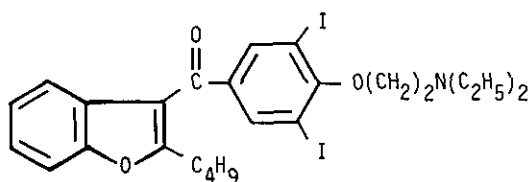
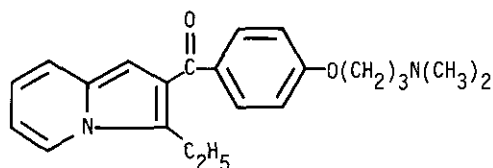


SYNTHESES OF 2-ALKYL-3-(4-DIALKYLAMINOALKOXY-BENZOYL)-THIENO(3,2-c)PYRIDINES

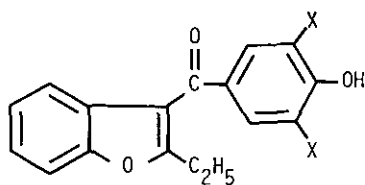
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Abstract - This paper deals with the syntheses of thieno(3,2-c)pyridinic isosteres 4 of two potent anti-anginal and/or antiarrhythmic agents : amiodarone 1 and butoprazin 2. The corresponding tetrahydrogenated analogs are also synthesized.

The grafting on various heterocycles (indole¹, benzo(b)furan², benzo(b)thiophene³, indolizine⁴) of the pharmacophoric 4-dialkylaminoalkoxy-benzoyl group gives compounds with remarkable anti-anginal and/or anti-arrhythmic⁵ activities such as amiodarone⁶ 1 and butoprazin⁶ 2.

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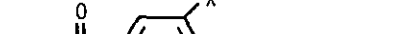
In this class of pharmacologically interesting products, we can add the phenols 3 which are potent uricosuric agents.

3

X = Br : benzbromarone⁶

X = I : benziodarone⁶

Furthermore, the platelet antiaggregating and antithrombotic⁷ activities of ticlopidine⁸ 6 lead us to synthesize various thieno(3,2-c)pyridines.

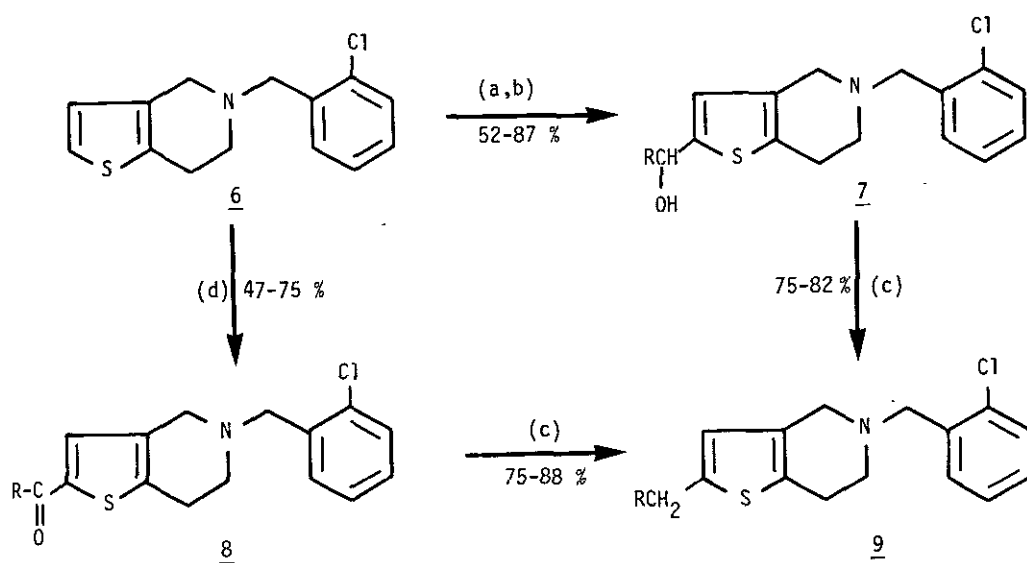


 4



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Scheme 1



— 1236 —

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 = CH₂CH₃) 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

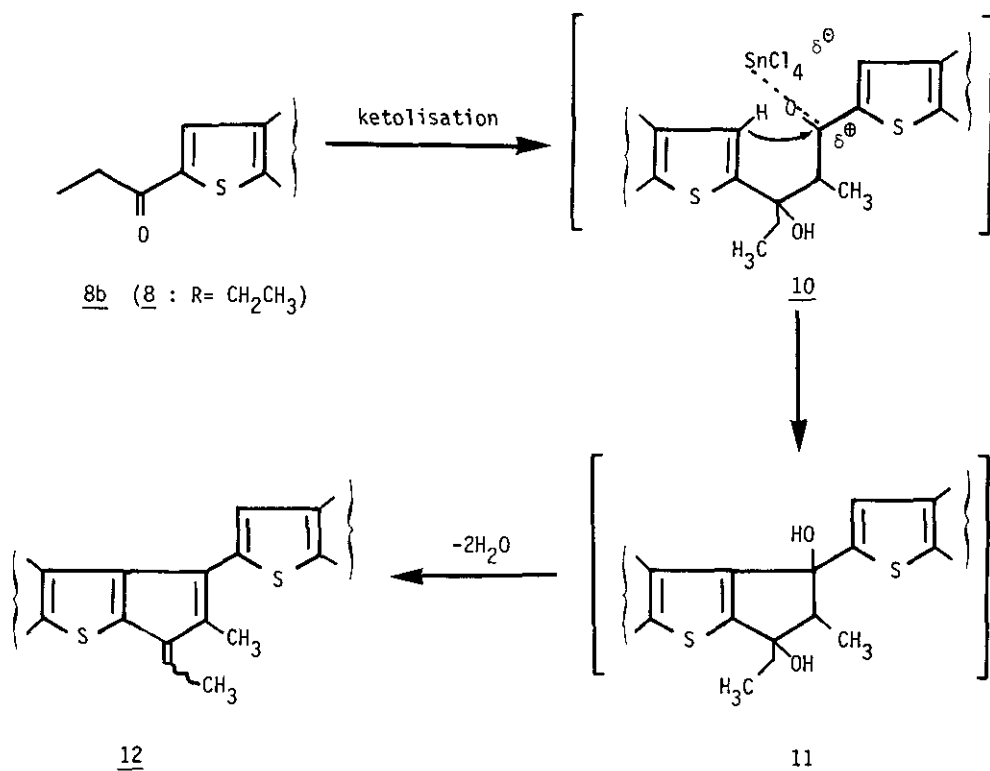
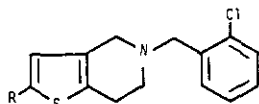


Table I summarizes the physicochemical characteristics of the new C₂-alkylated tetrahydro-thieno(3,2-c)pyridines.

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.
<u>7a</u>	CH(OH)CH ₃	-	oil	87	CDCl ₃ : 1.37(d, J=6, 3H, CH ₃) ; 2.70(bs, 4H, NCH ₂ CH ₂) ; 3.43(bs, 2H, NCH ₂ -thienyl) ; 3.70(s, 2H, NCH ₂ Ar) ; 4.80(q, 1H, CHOHCH ₃) ; 6.40(s, 1H, thiophen) ; 6.93-7.27(m, 4H, arom.).
<u>7b</u>	CH(OH)CH ₂ CH ₃	-	oil	52	CDCl ₃ : 0.80-1.93(m, 7H, (CH ₂) ₂ CH ₃) ; 2.80(bs, 4H, NCH ₂ CH ₂) ; 3.53(bs, 2H, NCH ₂ -thienyl) ; 3.60(s, 2H, NCH ₂ Ar) ; 4.73(t, J=7, 1H, CHOHCH ₂) ; 6.50(s, 1H, thiophen) ; 7.06-7.60(m, 4H, arom.).
<u>8a</u>	COCH ₃	oxalate	152 (iPrOH-AcOEt)	55	CDCl ₃ : 2.43(s, 3H, COCH ₃) ; 2.87(bs, 4H, NCH ₂ CH ₂) ; 3.60(bs, 2H, NCH ₂ -thienyl) ; 3.80(s, 2H, NCH ₂ Ar) ; 7.06-7.60(m, 5H, thiophen and arom.).
<u>8b</u>	COCH ₂ CH ₃	maleate	120 (iPrOH-iPr ₂ O)	47	CDCl ₃ : 1.17(t, J=7, 3H, CH ₂ CH ₃) ; 2.80(q, J=7, 2H, CH ₂ CH ₃) ; 2.87(bs, 4H, NCH ₂ CH ₂) ; 3.60(bs, 2H, NCH ₂ -thienyl) ; 3.80(s, 2H, NCH ₂ Ar) ; 7.00-7.57(m, 5H, thiophen and arom.).
<u>8c</u>	CO(CH ₂) ₂ CH ₃	maleate	188 (MeOH)	75	CDCl ₃ : 0.76-1.13(m, 3H, CH ₂ CH ₃) ; 1.33-2.00(m, 2H, CH ₂ CH ₃) ; 2.47-3.00(m, 6H, COCH ₂ and NCH ₂ CH ₂) ; 3.47(bs, 2H, NCH ₂ -thienyl) ; 3.57(s, 2H, NCH ₂ Ar) ; 7.01-7.17(m, 5H, thiophen and arom.).
<u>8d</u>	CO(CH ₂) ₅ CH ₃	maleate	110 (EtOH-Et ₂ O)	73	CDCl ₃ : 0.73-1.93(m, 11H, (CH ₂) ₄ CH ₃) ; 2.57-3.00(m, 6H, COCH ₂ and NCH ₂ CH ₂) ; 3.57(bs, 2H, NCH ₂ -thienyl) ; 3.80(s, 2H, NCH ₂ Ar) ; 7.00-7.57(m, 4H, arom.).
<u>9a</u>	C ₂ H ₅	hydrochloride	140 (H ₂ O)	82(1)	CDCl ₃ : 1.23(t, J=7, 3H, CH ₂ CH ₃) ; 2.73(q, J=7, 2H, CH ₂ CH ₃) ; 2.80(bs, 4H, NCH ₂ CH ₂) ; 3.50(bs, 2H, NCH ₂ -thienyl) ; 3.73(s, 2H, NCH ₂ Ar) ; 6.33(s, 1H, thiophen) ; 7.00-7.67(m, 4H, arom.).
<u>9b</u>	n-C ₄ H ₉	hydrochloride	195 (MeOH)	75(2)	CDCl ₃ : 0.73-1.73(m, 9H, (CH ₂) ₃ CH ₃) ; 2.40-2.93(m, 4H, NCH ₂ CH ₂) ; 3.47(bs, 2H, NCH ₂ -thienyl) ; 3.73(s, 2H, NCH ₂ Ar) ; 6.33(s, 1H, thiophen) ; 7.00-7.67(m, 4H, arom.).
<u>9c</u>	n-C ₇ H ₁₅	hydrochloride	150 (iPrOH-iPr ₂ O)	88(2)	CDCl ₃ : 0.67-1.93(m, 15H, (CH ₂) ₆ CH ₃) ; 2.60-3.00(m, 4H, NCH ₂ CH ₂) ; 3.60(bs, 2H, NCH ₂ -thienyl) ; 3.87(s, 2H, NCH ₂ Ar) ; 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 medium¹², were unsuccessful. Careful oxidation, with N-chlorosuccinimide in an alkaline medium¹³, of tetrahydrothieno(3,2-c)pyridine 16b (16 : R = n-C₄H₉) gives dihydrothieno(3,2-c)pyridine 17, but this one could not be aromatized, with 10 % Pd/C in refluxed ethanol¹⁴, in thieno(3,2-c)pyridine 14b (14 : R = n-C₄H₉). However, careful oxidation, with N-bromosuccinimide in chloroform¹⁵, 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]octane¹⁶ 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 medium¹⁷, demethylation of thieno(3,2-c)pyridines 14 gives phenols 20 (Scheme 4).

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

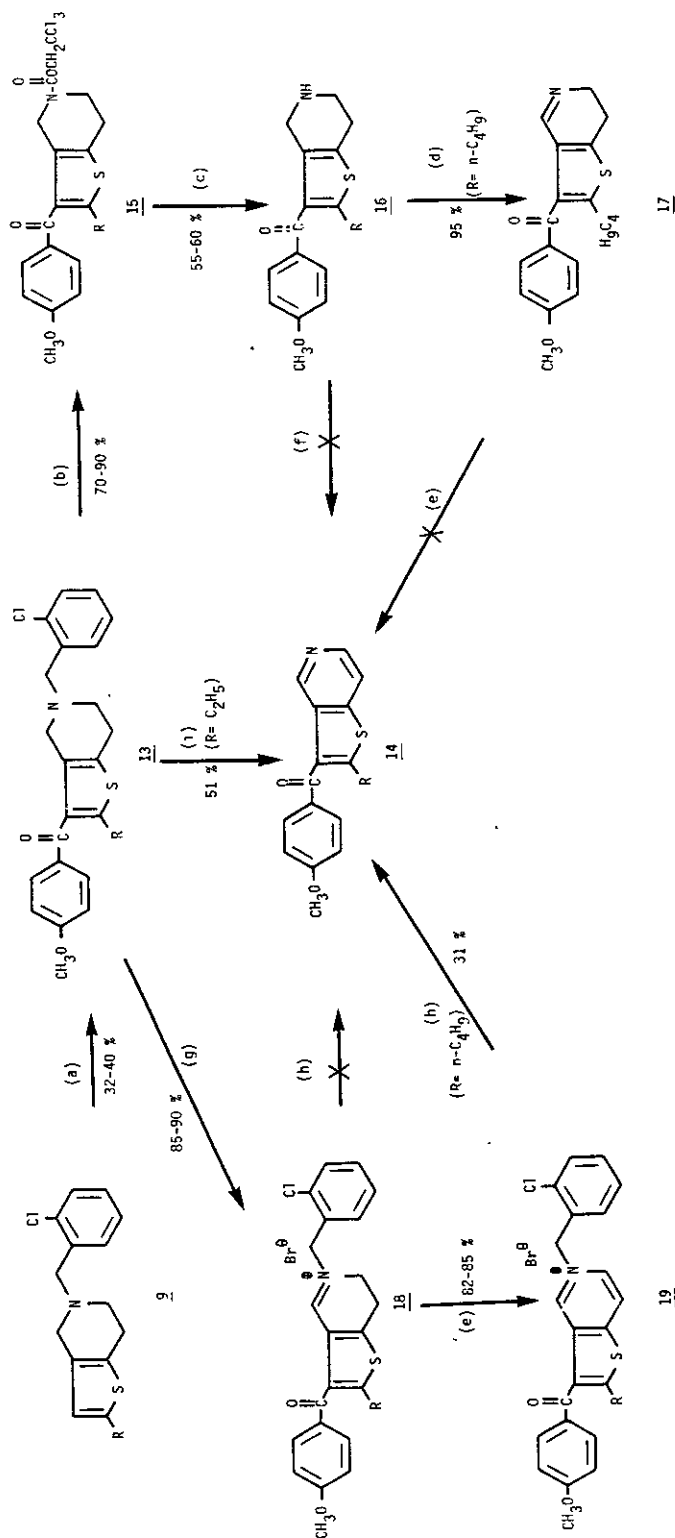
- direct alkylation of phenates with N-chloroalkyl N,N-dialkylamines¹⁸, easy to access, giving thieno(3,2-c)pyridines 22 (4 : X = H).
- alkylation of phenates with 1,2-dichloroethane or 1,3-dichloropropane¹⁸, giving O-chloroalkyl thieno(3,2-c)pyridines 21 (X = Cl) : those condense with secondary amines 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 medium¹⁸. 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-OCH₃)C₆H₄COCl (1.3 eq.), SnCl₄ (3.4 eq.), 1,2-dichloroethane, r.t., 20 h.

(b) : Cl₃CH₂COCl (1.3 eq.), toluene, reflux, 5 h.

(c) : Zn powder (2.3 eq.), acetic acid, 50°C, 5 h.

(d) : N-chlorosuccinimide (1.5 eq.), diethyl oxide, r.t., 2 h.; then 1.1 N ethanolic KOH (1 eq.), diethyl oxide, r.t., 3 h.

(e) : 10% Pd/C (0.6 eq.), ethanol, reflux, overnight.

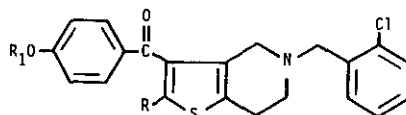
(f) : K₃Fe(CN)₆ (4 eq.), KOH (2.2 eq.), water-dioxane, r.t., overnight.

(g) : N-bromosuccinimide (1.1 eq.), chloroform, r.t., 3 h.

(h) : 1,4-diazabicyclo[2.2.2]octane (2 eq.), dimethylformamide, 120°C, 6 h.

(i) : 10% Pd/C (0.8 eq.), diphenyl oxide, 260°C, 0.5 h.

Table II



Compound (2)	R ₁	R	Salt	mp. (°C) Solvent	Yield (%)	60MHz ¹ H-NMR(solvent) ; δ(ppm) ; J(Hz) s: singlet; bs: broad singlet; d: doublet; t: triplet; m: multiplet
<u>13a</u>	CH ₃	C ₂ H ₅		80 (iPrOH)	32	CDCl ₃ : 1.13(t, J=7, 3H, CH ₂ CH ₃); 2.63(q, J=7, 2H, CH ₂ CH ₃); 2.83(bs, 4H, NCH ₂ CH ₂); 3.43(bs, 2H, NCH ₂ -thienyl); 3.70(s, 2H, NCH ₂ Ar); 3.83(s, 3H, OCH ₃); 6.87 and 7.73(2d, J=8, 4H, ArOCH ₃); 7.00-7.57(m, 4H, arom.).
<u>13b</u>	CH ₃	n-C ₄ H ₉	hydrochloride	180 (EtOH-iPrOH)	42	CDCl ₃ : 0.60-1.80(m, 7H, (CH ₂) ₂ CH ₃); 2.60(t, J=7, 2H, CH ₂ (CH ₂) ₂ CH ₃); 2.80(bs, 4H, NCH ₂ CH ₂); 3.40(bs, 2H, NCH ₂ -thienyl); 3.67(s, 2H, NCH ₂ Ar); 3.83(s, 3H, OCH ₃); 6.87 and 7.73(2d, J=8, 4H, ArOCH ₃); 7.00-7.53(m, 4H, arom.).
<u>26a</u>	H	C ₂ H ₅	hydrochloride	240 (EtOH-MeOH)	40	DMSO-d ₆ : 1.07(t, J=7, 3H, CH ₂ CH ₃); 2.57(q, J=7, 2H, CH ₂ CH ₃); 2.80(bs, 4H, NCH ₂ CH ₂); 3.33(bs, 2H, NCH ₂ -thienyl); 3.67(s, 2H, NCH ₂ Ar); 6.80 and 7.53(2d, J=8, 4H, ArOH); 7.00 and 7.47(m, 4H, arom.).
<u>26b</u>	H	n-C ₄ H ₉	hydrochloride	202 (CH ₃ CN)	22	CDCl ₃ : 0.60-1.60(m, 7H, CH ₂ (CH ₂) ₂ CH ₃); 2.47(t, J=7, 2H, CH ₂ (CH ₂) ₂ CH ₃); 2.93(bs, 4H, NCH ₂ CH ₂); 3.57(bs, 2H, NCH ₂ -thienyl); 3.83(s, 2H, NCH ₂ Ar); 6.50 and 7.50(2d, J=8, 4H, ArOH); 7.00-7.47(m, 4H, arom.).
<u>27a</u>	(CH ₂) ₂ N(CH ₃) ₂	C ₂ H ₅	dioxalate	134 (iPrOH)	36	CDCl ₃ : 1.17(t, J=7, 3H, CH ₂ CH ₃); 2.57(q, J=7, 2H, CH ₂ CH ₃); 2.80(s, 6H, N(CH ₃) ₂); 3.00-3.73(m, 8H, NCH ₂ CH ₂ OCH ₂ CH ₂ N and NCH ₂ -thienyl); 3.80(s, 2H, NCH ₂ Ar); 4.40(t, J=7, 2H, OCH ₂ CH ₂); 7.00 and 7.67(2d, J=9, 4H, ArO-); 7.13-7.57(m, 4H, arom.).
<u>27b</u>	(CH ₂) ₂ N(C ₂ H ₅) ₂	C ₂ H ₅	dioxalate	128 (CH ₃ CN-iPrOH)	51	CDCl ₃ : 0.90-1.33(m, 9H, CH ₂ CH ₃ and N(CH ₂ CH ₃) ₂); 2.40-3.00(m, 12H, CH ₂ CH ₂ OCH ₂ CH ₂ N(CH ₂ CH ₃) ₂ and NCH ₂ CH ₂); 3.43(bs, 2H, NCH ₂ -thienyl); 3.67(s, 2H, NCH ₂ Ar); 4.13(t, J=7, 2H, OCH ₂ CH ₂); 6.90 and 7.80(2d, J=9, 4H, ArO-); 7.00-7.50(m, 4H, arom.).
<u>27c</u>	(CH ₂) ₂ N(nC ₄ H ₉) ₂	C ₂ H ₅	dioxalate	137 (EtOH)	31	CF ₃ COOH(1) : 0.60-1.83(m, 13H, CH ₂ (CH ₂) ₂ CH ₃ and N(CH ₂ CH ₃) ₂); 2.67(t, J=7, 2H, CH ₂ CH ₃); 3.13-4.07(m, 12H, NCH ₂ CH ₂ OCH ₂ CH ₂ N(CH ₂ CH ₃) ₂); 4.50(bs, 2H, NCH ₂ -thienyl); 4.67(s, 2H, NCH ₂ Ar); 7.07 and 7.83(2d, J=9, 4H, ArO-); 7.50(bs, 4H, arom.).

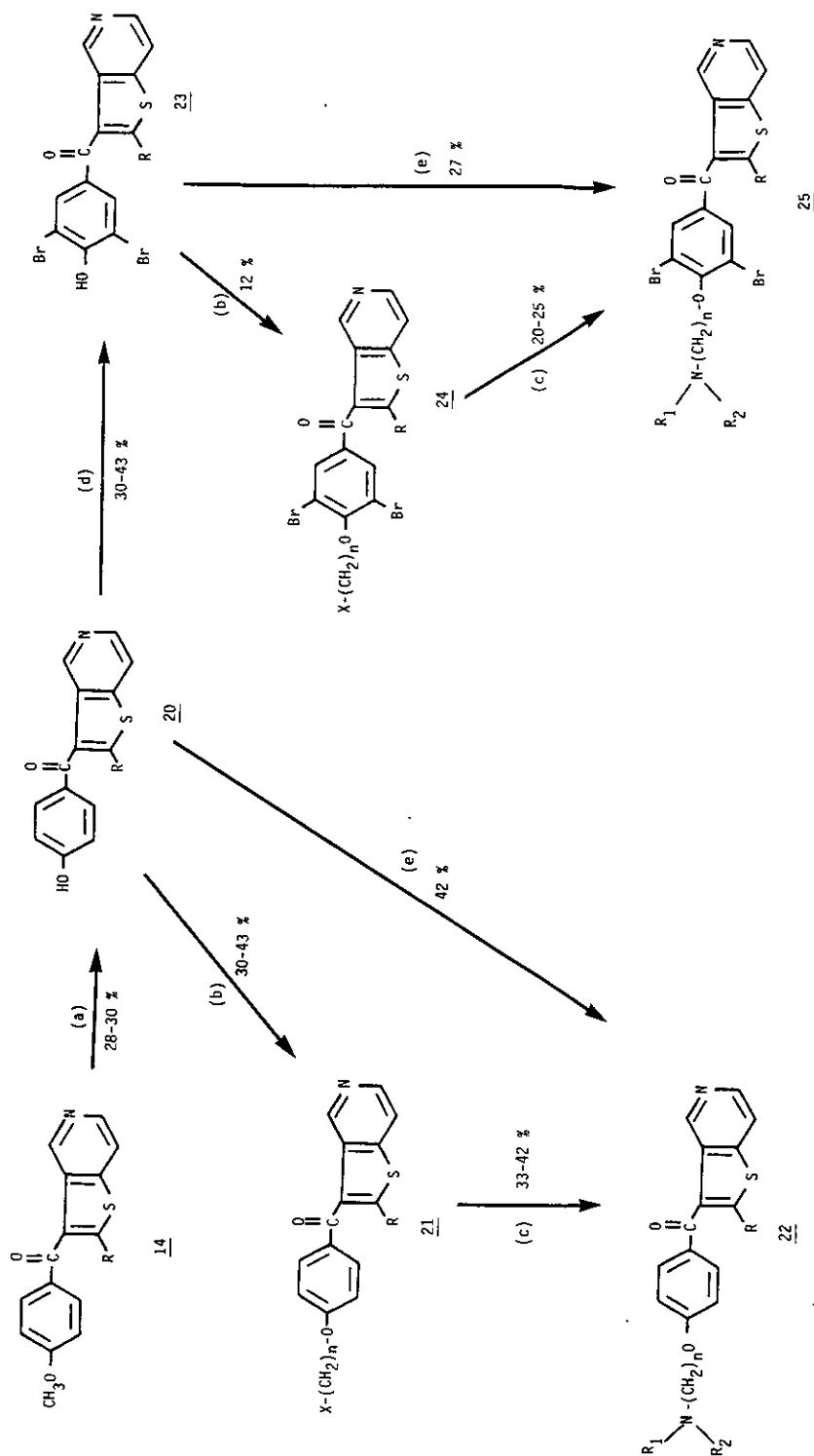
(1): ¹H-NMR spectrum of dioxalate (2). satisfactory elementary analyses for the synthesized compounds are obtained.

Table III

Compounds (3)	m.p.(°C) Solvent	Yield (%)	60 MHz ^1H NMR (solvent) , δ (ppm), J(Hz) bs: broad singlet; s:singlet; d: doublet; t: triplet; q: quartet; m: multiplet
<u>15</u> (R = C_2H_5)	70 (iPr ₂ O)	90	CDCl_3 : 1.13(t, J=7, 3H, CH_2CH_3); 2.63(q, J=7, 2H, CH_2CH_3); 2.77-3.07(m, 2H, 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, 2H, OCH_2CCl_3); 6.87-7.73(2d, J=8, 4H, ArOCH_3).
<u>15</u> (R = n- C_4H_9)	96 (pentane)	88	CDCl_3 : 0.60-1.80(m, 7H, $(\text{CH}_2)_2\text{CH}_3$); 2.43-3.00(m, 4H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$ 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).
<u>16</u> (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).
<u>16</u> (R = n- C_4H_9)	114 (1) (iPrOH-EtOH)	55	CDCl_3 : 0.58-1.56(m, 7H, $(\text{CH}_2)_2\text{CH}_3$); 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).
<u>17</u>	oil	95	CF_3COOD : 0.67-2.00(m, 7H, $(\text{CH}_2)_2\text{CH}_3$); 2.57-3.00(m, 2H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$); 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 ² and 7.83(2d, J=8, 4H, ArOCH_3); 8.67(s, 1H, $\text{N}=\text{CH}$).
<u>18</u> (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, $\text{NCH}=\text{}$).
<u>18</u> (R = n- C_4H_9)	(2)	90	CF_3COOD : 0.70-2.00(m, 7H, $(\text{CH}_2)_2\text{CH}_3$); 2.60-3.13(m, 2H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$); 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, $\text{NCH}=\text{}$).
<u>19</u> (R = C_2H_5)	(2)	85	CF_3COOD : 1.17-1.60(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, $\text{NCH}=\text{}$); 9.00(s, 1H, $\text{NCH}=\text{CH}$).
<u>19</u> (R = n- C_4H_9)	(2)	82	CF_3COOD : 0.77-2.07(m, 7H, $(\text{CH}_2)_2\text{CH}_3$); 2.83-3.27(m, 2H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$); 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, $\text{NCH}=\text{}$); 9.00(s, 1H, $\text{NCH}=\text{CH}$).

(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.

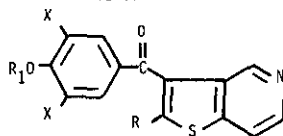
 (b) : H NaOH (1 eq.), r.t., 1 h; then Cl(CH₂)_nCl (5 eq.), dimethylformamide, r.t., 48 h.

 (c) : R₁R₂NH (4 eq.), dimethylformamide, 100°C, 18 h.

 (d) : CH₃COONa.H₂O (2.1 eq.), methanol, reflux, 2 h; then Br₂ (2.2 eq.), acetic acid, r.t., 2 h.

 (e) : K₂CO₃ (3 eq.), water-dichloroethane, reflux, 1 h; then Cl(CH₂)_nNR₁R₂ (1.2 eq.), water-dichloroethane, reflux, 4 h.

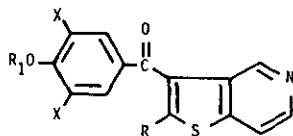
Table IV



Compound (1)	X	R ₁	R	Salt	m.p. (°C) solvent	Yield (%)	60 MHz ¹ H-NMR (solvent); δ (ppm); J(Hz) s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet
<u>14a</u>	H	CH ₃	C ₂ H ₅	hydrochloride	165 (iPrOH)	51	CDCl ₃ : 1.30(t, J=7.3H, CH ₂ CH ₃); 2.90(q, J=7.2H, CH ₂ CH ₃); 3.83(s, 3H, OCH ₃) 6.70-8.83 (m, 7H, arom.).
<u>14b</u>	H	CH ₃	n-C ₄ H ₉	-	oil	31	CDCl ₃ : 0.67-1.93(m, 9H, C ₄ H ₉); 3.83(s, 3H, OCH ₃); 6.80-8.00(m, 5H, ArOCH ₃ and NCH=CH), 8.33 (d, J=6.1H, NCH=CH); 8.60(s, 1H, N=CH).
<u>20a</u>	H	H	C ₂ H ₅	hydrochloride	188 (EtOH)	28	DMSO-d ₆ : 1.27(t, J=7.3H, CH ₂ CH ₃); 2.87(q, J=7.2H, CH ₂ CH ₃); 7.00 and 7.83(2d, J=9.4H, ArOH), 8.07(d, J=6.1H, NCH=CH); 8.47(d, J=6.1H, NCH=CH); 8.73(s, 1H, N=CH).
<u>20b</u>	H	H	n-C ₄ H ₉	hydrochloride	181 (iPrOH)	30	DMSO-d ₆ : 0.60-2.00(m, 7H, (CH ₂) ₂ CH ₃); 2.57-3.00(m, 2H, CH ₂ (CH ₂) ₂ CH ₃); 6.80 and 7.60(2d, J=9.4H, ArOH); 7.93(d, J=6.1H, NCH=CH); 8.33(d, J=6.1H, NCH=CH); 8.56(s, 1H, N=CH).
<u>21a</u>	H	(CH ₂) ₃ Br	C ₂ H ₅	-	oil	30	DMSO-d ₆ : 1.23(t, J=7.3H, CH ₂ CH ₃); 2.00-2.57(m, 2H, OCH ₂ CH ₂ CH ₂ Br); 2.83(q, J=7.2H, CH ₂ CH ₃); 3.16-4.00(m, 2H, OCH ₂ CH ₂ CH ₂ Br); 4.20(t, J=6.2H, OCH ₂ (CH ₂) ₂ Br); 7.07 and 7.73 (2d, J=9.4H, ArO-); 8.03(d, J=6.1H, NCH=CH); 8.40(d, J=6.1H, NCH=CH); 8.60(s, 1H, N=CH).
<u>21b</u>	H	(CH ₂) ₃ Cl	C ₂ H ₅	-	oil	43	DMSO-d ₆ : 1.20(t, J=7.3H, CH ₂ CH ₃); 2.00-2.47(m, 2H, OCH ₂ CH ₂ CH ₂ Cl); 2.83(q, J=7.2H, CH ₂ CH ₃); 3.57-4.00(m, 2H, OCH ₂ CH ₂ CH ₂ Cl); 4.20(t, J=6.2H, OCH ₂ CH ₂ CH ₂ Cl); 7.07 and 7.77(2d, J=9.4H, ArO-); 8.00(d, J=6.1H, NCH=CH); 8.40(d, J=6.1H, NCH=CH); 8.67(s, 1H, N=CH).
<u>22a</u> (2)	H	(CH ₂) ₂ N(C ₂ H ₅) ₂	C ₂ H ₅	dioxalate	132 (EtOH)	42	CDCl ₃ : 1.07(t, J=7.3H, CH ₂ CH ₃); 1.17(t, J=7.6H, N(CH ₂ CH ₃) ₂); 2.33-3.13(m, 8H, CH ₂ CH ₃ , N(CH ₂ CH ₃) ₂ and NCH ₂ CH ₂ O); 4.07(t, J=6.2H, OCH ₂ CH ₂); 6.83 and 7.80(2d, J=9.4H, ArO-); 7.93(d, J=6.1H, NCH=CH); 8.33(d, J=6.1H, NCH=CH); 8.67(s, 1H, N=CH).
<u>22b</u> (3)	H	(CH ₂) ₃ N(CH ₃) ₂	C ₂ H ₅	dioxalate	112 (EtOH)	33	CDCl ₃ : 1.17(t, J=7.3H, CH ₂ CH ₃); 2.20(s, 6H, N(CH ₃) ₂); 1.73-2.60(m, 4H, OCH ₂ CH ₂ CH ₂ N< and >NCH ₂ -); 2.87(q, J=7.2H, CH ₂ CH ₃); 4.07(t, J=6.2H, OCH ₂ -); 6.87 and 7.63(2d, J=9.4H, ArO-); 7.90(d, J=6.1H, NCH=CH); 8.33(d, J=6.1H, NCH=CH); 8.67(s, 1H, N=CH).
<u>22c</u> (3)	H	(CH ₂) ₃ N(nC ₄ H ₉) ₂	C ₂ H ₅	dioxalate	68 (EtOH)	42	DMSO-d ₆ : 0.67-2.67(m, 27H, CH ₂ CH ₃ and OCH ₂ CH ₂ CH ₂ N(nC ₄ H ₉) ₂); 2.80(q, J=7.2H, CH ₂ CH ₃); 4.07(t, J=6.2H, OCH ₂ -); 6.93 and 7.67(2d, J=9.4H, ArO-); 7.90(d, J=6.1H, NCH=CH); 8.33(d, J=6.1H, NCH=CH); 8.57(s, 1H, N=CH).

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

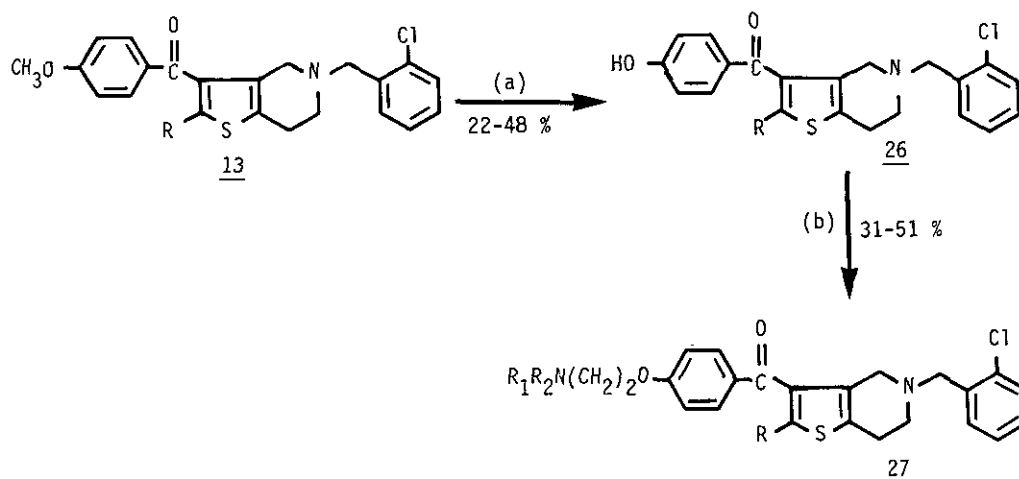
Table IV (suite)



Compound (1)	X	R ₁	R	Salt	m.p. (°C) solvent	Yield (%)	60 MHz ¹ H-NMR (solvent); δ(ppm); J(Hz) s : singlet; d : doublet; t : triplet; q : quartet; m: multiplet
<u>23a</u>	Br	H	C ₂ H ₅	hydrochloride	216 (EtOH-MeOH)	30	DMSO-d ₆ : 1.23(t, J=7, 3H, CH ₂ CH ₃); 2.87(q, J=7, 2H, 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).
<u>23b</u>	Br	H	C ₄ H ₉	hydrochloride	198 (iPrOH-EtOH)	43	CDCl ₃ : 0.80-2.00(m, 7H, CH ₂ (CH ₂) ₂ CH ₃); 2.90(t, J=7, 2H, CH ₂ (CH ₂) ₂ CH 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).
<u>24a</u>	Br	(CH ₂) ₃ Cl	C ₂ H ₅	-	oil	12	DMSO-d ₆ : 1.27(t, J=7, 3H, CH ₂ CH ₃); 2.23(t, J=6, 2H, OCH ₂ CH ₂ CH ₂ Cl); 2.83(t, J=7, 2H, CH ₂ CH ₃); 3.83(t, J=6, 2H, OCH ₂ CH ₂ CH ₂ Cl); 4.33(t, J=6, 2H, OCH ₂ CH ₂ CH ₂ Cl); 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).
<u>25a</u> (2)	Br	(CH ₂) ₂ N(C ₂ H ₅) ₂	C ₂ H ₅	dioxalate	130 (iPrOH)	27	CDCl ₃ : 1.07(t, J=7, 3H, CH ₂ CH ₃); 1.20(t, J=7, 6H, N(CH ₂ CH ₃) ₂); 2.40-3.13(m, 10H, CH ₂ CH ₃ and OCH ₂ (CH ₂) ₂ N(CH ₂ CH ₃) ₂); 4.13(t, J=6, 2H, OCH ₂ CH ₂ CH ₂ N<); 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).
<u>25b</u> (3)	Br	(CH ₂) ₃ N(CH ₃) ₂	C ₂ H ₅	dioxalate	120 (iPrOH)	20	CDCl ₃ : 1.27(t, J=7, 3H, CH ₂ CH ₃); 1.93-3.67(m, 6H, CH ₂ CH ₃ and OCH ₂ (CH ₂) ₂ N<); 2.50(s, 6H, N(CH ₃) ₂); 4.33(t, J=6, 2H, OCH ₂ CH ₂ CH ₂ N<); 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).
<u>25c</u> (3)	Br	(CH ₂) ₃ N(nC ₄ H ₉) ₂	C ₂ H ₅	-	oil	25	CDCl ₃ : 0.73-1.83(m, 19H, CH ₂ CH ₃ and OCH ₂ CH ₂ CH ₂ N(CH ₂) ₂ (CH ₂) ₂ CH ₃); 2.57-3.13(m, 8H, CH ₂ CH ₃ & -CH ₂ N(CH ₂ (CH ₂) ₂ CH 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 $\text{R}_1\text{R}_2\text{N}(\text{CH}_2)_2\text{Cl} \cdot \text{HCl}$ (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.

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