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Bronchodilators Giving Reduced Cardiovascular Effects. Relative Biological Activities of the Four Isomers of 1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutanol

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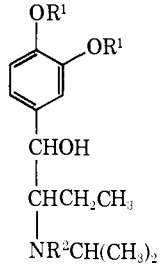
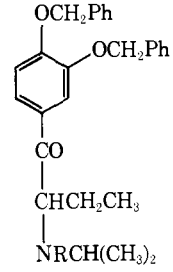
It is shown that isoetharine is the racemic erythro form of 1-(3,4-dihydroxyphenyl)-2-isopropylaminobutanol (1). The compound (1) was separated into its isomers. The (−)-erythro isomer exhibited greater antiallergic and β-adrenoceptor stimulating activity than did the (+)-erythro or either threo form. It also showed the highest β_2-adrenoceptor selectivity of the isomers of 1.

Isoetharine is a bronchodilator which was shown, as early as 1950, to give fewer cardiac effects for a given degree of bronchodilatation than did isoproterenol.[1] It has the chemical structure of 1-(3,4-dihydroxyphenyl)-2-isopropylaminobutanol (**1**), and the latter has two asymmetric centers and can therefore exist in four isomeric forms. It seemed to us to be of interest to compare some of the biological activities of the four isomers of **1** and to determine which of these isomers was present in isoetharine.



1, $R^1 = R^2 = H$
2, $R^1 = CH_2Ph$; $R^2 = H$
3, $R^1 = R^2 = CH_2Ph$
4, $R^1 = CH_2Ph$; $R^2 = CH_3CO$



5, R = H
6, $R = CH_2Ph$

The ability of different drugs selectively to stimulate β-adrenoceptors led Lands and his colleagues to suggest the subdivision of these receptors into β_1 and β_2 subclasses; whereas the bronchodilatory effects of the sympathomimetic amines were shown to be served by the β_2 receptors, mammalian cardiac excitation was mediated by the β_1 receptors.[2,3] Interest in the ability to produce bronchodilators with reduced side effects was stimulated when it was shown that the use of bronchodilator drugs, particularly isoproterenol in pressurized aerosol form, was associated with an increase in deaths from asthma.[4,5] The cardiac effects of bronchodilators, whether they have been responsible for deaths or not, are undesirable and for this reason considerable effort has been directed toward producing bronchodilators showing β_2-adrenoceptor specificity. Despite this effort none of the recently introduced drugs have demonstrated any significant increase in β_2-adrenoceptor specificity over that shown by isoetharine.[6,7,†]

Disodium cromoglycate has recently been introduced as a treatment for asthma. It is not a bronchodilator. The main activity that has been demonstrated for it in a variety of *in vitro* and *in vivo* tests is its ability to inhibit the release of mediators of immediate-type allergic reactions.[8] That the sympathomimetic amines will do this was reported in 1936[9] but the significance of this work was largely ignored until after the introduction of disodium cromoglycate. Since then this particular activity of sympathomimetic amines has been demonstrated in a variety of test systems.[10-15] In most of these systems the sympathomimetic amines are considerably more active in protecting against mediator release (*i.e.*, antianaphylactic activity) than is disodium cromoglycate.

In this paper we attempt to show that isoetharine is the (±)-erythro form of **1** and to compare the four isomers of **1** for relative β_2-adrenoceptor specificity and antianaphylactic activity.

Chemistry. Isoetharine can be prepared by the catalytic hydrogenation of 3,4-dibenzyloxy-α-isopropylamino-

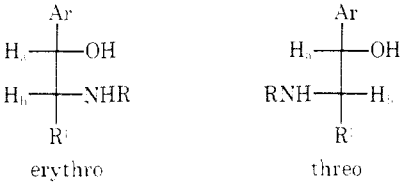
† R. H. Poyser and M. I. Robertson, unpublished results.

Table I

Compound	Coupling constants, $J_{H(a)H(b)}$, Hz[a]
Ephedrine[c]	2.8[d]
ψ-Ephedrine	9.0
Isoetharine[b]	3.0[d]
"Inverted" isoetharine[c]	8.0

[a]Spectra were determined in $(CD_3)_2SO$ using a Varian A-60 at 60 MHz with tetramethylsilane as internal standard. [b]Dilabron from Sterling Winthrop and prepared by catalytic hydrogenation of **5**. [c]The asymmetric center carrying the OH group was inverted as described in the text. [d]After the addition of D_2O. [e]R. H. Uloth, J. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).

butyrophenone (**5**).[16] It has been recognized for some time that catalytic hydrogenation of compounds of this type produces mainly the erythro form of the substituted ethanolamine,[17,18] and rules have been suggested to predict the predominant isomer that will be produced by reduction of ketones α to an asymmetric center carrying a polar group.[19] It is therefore to be expected that isoetharine will be mainly the erythro form of **1**. Nmr data for the hydrogen–hydrogen interactions on the two adjacent asymmetric centers for isoetharine prepared in this way were compared with that for ephedrine (Table I) which is known to be the erythro configuration.[20] This sample of isoetharine gave a spin–spin coupling constant expected for the erythro isomer and a sample of commercial isoetharine‡ gave the same result. Confirmation that isoetharine is the racemic erythro form of **1** was provided by inverting the asymmetric center carrying the OH group. This would be expected to produce the threo isomer with a change in coupling constant which should then be close to that for pseudo-ephedrine. This was the result obtained (Table I).



The inversion was carried out by first reducing the carbonyl group of **5** to hydroxymethylene with sodium borohydride. This gave **2** with the erythro configuration as was shown by catalytic hydrogenation to give isoetharine. The erythro (**2**) was N-acetylated and allowed to react with thionyl chloride to replace OH by Cl. Alkaline hydrolysis replaced Cl by OH with inversion and also removed the *N*-acetyl group to give mainly threo (**2**). This was debenzylated by catalytic hydrogenation to give threo (**1**).

The configuration of amino alcohols produced by metal hydride reduction of α-amino-α-alkylacetophenones is dependent on the degree of substitution of the amino group. With tertiary amino groups carrying bulky substituents the threo form usually predominates while with secondary amino groups the main form produced is the erythro.[18] Reaction of *N*-isopropylbenzylamine with α-bromo-3,4-dibenzyloxybutyrophenone gave **6**. This was reduced with sodium borohydride to the alcohol **3** and debenzylated by reduction with hydrogen in the presence of palladium to give **1** identical with the product obtained by inversion of the OH substituted asymmetric center of isoetharine confirming that this product had the threo configuration.

The enantiomorphs of isoetharine were separated by recrystallizing the (+)- and (−)-mandelic acid salts of its dibenzyl derivative **2** from ethanol, to constant rotation, followed by debenzylation. The separated enantiomorphs of **2** were N-acetylated, allowed to react with thionyl chloride, hydrolyzed to give inversion, and debenzylated to give the enantiomorphs of threo (**1**).

‡ Dilabron from Sterling Winthrop.

β_2-Adrenoceptor Selectivity. The β-adrenoceptor stimulant activities of the isomeric forms of **1** were investigated and compared with isoproterenol using isolated atria and isolated trachea of guinea pigs. β_1-Adrenoceptor stimulant effects were observed as dose-dependent increases in the rate and force of contraction of spontaneously beating atria, whereas β_2 effects were recorded as dose-dependent decreases in the spasmogenic response of the trachea to electrical stimulation.[21] Increasing doses of each compound were examined on three to six atria and trachea and from the dose–response curves obtained, doses to cause equivalent effects were determined. These effects for each type of preparation were chosen to be approximately half the maximum response to isoproterenol and all doses were expressed relative to isoproterenol.

The results in Table II show that for all three effects the racemic erythro and (−)-erythro isomers of **1** were more active than the other forms. On the trachea the racemic erythro and (−)-erythro isomers of **1** were slightly less active than racemic isoproterenol, whereas on the atria both isomers were much less active than isoproterenol. These results therefore confirm the β_2-adrenoceptor selectivity of isoetharine and indicate that both its activity and selectivity are due to the (−)-erythro isomer of **1**. The activities shown by the threo isomers are relatively low and it is possible that some of these activities might be due to contamination with the active erythro isomer.

Rat Passive Cutaneous Anaphylaxis. The results presented in Table II show that the racemic and (−)-erythro forms show the highest activity of the isomers of **1** in the rat PCA test and that these active isomers are much more active than is disodium cromoglycate. The system has been used previously to assess the activity of substituted chromones as potential antiallergic drugs.[22]

Experimental Section

Chemistry. Melting points (uncorrected) were determined on a Büchi capillary melting point apparatus. Optical rotations were measured in a Perkin-Elmer 141 polarimeter using a 1% solution in EtOH and a 10-cm cell. Microanalyses were determined on a Perkin-Elmer 240 CHN analyzer and are within ±0.4% of required values. A Varian A-60 spectrophotometer was used for nmr data, all spectra being run in $(CD_3)_2SO$ or $(CD_3)_2SO$–D_2O.

erythro-1-(3,4-Dibenzyloxyphenyl)-2-isopropylaminobutanol (**2**). A solution of 3,4-dibenzyloxy-α-isopropylaminobutyrophenone (**5**) hydrochloride (227 g, 0.5 mol) in MeOH (700 ml) was cooled to 5–10° and $NaBH_4$ (19 g, 0.5 mol) added over a period of *ca.* 2 hr. After a further 1 hr of stirring, H_2O (2 l.) was added and the mixture was extracted with CH_2Cl_2. The extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was dissolved in Et_2O and HCl gas passed through. Compound **2** was obtained as its hydrochloride: yield, 180 g (80%); mp 167–168° (MeOH–Et_2O). *Anal.* ($C_{27}H_{34}ClNO_3$) C, H, Cl, N.

Resolution of *erythro*-1-(3,4-Dibenzyloxyphenyl)-2-isopropylaminobutanol (**2**). *erythro*-1-(3,4-Dibenzyloxyphenyl)-2-isopropylaminobutanol hydrochloride was converted to free base with aqueous NaOH and extracted with CH_2Cl_2. After drying ($MgSO_4$) and evaporating at reduced pressure, the residual oil (210 g, 0.5 mol) was dissolved in EtOH (750 ml) and a solution of (+)-mandelic acid (76 g, 0.5 mol) in H_2O (*ca.* 75 ml) was added. After up to 5 days at ambient temperature crystallization began and was then rapidly complete. The solid ($[\alpha]^{21}D$ +15–20°) was recrystallized from a 10% solution in EtOH to constant rotation ($[\alpha]^{21}D$ +9.7°): yield, 19 g (13.5%); mp 126–127°. *Anal.* ($C_{35}H_{41}NO_6$) C, H, N. The isomer from (−)-mandelic acid was prepared similarly ($[\alpha]^{21}D$ −9.7°): yield 20.6 g (14.5%); mp 126–127°. *Anal.* ($C_{35}H_{41}NO_6$) C, H, N.

Table II. Biological Activities of the Isomers of **1**

Compound	Activities on β-adrenoceptors in guinea-pig isolated tissues, ratio of doses (with 95% confidence limits) for equivalent effects: Trachea (β_2), 50% inhibition of electrically induced spasmogenic response[a]	Atrial rate (β_1), 25% increase[a]	Atrial force of contraction (β_1), 80% increase[a]	Rat PCA activity, dose for 50% inhibition (with 95% confidence limits, and slope)
Disodium cromoglycate				6.7 (4.9–9.3, 147)
Isoproterenol	1	1	1	0.01 (0.002–0.06, 36)
Racemic erythro **1**	7.2 (4.7–11)	570 (410–800)	710 (470–1,100)	0.1 (0.02–0.7, 31)
(−)-Erythro **1**	1.9 (1.2–3.2)	310 (230–430)	270 (142–450)	0.1 (0.01–1.0, 29)
(+)-Erythro **1**	1200 (520–2500)	8,900 (5,200–14,000)	10,000 (6,700–16,000)	>20
Racemic threo **1**	780 (530–1200)	25,000 (18,000–35,000)	>97,000[b]	>20
(−)-Threo **1**	180 (75–360)	6,400 (5,100–8,400)	28,000 (21,000–38,000)	>20
(+)-Threo **1**	940 (370–1900)	4,400 (3,600–5,800)	62,000 (50,000–81,000)	>20

[a]These effects for each type of preparation approximated to half the maximum response to isoprenaline. [b]80% increase not obtained with doses used.

Optical Isomers of *erythro*-1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutanol (1). The resolved mandelate salts of **2** were converted to their free amines by treatment with aqueous NaOH and extracting with CH_2Cl_2. After evaporating the extracts *in vacuo*, the residue was dissolved in Et_2O and $MeSO_3H$ added in excess. The precipitated oils rapidly solidified on scratching giving the $MeSO_3H$ salts in 80% yields: mp 139–139.5° (EtOH); $[\alpha]^{21}D$ +16.7° [from (−)-mandelate salt] and $[\alpha]^{21}D$ −16.6° [from (+)-mandelate salt]. *Anal.* ($C_{28}H_{37}NO_6S$) C, H, N, S.

The $MeSO_3H$ salts in MeOH were catalytically debenzylated at ambient temperature and pressure using 10% Pd/C. The required title compounds were obtained as their $MeSO_3H$ salts in *ca.* 90% yield: mp 170–171° (MeOH–Et_2O); $[\alpha]^{21}D$ ±22.9°; nmr δ 9.00–7.70 (m, 4, exch), 6.86 (s, 1), 6.75 (s, 2), 6.10–5.60 (broad, 1, exch), 4.92§ (m, after D_2O, d, 1), 3.60–3.00 (m, 2), 2.44 (s, 3), 1.75–1.15 (m, 2), 1.34 (d, 6), 0.72 (t, 3). *Anal.* ($C_{14}H_{25}NO_6S$) C, H, N, S.

***erythro*-*N*-Acetyl-1-(3,4-dibenzyloxyphenyl)-2-isopropylaminobutanol (4).** To a stirred solution of *erythro*-1-(3,4-dibenzyloxyphenyl-2-isopropylaminobutanol (**2**, 42 g, 0.1 mol) and Et_3N (10.1 g, 0.1 mol) in C_6H_6 (200 ml) was added AcCl (7.85 g, 0.1 mol) in one portion. After 0.5 hr Et_3N·HCl was removed by filtration and the filtrate evaporated *in vacuo*. Trituration of the yellow oil with MeOH gave the title compound: yield, 36.5 g (79%); mp 116° (MeOH). *Anal.* ($C_{29}H_{35}NO_4$) C, H, N.

Resolved samples of 1-(3,4-dibenzyloxyphenyl)-2-isopropylaminobutanol were acetylated in the same way. These *N*-acetyl compounds were intractable yellow oils having ir spectra identical with the unresolved *N*-acetyl derivative.

***threo*-1-(3,4-Dibenzyloxyphenyl)-2-isopropylaminobutanol (2) Hydrochloride.** To the unresolved *N*-acetyl derivative **4** was added 2 vol of $SOCl_2$. An instantaneous exothermic reaction occurred giving a yellow solution. After 0.5 hr excess $SOCl_2$ was removed *in vacuo* and an excess of aqueous NaOH added to the residue. Sufficient MeOH was then added to solubilize the oil and the mixture left overnight at ambient temperature.

The mixture was evaporated *in vacuo* and the residue was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated *in vacuo*, the residue was dissolved in Et_2O, and HCl gas was passed through to precipitate racemic threo (**2**) hydrochloride. It was crystallized from MeOH–Et_2O: yield, 85%; mp 113–114° (MeOH–Et_2O). *Anal.* ($C_{27}H_{34}ClNO_3$) C, H, Cl, N.

The *N*-acetyl derivatives of the resolved isomers **4** were treated in exactly the same manner, and the enantiomorphs of **2** were obtained at HCl salts: mp 147–148° (MeOH–Et_2O); $[\alpha]^{21}D$ −34.5 and +34.6°. *Anal.* ($C_{27}H_{34}ClNO_3$) C, H, Cl, N.

The (+)-erythro isomer of **4** gave the (−)-threo isomer of **2**.

Attempts were made to purify the yellow oil obtained by adding $SOCl_2$ to racemic **4**. After reaction excess $SOCl_2$ was evaporated, the residual oil was taken up in CH_2Cl_2 and washed with H_2O. The CH_2Cl_2 layer was dried ($MgSO_4$) and evaporated *in vacuo* to give *O*-acetyl-1-(3,4-dibenzyloxyphenyl)-2-isopropylaminobutanol identified by nmr, ir (CO 1735 cm^{-1}), and analyses. *Anal.* ($C_{29}H_{35}NO_4$) C, H, N. This phenomena of N → O migration in threo compounds of this type is well documented.[23] Base hydrolysis of this *O*-acetyl derivative gave the title compound: overall yield, 82%; mp 113–114° (MeOH–Et_2O). *Anal.* ($C_{29}H_{35}NO_4$) C, H, N.

***threo*-1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutanol (1) Hydrochloride. Method 1.** Catalytic (10% Pd/C) debenzylation of the isomers of the threo dibenzyloxy compounds **2** hydrochlorides in MeOH at ambient temperature and pressure gave the three isomers of **1** hydrochlorides. Racemic **1** gave an 80% yield and mp 188–189° (MeOH–Et_2O). (−) and (+) isomers gave yields of 82 and 87%, respectively; both gave mp 200°; $[\alpha]^{21}D$ −58.3 and +58.4°; nmr δ 9.25–7.00 (broad, 5, exch), 6.83 (s, 1), 6.72 (s, 2), 4.54# (d, 1), 3.60–2.80 (broad, 2), 1.60–1.00 (broad, 2), 1.30 (d, 6), 0.78 (t, 3). *Anal.* ($C_{13}H_{22}ClNO_3$) C, H, Cl, N.

Method 2. A mixture of 3,4-dibenzyloxy-α-bromobutyrophenone (43.9 g, 0.1 mol) and *N*-benzylisopropylamine (15 g, 0.1 mol) in EtOH was refluxed 24 hr. The solution was then evaporated *in vacuo* and the residue extracted with Et_2O. After filtering, HCl gas was passed through the filtrate precipitating an oil. The oil was triturated with several lots of ether and dried *in vacuo* producing a foamy solid, yield 19 g (37%), mp 64–68°, containing mainly 3,4-dibenzyloxy-α-*N*-benzylisopropylaminobutyrophenone (**6**) hydrochloride, as shown by nmr and ir. Attempted recrystallization of this material failed.

This amino ketone **6** (15.2 g, 0.03 mol) was dissolved in MeOH and cooled to 5–10°, and $NaBH_4$ (2 g, 0.05 mol) was added during *ca.* 1 hr, maintaining the temperature below 15°. After a further 1 hr H_2O was added and the mixture extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated *in vacuo*, the residue was dissolved in Et_2O, and HCl gas was passed through the solution. The precipitated oil was separated, washed with ether, and dried to give a solid, yield 11.9 g (78%), mp 72–75°, containing *threo*-(3,4-dibenzyloxyphenyl)-2-*N*-benzylisopropylaminobutanol (**3**) hydrochloride.

Catalytic (10% Pd/C) debenzylation of the crude amino alcohol **3** (10 g) in MeOH at ambient temperature and pressure gave racemic threo (**1**): yield, 3.9 g (78%); mp 187–188° (MeOH–Et_2O); nmr identical with that for the compound by method 1. *Anal.* ($C_{13}H_{22}ClNO_3$) C, H, Cl, N.

Guinea-Pig Isolated Atria and Trachea. Guinea pigs were killed by a blow on the head and the heart and trachea removed. The atria were dissected from the heart and suspended in McEwan's solution[24] at 32°, aerated with 95% O_2 + 5% CO_2. A resting tension of 1 g was applied and contractions were recorded with an isometric force transducer (Dynamometer UF1). The rate of beating was monitored with a Devices instantaneous ratemeter. Dose–response curves for the isomers of **1** and isoprenaline were determined by adding increasing doses of drug, the bath fluid being changed between each dose.

The trachea of the guinea pig was set up essentially as described by Farmer and Coleman[21] to allow measurements of changes in intraluminal pressure in response to transmural stimulation. This stimulation consisted of square wave monophasic pulses of 1-msec duration and supramaximal voltage applied to the tissue for 10-sec periods at a frequency of between 50 and 60 Hz. Pressure changes were detected with a Bell and Howell, Ltd., pressure transducer, type 4-327-L221. The interval needed for recovery of base-line pressure between stimulations was usually

§ Proton H_a $J_{H(a)H(b)}$ = 2.8 Hz [(−) isomer], 3.0 Hz [(+) isomer].

Proton H_a $J_{H(a)H(b)}$ = 8.0 Hz.

about 5 min and never more than 8 min. The effects on the trachea of either the isomers of 1 or isoproterenol given in increasing doses were assessed by inhibition of the rapid increase in intraluminal pressure to stimulation. Before stimulations were applied, each dose of drug was allowed to produce its maximal relaxant effect. The bathing fluid was changed immediately after each stimulation. All responses were recorded on a Devices M2 or M4 pen recorder.

Rat Passive Cutaneous Anaphylaxis Test. The PCA test was carried out by a method similar to that previously described.[25,26] Serum containing heat labile homocytotropic antibody was raised in rats to ovalbumin by a method similar to that described by Mota.[27] A 72-hr sensitization period was used and dilutions of drugs were injected sc prior to iv challenge with antigen, each dose of drug into groups of six rats; for each drug four doses giving between 0 and 100% inhibition were used and each dose was repeated at least once on separate occasions. The drugs were most active if given sc 0–10 min before iv challenge. Isoproterenol and the isomers of 1 were given just before challenge while disodium cromoglycate was given 10 min before challenge at which time it showed its highest activity.

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Naphthothiophenes. 4. Preparation of Multisubstituted 4-Naphtho[2,1-*b*]thiophenemethanols and the Effect of Side Chain Modification on Antimalarial Activity of 8-Trifluoromethyl-4-naphtho[2,1-*b*]thiophenemethanols

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Eighteen substituted 4-naphtho[2,1-*b*]thiophenemethanols, including a series bearing substituents in the thiophene and naphthlene rings and a series in which the side chain has been modified, have been prepared and screened for antimalarial activity. Their synthesis was achieved by photocyclization of α-(2-thienyl)-β-(phenyl)acrylic acids to naphtho[2,1-*b*]thiophene-4-carboxylic acids followed by conversion of the latter into the title compounds *via* the conventional five-step route involving bromomethyl ketone intermediates. The greatest activity was observed for **21**, **23**, and **25** which gave cures against *Plasmodium berghei* at 160, 80, and 160 mg/kg dosage levels, respectively. A limited side chain modification study showed that the *N,N*-di-*n*-butylamino system is the side chain of choice among nine studied.

Previous reports from this laboratory have described the synthesis and antimalarial activity against *Plasmodium berghei* in mice and the *in vitro* DNA binding properties of several series of naphthothiophenemethanols.[1-3] Our prior work has dealt with naphthothiophenemethanols substituted only in the naphthalene ring. In view of the significant increase in activity on multisubstitution of the isosteric phenanthrenemethanol system,[4,5] particularly with substituents with positive Hammett σ constants, we have prepared a limited series of multi-substituted 4-naphtho[2,1-*b*]thiophenemethanols bearing substituents in both the naphthalene and thiophene rings.

Extensive side chain modifications in various arylcarbinolamine antimalarials have been previously reported.[6-8] It appears for *N,N*-di-*n*-alkylamino side chain types that the alkyl group which leads to optimum activity varies with the aryl system and, indeed, within a given system. The result is probably a function of transport and not due to effects on DNA binding, except in the case of drastic modification, since we have shown for the two side chain systems *N,N*-di-*n*-butylamino and *N*-piperidino in the 4-naphtho[2,1-*b*]thiophenemethanol series compounds that both bind to DNA *in vitro*[3] with comparable efficiency. Interestingly, no *in vivo* activity was found for the latter types. To obtain a general idea of the effect of side chain modifications for the naphthothiophenemethanols we report here a series of 8-trifluoromethyl-α-(alkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols in which limited side chain modifications have been carried out.

Chemistry. The synthetic route employed to prepare