,1941,6,852.

18. C. Goldenberg, R. Wanderstrick, C. van Meerbeek, N. Claeys, E. Deray, M. Descamps, G. Delannois, J. Bauthier and R. Charlier, Chim.Therap.,1972,7,369.

Received, 13th February, 1984