Synthesis of Thyroid Hormone Analogues. Part 1. Preparation of 3′-Heteroarylmethyl-3,5-di-iodo-L-thyronines *via* Phenol–Dinitrophenol Condensation and Relationships between Structure and Selective Thyromimetic Activity

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3′-Heteroarylmethyl analogues (**1**)—(**8**) of the natural thyroid hormone 3,3′,5-tri-iodo-L-thyronine (T_3) were synthesized as potential selective (cardiac-sparing) thyromimetics. The diphenyl ether moiety was constructed by condensation of 3-substituted 4-methoxyphenols with a 3,5-dinitro-L-tyrosine derivative. Synthesis of the key phenols (**28**)—(**32**) required the *in situ* preparation, at low temperatures, of the novel metallated species 2-lithio-5-methoxypyridine (**14**), 5-lithio-2-methoxypyrimidine (**15**), 5-lithio-2-methylpyridine (**16**), 5-bromo-4-lithio-2-methoxypyridine (**18**), and 2,6-difluoro-3-lithiopyridine (**19**), followed by reaction with the benzaldehyde (**20**). Alternative routes to the pyridazinone (**36**) and thiazolone (**37**) phenols were developed from the benzyl bromide (**33**). Structure–activity relationships indicate that selective thyromimetic activity is associated with 2-oxyheteroaren-5-ylmethyl 3′-substitution, as found in the pyridone (**1**), pyridazinone (**2**), hydroxypyridine (**4**) and thiazolone (**8**). The location of the oxy substituent in the heterocycle is critical for both hormonal activity and for binding to the T_3 receptor.

It is well established that the thyroid hormones L-3,3′,5-tri-iodothyronine (T_3) and L-thyroxine reduce circulating cholesterol levels in animal models of hypercholesterolaemia and in man.[1] However, the adverse cardiac effects of the hormones and some of their analogues have precluded their therapeutic use in the treatment of hyperlipidaemia.[2] Recently we have demonstrated that a novel class of 3′-arylmethyl analogues of T_3, exemplified by the pyridone (**1**) and the pyridazinone (**2**), are highly effective in reducing plasma cholesterol levels but have little or no effect on cardiac function.[3] Herein we report the synthesis of compounds (**1**) and (**2**), and of the related heterocyclic analogues (**3**)—(**8**). These compounds were required as part of a wider study designed to explore the effects of 3′-substituent structure on selective thyromimetic activity. The important aspects of the structure–activity relationships which emerged are also discussed.

Results and Discussion

Synthesis.—The key step in the synthesis of thyroid hormone analogues is the formation of the hindered diphenyl ether moiety. There is substantial precedent, exemplified by the syntheses of many thyroid hormone analogues,[4] for two general approaches, routes A and B. We have routinely used both routes for the preparation of a wide range of 3′-substituted T_3 analogues.[5] The coupling of a diaryliodonium salt with a 2,6-dihalogenophenol (route A) (Scheme 1) is generally preferred, since the alternative condensation of a phenol with a 2,6-dinitrophenol (route B) requires subsequent steps to convert the nitro groups into halogen. In addition, the precursor 1,2-disubstituted benzenes required for route A are more readily available than are the 3,4-disubstituted phenols needed for route B. However, we have found that application of route A to the synthesis of structurally diverse 3′-arylalkyl T_3 derivatives gave poor yields in certain instances. Particular problems were encountered with the preparation of diaryliodonium salts from

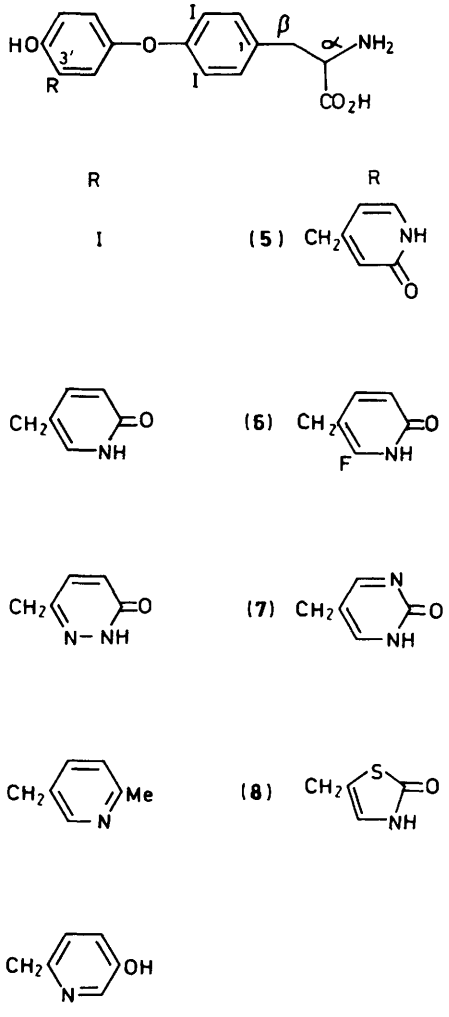

Figure. Structures of T_3 and selective thyromimetics

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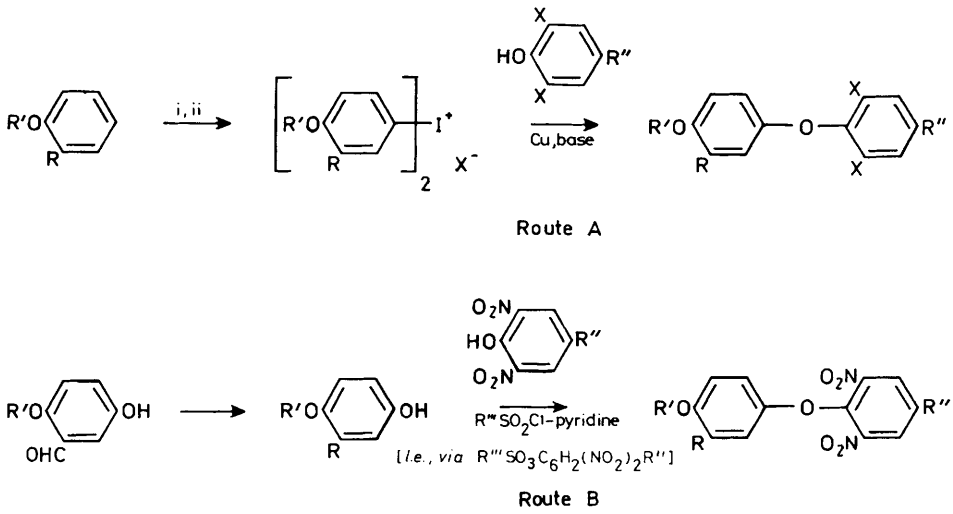
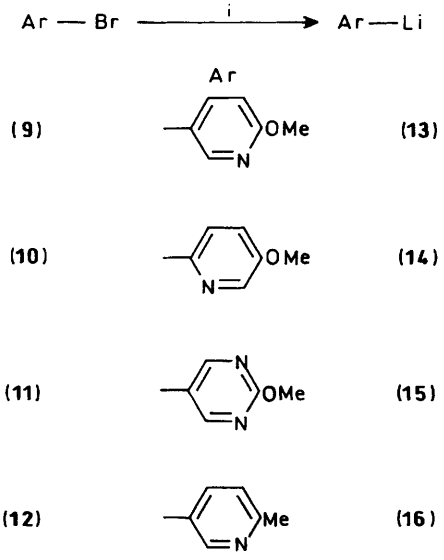


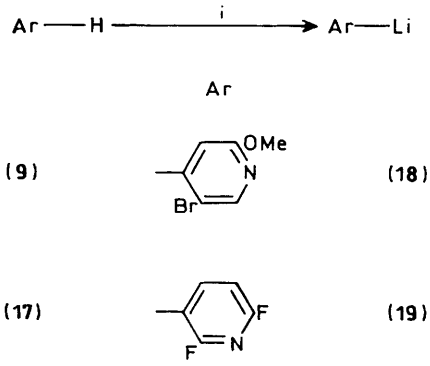
Scheme 1. *Reagents:* i, I^{III}; ii, MX

1,2-disubstituted benzenes containing electron-rich or nucleophilic arylalkyl R groups (route A) which can compete for the electrophilic iodine(III) reagent. In contrast, route B, although lengthier, proved to be a robust method for preparing 3′-arylalkyl T_3 analogues and was used to prepare the 3,5-diiodothyronines (**1**)—(**8**). A significant drawback with route B is that conversion of the 3,5-dinitrothyronines into the 3,5-dibromo compounds generally gave low yields, and complex product mixtures from which pure products were difficult to isolate. The improved biological activity seen with 3,5-dibromo analogues, exemplified by SK&F L-94901,[3] required the development of both route A and a phenolic oxidative coupling approach, and these are described in Parts 2 and 3 of this series.

We have previously used the aldehyde (**20**) (Scheme 4) for the preparation of 3′-substituted T_3 analogues [5] and this compound was used to prepare the key 3,4-disubstituted phenolic precursors required for route B, as outlined in Schemes 2—5. Six of the desired phenols were prepared from addition reactions of the appropriate metallated heterocycle with aldehyde (**20**) at low temperature (Scheme 4). Several of these metalled systems are novel, and were prepared *in situ* as outlined in Schemes 2 and

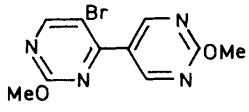


Scheme 2. *Reagent and conditions:* i, Bu^nLi–THF, −90 to −100 °C



Scheme 3. *Reagent and conditions:* i, $LiNPr^i_2$–THF, −78 °C

3. Bromo–lithium exchange reactions of the bromides (**9**)—(**12**) occurred rapidly at −100 °C [6] with butyl-lithium in tetrahydrofuran (THF), giving aryl-lithiums (**13**)—(**16**) respectively (Scheme 2). Formation of compound (**13**) has precedent,[7] and its isomer (**14**) was prepared from 2-bromo-5-methoxypyridine (**10**) under similar conditions. Reaction of 5-bromo-2-methoxypyrimidine (**11**) with butyl-lithium at −78 °C has been reported to give compound (**I**).[8] We found that by lowering the temperature of the reaction to −100 °C [9] compound (**15**) was more stable and did not produce the bipyrimidine (**I**). Similarly,



(**I**)

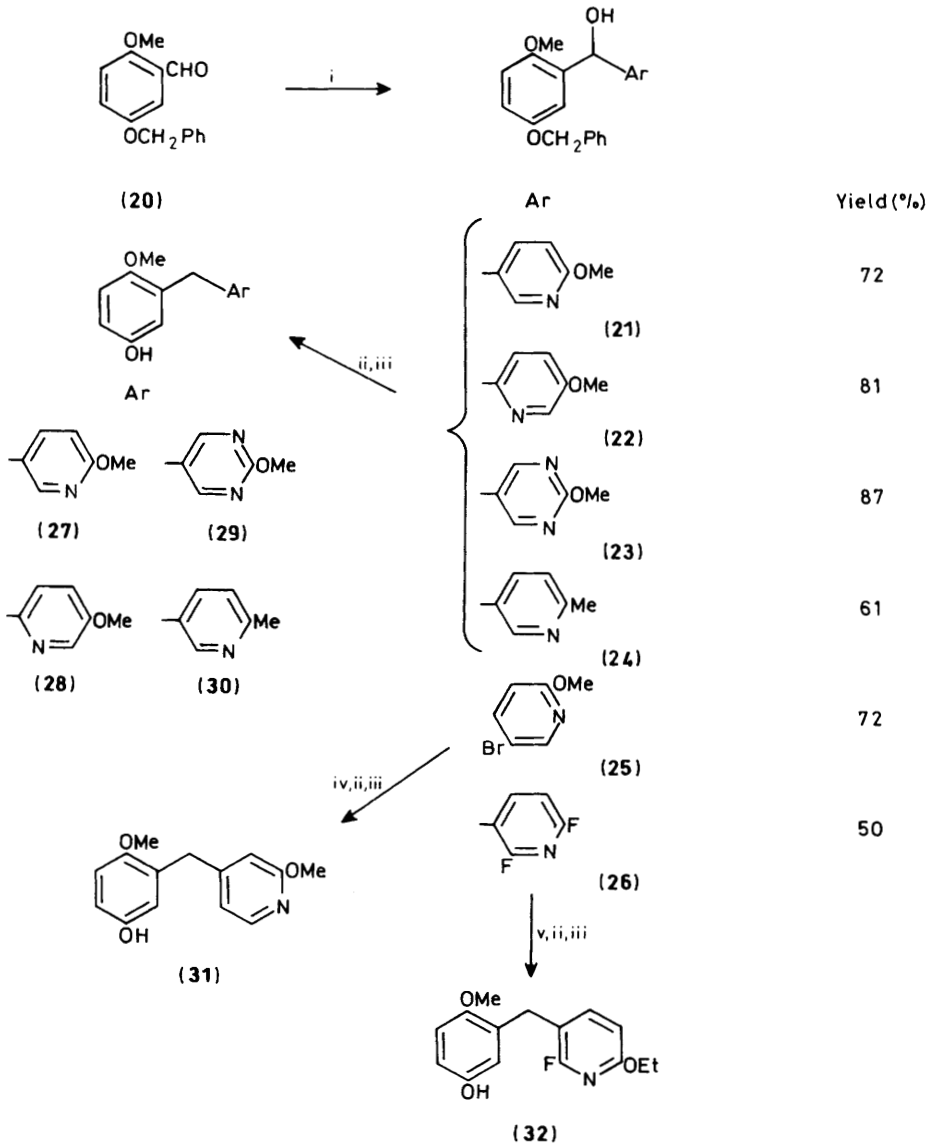
5-bromo-2-methylpyridine (**12**) underwent selective halogen–lithium exchange at −100 °C to give compound (**16**) *without* deprotonation of the 2-methyl group. The lithio derivative (**16**), which appears to be the first example of a methyl-substituted lithiopyridine, was found to be stable at −100 °C, but at temperatures above −80 °C decomposition occurred. The absence of lateral metallation of the bromide (**12**) might be expected at these temperatures, since most of the reported procedures for this conversion require higher temperatures.[10]

In contrast to the rapid bromo–lithium exchange reaction of

the pyridine (**9**) with butyl-lithium,[7] treatment of compound (**9**) with lithium di-isopropylamide (LDA) resulted in metallation exclusively at the 4-position, giving compound (**18**) (Scheme 3). This reaction has analogy in the metallation of 3-bromopyridine itself, which is known to give the 4-lithio derivative with LDA.[11] Evidently, the 5-bromo group in the pyridine (**9**) is more effective in directing metallation than is the 2-methoxy group. The relatively reduced kinetic acidity of the proton *ortho* to the methoxy group in (**9**) is further supported by the lack of reactivity of 2-methoxypyridine, which we were unable to deprotonate with LDA. 2,6-Difluoropyridine (**17**) readily gave the 3-lithio species (**19**) with LDA, as would be expected from the known metallation reactions of 2-fluoropyridine.[11]

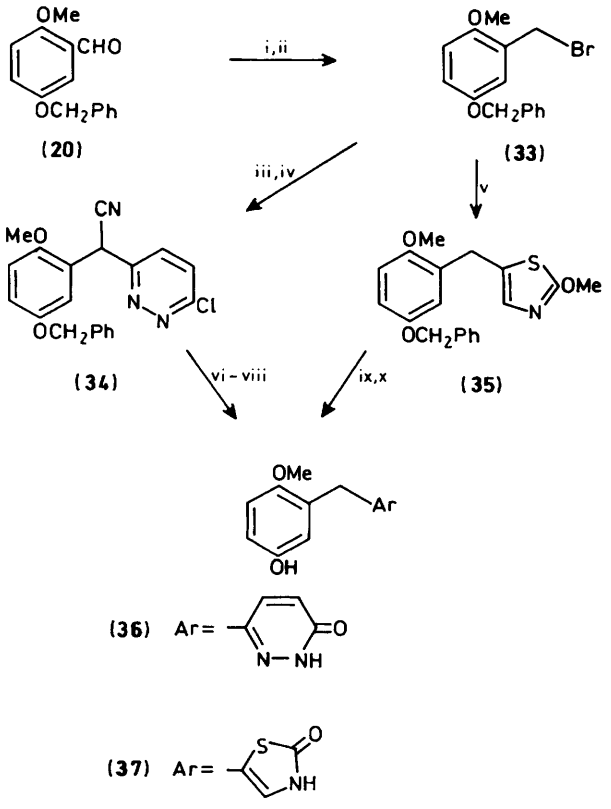
The lithioheterocycles, prepared *in situ* according to Schemes 2 and 3, reacted smoothly with the aldehyde (**20**)[5] to give the required alcohols (**21**)—(**26**) (Scheme 4, yields not optimised). Considerably lower yields were obtained if the reactions were carried out at temperatures above −70 °C, probably as a consequence of the instability of the lithiated species at these temperatures. The identity of the alcohols (**21**)—(**26**) confirmed the structures of the intermediate lithioheterocycles. The bromo substituent in the compound (**25**), having served to direct the regiochemistry of the metallation reaction, was subsequently removed by exchange with lithium, followed by protonation. The required oxygen functionality was selectively introduced into the difluoride (**26**) by displacement of the least hindered fluoro group with ethoxide (Scheme 4). The desired phenols (**27**)—(**32**) were obtained from the alcohols by acetylation followed by catalytic hydrogenolysis; the free alcohols themselves were resistant to hydrogenolysis. Reduction of the pyrimidine ring in the acetate derivative of alcohol (**23**) occurred readily in methanol, probably because of the solvent increasing in acidity upon release of acetic acid; addition of triethylamine allowed successful conversion into the phenol (**29**). The acetates from alcohols (**22**) and (**24**) were effectively hydrogenolysed in acetic acid containing hydrochloric acid. In these cases little or no hydrogenolysis occurred in the absence of the added mineral acid.

Attempts to effect lithium–halogen exchange in 3-bromo-6-methoxypyridazine were without success, and the required



Scheme 4. *Reagents and conditions:* i, ArLi (Schemes 2 and 3)–THF; ii, Ac_2O–pyridine; iii, H_2–Pd–C; iv, BuLi–THF, −78 °C; then water; v, EtONa–EtOH

phenol (**36**) was therefore prepared by an alternative route (Scheme 5). The phenylacetonitrile prepared from the bromide (**33**) was arylated with 3,6-dichloropyridazine to yield compound (**34**). Conversion of the chloropyridazine (**34**) into the corresponding pyridazinone was effected with sodium acetate in acetic acid, and conversion into the phenol (**36**) was completed by successive hydrolyses with hydrochloric and acetic acids (for debenzylation) then aqueous hydrochloric acid (for decyanation). Although the bromide (**33**) is a less reactive electrophile than the aldehyde (**20**), it could be used to alkylate lithioheterocycles which have greater thermal stability than those prepared in Schemes 2 and 3. Thus 2-methoxy-5-lithiothiazole[12] with bromide (**33**) gave the thiazole (**35**) in 74% yield. Hydrolysis followed by debenzylation with boron trichloride gave the desired phenol (**37**) (Scheme 5).



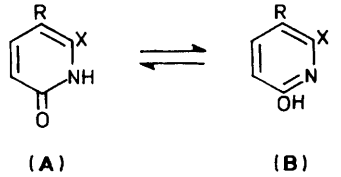
Scheme 5. *Reagents and conditions:* i, $NaBH_4$; ii, PBr_3; iii, NaCN; iv, 3,6-dichloropyridazine–NaH–DMF; v, 2-methoxythiazole–Bu^{n}Li–THF, −78 °C; vi, NaOAc–HOAc; vii, HCl–HOAc; viii, aq. HCl; ix, HCl–MeOH; x, BCl_3

In situ reaction of 3,5-dinitro-*N*-trifluoroacetyl-L-tyrosine ethyl ester with methanesulphonyl chloride[13] followed by reaction with the phenols (**27**)—(**32**), (**36**), and (**37**) gave the diphenyl ethers (**38**)—(**45**) (Scheme 6). The dinitro compounds (**38**)—(**45**) were converted into the corresponding di-iodo derivatives (**46**)—(**53**) by successive catalytic hydrogenation, bisdiazotisation, then iodination. We found that the conditions used for the bisdiazotisation step were critical. Under the reported preferred conditions (sodium nitrite in anhydrous acetic acid and sulphuric acid[4,13]) the diamines derived from nitro compounds (**38**)—(**45**) failed to give the desired products. However, use of acetic acid–sulphuric acid–water solvent mixtures resulted in the formation of di-iodides (**46**)—(**53**) in acceptable yields after purification by column chromatography.

The 3,5-di-iodothyronines (**46**)—(**53**) were subsequently deprotected to yield the desired hormone analogues (Scheme 7). The 2-methoxypyridines (**46**) and (**50**), and the pyridine (**49**), were converted in one step into the target compounds (**1**), (**5**), and (**3**) respectively by treatment with refluxing hydrobromic acid and aqueous acetic acid. These conditions effectively cleave the 4′-methoxy group, and remove the L-alanyl protective groups,[4,5] but when they were applied to the pyrimidine (**48**), decomposition occurred. Consequently, compound (**48**) was converted into analogue (**7**) by a two-step procedure involving initial cleavage of the 4′-methoxy group with 5 mol equiv. of boron tribromide in dichloromethane,[5] followed by side-chain deprotection and 2-methoxypyrimidine hydrolysis with refluxing aqueous hydrochloric acid. Compounds (**52**) and (**53**) were converted into amino acids (**2**) and (**8**) respectively by, first, 4′-methoxy group cleavage with boron tribromide, followed by basic hydrolysis of the L-alanyl protecting groups. The dealkylation reaction with boron tribromide also resulted in cleavage of the ethyl ester group, but this was considerably slower than the accompanying aryl methyl ether cleavage. Where ester–acid mixtures were obtained, separation was unnecessary since the mixture could be easily converted into the single desired T_3 analogue. Conversion of pyridines (**47**) and (**51**) into targets (**4**) and (**6**) respectively was best accomplished by initial cleavage of the alkoxy groups on the pyridine rings, as well as the 4′-methoxy and ester groups, by using excess of boron tribromide at room temperature, followed by basic hydrolysis of the *N*-trifluoroacetyl groups.

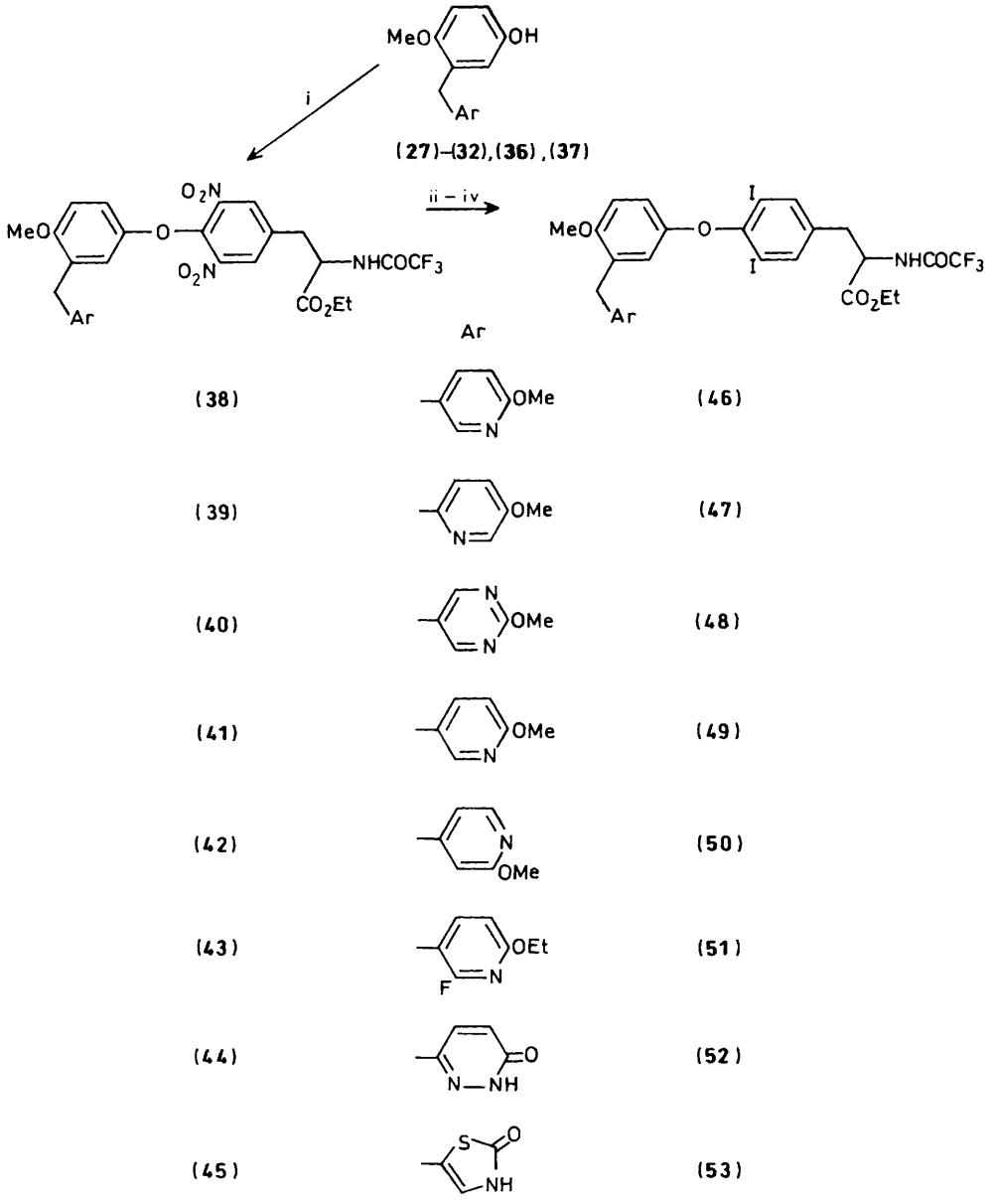
Structure–Activity Relationships.—Thyromimetic activities were determined *in vivo* and *in vitro* in rat heart and liver using established assay procedures[3,14] (Table). Relative *in vivo* potency comparisons in these tissues provide an assessment of selective activity. Relative *in vitro* receptor binding, being free from the complicating pharmacokinetic factors operative *in vivo*, gives key information concerning the nature of the ligand–receptor interactions.[15] The results (Table) show that none of the analogues possesses significant *in vivo* thyromimetic potency in the heart. In contrast, compounds (**1**), (**2**), (**4**), and (**8**) possess significant liver activity *in vivo* and are therefore selective thyromimetics. For each compound, receptor-binding affinity *in vitro* is essentially the same in both tissues, providing further evidence that receptors in heart and liver are identical, and that the observed selective activity depends on differential tissue uptake or penetration to the nuclear receptors.[3]

Compounds (**3**)—(**6**) were synthesized to evaluate the importance for activity of the *para*-oxygen substituent in the active heterocyclic analogues (**1**) and (**2**). The complete loss of *in vivo* potency seen with the pyridine (**3**) and the pyridone (**5**) show that the *para*-oxo group is critical for activity. The much reduced receptor binding of compound (**5**) relative to the active isomer (**1**) probably contributes to the reduced activity *in vivo*. It is well established that 2-hydroxypyridines and 2-hydroxypyridazines predominantly exist in aqueous solution as the oxo tautomers (A). In contrast, in 6-halogeno-2-hydroxypyridines (*e.g.* X = Cl) the hydroxy tautomer (B) is favoured.[16] The fluoro



(A) (B)

analogue (**6**) was synthesized in an attempt to define which tautomer of (**1**) is responsible for activity. The loss of both activity and receptor binding seen with compound (**6**) implies that the oxo tautomer of (**1**) may be the active species. However, the pyridin-3-ol (**4**) retains activity and has high receptor



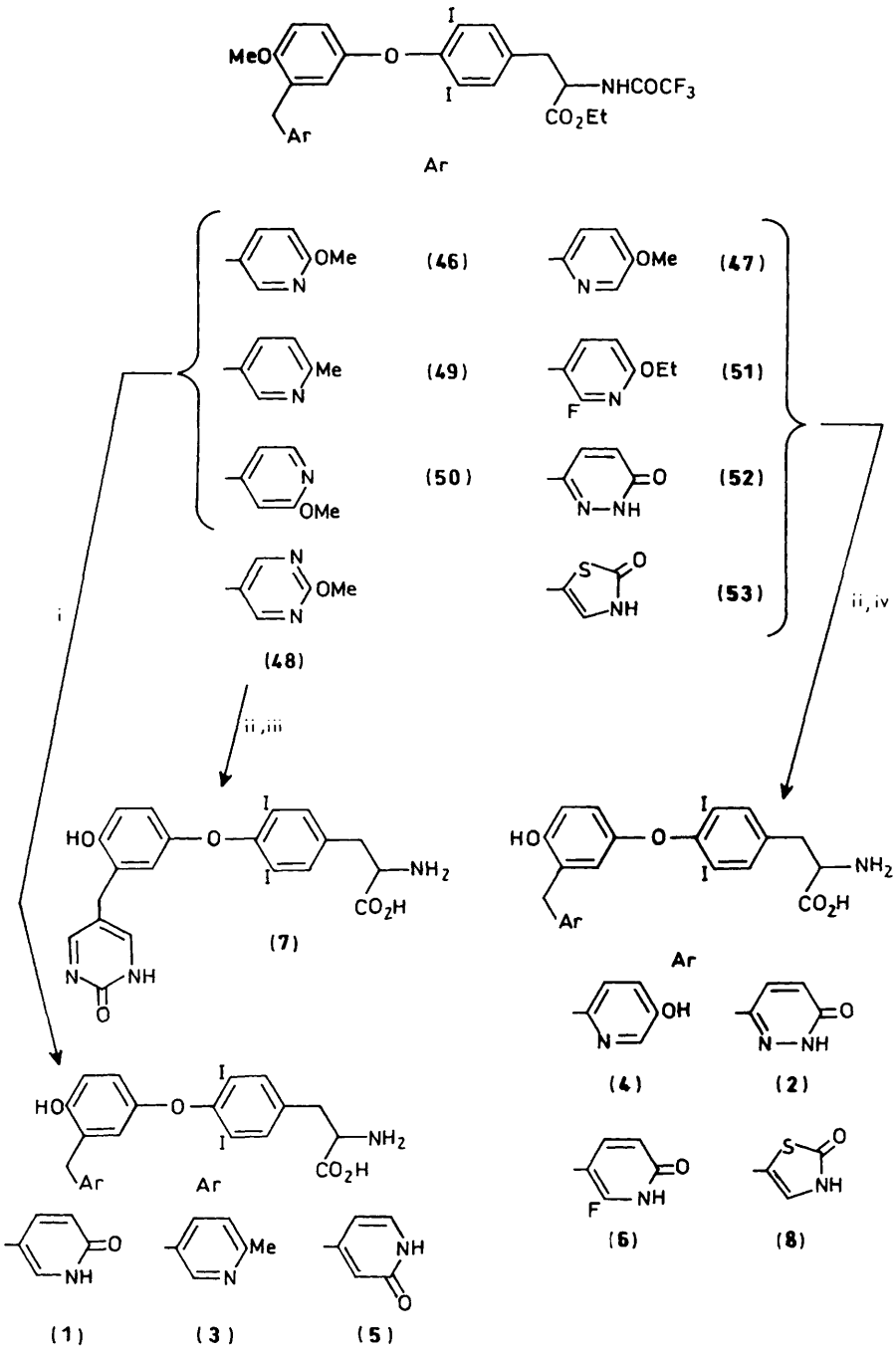
Scheme 6. *Reagents:* i, 3,5-dinitro-*N*-trifluoroacetyl-L-tyrosine ethyl ester–$MeSO_2Cl$–pyridine; ii, H_2/Pd–C; iii, $NaNO_2$–aq.H_2SO_4; iv, NaI–I_2

affinity, suggesting that both *para*-oxo and *para*-hydroxy groups are effective, and that the fluoro group in compound (**6**) has an additional deleterious effect on activity. The importance of additional properties of the heterocyclic group is further emphasised by the loss of activity seen with the pyrimidone (**7**) in comparison with the isomeric pyridazinone (**2**). In contrast, the thiazolone moiety in compound (**8**), which exists predominantly as the oxo tautomer,[17] is an excellent bioisosteric replacement for the pyridone in compound (**1**).

Extensive quantitative structure–affinity and conformational studies[5,15] using *in vitro* relative receptor binding have provided insights into those 3′-substituent physicochemical properties related to receptor recognition. These studies suggest that the 3′-substituent binding pocket on the T_3 receptor is hydrophobic and is limited in depth to the length of the natural iodo substituent, but has sufficient width to accommodate a phenyl or cyclohexyl ring. Extension of bulk beyond the volume occupied by 3′-benzyl or 3′-cyclohexylmethyl substituents leads to loss of binding.[5] The *in vitro* receptor affinities of the compounds in the Table, and related compounds,[3] are in accord with the model, and additionally suggest that there is a dipolar element of the receptor which interacts specifically with *para*-oxo or *para*-hydroxy groups present in 3′-arylmethyl substituents, leading to enhanced receptor affinity. Quantitative structure–activity studies of *in vitro* and *in vivo* thyromimetic activities, and selectivity, will by reported elsewhere. However, these studies revealed the 3,5-dibromo analogue of compound (**2**) (SK&F L-94901) to be a potent selective thyromimetic suitable for further development. The synthesis of this compound is discussed in Parts 2 and 3 of this series.

Experimental

M.p.s were determined with a Büchi capillary oil-immersion apparatus and are uncorrected. Optical rotations were measured at 25 °C on a Perkin-Elmer 241 polarimeter. I.r.

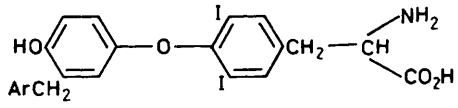


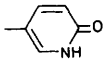
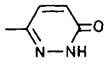
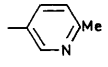
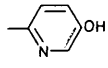
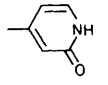
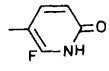
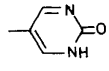
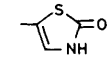
Scheme 7. *Reagents:* i, HBr–aq. HOAc; ii, BBr_3; iii, aq. HCl; iv, NaOH

spectra were recorded on Perkin-Elmer 580B and 577 spectrophotometers. ^{1}H N.m.r. spectra were recorded with JEOL JNM PFT 100 and JNM FX60Q spectrometers with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) as the internal standard. High-performance liquid chromatography (h.p.l.c.) was performed using a Perkin-Elmer Series 3B/LC 75 or a Constametric/LC 75 system. Organic extracts were dried with anhydrous magnesium sulphate. Column chromatography was performed with Merck Kieselgel 60 (Art 7734) and Kieselgel 60 (Art 15111). Light petroleum refers to the fraction boiling between 60 and 80 °C except where otherwise indicated.

2-Bromo-5-methoxypyridine (**10**).—2-Amino-5-methoxypyridine[18] (14.8 g) was dissolved in 60% HBr (150 ml) and bromine (47.47 g) was added dropwise to the cooled (−10 °C), stirred solution. To the resulting yellow suspension was added, dropwise, a solution of sodium nitrite (20.53 g) in water (40 ml), while the temperature was kept below −5 °C. The mixture was stirred to room temperature, and after 0.5 h cooled to 0 °C, and a solution of sodium hydroxide (120 g) in water (100 ml) was slowly added. The mixture was extracted with ether, and the extracts were dried and evaporated. The residue was chromatographed on silica gel (150 g; dichloromethane) then distilled under reduced pressure to give 2-*bromo*-5-*methoxy*-

Table. Thyromimetic activities in the rat



Cmpd.	Ar	Heart		Liver	
		Relative potency *in vivo*[a]	Relative receptor binding *in vitro*[b]	Relative potency *in vivo*[a]	Relative receptor binding *in vitro*[b]
T_3		100	100	100	100
(1)		inactive	2.7	1.7	2.3
(2)		0.1	4.0	2.4	2.0
(3)		inactive	2.5	inactive	0.63
(4)		*c*	15.0	1.7	19.6
(5)		inactive	0.045	*c*	0.042
(6)		inactive	1.65	inactive	0.27
(7)		inactive	0.58	inactive	0.14
(8)		*c*	6.2	3.3	10.6

[a] GPDH induction. [b] Receptors in isolated nuclei. [c] Low maximum response. See refs. 3 and 14 for descriptions of methodology used.

pyridine (**10**) (14.1 g, 63%), b.p. 76—78 °C/0.6 Torr (Found: C, 38.3; H, 3.3; N, 7.4; Br, 42.5. C_6H_6BrNO requires C, 38.3; H, 3.2; N, 7.5; Br, 42.5%); δ($CDCl_3$) 3.83 (3 H, s, OMe), 7.09 (1 H, d, 4-H), 7.37 (1 H, d, 3-H), and 8.04 (1 H, d, 6-H).

(5-*Benzyloxy*-2-*methoxyphenyl*)-(2-*methoxypyrimidin*-5-*yl*)-*methanol* (**23**).—A solution of butyl-lithium in hexane (47 ml of a 1.55M solution) was cooled to −90 °C and added dropwise, under N_2, to a stirred, cooled (−95 °C) solution of 5-bromo-2-methoxypyrimidine (**11**) (13.61 g, 0.072 mol) in dry THF (500 ml). To the resulting yellow solution was immediately added a solution of aldehyde (**20**)[5] (14.5 g, 0.060 mol) in dry THF (150 ml), with the temperature of the reaction mixture being kept below −90 °C. The solution was stirred and allowed to warm to room temperature (2 h), and was then treated with saturated aqueous ammonium chloride (500 ml). The mixture was extracted with ethyl acetate, and the extract was dried and evaporated to dryness. The residue was crystallised from dichloromethane–light petroleum to give the *product* (**23**) (18.5 g, 87%), m.p. 118—120 °C (Found: C, 67.9; H, 5.8; N, 7.7. $C_{20}H_{20}N_2O_4$ requires C, 68.2; H, 5.7; N, 8.0%); $\nu_{max.}$(Nujol) 3 220 cm^{-1} (OH); δ($CDCl_3$) 2.8 (1 H, br s, OH), 3.72 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.99 (2 H s, OCH_2), 5.94 (1 H, s, CH), ~6.9 (3 H, m, ArH), ~7.4 (5 H, m, benzyl Ph), and 8.43 (2 H, s, Pyrim-H).

(5-*Benzyloxy*-2-*methoxyphenyl*)-(6-*methylpyridin*-3-*yl*)*methanol* (**24**).—To a cooled (−95 °C), stirred solution of 5-bromo-2-methylpyridine (**12**) (7.74 g, 0.045 ml) in dry THF (125 ml) under N_2 was added, dropwise, a solution of butyl-lithium in hexane (30 ml of a 1.5M solution). The resultant clear orange solution was warmed to −80 °C whereupon an orange precipitate formed, and after a further 10 min a solution of aldehyde (**20**) (5.07 g, 0.021 mol) in dry THF (65 ml) was added, with the temperature of the reaction mixture being maintained at −80 °C. The resultant yellow solution was stirred and allowed to warm to room temperature, then treated with saturated aqueous ammonium chloride (100 ml). The mixture was extracted with ethyl acetate and the extract was dried and evaporated. The residue was crystallised from dichloromethane–light petroleum (40—60 °C) to give the *product* (**24**) (4.3 g, 61%), m.p. 138 °C (Found: C, 75.0; H, 6.2; N, 4.0. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%); $\nu_{max.}$(Nujol) 3 060 cm^{-1} (OH); δ($CDCl_3$) 2.50 (3 H, s, Py-Me), 3.70 (3 H, s, OMe), ~3.7 (1 H, br s, OH), 4.98 (2 H, s, OCH_2), 6.00 (1 H, s, CH), ~6.9 (3 H, m, ArH), 7.05 (1 H, d, Py 5-H), 7.36 (5 H, m, benzyl Ph), 7.56 (1 H, dd, Py 4-H), and 8.44 (1 H, d, Py 2-H).

Similarly prepared were (5-*benzyloxy*-2-*methoxyphenyl*)-(6-*methoxypyridin*-3-*yl*)*methanol* (**21**) [from 5-bromo-2-methoxypyridine (**9**), 72%], m.p. 80—82 °C (Found: C, 71.7; H, 6.0; N, 3.9. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%); $\nu_{max.}$(Nujol)

3 080 cm^{-1} (OH); δ($CDCl_3$) 3.15 (1 H, s, OH), 3.73 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.99 (2 H, s, CH_2O), 5.95 (1 H, s, CH), 6.7—7.6 (10 H, m, ArH), and 8.12 (1 H, d, Py 2-H), and (5-benzyloxy-2-methoxyphenyl)-(5-methoxypyridin-2-yl)-methanol (**22**) [from 2-bromo-5-methoxypyridine (**10**), 81%]. Crude alcohol (**22**) was acetylated with acetic anhydride in pyridine to give the *acetate*, m.p. 105—110 °C (Found: C, 69.8; H, 5.6; N, 3.2. $C_{23}H_{23}NO_5$ requires C, 70.2; H, 5.8; N, 3.6%); $\nu_{max.}$(Nujol) 1 720 cm^{-1} (ester CO); δ($CDCl_3$) 2.18 (3 H, s, COMe), 3.78 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.01 (2 H, s, CH_2O), 6.8—7.3 (11 H, m, ArH), and 8.28 (1 H, d, Py 6-H).

(5-*Benzyloxy*-2-*methoxyphenyl*)-(5-*bromo*-2-*methoxypyridin*-4-*yl*)*methanol* (**25**).—To a stirred solution of di-isopropylamine (27.83 g, 0.275 mol) in dry THF (110 ml) at −70 °C under N_2 was added, dropwise, during 20 min, a solution of butyl-lithium (172 ml of a 1.6M solution in hexane) containing THF (60 ml). A solution of 5-bromo-2-methoxypyridine (**9**) (50.77 g, 0.270 mol) in dry THF (160 ml) was added during 0.5 h, with the temperature of the reaction mixture being kept at −70 °C. This mixture was treated, during 0.75 h at −70 °C, with a solution of aldehyde (**20**) (47.63 g, 0.197 mol) in dry THF (310 ml). The reaction mixture was allowed to warm to 0 °C, then saturated aqueous ammonium chloride (300 ml) was added. The mixture was extracted with ethyl acetate, the combined extracts were dried and evaporated, and the residue was crystallised from dichloromethane–light petroleum–ethyl acetate to give the *product* (**25**) (60.82 g, 72%), m.p. 107—109 °C (Found: C, 58.3; H, 4.7; N, 3.2; Br, 18.8. $C_{21}H_{20}BrNO_4$ requires C, 58.6, H, 4.7; N, 3.3; Br, 18.6%); $\nu_{max.}$($CHBr_3$) 3 580 cm^{-1} (OH); δ($CDCl_3$) 3.15 (1 H, s, OH), 3.82 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.93 (2 H, s, OCH_2), 6.19 (1 H, s, CH), ~6.7 (3 H, m, ArH), 6.99 (1 H, s, Py 3-H), 7.32 (5 H, m, benzyl Ph), and 8.16 (1 H, s, Py 6-H).

Similarly prepared from 2,6-difluoropyridine (**17**) was (5-*benzyloxy*-2-*methoxyphenyl*)-(2,6-*difluoropyridin*-3-*yl*)*methanol* (**26**) (50%), m.p. 87—90 °C (Found: C, 67.5; H, 4.9; N, 3.9. $C_{20}H_{17}F_2NO_3$ requires C, 67.2; H, 4.8; N, 3.9%); $\nu_{max.}$(Nujol) 3 350 cm^{-1} (OH); δ($CDCl_3$) 3.22 (1 H, d, OH), 3.78 (3 H, s, OMe), 4.99 (2 H, s, OCH_2), 6.18 (1 H, d, CH), 6.85 (4 H, m, ArH), 7.35 (5 H, m, benzyl Ph), and 7.92 (1 H, q, Py 4-H).

(5-*Benzyloxy*-2-*methoxyphenyl*)-(2-*methoxypyridin*-4-*yl*)*methanol*.—To a stirred solution of the alcohol (**25**) (60.8 g, 0.141 mol) in dry THF (400 ml) at −70 °C was added, during 0.5 h at −70 °C, a solution of butyl-lithium (221 ml of a 1.6M solution in hexane, 0.353 mol). Water (25.46 g, 1.41 mol) in THF (150 ml) was added to the mixture at −65 °C. The mixture was warmed to room temperature, saturated aqueous ammonium chloride was added, and the mixture was extracted with ethyl acetate. The extracts were dried and evaporated, and the residue was recrystallised from dichloromethane–light petroleum to give the *title product* (33.11 g, 67%), m.p. 99—100 °C (Found: C, 71.4; H, 6.0; N, 3.7. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%); $\nu_{max.}$(Nujol) 3 160 cm^{-1} (OH); δ($CDCl_3$) 3.73 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.30 (1 H, br s, OH), 4.97 (2 H, s, CH_2O), 5.90 (1 H, s, CH), ~6.8 (5 H, m, ArH), 7.34 (5 H, m, benzyl Ph), and 8.04 (1 H, d, Py 6-H).

4-*Methoxy*-3-[(2-*methoxypyrimidin*-5-*yl*)*methyl*]*phenol* (**29**).—The alcohol (**23**) (14.96 g, 0.0425 mol) was dissolved in a mixture of pyridine (50 ml) and acetic anhydride (50 ml). The solution was heated to 100 °C for 0.25 h, then evaporated to dryness. The residue was azeotroped with toluene, then crystallised from ether–light petroleum to give the corresponding *acetate* (16.16 g, 96%), m.p. 102—103 °C (Found: C, 66.7; H, 5.7; N, 6.9. $C_{22}H_{22}N_2O_5$ requires C, 67.0; H, 5.6; N, 7.1%); $\nu_{max.}$(Nujol) 1 735 cm^{-1} (ester CO); δ($CDCl_3$) 2.09 (3 H, s, Ac), 3.70 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.98 (2 H, s, OCH_2), ~6.9 (4 H, m, ArH, CH), 7.40 (5 H, m, benzyl Ph), and 8.44 (2 H, s, Pyrim-H).

This acetate (15.01 g, 0.0381 mol) was hydrogenated at 50 p.s.i. in methanol (100 ml) containing triethylamine (7.69 g, 0.076 mol) and 10% palladium–charcoal (3.5 g). After hydrogen uptake had ceased, the mixture was filtered and the filtrate was evaporated to dryness. The residue was crystallised from aqueous methanol to give the *phenol* (**29**) (8.55 g, 91%), m.p. 132—133 °C (Found: C, 63.3; H, 5.7; N, 11.4. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); $\nu_{max.}$(Nujol) 3 115 cm^{-1} (OH); δ($CHCl_3$) 3.74 (3 H, s, OMe), 3.77 (2 H, s, CH_2), 3.98 (3 H, s, OMe), ~6.0 (1 H, br s, OH), 6.65 (3 H, m, ArH), and 8.34 (2 H, s, Pyrim-H).

Similarly prepared, by hydrogenolysis of the corresponding acetate in methanol, was 4-*methoxy*-3-[(6-*methoxypyridin*-3-*yl*)*methyl*]*phenol* (**27**) (92%), m.p. 121—124 °C (Found: C, 67.8; H, 6.1; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%); $\nu_{max.}$(Nujol) 3 000 cm^{-1} (OH); δ($CDCl_3$) 3.74 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.76 (2 H, s, CH_2), 5.50 (1 H, s, OH), ~6.6 (4 H, m, ArH), 7.42 (1 H, dd, Py 4-H), and 7.94 (1 H, d, Py 2-H).

4-*Methoxy*-3-[(2-*methoxypyridin*-4-*yl*)*methyl*]*phenol* (**31**).—(5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)-methanol (33.0 g, 0.094 mol) was acetylated with pyridine (80 ml) and acetic anhydride (100 ml) [as described for compound (**29**), above]. The acetate so obtained was hydrogenated at 50 p.s.i. in glacial acetic acid (110 ml) containing 10% palladium–charcoal (15 g of catalyst containing 42% water, from Hoechst Ltd.) and 10M HCl (1.0 ml, 0.010 mol). After 1.5 h, uptake of 2 equiv. of hydrogen was complete. The mixture was filtered, a solution of sodium acetate (1.0 g) in water (10 ml) added to the filtrate, and the mixture was evaporated to dryness. The residue was partitioned between chloroform and saturated aqueous potassium hydrogen carbonate, and the organic layer was removed, dried, and evaporated to dryness. The residue was crystallised from chloroform–light petroleum to give the *phenol* (**31**) (17.35 g, 75%), m.p. 98—99 °C (Found: C, 68.7; H, 6.4; N, 5.5. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%); $\nu_{max.}$(Nujol) 3 120 cm^{-1} (OH); δ($CDCl_3$) 3.75 (3 H, s, OMe), 3.84 (2 H, s, CH_2), 3.89 (3 H, s, OMe), ~6.7 (5 H, m, ArH), and 7.96 (1 H, d, Py 6-H).

Similarly prepared were 4-*methoxy*-3-[(6-*methylpyrid*-3-*yl*)*methyl*]*phenol* (**30**) [from compound (**24**), 69%], m.p. 146—148 °C (Found: C, 73.5; H, 6.6; N, 5.7. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%); $\nu_{max.}$(Nujol) 3 300—2 200 cm^{-1} (OH); δ($CDCl_3$) 2.45 (3 H, s, Me), 3.79 (3 H, s, OMe), 3.82 (2 H, s, CH_2), 6.36 (1 H, m, Ar 2-H), 6.73 (2 H, m, Ar 5- and 6-H), 7.05 (1 H, d, Py 5-H), 7.52 (1 H, dd, Py 4-H), and 8.21 (1 H, d, Py 2-H), and 4-*methoxy*-3-[(5-*methoxypyridin*-2-*yl*)*methyl*]*phenol* (**28**) [from compound (**22**), 64%], m.p. 115—122 °C (Found: C, 67.5; H, 6.2; N, 5.3. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%); δ($CDCl_3$) 3.75 (3 H, s, OMe), 3.76 (3 H, s, OMe), 4.01 (2 H, s, CH_2), ~6.9 (5 H, m, ArH), and 7.97 (1 H, dd, Py 6-H).

3-[(6-*Ethoxy*-2-*fluoropyridin*-3-*yl*)*methyl*]-4-*methoxyphenol* (**32**).—To a solution of sodium ethoxide [from sodium (0.553 g, 0.024 mol)] in dry ethanol (20 ml) was added a solution of the alcohol (**26**) (3.91 g, 0.011 mol) in dry ethanol (20 ml). The solution was refluxed for 0.5 h, then evaporated to dryness. The residue was partitioned between water and chloroform, and the organic layer was removed, dried, and evaporated to dryness. The n.m.r. spectrum of the crude product in $CDCl_3$ showed that the 6-fluoro group in compound (**26**) was selectively replaced by ethoxy: δ 6.44 (1 H, dd, J_{HH} 8, J_{HF} 3 Hz, Py 5-H). This material was successively acetylated then hydrogenolysed (10% palladium–charcoal in ethanol) as described above to give, after chromatography on silica gel with ethyl acetate–light petroleum (1:5) as eluant, the *phenol* (**32**) (1.52 g, 50% overall), m.p. 84–

87 °C (from dichloromethane–light petroleum) (Found: C, 64.8; H, 6.0; N, 4.9. $C_{15}H_{16}FNO_3$ requires C, 65.0; H, 5.8; N, 5.1%); $\nu_{max.}$(Nujol) 3 255 cm^{-1} (OH); δ($CHCl_3$) 1.38 (3 H, t, Me), 3.77 (3 H, s, OMe), 3.80 (2 H, s, CH_2), 4.36 (2 H, q, OCH_2), 4.62 (1 H, br s, OH), 6.35 (1 H, dd, J_{HH} 8, J_{HF} 3 Hz, Py 5-H), ~6.7 (3 H, m, ArH), and 7.37 (1 H, dd, Py 4-H).

5-Benzyloxy-2-methoxybenzyl Bromide (**33**).—Sodium borohydride (15 g) was added in portions to a gently warmed, stirred suspension of 5-benzyloxy-2-methoxybenzaldehyde (**20**) (150.4 g) in methanol (500 ml). The resulting clear solution was evaporated to dryness, the residue partitioned between dichloromethane and water, and the organic layer removed and washed with saturated aqueous sodium chloride. The dried organic phase was evaporated to dryness and the residue was crystallised from dichloromethane–light petroleum to give *5-benzyloxy-2-methoxybenzyl alcohol* (143.8 g, 95%), m.p. 50—51 °C (Found: C, 74.0; H, 6.9. $C_{15}H_{16}O_3$ requires C, 73.8; H, 6.6%); $\nu_{max.}$(Nujol) 3 360 cm^{-1} (OH); δ($CDCl_3$) 3.79 (3 H, s, OMe), 4.63 (2 H, s, CH_2OH), 4.99 (2 H, s, benzyl CH_2O), 6.85 (3 H, m, ArH), and 7.35 (5 H, m, benzyl Ph).

To a stirred, cooled (−5 °C) solution of this alcohol (143.8 g) in dry dichloromethane (500 ml) was added, dropwise, a solution of phosphorus tribromide (58.5 g) in dry dichloromethane (100 ml), while the reaction temperature was kept below 0 °C. The mixture was stirred and allowed to warm to 10 °C, then quenched with water (500 ml), and the organic layer was removed and thoroughly washed with water and dried. Evaporation, followed by crystallisation of the residue from dichloromethane–light petroleum yielded the *bromide* (**33**) (146.8 g, 81%), m.p. 88—90 °C (Found: C, 58.9; H, 4.9; Br, 25.9. $C_{15}H_{15}BrO_2$ requires C, 58.7; H, 4.9; Br, 26.0%); δ($CDCl_3$) 3.83 (3 H, s, OMe), 4.51 (2 H, s, CH_2Br), 4.99 (2 H, s, CH_2O), 6.85 (3 H, m, ArH), and 7.35 (5 H, m, benzyl Ph).

(5-Benzyloxy-2-methoxyphenyl)-(6-chloropyridazin-3-yl)-acetonitrile (**34**).—To a warm stirred solution of sodium cyanide (16.12 g) in dimethyl sulphoxide (250 ml) was added, in portions, the bromide (**33**) (100 g); a precipitate appeared. The cooled solid mixture was treated with water (1 l), the mixture was stirred vigorously, and the precipitate was collected, and then recrystallised from aqueous methanol to give *(5-benzyloxy-2-methoxyphenyl)acetonitrile* (72.2 g, 87%), m.p. 63—65 °C (Found: C, 75.6; H, 6.1; N, 5.2. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%); $\nu_{max.}$(Nujol) 2 245 cm^{-1} (CN); δ($CDCl_3$) 3.66 (2 H, s, CH_2CN), 3.80 (3 H, s, OMe), 5.01 (2 H, s, CH_2O), ~6.9 (3 H, m, ArH), and 7.39 (5 H, m, benzyl Ph).

To a stirred solution of this nitrile (14.84 g, 0.0587 mol) and 3,6-dichloropyridazine (8.69 g, 0.0587 mol) in dry dimethylformamide (50 ml) was added, in portions during 2 h, sodium hydride (5.92 g of a 50% dispersion in oil, 0.123 mol). The mixture was poured onto excess of crushed ice and extracted with dichloromethane. The extracts were washed with water, dried, charcoaled, and then evaporated to dryness. Crystallisation of the residue from chloroform–light petroleum gave the *nitrile* (**34**) (13.8 g, 64%), m.p. 152—156 °C (decomp.) (Found: C, 65.0; H, 4.3; N, 11.3; Cl, 10.2. $C_{20}H_{16}ClN_3O_2 \cdot 0.04CHCl_3$ requires C, 64.9; H, 4.4; N, 11.3; Cl, 10.7%); $\nu_{max.}$(Nujol) 2 250 cm^{-1} (CN); δ[$(CD_3)_2SO$] 3.70 (3 H, s, OMe), 5.05 (2 H, s, OCH_2), 6.12 (1 H, s, CH), 7.03 (3 H, m, ArH), 7.37 (5 H, m, benzyl Ph), 7.62 (1 H, d, Pyrid-H), and 7.89 (1 H, d, Pyrid-H).

4-Benzyloxy-2-[(2-methoxythiazol-5-yl)methyl]anisole (**35**).—To a stirred solution of 2-methoxythiazole (8.13 g, 0.0706 mol) in dry THF at −78 °C under N_2 was added butyl-lithium (45 ml of a 1.6M solution in hexane, 0.071 mol). A solution of the bromide (**33**) (19.72 g, 0.0642 mol) in dry THF (80 ml) was added, with the reaction temperature maintained below −70 °C. The solution was stirred, allowed to warm to room temperature, and worked up as described above for compound (**23**). The crude product was purified by chromatography on silica gel, with ethyl acetate–light petroleum (1:6) as eluant, to give the *thiazole* (**35**) (16.15 g, 74%), m.p. 53—55 °C (from light petroleum) (Found: C, 66.6; H, 5.9; N, 4.1; S, 9.2. $C_{19}H_{19}NO_3S$ requires C, 66.8; H, 5.6; N, 4.1; S, 9.4%); δ($CDCl_3$) 3.79 (3 H, s, OMe), 3.92 (2 H, s, CH_2), 4.01 (3 H, s, thiazole OMe), 4.98 (2 H, s, CH_2O), ~6.8 (4 H, m, ArH), and 7.35 (5 H, m, benzyl Ph).

6-[(5-Hydroxy-2-methoxyphenyl)methyl]pyridazin-3(2H)-one (**36**).—A solution of the nitrile (**34**) (11.00 g) in conc. hydrochloric acid (50 ml) containing glacial acetic acid (10 ml) was refluxed for 20 min, then evaporated to dryness. The residue was dissolved in 6M hydrochloric acid (100 ml) and the solution was refluxed and stirred for 6 h. On cooling, the *phenol* (**36**) was precipitated as the *hydrochloride salt* (2.36 g), m.p. 175—182 °C (Found: C, 53.7; H, 4.9; N, 10.4; Cl, 13.0. $C_{12}H_{12}N_2O_3 \cdot HCl$ requires C, 53.6; H, 4.9; N, 10.4; Cl, 13.2%); $\nu_{max.}$(Nujol) 3 250 (OH) and 3 150—2 100 cm^{-1} (NH^+); δ[$(CD_3)_2SO$] 3.70 (3 H, s, OMe), 3.77 (2 H, s, CH_2), ~6.6 (3 H, m, ArH), 6.83 (1 H, d, Pyrid 5-H), and 7.25 (1 H, d, Pyrid 4-H). A second crop of product (4.6 g, total yield 82%) was obtained upon concentration of the mother liquors.

5-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H)-one (**37**).—To a solution of the methoxythiazole (**35**) (8.62 g, 0.0253 mol) in methanol (50 ml) was added 10M hydrochloric acid (50 ml). The solution was heated for a few minutes on a steam-bath, then cooled and diluted with water (100 ml). The precipitate was collected, and recrystallised from methanol to give *5-[(5-benzyloxy-2-methoxyphenyl)methyl]thiazol-2(3H)-one* (5.96 g, 72%), m.p. 175—180 °C (Found: C, 65.9; H, 5.2; N, 4.4; S, 9.9. $C_{18}H_{17}NO_3S$ requires C, 66.0; H, 5.2; N, 4.3; S, 9.8%); $\nu_{max.}$(Nujol) 3 150 (NH) and 1 645 cm^{-1} (amide CO); δ($CDCl_3$) 3.71 (2 H, s, CH_2), 3.78 (3 H, s, OMe), 4.99 (2 H, s, CH_2O), 6.26 (1 H, m, Thiaz 4-H^{17}), 6.80 (3 H, app s, ArH), 7.38 (5 H, m, benzyl Ph), and 9.68 (1 H, br, NH).

To a stirred suspension of this 2-oxothiazole (5.87 g, 0.0179 mol) in dry dichloromethane (30 ml) at −78 °C was added boron trichloride (35.9 ml of a 1M solution in dichloromethane, 0.0359 mol). The solution was warmed to −20 °C and after 1 h at this temperature the homogeneous mixture was quenched with ice. The mixture was extracted with excess of ethyl acetate, and the combined extracts were washed successively with water and saturated aqueous sodium chloride. Evaporation of the dried solution and crystallisation of the residue from ethyl acetate–light petroleum gave the *phenol* (**37**) (2.54 g, 60%), m.p. 159 °C (Found: C, 55.7; H, 4.4; N, 5.9; S, 13.3. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.7; N, 5.9; S, 13.5%); $\nu_{max.}$($CHBr_3$) 3 580 (OH), 3 410 (NH), and 1 667 cm^{-1} (amide CO); δ[$(CD_3)_2SO$] 3.66 (2 H, s, CH_2), 3.71 (3 H, s, OMe), ~6.6 (4 H, m, ArH), ~8.7 (1 H, br, OH), and ~10.5 (1 H, br, NH).

3′-Heteroarylmethyl-4′-O-methyl-3,5-dinitro-N-trifluoroacetyl-L-thyronine Ethyl Esters (**38**)—(**45**).—*General procedure.* A stirred solution of 3,5-dinitro-*N*-trifluoroacetyl-L-tyrosine ethyl ester (0.077 mol) in dry pyridine (100 ml) was treated with methanesulphonyl chloride (0.077 mol) and then refluxed for 10 min. A solution of the phenol [(**27**)—(**32**), (**36**), or (**37**)] (0.070 mol) in dry pyridine (60 ml) was added, and the mixture was refluxed for 1 h. The pyridine was evaporated off, the residue was dissolved in chloroform, and the solution was washed successively with water, 2M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, 2M-aqueous sodium hydroxide, and water. The dried organic solution was evaporated and the following products obtained by crystallisation from aqueous ethanol:

3′-[(6-*Methoxypyridin*-3-*yl*)*methyl*]-4′-O-*methyl*-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**38**) (48%), m.p. 123–124 °C (Found: C, 51.9; H, 4.1; N, 9.0. $C_{27}H_{35}F_3N_4O_{10}$ requires C, 52.1; H, 4.1; N, 9.0%); $\nu_{max.}$(Nujol) 3 130 (NH), 1 730 (ester CO), and 1 705 cm^{-1} (amide CO); δ($CDCl_3$) 1.31 (3 H, t, ester Me), 3.35 (2 H, m, β-H_2), 3.74 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.79 (2 H, s, CH_2), 4.31 (2 H, q, ester CH_2), 4.82 (1 H, m, α-H), ~7.0 (5 H, m, ArH), 7.89 (2 H, s, 2- and 6-H), and 7.94 (1 H, dd, Py 2-H).

3′-[(5-*Methoxypyridin*-2-*yl*)*methyl*]-4′-O-*methyl*-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**39**) (68%), as a froth after column chromatography (Found: C, 51.9; H, 4.1; N, 8.5%); $\nu_{max.}$(Nujol) 3 310 (NH), 1 740 (ester CO), and 1 720 cm^{-1} (amide CO); δ($CDCl_3$) 1.32 (3 H, t, ester Me), 3.35 (2 H, m, β-H_2), 3.76 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.01 (2 H, s, CH_2), 4.31 (2 H, q, ester CH_2), 4.85 (1 H, m, α-H), 6.75 (3 H, m, ArH), 6.98 (1 H, d, Py 3-H), 7.12 (1 H, dd, Py 4-H), 7.64 (1 H, d, NH), 7.89 (2 H, s, 2- and 6-H), and 8.17 (1 H, d, Py 6-H).

3′-[(2-*Methoxypyrimidin*-5-*yl*)*methyl*]-4′-O-*methyl*-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**40**) (60%), m.p. 127—129 °C (Found: C, 49.8; H, 3.9; N, 11.1. $C_{26}H_{24}F_3N_5O_{10}$ requires C, 50.1; H, 3.99; N, 11.2%); $\nu_{max.}$(Nujol) 3 400 (NH), 1 745 (ester CO), and 1 700 cm^{-1} (amide CO); δ($CDCl_3$) 1.32 (3 H, t, ester Me), 3.35 (2 H, m, β-H_2), 3.77 (3 H, s, OMe), 3.79 (2 H, s, CH_2), 3.99 (3 H, s, OMe), 4.32 (2 H, q, ester CH_2), 4.85 (1 H, m, α-H), 6.70 (3 H, m, ArH), 7.64 (1 H, d, NH), 7.94 (2 H, s, 2- and 6-H), and 8.32 (2 H, s, Pyrim-H).

4′-O-*Methyl*-3′-[(6-*methylpyridin*-3-*yl*)*methyl*]-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**41**) (54%), m.p. 151 °C (Found: C, 53.5; H, 4.2; N, 9.0. $C_{27}H_{25}F_3N_4O_9$ requires C, 53.5; H, 4.2; N, 9.2%); $\nu_{max.}$(Nujol) 3 300 (NH), 1 730 (ester CO), and 1 700 cm^{-1} (amide CO); δ($CDCl_3$) 1.31 (3 H, t, ester Me), 2.50 (3 H, s, Py-Me), 3.34 (2 H, m, β-H_2), 3.74 (3 H, s, OMe), 3.83 (2 H, s, CH_2), 4.32 (2 H, q, ester CH_2), 4.77 (1 H, m, α-H), 6.65 (3 H, m, ArH), 7.05 (1 H, d, Py 5-H), 7.34 (1 H, dd, Py 4-H), 7.80 (1 H, d, NH), 7.90 (2 H, s, 2- and 6-H), and 8.31 (1 H, d, Py 2-H).

3′-[(2-*Methoxypyridin*-4-*yl*)*methyl*]-4′-O-*methyl*-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**42**) (37%), m.p. 98—99 °C (Found: C, 52.0; H, 4.0; N, 9.0. $C_{27}H_{25}F_3N_4O_{10}$ requires C, 52.1; H, 4.1; N, 9.0%); $\nu_{max.}$(Nujol) 3 200 (NH), 1 735 (ester CO), and 1 717 cm^{-1} (amide CO); δ($CDCl_3$) 1.33 (3 H, t, ester Me), 3.34 (2 H, m, β-H_2), 3.74 (3 H, s, OMe), 3.83 (2 H, s, CH_2), 3.90 (3 H, s, OMe), 4.33 (2 H, q, ester CH_2), 4.84 (1 H, m, α-H), ~6.65 (5 H, m, ArH and Py 3- and 5-H), 7.29 (1 H, d, NH), 7.91 (2 H, s, 2- and 6-H), and 8.03 (1 H, d, Py 6-H).

3′-[(6-*Ethoxy*-2-*fluoropyridin*-3-*yl*)*methyl*]-4′-O-*methyl*-3,5-*dinitro*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**43**) (48%), m.p. 99—102 °C (Found: C, 51.9; H, 4.1; N, 8.6. $C_{28}H_{26}F_4N_4O_{10}$ requires C, 51.5; H, 4.0; N, 8.6%); $\nu_{max.}$(Nujol) 3 295 (NH), 1 732 (ester CO), and 1 702 cm^{-1} (amide CO); δ($CDCl_3$) 1.34 and 1.35 (each 3 H, t, ester and ether Me), 3.1—3.6 (2 H, m, β-CH_2), 3.76 (3 H, s, OMe), 3.80 (2 H, s, CH_2), 4.33 and 4.34 (each 2 H, q, ester and ether CH_2), 4.85 (1 H, m, α-H), 6.36 (1 H, dd, Py 5-H), ~6.65 (3 H, m, ArH), 7.13 (1 H, d, NH), 7.30 (1 H, dd, Py 4-H), and 7.90 (2 H, s, 2- and 6-H).

4′-O-*Methyl*-3,5-*dinitro*-3′-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**44**) (36%), m.p. 170—172 °C (from ethyl acetate–light petroleum) (Found: C, 49.3; H, 3.5; N, 11.0. $C_{25}H_{22}F_3N_5O_{10}$ requires C, 49.3; H, 3.6; N, 11.5%); $\nu_{max.}$(Nujol) 3 260 (NH), 1 750 (ester CO), 1 710 (amide CO), and 1 690 cm^{-1} (pyridazinone CO); δ($CDCl_3$) 1.32 (3 H, t, ester Me), 3.0—3.6 (2 H, m, β-H_2), 3.80 (3 H, s, OMe), 3.85 (2 H, s, CH_2), 4.31 (2 H, q, ester CH_2), 4.87 (1 H, m, α-H), ~6.7 (3 H, m, ArH), 6.93 and 7.15 (each 1 H, d, Pyrid-H), 7.97 (2 H, s, 2- and 6-H), 8.18 (1 H, d, NH), and 11.85 (1 H, s, pyridazinone NH).

4′-O-*Methyl*-3,5-*dinitro*-3′-[(2-*oxo*-2,3-*dihydrothiazol*-5-*yl*)*methyl*]-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**45**) (41%), m.p. 159—160 °C (Found: C, 46.9; H, 3.2; N, 8.6; S, 5.4. $C_{24}H_{21}F_3N_4O_{10}S$ requires C, 46.9; H, 3.4; N, 9.1; S, 5.2%); $\nu_{max.}$(Nujol) 3 300 (NH), 1 730 (ester CO), 1 703 (amide CO), and 1 670 cm^{-1} (thiazolone CO); δ($CDCl_3$) 1.18 (3 H, t, ester Me), ~3.3 (2 H, m, β-H_2), 3.67 (2 H, s, CH_2), 3.77 (3 H, s, OMe), 4.18 (2 H, q, ester CH_2), 4.80 (1 H, m, α-H), 6.45 (1 H, s, Thiaz 4-H), 6.68 (1 H, dd, 6′-H), 6.80 (1 H, d, 2′-H), 6.94 (1 H, d, 5′-H), and 8.37 (2 H, s, 2- and 6-H).

3′-*Heteroarylmethyl*-3,5-*di-iodo*-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine Ethyl Esters* (**46**)—(**53**).—*General procedure*. A dinitrothyronine (**38**), (**39**), (**41**)—(**45**) (0.020 mol) was hydrogenated at 50 p.s.i. in glacial acetic acid (45 ml) containing 10% palladium–charcoal. The required uptake of hydrogen was complete within 1 h. The mixture was filtered and the filtrate and washings (~80 ml) were added to a cold (0 °C) mixture of sulphuric acid (120 ml) and water (120 ml). [In the case of dinitro compound (**40**), reduction was performed in methanol containing triethylamine (10 mol equiv.). The solvents were then removed and replaced with glacial acetic acid.] The diamine solution was cooled and *vigorously* mechanically stirred to −10 °C and a solution of sodium nitrite (0.050 mol) in water (75 ml) was added dropwise, with the temperature being kept between −10 and −15 °C during this addition. After a further 0.25 h at −10 °C, the reaction mixture was poured into a stirred mixture containing potassium iodide (0.20 mol), iodine (0.020 mol), and urea (0.03 mol) in chloroform (400 ml) and water (400 ml). The resulting mixture was stirred to room temperature for 1—2 h, then cautiously treated with excess of solid sodium metabisulphite. The organic layer was removed, and washed thoroughly with water and then with saturated aqueous sodium hydrogen carbonate. The dried organic solution was evaporated and the residue was purified by column chromatography on silica gel, with ethyl acetate–light petroleum to give the following 3,5-*di-iodo* derivatives:

3,5-*Di-iodo*-3′-[(6-*methoxypyridin*-3-*yl*)*methyl*]-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**46**) (35%), m.p. 105—109 °C (from aqueous ethanol) (Found: C, 41.5; H, 3.3; N, 3.6; I, 32.1. $C_{27}H_{25}F_3I_2N_2O_6$ requires C, 41.3; H, 3.2; N, 3.6; I, 32.4%); $\nu_{max.}$(Nujol) 3 130 (NH), 1 735 (ester CO), and 1 715 cm^{-1} (amide CO); δ($CDCl_3$) 1.33 (3 H, t, ester Me), 3.15 (2 H, m, β-H_2), 3.78 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.83 (2 H, s, CH_2), 4.29 (2 H, q, ester CH_2), 4.80 (1 H, m, α-H), ~6.9 (6 H, m, ArH and NH), 7.61 (2 H, s, 2- and 6-H), and 8.02 (1 H, d, Py 2-H).

3,5-*Di-iodo*-3′-[(5-*methoxypyridin*-2-*yl*)*methyl*]-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**47**) (9%), m.p. 108—110 °C (from aqueous ethanol) (Found: C, 41.5; H, 3.5; N, 3.5; I, 32.1%); $\nu_{max.}$(Nujol) 3 280 (NH), 1 735 (ester CO), and 1 705 cm^{-1} (amide CO); δ($CDCl_3$) 1.31 (3 H, t, ester Me), 3.15 (2 H, m, β-H_2), 3.76 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.06 (2 H, s, CH_2), 4.29 (2 H, q, ester CH_2), 4.80 (1 H, m, α-H), ~6.65 (3 H, m, ArH), 7.05 (3 H, m, Py 3- and 4-H and NH), 7.58 (2 H, s, 2- and 6-H), and 8.20 (1 H, d, Py 6-H).

3,5-*Di-iodo*-3′-[(2-*methoxypyrimidin*-5-*yl*)*methyl*]-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**48**) (19%), m.p. 135—136 °C (from aqueous ethanol) (Found: C, 39.5; H, 2.9; N, 5.3; I, 32.4. $C_{26}H_{24}F_3I_2N_3O_6$ requires C, 39.8; H, 3.1; N, 5.4; I, 32.3%); $\nu_{max.}$(Nujol) 3 230 (NH), 1 750 (ester CO), and 1 738 cm^{-1} (amide CO); δ($CDCl_3$) 1.29 (3 H, t, ester Me), 3.10 (2 H, m, β-H_2), 3.72 (3 H, s, OMe), 3.78 (2 H, s, CH_2), 3.96 (3 H, s, OMe), 4.27 (2 H, q, ester CH_2), 4.75 (1 H, m, α-H), 6.64 (3 H, m, ArH), 7.13 (1 H, d, NH), 7.59 (2 H, s, 2- and 6-H), and 8.32 (2 H, s, Pyrim-H).

3,5-*Di-iodo*-4′-O-*methyl*-3′-[(6-*methylpyridin*-3-*yl*)*methyl*]-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**49**) (33%), m.p. 129 °C (from ethyl acetate–light petroleum) (Found: C, 42.6; H, 3.2; N,

3.8; I, 32.8. $C_{27}H_{25}F_3I_2N_2O_5$ requires C, 42.2; H, 3.3; N, 3.7; I. 33.0%); $\nu_{max.}$(Nujol) 3 260 (NH), 1 735 (ester CO), and 1 710 cm^{-1} (amide CO); δ($CDCl_3$) 1.31 (3 H, t, ester Me), 2.48 (3 H, s, Py-Me), 3.12 (2 H, m, β-H_2), 3.32 (3 H, s, OCH_2), 3.84 (2 H, s, CH_2), 4.26 (2 H, q, ester CH_2), 4.74 (1 H, m, α-H), ~6.6 (3 H, m, ArH), 7.02 (1 H, d, Py 5-H) ~7.3 (1 H, d, NH), 7.38 (1 H, dd, Py 4-H), 7.60 (2 H, s, 2- and 6-H), and 8.33 (1 H, d, Py 2-H).

3,5-*Di-iodo*-3′-[(2-*methoxypyridin*-4-*yl*)*methyl*]-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**50**) (16%), m.p. 127—129 °C (from ethyl acetate–light petroleum) (Found: C, 41.3; H, 3.15; N, 3.6; I, 32.1. $C_{27}H_{25}F_3I_2N_2O_6$ requires C, 41.3; H, 3.3; N, 3.6; I, 32.4%); $\nu_{max.}$(Nujol) 3 305 (NH), 1 730 (ester CO), and 1 704 cm^{-1} (amide CO); δ($CDCl_3$) 1.31 (3 H, t, ester Me), 3.15 (2 H, m, β-H_2), 3.72 (3 H, s, OMe), 3.84 (2 H, s, CH_2), 3.89 (3 H, s, OMe), 4.26 (2 H, q, ester CH_2), 4.80 (1 H, m, α-H), ~6.65 (5 H, m, ArH and Py 3- and 5-H), 6.95 (1 H, d, NH), 7.59 (2 H, s, 2- and 6-H), and 8.00 (1 H, d, Py 6-H).

3′-[(6-*Ethoxy*-2-*fluoropyridin*-3-*yl*)*methyl*]-3,5-*di-iodo*-4′-O-*methyl*-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**51**) (24%), m.p. 121 °C (from ethyl acetate–light petroleum) (Found: C, 41.1; H, 3.1; N, 3.5; I, 31.3. $C_{28}H_{26}F_4I_2N_2O_6$ requires C, 41.2; H, 3.2; N, 3.4; I, 31.1%); $\nu_{max.}$(Nujol) 3 285 (NH), 1 755 (ester CO), and 1 708 cm^{-1} (amide CO); δ($CDCl_3$) 1.30 and 1.36 (each 3 H, t, ether and ester Me), 3.12 (2 H, m, β-H_2), 3.75 (3 H, s, OMe), 3.80 (2 H, s, CH_2), 4.27 and 4.34 (each 2 H, q, ether and ester CH_2), 4.78 (1 H, m, α-H), 6.33 (1 H, dd, Py 5-H), 6.47 (1 H, dd, 6′-H), 6.68 (1 H, d, 2′-H), 6.75 (1 H, d, 5′-H), 6.94 (1 H, d, NH), 7.35 (1 H, dd, Py 4-H), and 7.58 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-4′-O-*methyl*-3′-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**52**) (24%), m.p. 220—223 °C (decomp.) (from aqueous ethanol) (Found: C, 38.9; H, 2.8; N, 5.5; I, 32.6. $C_{25}H_{22}F_2I_2N_3O_6$ requires C, 38.9; H, 2.9; N, 5.5; I, 32.9%); $\nu_{max.}$(Nujol) 3 240 (NH), 1 740 (ester CO), 1 710 (amide CO), and 1 670 cm^{-1} (pyridazinone CO); δ($CDCl_3$) 1.33 (3 H, t, ester Me), 3.15 (2 H, m, β-H_2), 3.80 (3 H, s, OMe), 3.89 (2 H, s, CH_2), 4.31 (2 H, q, ester CH_2), 4.85 (1 H, m, α-H), ~6.7 (3 H, m, ArH), 6.89 and 7.17 (each 1 H, d, Pyrid-H), 7.55 (1 H, d, NHCOCF_3), 7.62 (2 H, s, 2- and 6-H), and 8.0 (1 H, s, pyridazinone NH).

3,5-*Di-iodo*-4′-O-*methyl*-3′-[(2-*oxo*-2,3-*dihydrothiazol*-5-*yl*)-*methyl*]-N-*trifluoroacetyl*-L-*thyronine ethyl ester* (**53**) (27%), m.p. 137—139 °C (from ethyl acetate–light petroleum) (Found: C, 37.2; H, 2.7; N, 3.6; S, 4.3; I, 32.8. $C_{24}H_{21}F_3I_2N_2O_6S$ requires C, 37.1; H, 2.7; N, 3.6; S, 4.1; I, 32.7%); $\nu_{max.}$(Nujol) 3 270 (NH), 1 730 (ester CO), 1 700 (amide CO), and 1 657 cm^{-1} (thiazolone CO); δ[(CD_3)$_2$SO] 1.99 (3 H, t, ester Me), ~3.2 (2 H, m, β-H_2), 3.67 (2 H, s, CH_2), 3.76 (3 H, s, OMe), 4.15 (2 H, q, ester CH_2), 4.64 (1 H, m, α-H), 6.45 (1 H, d, 6′-H), 6.47 (1 H, s, Thiaz 4-H), 6.62 (1 H, d, 2′-H), 6.91 (1 H, d, 5′-H), and 7.80 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-3′-[(6-*oxo*-1,6-*dihydropyridin*-3-*yl*)*methyl*]-L-*thyronine* (**1**).—A solution of the thyronine (**46**) (2.64 g) in glacial acetic acid (270 ml) and 48% aqueous hydrobromic acid (135 ml) was refluxed for 5 h. The solvents were removed under reduced pressure and the residue was recrystallised twice from aqueous ethanolic sodium hydroxide on addition of acetic acid (to pH 6) to give the *thyronine* (**1**) (1.76 g, 82%), m.p. 253—255 °C (decomp.) (Found: C, 38.8; H, 2.8; N, 4.3; I, 39.2. $C_{21}H_{18}I_2N_2O_5$·H_2O requires C, 38.8; H, 3.1; N, 4.3; I, 39.0%); $[\alpha]_D$ −7.2° (*c* 1.0 in 0.1M-NaOH–EtOH, 1:2); $\nu_{max.}$(Nujol) 3 610 (H_2O), 3 600—2 300 (OH, NH, NH_3^+), 1 655 (pyridone CO), and 1 610 cm^{-1} (acid anion CO); δ(1M-NaOD–D_2O) 2.75 (2 H, m, β-H_2), 3.45 (1 H, m, α-H), 3.58 (2 H, s, CH_2), 6.25—6.60 (4 H, m, ArH), 7.21 (1 H, dd, Py 4-H), 7.58 (1 H, d, Py 2-H), and 7.69 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-3′-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-L-*thyronine* (**2**).—A solution of the thyronine (**52**) (1.82 g, 0.00236 mol) in dry dichloromethane (40 ml) was stirred and cooled 0 °C and boron tribromide (4.14 g, 0.0165 mol) was added. The mixture was stirred at room temperature for 1.5 h, then excess of crushed ice was added. The mixture was filtered, and the precipitate was collected and dissolved in 2M-NaOH (20 ml). The solution was heated (steam-bath) for 0.25 h, then acetic acid was added (to pH 5). The precipitate was collected, and recrystallised from aqueous ethanolic sodium hydroxide on addition of acetic acid to give the *thyronine* (**2**) (1.00 g, 67%), m.p. 258—262 °C (decomp.) (Found: C, 37.2; H, 2.6; N, 6.7; I, 38.9. $C_{20}H_{17}I_2N_3O_5$·0.7H_2O requires C, 37.2; H, 2.9; N, 6.5; I, 39.3%); $[\alpha]_D$ +10.8° (*c* 1.0 in EtOH–H_2O–conc. HCl, 17:2:1); $\nu_{max.}$(Nujol) 3 700—2 500 (NH, OH, NH_3^+), 1 652 (pyridazinone CO), and 1 589 cm^{-1} (acid anion CO); δ(1M-NaOD–D_2O) 2.80 (2 H, m, β-H_2), 3.45 (1 H, m, α-H), 3.89 (2 H, s, CH_2), 6.15 (1 H, m, 2′-H), 6.60 (2 H, m, ArH), 6.67 and 7.06 (each 1 H, d, Pyrid-H), and 7.72 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-3′-[(6-*methylpyridin*-3-*yl*)*methyl*]-L-*thyronine* (**3**).—The thyronine (**49**) (3.14 g) was deprotected as described for compound (**46**) to give the *thyronine* (**3**) (1.74 g, 68%), m.p. 254 °C (Found: C, 41.4; H, 3.2; N, 4.1. $C_{22}H_{20}I_2N_2O_4$·0.5H_2O requires C, 41.3; H, 3.3; N, 4.4%); $[\alpha]_D$ +19.1° (*c* 1.0 in EtOH–H_2O–conc. HCl, 17:2:1); $\nu_{max.}$(2.1% KBr disc) 3 310—2 100 (OH, NH_3^+), 1 650 and 1 610 cm^{-1} (acid anion CO); δ(1M-NaOD–D_2O) 2.33 (3 H, s, Py-Me), 2.80 (2 H, m, β-H_2), 3.40 (1 H, m, α-H), 3.76 (2 H, s, CH_2), 6.2—6.6 (3 H, m, ArH), 6.92 (1 H, d, Py 5-H), 7.31 (1 H, dd, Py 4-H), 7.58 (2 H, s, 2- and 6-H), and 8.11 (1 H, d, Py 2-H).

3′-[(5-*Hydroxypyridin*-2-*yl*)*methyl*]-3,5-*di-iodo*-L-*thyronine* (**4**).—A solution of the thyronine (**47**) (0.72 g) in dichloromethane (4 ml) was added dropwise to a cooled (0 °C), stirred solution of boron tribromide (27.6 g) and dichloromethane (4 ml); a brown precipitate formed instantly. The mixture was stirred at room temperature for 17 h, diluted with dichloromethane (50 ml), and cautiously added to stirred ice–water (300 ml). The pH of the mixture was adjusted to 4 and the mixture was thoroughly extracted with ethyl acetate. The combined, dried extracts were evaporated to dryness and the residue was hydrolysed with sodium hydroxide [as described for compound (**1**) above] to give the *thyronine* (**4**) (0.43 g, 74%), m.p. 277 °C (decomp.) (Found: C, 39.4; H, 2.9; N, 4.4; I, 39.7%. $C_{21}H_{18}I_2N_2O_5$·0.35H_2O requires C, 39.5; H, 3.0; N, 4.4; I, 39.8%); $[\alpha]_D$ +14° (*c* 1.0 in EtOH–H_2O—conc. HCl, 17:2:1); $\nu_{max.}$(Nujol) 3 300—2 300 (OH, NH_3^+), 1 626, 1 600, and 1 580 cm^{-1} (amino acid and aryl rings); δ(1M-NaOD–D_2O) 2.75 (2 H, m, β-H_2), 3.45 (1 H, m, α-H), 3.78 (2 H, s, CH_2), 6.10 (1 H, m, 2′-H), 6.55 (2 H, m, ArH), 6.85 (2 H, m, Py 3- and 4-H), and 7.68 (3 H, m, 2- and 6-H and Py 6-H).

3,5-*Di-iodo*-3′-[(2-*oxo*-1,2-*dihydropyridin*-4-*yl*)*methyl*]-L-*thyronine* (**5**).—The thyronine (**50**) (1.18 g) was deprotected as described above for compound (**46**) to give the *thyronine* (**5**) (0.83 g, 87%), m.p. 275—276 °C (decomp.) (Found: C, 39.5; H, 2.7; N, 4.3; I, 39.6. $C_{21}H_{18}I_2N_2O_5$ requires C, 39.9; H, 2.9; N, 4.4; I, 40.2%); $[\alpha]_D$ +19.8° (*c* 1.1 in EtOH–H_2O–conc. HCl, 17:2:1); $\nu_{max.}$(1.0% KBr disc) 3 700—2 300 (OH, NH, NH_3^+), 1 655 (pyridone CO), and 1 605 cm^{-1} (acid anion CO); δ (1M-NaOD–D_2O) 2.79 (2 H, m, β-H_2), 3.44 (1 H, m, α-H), 3.63 (2 H, s, CH_2), 6.2—6.6 (5 H, m, ArH and Py 3- and 5-H), 7.63 (1 H, d, Py 6-H), and 7.72 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-3′-[(2-*fluoro*-6-*oxo*-1,6-*dihydropyridin*-3-*yl*)-*methyl*]-L-*thyronine* (**6**).—The thyronine (**51**) (0.167 g) was deprotected as described for compound (**47**) to give the *thyronine* (**6**) (0.120 g, 60%), m.p. > 290 °C (decomp.) (Found:

C, 37.8; H, 2.6; N, 4.2. $C_{21}H_{17}FI_2N_2O_5 \cdot H_2O$ requires C, 37.8; H, 2.9; N, 4.2%); $[\alpha]_D$ −9° (*c* 0.2 in EtOH–5M-NaOH, 5:3); $\nu_{max.}$(1.5% KBr disc) 3 700—2 000 (H_2O, OH, NH_3^+) and 1 620 cm^{-1} (amino acid CO); δ(1M-NaOD–D_2O) 2.80 (2 H, m, alanyl β-H_2), 3.45 (1 H, m, α-H), 3.56 (2 H, s, CH_2), 5.92 (1 H, dd, Py 5-H), 6.08 (1 H, d, 2′-H), 6.55 (2 H, m, ArH), 7.04 (1 H, dd, Py 4-H), and 7.70 (2 H, s, 2- and 6-H).

3,5-*Di-iodo*-3′-[(2-*oxo*-1,2-*dihydropyrimidin*-5-*yl*)*methyl*]-L-*thyronine* (**7**).—To a stirred solution of the thyronine (**48**) (2.26 g, 0.00288 mol) in dry dichloromethane (50 ml) at −78 °C was added boron tribromide (3.68 g, 0.0147 mol). The solution was warmed to room temperature and, after a further 1 h, cold water (50 ml) was added. The mixture was extracted with ethyl acetate, and the extracts were washed with saturated aqueous sodium chloride, dried, treated with charcoal, and evaporated to dryness. The residue was dissolved in a mixture of glacial acetic acid (200 ml) and 36% hydrochloric acid (100 ml) and the solution was refluxed for 4 h. The solvents were removed under reduced pressure and the residue was recrystallised twice from aqueous ethanolic sodium hydroxide by addition of acetic acid to give the *thyronine* (**7**) (1.32 g, 72%), m.p. > 260 °C (decomp.) (Found: C, 37.1; H, 2.6; N, 6.3; I, 39.1. $C_{20}H_{17}I_2N_3O_5 \cdot H_2O$ requires C, 36.9; H, 2.9; N, 6.5; I, 39.0%); $[\alpha]_D$ +10.6° (*c* 0.84 in EtOH–H_2O–conc. HCl, 17:2:1); $\nu_{max.}$(Nujol) 3 620 (H_2O), 3 600—2 300 (OH, NH, NH_3^+), and 1 639 cm^{-1} (pyrimidinone CO and amino acid CO); δ(1M-NaOD–D_2O) 2.80 (2 H, m, β-H_2), 3.45 (1 H, m, α-H), 3.52 (2 H, s, CH_2), 6.50 (3 H, m, ArH), 7.69 (2 H, s, 2- and 6-H), and 7.94 (2 H, s, Pyrim-H).

3,5-*Di-iodo*-3′-[(2-*oxo*-2,3-*dihydrothiazol*-5-*yl*)*methyl*]-L-*thyronine* (**8**).—The thyronine (**53**) (0.966 g) was deprotected as described for compound (**52**) to give the *thyronine* (**8**) (0.59 g, 75%), m.p. 228—233 °C (decomp.) (Found: C, 35.1; H, 2.4; N, 4.4; S, 5.2; I, 39.9. $C_{19}H_{16}I_2N_2O_5S \cdot 0.3H_2O$ requires C, 35.5; H, 2.6; N, 4.4; S, 5.0; I, 39.4%); $[\alpha]_D$ −3.2° (*c* 0.9 in EtOH–0.1M-NaOH, 2:1); $\nu_{max.}$ (1.0% KBr disc) 3 700—2 200 (OH, NH, NH_3^+) and 1 632 cm^{-1} (thiazolone CO and amino acid CO); δ(1M-NaOD–D_2O) 2.82 (2 H, m, β-H_2), 3.47 (1 H, m, α-H), 3.68 (2 H, s, CH_2), 6.39 (1 H, s, Thiaz 4-H), ~6.5 (3 H, m, ArH), and 7.78 (2 H, s, 2- and 6-H).

H.p.l.c.—The purity of compounds (**1**)—(**8**) was > 95% as assessed by high-pressure liquid chromatography using a C_{18}/μ-Bondapak column. The mobile phase was acetonitrile–1% aqueous acetic acid (containing 1 g of camphorsulphonic acid per litre). Chiral h.p.l.c. analysis of compound (**1**)[19] suggested < 5% racemisation had occurred.

Acknowledgements

Many discussions on synthesis with Messrs. V. P. Shah, G. A. Showell, R. Novelli, and H. D. Prain are gratefully acknowledged. We thank Mr. M. Graham for elemental analysis, Dr. E. S. Pepper for n.m.r. spectra, Dr. R. C. Mitchell for i.r. spectra and optical rotations, Dr. D. Darkin for h.p.l.c., Dr. D. M. B. Hickey for help with collating the experimental data, and Drs. A. H. Underwood and D. Ellis for the biological assays.

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Received 30*th November* 1987; *Paper* 7/00072C