Preparation and some Reactions of 4- and 5-Aryl-4,5-dihydropyridazin-3(2*H*)-ones

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Efficient preparations of 4- and 5-phenyl-4,5-dihydropyridazin-3(2*H*)-ones have been developed, the main reactions of these compounds have been studied, and the synthetic routes have been used to give analogues with substituents in the phenyl rings.

In the best synthesis of the 4-phenyldihydropyridazinone (72% overall yield) the product was obtained from phenylacetic acid by three simple stages. This approach was applied in preparations of the 2- and 4-hydroxyphenyl compounds and, in conjunction with a recent method for amine protection, the 4-aminophenyl analogue. A four stage synthesis starting from benzaldehyde gave the 5-phenyldihydropyridazinone in 47% overall yield; hydroxybenzaldehydes were similarly converted into 5-(allyloxyphenyl)dihydropyridazinones.

Oxidation to phenylpyridazinones occurred more readily with the 4- and 5-phenyldihydropyridazinones than with the 6-phenyl isomer. The 4- and 5-dihydropyridazinones were smoothly reduced to tetrahydropyridazinones by hydrogenation over platinum but were unaffected by palladium in the presence of hydrazine or cyclohexene.

6-Aryl-4,5-dihydropyridazin-3(2*H*)-ones are readily obtained by treating 4-aryl-4-oxocarboxylic acids with hydrazine,[1] and since the required acids are easily accessible (from Friedel-Crafts reactions with succinic anhydrides) many 6-aryl compounds have been prepared.[2] Pharmacological interest in these products was stimulated by the observation that some of them have considerable and long-lasting antihypertensive activity.[3] Subsequently it was found that introduction of a 3-alkylamino-2-hydroxypropoxy group into the phenyl ring gives compounds which retain the antihypertensive activity and function also as β-adrenergic receptor blocking agents.[4] While some of these compounds have further substituents in the phenyl ring, the 4- and 5-positions of the heterocycle are unsubstituted. This work prompted interest in the possible pharmacological activity of 4- and 5-aryldihydropyridazinones and, in order to make the comparison with the 6-aryl analogues as close as possible, it was intended that the 4- or 5-aryl group should be the only substituent in the heterocyclic system. No 4-aryl-4,5-dihydropyridazin-3-one with a free 6-position appears to have been described, and in the 5-aryl series there is but one such example (a complex 2,5-disubstituted compound obtained during the degradation of flavellagic acid).[5] The object of the present study was, then, to devise methods for synthesising the required 4- and 5-aryldihydropyridazinones. Initially the parent 4- and 5-phenyl compounds were to be prepared, and since these represent new basic systems the main features of their chemistry were to be investigated. It was essential that the synthetic routes should be suitable for obtaining products with substituents in the phenyl rings; in this respect hydroxy and allyloxy groups were deemed the most important as being possible progenitors of the 3-alkylamino-2-hydroxypropoxy substituent characteristic of many potent β-blocking agents.[6]

The results are presented in Schemes 1—6; in view of their detailed nature and in general, the absence of theoretical problems, only a brief commentary on the main features of each section is required. There are a few instances in which the structures of products do not follow automatically from the nature of the reactions leading to them; in these cases the structures shown are established by the spectrometric results reported in the experimental section.

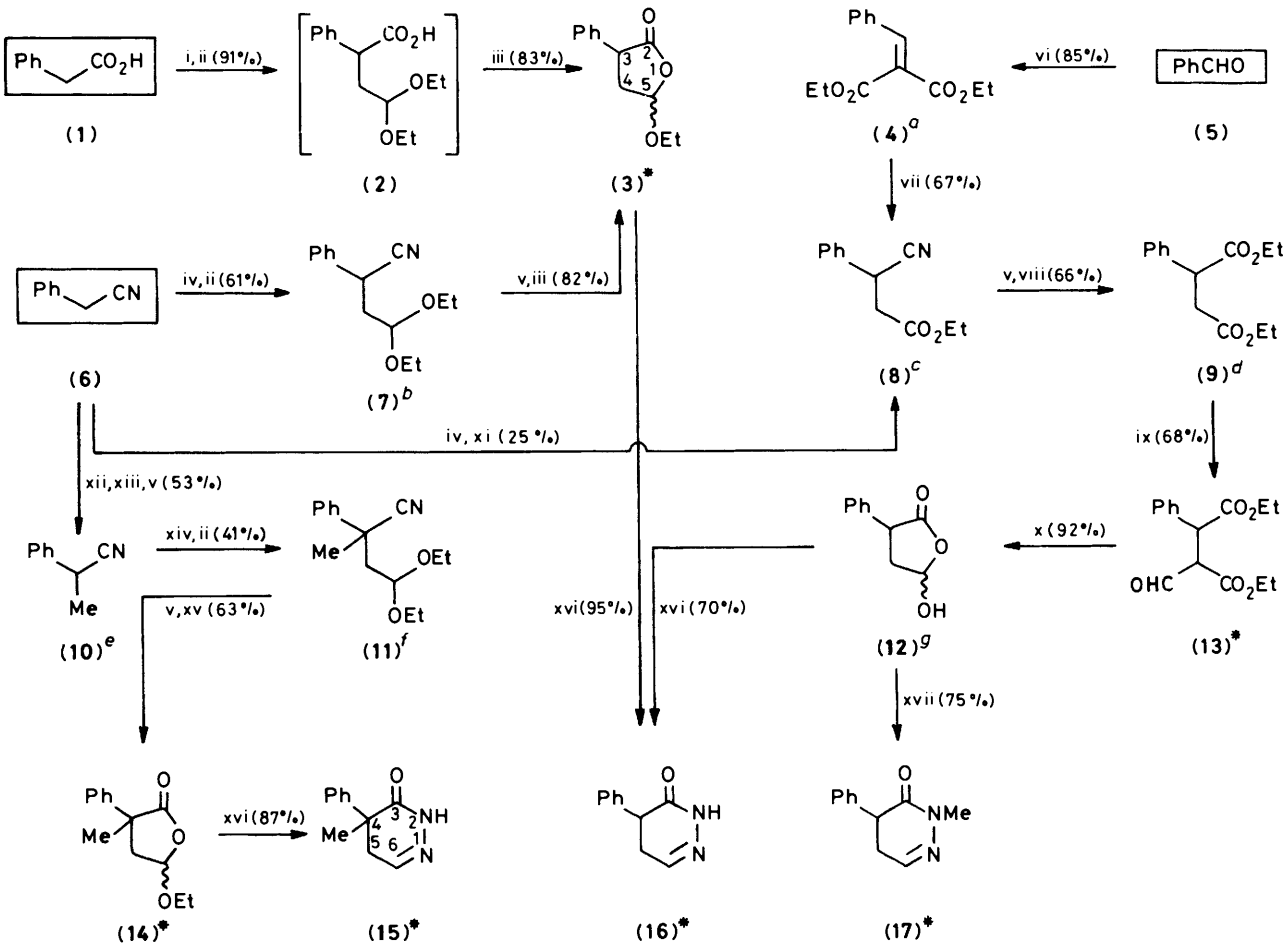
In the first route to the 4-phenyldihydropyridazinone (**16**) (six stages from benzaldehyde, Scheme 1) the crucial intermediate is the hydroxy lactone (**12**). This was originally prepared[7] from dimethyl phenylsuccinate (in 22% yield) by formylation, which resulted in partial transesterification, followed by hydrolysis and decarboxylation. The key improvement now introduced was to use an excess of ethyl formate, as reactant and solvent, with the diethyl ester (**9**). More recently the hydroxy lactone (**12**) was obtained from ethyl phenylacetate in four stages[8] by a sequence as efficient as the present one but involving less readily available reagents (such as the mono *N*,*N*-dimethylhydrazone of glyoxal). Preparation of the cyano ester (**8**) from phenylacetonitrile shortened the approach to the hydroxy lactone but the overall yield was thereby lowered. The alternative route to the 4-phenyldihydropyridazinone (**16**) *via* the ethoxy lactone (**3**) is much more efficient. This intermediate was initially obtained from phenylacetonitrile, but a better preparation, based on the α-alkylation of dianions of carboxylic acids,[9] was developed using phenylacetic acid as the starting material. Thus, the sequence (**1**) ⟶ (**2**) ⟶ (**3**) ⟶ (**16**) gives the 4-phenyldihydropyridazinone in 72% overall yield in three simple stages.

The ^{1}H n.m.r. spectrum of the 4-methyl-4-phenyl derivative (**15**) establishes the presence of the CH=N unit, and although the characteristic signal is overlapped by the signals of the aromatic protons in the related compounds (**16**) and (**17**) the three dihydropyridazinones show the expected spectrometric similarities. Detailed consideration of the data establishes that they all have the $\Delta^{1(6)}$-structures shown.

Development of the phenylacetic acid route for the preparation of 4-phenyldihydropyridazinones with a hydroxy group at position 2- or 4-of the phenyl ring is summarised in Scheme 2. After unsuccessful attempts to introduce the diethoxymethyl unit directly into the methylene group of 4-hydroxyphenylacetic acid by way of its trilithio-derivative, three methods for protecting the phenolic group were studied. The allyloxy group, chosen first for the reason mentioned earlier, underwent clean rearrangement to the *cis*-propenyloxy system when the protected acid (**18**; R = $CH_2CH{:}CH_2$) was treated with lithium di-isopropylamide even under mild conditions. (This rearrange-

In the Schemes starting materials are shown in boxes; intermediates which were not purified and characterised are shown in parentheses. References are given to known compounds which are not commercially available. New compounds are marked with an asterisk. Yields (%) of stages, or of sequences of stages, are shown with the reagent numbers.

Scheme 1. Preparation of 4,5-dihydro-4-phenylpyridazin-3(2*H*)-ones

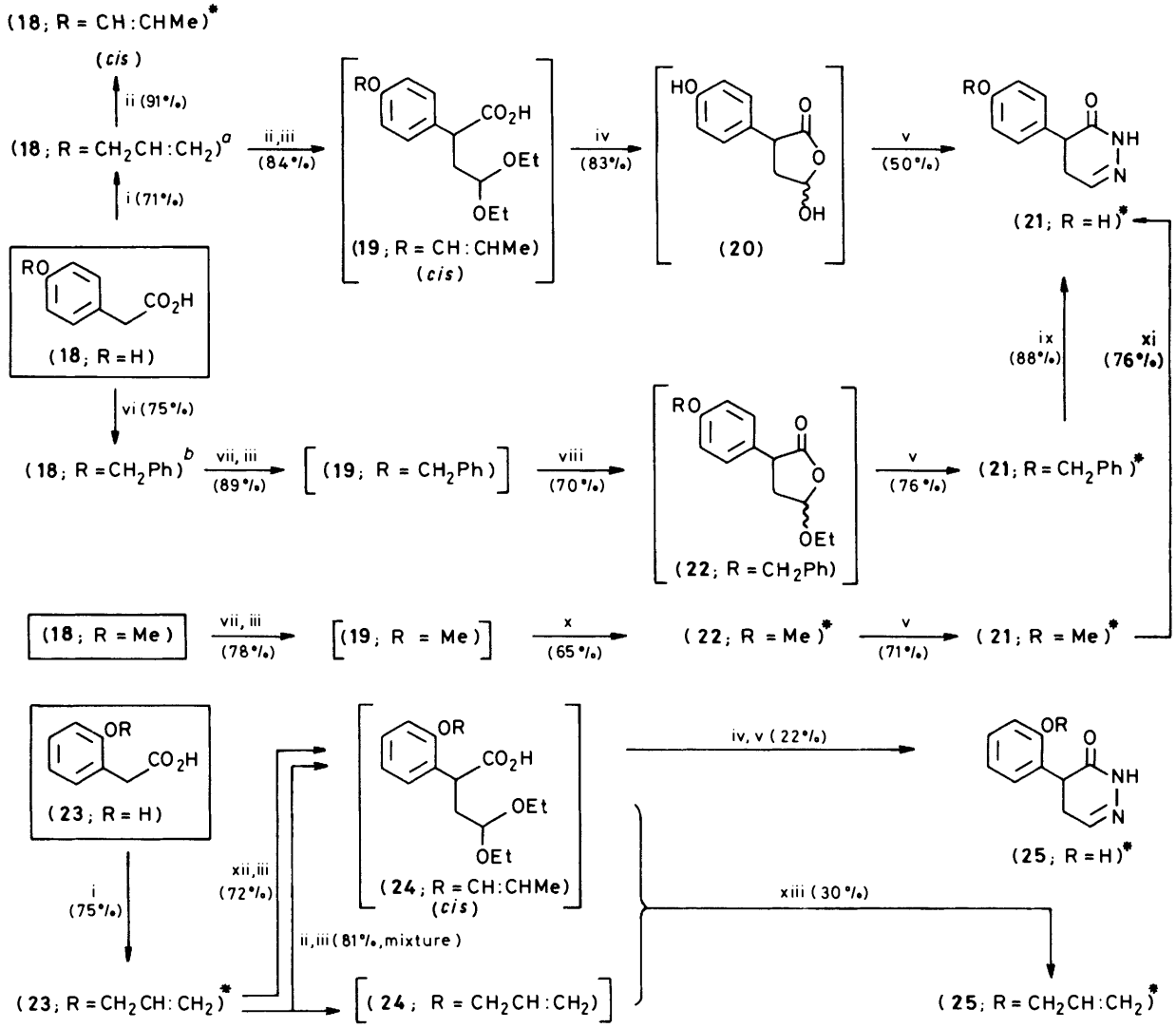


Reagents: i, $LiNPr^i_2$, −70 °C, then ⟶ 20 °C. ii, $BrCH_2CH(OEt)_2$. iii, Distil. iv, NaH. v, KOH. vi, $CH_2(CO_2Et)_2$–piperidine. vii, KCN–water. viii, EtOH–H_2SO_4. ix, HCO_2Et(excess)–Na. x, HCl–AcOH–water. xi, $BrCH_2CO_2Et$. xii, NaOEt–$(EtO)_2CO$. xiii, NaOEt–MeI. xiv, $NaNH_2$. xv, HCl–water. xvi, N_2H_4–AcOH–water. xvii, $MeNHNH_2$–AcOH–water. *References:* [a] 18, [b] 21, [c] 19, [d] 20, [e] 23, [f] 24, [g] 8.

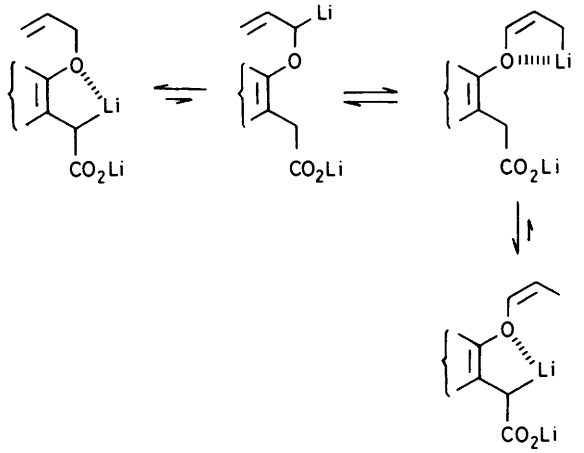
ment is discussed later; reagents such as potassium t-butoxide in hot dimethyl sulphoxide have generally been used to induce the corresponding transformation of other allyl ethers.[10]) However, some advantage accrued from this isomerisation: subsequent reaction with bromoacetal gave the *cis*-propenyloxy-compound (**19**; R = CH:CHMe), treatment of which with acid led not only to cyclisation but also to regeneration of the phenolic group in the hydroxy lactone (**20**). Success in using the benzyl group for protection depended on finding conditions for deprotection (palladium with cyclohexene) which did not reduce or degrade the dihydropyridazinone system. This problem was more acute with the methoxy group. While the protected aryldihydropyridazinone (**21**; R = Me) was unaffected by boron trichloride, both iodotrimethylsilane and sodium thioethoxide led to extensive decomposition; fortunately, smooth demethylation occurred with boron tribromide. The overall yields of 4,5-dihydro-4-(4-hydroxyphenyl)pyridazin-3(2*H*)-one (**21**; R = H) from the three routes are 25% (allyl), 31% (benzyl), and 27% (methyl), and since 4-methoxyphenylacetic acid is considerably cheaper than 4-hydroxyphenylacetic acid the third approach is to be preferred. (It may be significant that the final stage, reaction with hydrazine, proceeds more satisfactorily with the ethoxy lactones than with the hydroxy lactones in Schemes 1 and 2; the suitability of ethoxy lactones for generating dihydropyridazinones emerges also from the work in Scheme 4.)

In the 2-hydroxyphenyl series only the allyloxy compounds were investigated. Treatment of the protected acid (**23**; R = $CH_2CH{:}CH_2$) with 2 equivalents of lithium di-isopropylamide at 20 °C caused partial conversion into the *cis*-propenyloxy isomer, but at 68 °C the rearrangement appeared to be complete after a short time. Thus while both acids (**18** and **23**; R = $CH_2CH{:}CH_2$) undergo the base-induced allyloxy ⟶ *cis*-propenyloxy transformation very readily, there is a minor difference between them in this respect. Previous work [10] suggests that removal of a proton from the α-methylene group of the allyl ether gives a system in which rearrangement to the derivative of the *cis*-propenyloxy isomer is induced by the consequential stabilisation from metal–oxygen bonding. With the substituted phenylacetic acids studied here the benzylic anions (formed by the second equivalent of base) probably facilitate deprotonation of the allyloxy group by inter- or intramolecular proton exchange. However, in the case of (2-allyloxyphenyl)acetic acid the benzylic anions of both the allyloxy

Scheme 2. 4,5-Dihydro-4-(hydroxyphenyl)pyridazin-3(2*H*)-ones



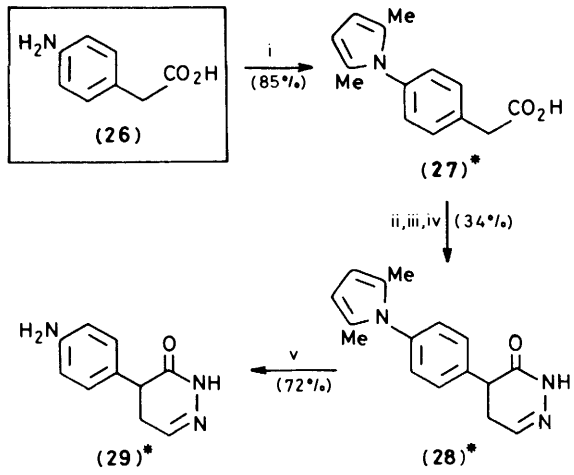
Reagents: i, CH_2:$CHCH_2Br$–KOH. ii, $LiNPr^i_2$, −70 °C then ⟶ 20 °C. iii, $BrCH_2CH(OEt)_2$. iv, HCl–water–Me_2CO. v, N_2H_4–AcOH–water. vi, $PhCH_2Cl$–KOH. vii, $LiNPr^i_2$, −20 °C, then ⟶ 45 °C. viii, heat (200 °C/0.4 mmHg). ix, Pd-on-C–cyclohexene. x, Distil. xi, BBr_3. xii, $LiNPr^i_2$, −20 °C, then ⟶ 68 °C. xiii, N_2H_4–HCl–AcOH–water. *References:* [a] 25, [b] 26.



and *cis*-propenyloxy compounds should also exhibit metal–oxygen bonding (see diagrams); such stabilisation of the allyloxy derivative could account for the somewhat slower rearrangement of this acid. Whatever the details, the equilibria presumably lie towards the benzylic anions (allyloxy or *cis*-propenyloxy) since reaction with bromoacetal occurs at these centres. The mixture of acetal acids (**24**) obtained from the partial isomerisation experiments was used to generate the allyoxyphenyldihydropyridazinone (**25**; R = CH_2CH:CH_2) in modest yield. An alternative procedure was employed with the *cis*-propenyloxy compound (**24**; R = CH:CHMe): the protecting group was removed before the treatment with hydrazine, but this route to the hydroxyphenyldihydropyridazinone (**25**; R = H) was disappointingly inefficient.

The method for protecting primary amines as *N*-substituted 2,5-dimethylpyrroles, which has been applied subsequently to a variety of substrates,[11] was originally developed after the failure of standard approaches to the 4-(4-aminophenyl)dihydropyridazinone (**29**) (Scheme 3). While use of the new amino-protecting group is the key feature of the successful synthesis, the overall yield (21%) is adversely affected by one unsatisfactory stage. Elsewhere in the present work the acetal-acids such as compounds (**2**) (Scheme 1) and (**19**; R = CH:CHMe) (Scheme 2) could be distilled or warmed with mineral acid to

Scheme 3. 4-(4-Aminophenyl-4,5-dihydropyridazin-3(2*H*)-one



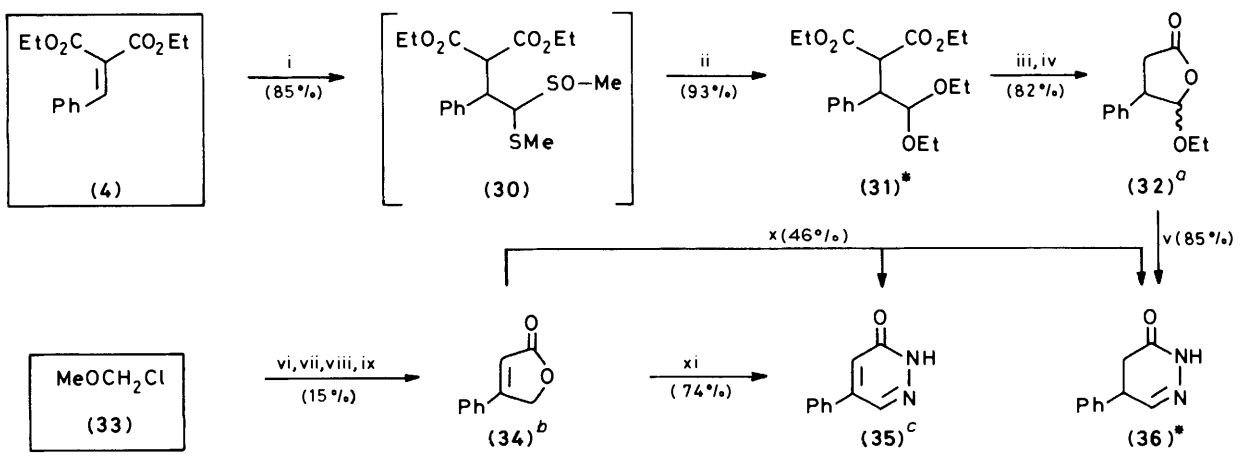
Reagents: i, $MeCO[CH_2]_2COMe$. ii, $LiNPr^i_2$, −70 °C, then ⟶ 20 °C. iii, $BrCH_2CH(OEt)_2$. iv, N_2H_4–AcOH–water. v, H_2NOH–H_2NOH HCl.

give the ethoxy or hydroxy lactones which serve as precursors of the dihydropyridazinones. Neither operation is compatible with the presence of a pyrrole system having a complex *N*-substituent and formation of the dihydropyridazinone ring had to be carried out directly from the acetal acid derived from the protected acid (**27**). Ring closure was slow, and gave only a modest yield (40%) of the product (**28**).

In the 5-phenyl series (Scheme 4) the initial approach was based on 4-phenylfuran-2(5*H*)-one (**34**)[12a] which had been shown[12b] to react with propylamine to give a product formally derived from the isomeric 3*H*-form. However, since the lactone was found to react only slowly with hydrazine in the standard aqueous acetic acid medium (*ca.* 60% AcOH) the proportion of acetic acid was increased (to *ca.* 85%). Boiling for 1 h gave mainly the required 5-phenyldihydropyridazinone (**36**) accompanied by some of the related 5-phenylpyridazinone (**35**)[13] (an alternative synthesis of which has been carried out[14]). Prolonged boiling led to a mixture of the 5-phenylpyridazinone (**35**) and a by-product, probably 3-acetoxy-5-phenylpyridazine; alkaline hydrolysis of the mixture afforded the 5-phenylpyridazinone (**35**) efficiently. It may be that under these conditions the dihydropyridazinone (**36**) is slowly acetylated and the product then oxidised, but in view of the relative inaccessibility of the lactone (**34**)[12a,7] this line was not pursued. Attention was turned to an alternative approach *via* the ethoxy lactone (**32**). This intermediate had been prepared[13] from phenylacetaldehyde, (42% overall yield), but such an approach did not appear promising for extension to the substituted phenyl analogues envisaged in the present work. Since substituted benzaldehydes were considered to be more convenient starting materials it was planned to use the related benzylidenemalonic esters in Michael addition reactions. After the failure of attempted base-catalysed addition reactions between diethyl benzylidenemalonate (**4**) and 1,3-dithiane or 1,3-dithiane 1-oxide the ester was found to undergo smooth addition with the lithio-derivative of methyl methylthiomethyl sulphoxide (thus further exemplifying the differences between cyclic and acyclic thioacetals in this respect).[15] Continuation as in Scheme 4 gave the required ethoxy lactone (**32**) (in overall yield of 55% from benzaldehyde) which reacted cleanly with hydrazine under the standard conditions to give the 5-phenyldihydropyridazinone (**36**) in 85% yield.

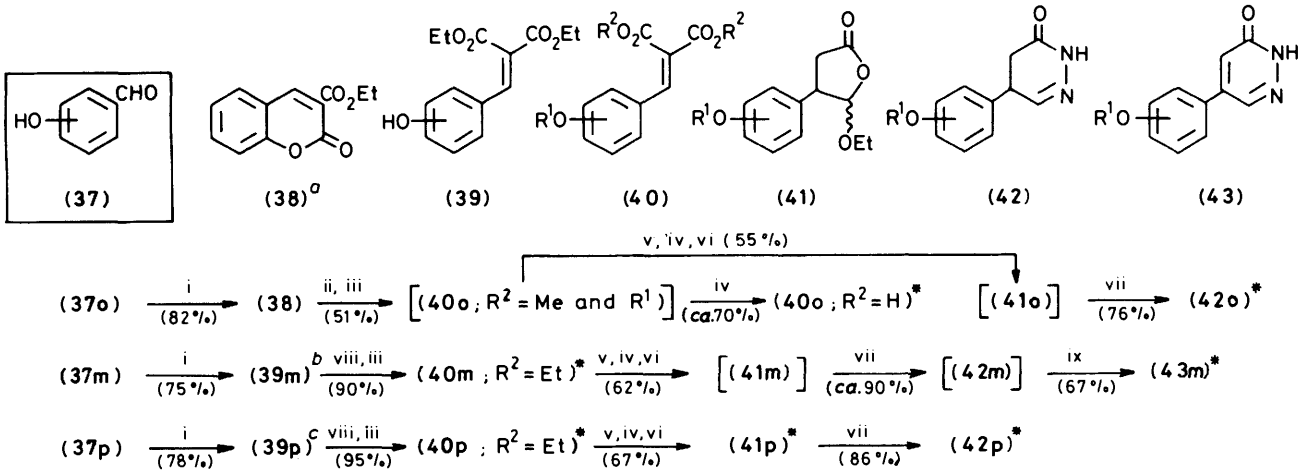
Application of the ethoxy lactone route to the preparation of 5-allyloxyphenyldihydropyridazinones is summarised in Scheme 5. Conversion of the 3- and 4-hydroxybenzaldehydes into the required allyloxybenzylidenemalonates (**40m**) and (**40p**) was straightforward. In the 2-hydroxyphenyl series a complication was caused by using methanolic potassium hydroxide to open the lactone ring of ethyl coumarin-3-carboxylate (**38**) preparatory to allylation of the aryloxy-anion: the incursion of various ester exchanges gave a mixture which appeared to consist largely of the methyl and allyl esters (**40o**; R^2 = Me and $CH_2CH{:}CH_2$). To support this conclusion, a portion of the mixture was hydrolysed and the product characterised as 2-allyloxybenzylidenemalonic acid (**40o**; R = H), and the remainder was used without purification for the ensuing reactions. All the ethoxy lactones (**41**) were obtained by a sequence in which the last stage, distillation, caused decarboxylation and ring closure. Although at the high temperatures used with these allyl phenyl ethers there is the possibility of Claisen rearrangement, the ^1H n.m.r. characteristics of the ethoxy lactones [reported for the isomer (**41p**) in the experimental section] showed that their allyloxy groups were intact. Thus, rearrangement does not occur to an appreciable extent

Scheme 4. 4,5-Dihydro-5-phenylpyridazin-3(2*H*)-one and 5-phenylpyridazin-3(2*H*)-one



Reagents: i, $MeSCH_2SOMe$–Bu^nLi. ii, $HC(OEt)_3$–EtOH–H_2SO_4. iii, KOH, then HCl. iv, Distil. v, N_2H_4–AcOH–water. vi, $Cu(CN)_2$. vii, PhMgBr. viii, Zn–$BrCH_2CO_2Et$. ix, HBr–AcOH. x, N_2H_4–AcOH (85%)–water (15%), reflux 1 h. xi, as x, reflux 1 day, then KOH–EtOH. *References:* [a] 13, [b] 12*a*, 7, [c] 13, 14.

Scheme 5. 5-Allyloxyphenyl-4,5-dihydropyridazin-3(2*H*)-ones (Substituted phenyl groups: *o* = *ortho*, *m* = *meta*, *p* = *para*. $R^1 = CH_2CH{:}CH_2$)



Reagents: i, $CH_2(CO_2Et)_2$–piperidine. ii, KOH–MeOH, heat. iii, $CH_2{:}CHCH_2Br$. iv, KOH, then HCl. v, $MeSCH_2SOMe$–Bu^nLi, then $HC(OEt)_3$–EtOH–H_2SO_4. vi, Distil. vii, N_2H_4–AcOH–water. viii, KOH–EtOH. ix, Air, 7 days. *References:* [a] 29, [b] 30, [c] 31.

under the conditions employed (*ca.* 30 min at 205 °C). Of the final products, the allyloxyphenyldihydropyridazinones (**42**), the 2- and 4-allyloxyphenyl compounds (**42o** and **42p**) crystallised readily. Spectrometric examination established that the oily product in the 3-allyloxyphenyl series was the dihydropyridazinone (**42m**) but this could not be induced to solidify and, on contact with air, was slowly transformed into the crystalline pyridazinone (**43m**). It is doubtful whether this contrast denotes any inherent difference between the isomers in their propensity for dehydrogenation.

Some reactions of the parent phenyldihydropyridazinones are set out in Scheme 6. Hydrogenation of the 4- and 5-phenyl compounds (**16**) and (**36**) readily gives the tetrahydropyridazinones (**45**) and (**46**) but, as utilised during the work in Scheme 2, reduction does not occur with palladium–cyclohexene. While all three phenyl compounds are dehydrogenated to pyridazinones by heating with bromine in acetic acid, only the 4-and 5-isomers are affected by *N*-bromosuccinimide in aqueous dimethyl sulphoxide: this difference and some of the previous observations suggest that conversion into pyridazinones occurs more easily with 4- and 5-aryldihydropyridazinones than with the 6-aryl analogues. [The 4-phenylpyridazinone (**44**) has also been obtained by a different route.[14]] The conversion $ArOCH_2CH{:}CH_2 \longrightarrow ArOCH_2CH(OH)CH_2NHR$ (a system which, as mentioned earlier, is of pharmacological interest) may be achieved by treatment with *N*-bromosuccinimide in aqueous dimethyl sulphoxide[16] followed by heating the bromohydrin with a primary amine.[4] With the 2-allyloxyphenyldihydropyridazinone (**42o**), oxidation of the heterocyclic system preceded bromohydrin formation and the sequence led to the substituted pyridazinone (**49**).

The reaction of phthalazin-1(2*H*)-one (**50**) with phenyllithium to give the 4-phenyl derivative (**51**)[17] suggested the possibility of similar conversions with the phenyldehydropyridazinones. Phthalazin-1(2*H*)-one is depicted as undergoing direct addition of phenyl-lithium to the C=N bond;[17] however, an excess of the reagent was used and the experiments of the present work indicate that the sequence in Scheme 6 occurs. The phenyldihydropyridazinones (**16**) and (**36**) were found to react with 2 (but no more than 2) equivalents of phenyl-lithium. Work-up regenerated the starting materials which suggests that the second equivalent of phenyl-lithium acts as a base, presumably removing the benzylic proton, rather than adding to the C=N bond.

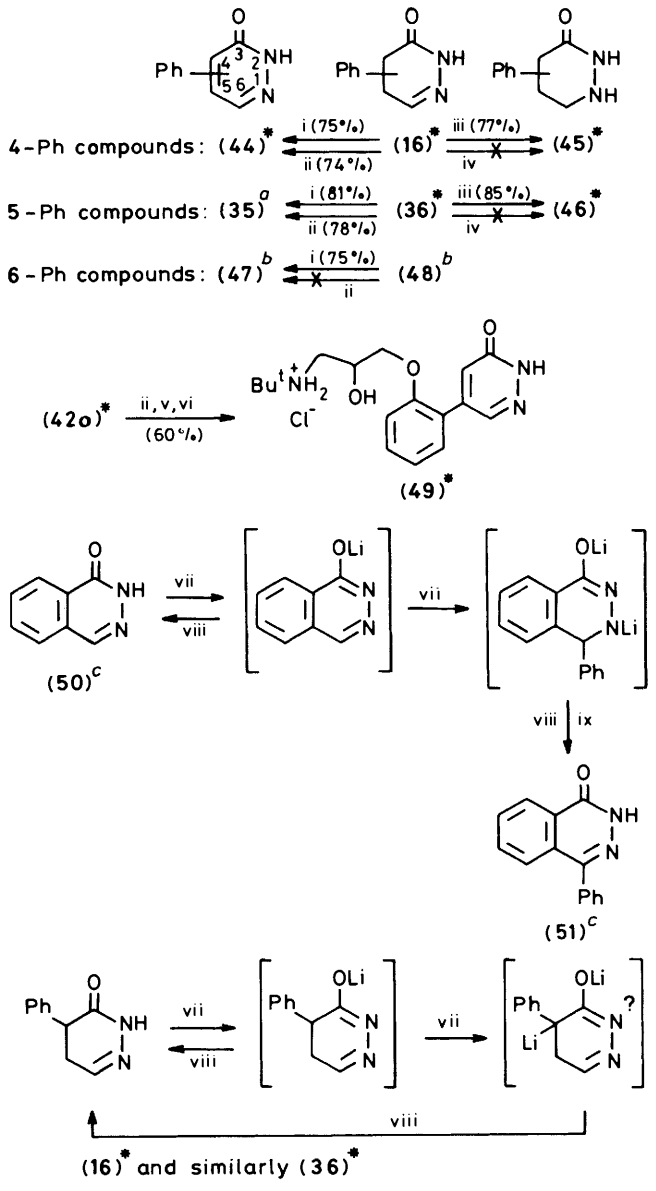
Experimental

Unless stated otherwise ^1H n.m.r., i.r., and u.v. spectra were recorded using Perkin-Elmer R32 (90 MHz), Perkin-Elmer 297, and Cary 14-M spectrometers with solutions in $CDCl_3$, CCl_4, and EtOH respectively. Preparative g.l.c. was carried out on a Pye 105 chromatograph (5 m column of 15% OV 17 on Diatomite C). General procedures are described where they are first used and then identified by capital letters. The preparations of known compounds, described briefly here, are better or more convenient than the literature methods. Light petroleum refers to the fraction of b.p. 40—60 °C, THF to tetrahydrofuran, and MMS to methyl methylthiomethyl sulphoxide.

Scheme 1. *Benzaldehyde* (**5**) ⟶ *Products* (**16**) *and* (**17**).—*Procedure A*. A solution of PhCHO (55 ml), $CH_2(CO_2Et)_2$ (76 ml), and piperidine (76 ml) in C_6H_6 (100 ml) was boiled under reflux for 4 h while water was removed in a Dean-Stark head. Et_2O was added, and the solution was washed (1M-H_2SO_4, then brine), dried, and evaporated. Distillation gave the ester (**4**) (98 g), b.p. 136—140 °C/0.3 mmHg (lit.,[18] 185—186 °C/11 mmHg). A solution of the ester (**4**) (64 g) and KCN (17 g) in EtOH (850 ml)–water (85 ml) was heated at 60 °C for 7 h. The addition of brine, isolation with Et_2O, and distillation gave the cyano ester (**8**) (36 g), b.p. 130—133 °C/0.3 mmHg (lit.,[19] 176 °C/16 mmHg). A solution of the cyano ester (20 g) and KOH (24 g) in EtOH (310 ml) was boiled under reflux for 4 h. After evaporation at 80 °C/17 mmHg the residue was dissolved in the minimum of water. The addition of 2M-HCl, collection of the precipitate, and crystallisation from water gave phenylsuccinic acid (14 g), m.p. 166—167 °C (lit.,[19] 167 °C). The foregoing acid (42 g), EtOH (150 ml), H_2SO_4 (7 ml), and C_6H_6 by procedure A (but with boiling for 3 days and washing with aqueous $NaHCO_3$) gave diethyl phenylsuccinate (**9**) (48.5 g), b.p. 128—129 °C/0.8 mmHg (lit.,[20] 166 °C/13 mmHg).

Na wire (3.3 g) was added to a solution of the ester (**9**) (12.4 g) in HCO_2Et (distilled from CaH_2; 35 ml) and the exothermic reaction which ensued was moderated by cooling the flask in ice; the mixture was then kept at 20 °C for 2 days. HCO_2Et (50 ml) was added and after 3 h the mixture was poured into ice–water (80 ml). The aqueous layer was washed with Et_2O and acidified with 2M-HCl. Isolation with Et_2O gave *diethyl 2-formyl-3-phenylbutanedioate* (**13**) (9.5 g), b.p. 152—153 °C/0.6 mmHg (Found: C, 65.0; H, 6.4. $C_{15}H_{18}O_5$ requires C, 64.7; H,

Scheme 6. Reactions of phenyl-4,5-dihydropyridazin-3(2*H*)-ones and related compounds



Reagents: i, Br_2–AcOH, 70 °C. ii, NBS–Me_2SO–water, 20 °C. iii, H_2–Pt. iv, Pd-on-C–N_2H_4·H_2O or cyclohexene. v, Bu^tNH_2. vi, HCl. vii, PhLi (1 equiv.). viii, water. ix, MeOH, heat. *References:* [a] 13, 14, [b] 1, [c] 17.

6.5%), δ 11.72 (d, *J* 9 Hz, OH of enolic form), 9.25 (d, *J* 3 Hz) and 9.58 (d, *J* 2 Hz) (CHO of diastereoisomeric ketonic forms; the combined integrals of these signals is approximately equal to that of the enolic OH signal); $\nu_{max.}$ 1 738 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 2 000), *m/z* 278 (M^+, 1%) and 131 (100). A solution of the ester (**13**) (4 g) in 10M-HCl (7 ml)–AcOH (7 ml) was boiled under reflux for 3 h. Isolation with Et_2O and distillation gave the hydroxyfuranone (**12**) as a viscous oil (2.5 g), b.p. 143—146 °C/0.1 mmHg (lit.,[8] 150 °C/0.4 mmHg), $\nu_{max.}$ 1 776 cm^{-1}.

Procedure B. A solution of the hydroxyfuranone (**12**) (1.8 g) and N_2H_4·H_2O (1.2 ml) in AcOH (8 ml)–water (5.5 ml) was boiled under reflux for 1.5 h, and poured into aqueous $NaHCO_3$. The material (1.4 g) isolated with Et_2O afforded 4,5-*dihydro*-4-*phenylpyridazin*-3(2H)-*one* (**16**) (1.2 g), m.p. 105—106 °C (from C_6H_6) (Found: C, 69.1; H, 5.7; N, 16.2. $C_{10}H_{10}N_2O$ requires C, 69.0; H, 5.8; N, 16.1%); δ 9.51 (1 H, br s, NH), 7.25 (6 H, m, C_6H_5 and CH=N), 3.65 (1 H, t, *J* 5 Hz, PhC*H*) and 2.8—2.6 (2 H, m, CH_2); $\nu_{max.}$ 3 430 and 1 730 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 5 500); *m/z* 174 (M^+, 73%) and 105 (100). The hydroxyfuranone (**12**) (1.6 g) and methylhydrazine (1 ml) by procedure B gave 4,5-*dihydro*-2-*methyl*-4-*phenylpyridazin*-3(2H)-*one* (**17**) (1.2 g), m.p. 78—79 °C (from CH_2Cl_2) (Found: C, 70.0; H, 6.5; N, 15.0. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%); δ 7.22 (6 H, m, C_6H_5 and CH=N), 3.67 (1 H, t, *J* 6 Hz, PhC*H*), 3.40 (3 H, s, CH_3), and 2.8—2.65 (2 H, m, CH_2); $\nu_{max.}$ 1 673 cm^{-1}; $\lambda_{max.}$ 252 nm (ε 5 400); *m/z* 188 (M^+, 100%).

Phenylacetic Acid (**1**) ⟶ *Product* (**16**).—*Procedure C.* A solution of Bu^nLi in hexane (1.6M; 150 ml) was added to a stirred solution of Pr^i_2NH (10 ml) in THF (100 ml) at −70 °C under N_2. A solution of $PhCH_2CO_2H$ (8.9 g) in THF (10 ml) was added and the temperature of the solution was allowed to reach 20 °C. Bromoacetal (20 ml) was added to the solution which was then boiled under reflux for 6 h and subsequently poured into water. The aqueous layer was washed with Et_2O and acidified with 10M-HCl. Isolation with Et_2O gave an oil (15 g) formulated, on spectrometric evidence, as the acid (**2**). Distillation of this oil afforded 5-*ethoxy*-4,5-*dihydro*-3-*phenylfuran*-2(3H)-*one* (**3**) (10.2 g), b.p. 133—136 °C/0.1 mmHg, a portion of which was further purified by g.l.c. (18 min/195 °C) (Found: C, 70.0, H, 6.8. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%); δ 5.60 (1 H, m, C*H*OEt) and 1.25 (3 H, t, *J* 7 Hz, CH_3); $\nu_{max.}$ 1 792 cm^{-1}, $\lambda_{max.}$ 207 nm (ε 8 300), *m/z* 206 (M^+, <1%) and 104 (100). The ethoxyfuranone (**3**) (2.1 g) and N_2H_4·H_2O (1.4 ml) by procedure B gave product (**16**) (1.69 g), m.p. 104—105 °C, identified by spectrometric examination.

Products from Phenylacetonitrile (**6**).—A suspension of NaH (0.3 g) in $PhCH_2CN$ (2 ml)–THF (15 ml) was stirred at 50 °C for 1.5 h. Ethyl bromoacetate (2.3 ml) was added to the mixture which was then boiled under reflux for 2 h. Dilution with water and isolation with Et_2O gave the cyano ester (**8**) (0.8 g), b.p. 140—143 °C/2 mmHg. A similar experiment with NaH (0.8 g)–$PhCH_2CN$ (2.9 g)–bromoacetal (4 ml) gave the cyano acetal (**7**) (3.5 g), b.p. 113—116 °C/0.15 mmHg (lit.,[21] 120—121 °C/0.2 mmHg). A solution of the cyano acetal (**7**) (1.5 g) and KOH (1.5 g) in EtOH (11 ml)–water (5 ml) was boiled under reflux for 1 day. Acidification with 10M-HCl and isolation with Et_2O gave the ethoxyfuranone (**3**) (1.1 g), b.p. 134—137 °C/0.13 mmHg.

$PhCH_2CN$ (distilled; 59 g) was treated with NaOEt and $(EtO)_2CO$ as in ref. 22 to give ethyl 2-cyano-2-phenylacetate (74 g), b.p. 119—122 °C/1.5 mmHg (lit.,[22] 125—135 °C/3—5 mmHg). Methylation of the foregoing ester (31.8 g) followed by hydrolysis and decarboxylation, as in ref. 23, gave 2-phenylpropanonitrile (**10**) (24 g), b.p. 111–112 °C/20 mmHg (lit.,[23] 109 °C/15 mmHg). Powdered $NaNH_2$ (6 g) was added to a solution of the foregoing nitrile (4.9 g) in Et_2O (52 ml), and the stirred suspension was boiled under reflux for 1 h. Bromoacetal (22 ml) was added to the mixture which was then boiled under reflux for 1 h, and then added slowly to ice–water. Isolation with Et_2O gave the acetal (**11**) (3.8 g), b.p. 128—130 °C/0.9 mmHg (lit.,[24] 104 °C/0.6 mmHg). A solution of the acetal (**11**) (1.8 g) and KOH (2 g) in EtOH (15 ml)–water (5 ml) was boiled under reflux for 1 day. Water (60 ml) was added, and the solution was washed with Et_2O. Acidification with 10M-HCl and isolation with Et_2O gave 5-*ethoxy*-4,5-*dihydro*-3-*methyl*-3-*phenylfuran*-2(3H)-*one* (**14**) (1 g), b.p. 144—146 °C/0.1 mmHg, a portion of which was further purified by g.l.c. (21 min/195 °C) (Found: *m/z* 220.1098. $C_{13}H_{16}O_3$ requires M^+ 220.1099); $\nu_{max.}$ 1 789 cm^{-1}. The furanone (**14**) (0.4 g) and N_2H_4·H_2O (0.3 ml) by procedure B gave 4,5-*dihydro*-4-*methyl*-4-*phenylpyridazin*-3(2H)-*one* (**15**) (0.2 g) (Found: C, 70.0; H, 6.4; N, 15.0. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%); δ 8.90 (1 H, s, NH), 7.31 (5 H, m, C_6H_5),

7.15 (1 H, m, CH=N), 2.9—2.6 (2 H, m, CH_2), and 1.55 (3 H, s, CH_3); $\nu_{max.}$($CHCl_3$) 3 410 and 1 680 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 5 100); *m/z* 188 (M^+, 100%).

Scheme 2. 4-*Hydroxyphenylacetic Acid* (**18**; R = H) ⟶ *Products* (**21**; R = H *and* CH_2Ph).—*Procedure D.* Allyl bromide (13 ml) was added during 20 min to a solution of the acid (**18**; R = H) (10 g) and KOH (8.4 g) in MeOH (60 ml), and the mixture was boiled under reflux for 2 h. A solution of KOH (8 g) in MeOH (40 ml) was added to the mixture which was then boiled under reflux for 1 h, poured into water, and washed with Et_2O. Acidification with 10M-HCl and extraction with Et_2O gave the acid (**18**; R = $CH_2CH{:}CH_2$) (9 g), m.p. 69—71 °C (from CCl_4) (lit.,[25] 68—69 °C). Treatment of the foregoing acid (1 g) with $LiNPr^i_2$ by procedure C, followed by the addition of water, acidification with 10M-HCl, and isolation with Et_2O gave (Z)-4-*propenyloxyphenylacetic acid* [**18**; R = CH:CHMe (*cis*)] (0.91 g), m.p. 99—100 °C (Found: C, 68.8; H, 6.3. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%), δ 10.11 (1 H, br s, CO_2H), 7.20 (2 H, d) and 6.93 (2 H, d) (C_6H_4), 6.35 (1 H, dq, *J* 6 and 2 Hz, OC*H*:CH), 4.85 (1 H, quint, *J* 6 Hz, OCH:C*H*), 3.58 (2 H, s, CH_2), and 1.68 (3 H, dd, *J* 6 and 2 Hz, CH_3); $\nu_{max.}$($CHCl_3$) 1 712 cm^{-1}, *m/z* 192 (M^+, 72%) and 147 (100). Treatment of the acid (**18**; R = $CH_2CH{:}CH_2$) (10.4 g) with $LiNPr^i_2$ then with bromoacetal by procedure C gave material (14 g) formulated, on spectrometric evidence, as the acid [**19**; R = CH:CHMe(*cis*)]. A solution of the foregoing acid (3.8 g) in 2M-HCl (0.7 ml)–water (4 ml)–Me_2CO (30 ml) was boiled under reflux for 1.5 h. Dilution with water (200 ml) and extraction with EtOAc gave material (2 g), $\nu_{max.}$ 1 771 cm^{-1}, formulated as the hydroxyfuranone (**20**). The foregoing material (3.2 g) and $N_2H_4{\cdot}H_2O$ (2.1 ml) in AcOH (24 ml)–water (9 ml) by procedure B (but using EtOAc for isolation) gave 4,5-*dihydro*-4-(4-*hydroxyphenyl*)*pyridazin*-3(2H)-*one* (**21**; R = H) (1.48 g), m.p. 214—216 °C (from MeOH) (Found: C, 62.9; H, 5.4; N, 14.7. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 14.7%); δ 7.18 (1 H, t, *J* 3 Hz, CH=N); $\nu_{max.}$(Nujol) 1 655 cm^{-1}; *m/z* 190 (M^+, 100%).

$PhCH_2Cl$ (15 ml) was added to a solution of the acid (**18**; R = H) (10 g) and KOH (8 g) in MeOH (100 ml), and the solution was boiled under reflux for 2.5 h. The mixture was poured into aqueous NaOH, washed with Et_2O, and acidified with 10M-HCl. Isolation with EtOAc gave the acid (**18**; R = CH_2Ph) (12.1 g), m.p. 122–122.5 °C (from EtOAc) (lit.,[26] 120—121 °C). Treatment of the foregoing acid (4 g) with $LiNPr^i_2$ (initial and final temperatures of −20 and 45 °C) and then with bromoacetal by procedure C gave an oil (5.4 g) formulated as the acid (**19**; R = CH_2Ph). This oil was heated at 200 °C/0.4 mmHg for 1 h, cooled, dissolved in Et_2O, and filtered through SiO_2 (50 g). Evaporation gave material (3.3 g), $\nu_{max.}$($CHBr_3$) 1 778 cm^{-1}, formulated as the ethoxyfuranone (**22**; R = CH_2Ph). A portion (2.6 g) of this oil and $N_2H_4{\cdot}H_2O$ (1.6 ml) by procedure B gave 4-(4-*benzyloxyphenyl*)-4,5-*dihydropyridazin*-3(2H)-*one* (**21**; R = CH_2Ph) (1.78 g), m.p. 194—196 °C (from AcOH) (Found: C, 72.6; H, 5.7; N, 9.8. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.75; N, 10.0%); $\nu_{max.}$(Nujol) 1 670 cm^{-1}; *m/z* 280 (M^+, 43%) and 91 (100). A solution of the foregoing compound (0.3 g) in EtOH (40 ml)–cyclohexene (40 ml) was boiled under reflux with Pd-on-C (10%; 0.06 g) under N_2 for 3 days. Filtration, evaporation, and crystallisation gave the 4-hydroxyphenol compound (**21**; R = H) (0.18 g), m.p. and mixed m.p. 213—215 °C.

4-*Methoxyphenylacetic Acid* (**18**; R = Me) ⟶ *Product* (**21**; R = H).—Treatment of the acid with $LiNPr^i_2$ (initial and final temperatures of −20 and 45 °C) then with bromoacetal by procedure C gave an oil (5.3 g) formulated as the acid (**19**; R = Me) which, on distillation, afforded 5-*ethoxy*-4,5-*dihydro*-3-(4-*methoxyphenyl*)*furan*-2(3H)-*one* (**22**; R = Me) (2.9 g), b.p. 209—211 °C/0.4 mmHg (Found: C, 66.1; H, 6.9. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); $\nu_{max.}$($CHBr_3$) 1 779 cm^{-1}, *m/z* 236 (M^+, 17%) and 135 (100). Treatment of compound (**22**; R = Me) (1.8 g) with $N_2H_4{\cdot}H_2O$ (1.2 ml) by procedure B gave 4,5-*dihydro*-4-(4-*methoxyphenyl*)*pyridazin*-3(2H)-*one* (**21**; R = Me) (1.1 g), m.p. 124—126 °C (from C_6H_6) (Found: C, 64.8; H, 5.9; N, 13.8. $C_{11}H_{12}N_2O_2$ requires C, 64.7; H, 5.9; N, 13.7%); $\nu_{max.}$ 3 430 and 1 702 cm^{-1}; *m/z* 204 (M^+, 75%) and 148 (100). BBr_3 (1 ml) was added to a solution of the foregoing compound (0.17 g) in dry CH_2Cl_2 (5 ml) at −70 °C under N_2. The temperature was allowed to reach 20 °C during 1 h, and after a further 3 h the mixture was poured into aqueous $NaHCO_3$. Extraction with EtOAc and crystallisation gave the 4-hydroxyphenyl compound (**21**; R = H) (0.12 g).

2-*Hydroxyphenylacetic Acid* (**23**; R = H) ⟶ *Products* (**25**; R = H *and* $CH_2CH{:}CH_2$).—Treatment of the acid (**23**; R = H) (18 g) by procedure D gave 2-*allyloxyphenylacetic acid* (**23**; R = $CH_2CH{:}CH_2$) (17 g), m.p. 80—81 °C (from C_6H_6) (Found: C, 68.9; H, 6.4. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%), *m/z* 192 (M^+, 45%) and 134 (100). Treatment of the foregoing acid (5 g) with $LiNPr^i_2$ and then with bromoacetal by procedure C gave an oil (6.5 g) formulated as a mixture of compounds [**24**; R = $CH_2CH{:}CH_2$ and CH:CHMe(*cis*)]. This oil and $N_2H_4{\cdot}H_2O$ (4.5 ml) were dissolved in AcOH (24 ml)–water (8 ml), 10M-HCl (4.2 ml) was added, and the solution was boiled under reflux for 2.5 h. Work-up as in procedure B afforded an oil (3.2 g) which on crystallisation from MeOH gave 4-(2-*allyloxyphenyl*)-4,5-*dihydropyridazin*-3(2H)-*one* (**25**; R = $CH_2CH{:}CH_2$) (1.2 g), m.p. 138.5—140 °C (Found: C, 67.5; H, 6.2; N, 12.2. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); $\nu_{max.}$(CH_2Cl_2) 3 420 and 1 690 cm^{-1}; *m/z* 230 (M^+, 18%) and 189 (100). Treatment of the acid (**23**; R = $CH_2CH{:}CH_2$) (2 g) with $LiNPr^i_2$ (the initial mixing at −20 °C being followed by boiling under reflux for 1 h) then with bromoacetal by procedure C gave an oil (2.3 g) indicated by spectrometric examination to be largely compound [**24**; R = CH:CHMe(*cis*)]. A solution of this oil in 10M-HCl (0.5 ml)–water (2.5 ml)–Me_2CO (17 ml) was boiled under reflux for 2 h, diluted with water, and extracted with EtOAc to give material (1.2 g) which was treated with $N_2H_4{\cdot}H_2O$ (8 ml) in AcOH (36 ml)–H_2O (30 ml) by procedure B. Chromatography of the product on SiO_2 (100 g), elution with Et_2O–MeOH (9:1), and crystallisation from EtOH gave 4,5-*dihydro*-4-(2-*hydroxyphenyl*)*pyridazin*-3(2H)-*one* (**25**; R = H) (0.31 g), m.p. 172—174 °C (Found: C, 62.9; H, 5.3; N, 14.7. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 14.7%); $\nu_{max.}$(Nujol) 3 270, 3 100, and 1 669 cm^{-1}; *m/z* 190 (M^+, 100%).

Scheme 3. 4-*Aminophenylacetic Acid* (**26**) ⟶ *Product* (**29**).—A suspension of the acid (**26**) (5 g) in hexane-2,5-dione (20 ml)–benzene (50 ml) by procedure A gave a solution which was diluted with Et_2O, and washed thrice with 2M-HCl and thrice with water. Crystallisation of the product from MeCN under N_2 gave 4-(2,5-*dimethylpyrrol*-1-*yl*)*phenylacetic acid* (**27**) (6.5 g), m.p. 115—117 °C (Found: C, 73.3; H, 6.6; N, 6.4. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%); *m/z* 229 (M^+, 100%). (A compound with m.p. 100 °C but not further characterised is reported[27] to have this structure.) Treatment of the acid (**27**) (7.3 g) with $LiNPr^i_2$ and then with bromoacetal by procedure C gave an oil (9.35 g). A solution of this oil (2.4 g) and $N_2H_4{\cdot}H_2O$ (1 ml) in AcOH (3 ml)–EtOH (7 ml)–water (6 ml) was boiled under reflux for 3 h, and poured into aqueous Na_2CO_3. The material isolated with Et_2O was sublimed at 200 °C/0.01 mmHg to give 4-[4-(2,5-*dimethylpyrrol*-1-*yl*)-*phenyl*]-4,5-*dihydropyridazin*-3(2H)-*one* (**28**) (0.74 g), m.p. 184—187 °C (from C_6H_6) (Found: C, 71.9; H, 6.4; N, 15.7. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); δ 9.30 (1 H, br s,

NH), 7.4—7.1 (5 H, m, C_6H_4 and CH=N), 5.85 (2 H, s, pyrrole H), 3.75 (1 H, t, *J* 7 Hz, ArC*H*), 2.9—2.7 (2 H, m, CH_2), and 2.00 (6 H, s, CH_3); *m/z* 267 (M^+, 100%). A solution of compound (**28**) (0.7 g), KOH (0.45 g), and H_2NOH·HCl (0.9 g) in EtOH (17 ml)–water (9 ml) was boiled under reflux for 24 h, and poured into 1M-H_2SO_4. Isolation with Et_2O gave 4-(4-*aminophenyl*)-4,5-*dihydropyridazin*-3(2H)-*one* (**29**) (0.36 g), m.p. 176—179 °C (from EtOH) (Found: *m/z* 189.0905. $C_{10}H_{11}N_3O$ requires M^+ 189.0908); $\nu_{max.}$(Nujol) 3 350, 3 210, and 1 671 cm^{-1}.

Scheme 4. *The Ester* (**4**) ⟶ *Product* (**36**).—*Procedure E.* A solution of Bu^nLi in hexane (1.6-M; 70 ml) was added to a solution of MMS (12 ml) in THF (80 ml) at 0 °C under N_2. The solution was cooled to −70 °C and a solution of the ester (**4**) (24 g) in THF (10 ml) was added. The temperature was allowed to reach 20 °C, and after 2 h the mixture was poured into aqueous NH_4Cl. Extraction with Et_2O gave an oil (34 g) formulated, on spectrometric evidence, as the adduct (**30**). A solution of this oil, $HC(OEt)_3$ (19 ml), and H_2SO_4 (1.3 ml) in dry EtOH (130 ml) was kept at 20 °C for 2 days, and poured into aqueous $NaHCO_3$. Extraction with Et_2O gave an oil (30 g), a portion (3 g) of which was distilled to give *diethyl* 2-(2,2-*diethoxy*-1-*phenylethyl*)*propane*-1,3-*dioate* (**31**) (2.5 g), b.p. 152—154 °C/0.05 mmHg (Found: C, 64.5; H, 7.9. $C_{19}H_{28}O_6$ requires C, 64.75; H, 8.0%); *m/z* 307 ($M^+ - 45$, 100%).

Procedure F. A solution of the remaining oil (27 g) and KOH (30 g) in EtOH (350 ml) was boiled under reflux for 4 h, poured into water, and acidified with 10M-HCl. Isolation with Et_2O and distillation gave 5-ethoxy-4,5-dihydro-4-phenylfuran-2(3*H*)-one (**32**) (13 g), b.p. 141—142 °C/1 mmHg (lit.,[13] 120 °C/0.05 mmHg); $\nu_{max.}$ 1 795 cm^{-1}. The ethoxyfuranone (**32**) (12.5 g) and N_2H_4·H_2O (6 ml) in AcOH (32 ml)–water (22 ml) by procedure B gave 4,5-*dihydro*-5-*phenylpyridazin*-3(2H)-*one* (**36**) (11 g), m.p. 114—116 °C (from EtOH) (Found: C, 69.0; H, 5.8; N, 16.2. $C_{10}H_{10}N_2O$ requires C, 69.0; H, 5.8; N, 16.1%), δ 9.2 (1 H, br s, NH), 7.25 (6 H, m, C_6H_5 and CH=N), 3.85 (1 H, m, PhC*H*), and 2.8—2.6 (2 H, m, CH_2); $\nu_{max.}$ 3 435 and 1 704 cm^{-1}; $\lambda_{max.}$ 242 nm (ε 6 100); *m/z* 174 (M^+, 100%).

The Lactone (**34**) ⟶ *Products* (**35**) *and* (**36**).—The lactone (**34**) was prepared from $MeOCH_2Cl$ (**33**) in four stages[28,12a] (15% overall yield). A solution of the lactone (**34**) (0.22 g) and N_2H_4·H_2O (0.15 ml) in AcOH (3 ml)–water (0.5 ml) was boiled under reflux for 1 h. Work-up gave material shown (by ^1H n.m.r.) to contain products (**36**) and (**35**) in a ratio of *ca.* 4:1. Two crystallisations from EtOH gave the dihydropyridazinone (**36**) (0.11 g), m.p. 113—115 °C. A solution of the lactone (**34**) (0.95 g) and N_2H_4·H_2O (0.75 ml) in AcOH (5 ml)–water (0.9 ml) was boiled under reflux for 1 day. Work-up gave material indicated by ^1H n.m.r. examination to contain the pyridazinone (**35**) and a compound formulated as 3-acetoxy-5-phenylpyridazine. A solution of this material in KOH (0.8 g)–EtOH (10 ml) was kept at 20 °C for 2 days, acidified, and extracted with EtOAc to give 5-phenylpyridazin-3(2*H*)-one (**35**) (0.76 g), m.p. 197—199 °C (from EtOAc) (lit.,[13] 194 °C and lit.,[14] 192—194 °C); δ[$(CD_3)_2SO$] 13.13 (1 H, br s, NH), 8.21 (1 H, d, *J* 2 Hz, CH=N), and 7.12 (1 H, d, *J* 2 Hz, CHCO); $\nu_{max.}$(Nujol) 1 665 cm^{-1}; *m/z* 172 (M^+, 100%).

Scheme 5. 2-*Hydroxybenzaldehyde* (**37o**) ⟶ *Product* (**42o**).—Procedure A with the aldehyde (**37o**) (102 g), $CH_2(CO_2Et)_2$ (168 ml), piperidine (10 ml) and C_6H_6 (150 ml) gave ethyl coumarin-3-carboxylate (**38**) (172 g), m.p. 94—96 °C (from CCl_4) (lit.,[29] 92—94 °C). A solution of the foregoing ester (10 g) and KOH (8.5 g) in MeOH (160 ml) was boiled under reflux for 1.5 h. A solution of allyl bromide (18 ml) in MeOH (20 ml) was added, and the mixture was boiled under reflux for 2 h. Dilution with water and extraction with Et_2O gave an oil (7 g) indicated by ^1H n.m.r. examination to be a mixture consisting mainly of the esters (**40o**; R^2 = Me or allyl). A solution of the foregoing oil (1.5 g) and KOH (0.8 g) in EtOH (10 ml)–water (4 ml) was boiled under reflux for 3 h. Acidification gave 2-*allyloxybenzylidenemalonic acid* (**40o**; R^2 = H) (0.83 g), m.p. 173—176 °C (evolution of gas) (from EtOH) (Found: C, 62.7; H, 4.9. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.9%); *m/z* 248 (M^+, 16%) and 146 (100). Treatment of the mixture of esters (**40o**; R^2 = Me and allyl) (23 g) by procedure E gave an oil (26 g). This oil by procedure F gave material (15.5 g) which, on distillation, afforded the ethoxyfuranone (**41o**) (10.9 g), b.p. 202—206 °C/0.01 mmHg; $\nu_{max.}$ 1 793 cm^{-1}. The foregoing compound (9.8 g) and N_2H_4·H_2O (3.6 ml) by procedure B gave 5-(2-*allyloxyphenyl*)-4,5-*dihydropyridazin*-3(2H)-*one* (**42o**) (6.5 g), m.p. 93—95 °C (from C_6H_6) (Found: C, 67.7; H, 6.1; N, 12.0. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); $\nu_{max.}$ 3 435 and 1 702 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 6 900); *m/z* 230 (M^+, 42%) and 189 (100).

3-*Hydroxybenzaldehyde* (**37m**) ⟶ *Product* (**43m**).—Procedure A with the aldehyde (**37m**) (100 g) gave the ester (**39m**) (187 g), m.p. 87—88.5 °C (from CCl_4) (lit.,[30] 86.5—87 °C).

Procedure G. A solution of KOH (3.5 g) in EtOH (22 ml) was added during 10 min to a stirred solution of the foregoing ester (16.5 g) in EtOH (65 ml) at 10 °C. After 15 min allyl bromide (8.8 ml) was added during 10 min, and the solution was boiled under reflux for 2 h. Et_2O was added, and the solution was washed with water, thrice with 1M-NaOH, and brine. The solution was dried, filtered through SiO_2, and evaporated to give *diethyl* 3-*allyloxybenzylidenemalonate* (**40m**; R^2 = Et) (17 g) (Found: C, 67.2; H, 6.7. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%), $\nu_{max.}$ 1 728 cm^{-1}; *m/z* 304 (M^+, 30%) and 41 (100). Procedure E with the foregoing ester (11 g) gave an oil (13.5 g) which, by procedure F, afforded the ethoxy lactone (**41m**) (5.9 g), b.p. 205—210 °C/0.01 mmHg, *m/z* 262 (M^+, 10%) and 160 (100). The ethoxy lactone (5.5 g) and N_2H_4·H_2O (2.1 ml) by procedure B gave an oil (4.5 g) formulated on spectrometric evidence as the 5-substituted dihydropyridazinone (**42m**). This oil slowly crystallised during 7 days. Recrystallisation from EtOH afforded 5-(3-*alloxyphenyl*)*pyridazin*-3(2H)-*one* (**43m**) (3.0 g), m.p. 138—140 °C (Found: C, 68.2; H, 5.4; N, 12.3. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%), δ 13.11 (1 H, s, NH), 8.27 (1 H, d, *J* 2 Hz, CH=N), 7.45—7.0 (5 H, m, C_6H_4 and CHCO), 6.10 (1 H, m, C*H*:CH_2), 5.38 (2 H, m, CH:CH_2), and 4.65 (2 H, m, OCH_2); $\nu_{max.}$ 1 655 cm^{-1}; $\lambda_{max.}$ 277 nm (ε 10 400) and 305 (5 800); *m/z* 228 (M^+, 50%) and 41 (100).

4-*Hydroxybenzaldehyde* (**37p**) ⟶ *Product* (**42p**).—Procedure A with the aldehyde (**37p**) (104 g) gave the ester (**39p**) (201 g), m.p. 92—93 °C (from CCl_4) (lit.,[31] 93 °C). Procedure G with the foregoing ester (15 g) gave *diethyl* 4-*allyloxybenzylidenemalonate* (**40p**; R^2 = Et) (16.8 g) (Found: C, 66.8; H, 6.5. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$ 1 724 cm^{-1}; *m/z* 304 (M^+, 95%) and 41 (100). Procedure E with the ester (**40p**; R^2 = Et) (12 g) gave an oil (16.9 g) which, by procedure F, afforded 4-(4-*allyloxyphenyl*)-5-*ethoxy*-4,5-*dihydrofuran*-2(3H)-*one* (**41p**) (7.1 g), b.p. 203—208 °C/0.01 mmHg (Found: C, 68.4; H, 6.8. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); δ 4.5 (2 H, m, OCH_2CH:CH_2), 5.35 (3 H, m, OCH_2CH:CH_2 and CHOEt), and 6.03 (1 H, m, OCH_2CH:CH_2); $\nu_{max.}$ 1 795 cm^{-1}; *m/z* 262 (M^+, 6%) and 160 (100). The ethoxy lactone (5.7 g) and N_2H_4·H_2O (2.4 ml) by procedure B gave 5-(4-*allyloxyphenyl*)-4,5-*dihydropyridazin*-3(2H)-*one* (**42p**) (4.3 g), m.p. 130—131.5 °C (from C_6H_6) (Found: C, 68.0; H, 6.2; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); $\nu_{max.}$ 3 430 and 1 705 cm^{-1}; *m/z* 230 (M^+, 47%) and 41 (100).

Scheme 6. *Oxidation and Reduction of* 4,5-*Dihydrophenylpyridazin*-3(2H)-*ones*.—A solution of Br_2 (0.2 ml) in AcOH (0.5 ml) was added during 2 min to a stirred solution of 4,5-dihydro-4-phenylpyridazin-3(2*H*)-one (**16**) (0.51 g) in AcOH (3.2 ml) at 70 °C, which was then poured into aqueous $NaHCO_3$. Isolation with EtOAc gave 4-*phenylpyridazin*-3(2H)-*one* (**44**) (0.38 g), m.p. 217—220 °C (alternative preparation,[14] 217—219 °C) (Found: C, 69.5; H, 4.8; N, 16.3. $C_{10}H_8N_2O$ requires C, 69.75; H, 4.7; N, 16.3%); δ[$(CD_3)_2SO$] 13.21 (1 H, s, NH), 7.91 (1 H, m, 6-H) and 7.45 (1 H, m, 5-H); $\nu_{max.}$(Nujol) 1 640 cm^{-1}; *m/z* 172 (M^+, 100%). Similarly, the dihydropyridazinones (**36**) and (**48**)[1] gave the pyridazinones (**35**) (81%, m.p. and mixed m.p. 194—196 °C) and (**47**) (75%, m.p. 199—200 °C) (lit.,[1] 200—201 °C), respectively.

Procedure H. *N*-Bromosuccinimide (0.6 g) was added to a solution of the dihydropyridazinone (**16**) (0.22 g) in Me_2SO (5 ml)–water (0.2 ml) at 5 °C. The cooling bath was removed, and after 2 h the solution was poured into aqueous $NaHCO_3$. Isolation with EtOAc gave the pyridazinone (**44**) (0.16 g). Similarly, the dihydropyridazinone (**36**) gave the pyridazinone (**35**) (78%) but the dihydropyridazinone (**48**) was recovered unchanged. A solution of the dihydropyridazinone (**16**) (0.36 g) in EtOH (8 ml)–AcOH (0.1 ml) was shaken over PtO_2 (0.12 g) in an atmosphere of H_2 for 6 h. Work-up gave 4-*phenyltetrahydropyridazin*-3(2H)-*one* (**45**) (0.28 g), m.p. 140—141 °C (from $CHCl_3$) (Found: C, 67.9; H, 6.8; N, 16.1. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.9; N, 15.9%); δ 7.57 (1 H, br s, CONH), 7.27 (5 H, s, Ph), 4.05 (1 H, br s, N*H*CH_2), 5.70 (1 H, dd, *J* 10 and 7 Hz, PhC*H*), 3.13 (2 H, t, *J* 7 Hz, 6-H), and 2.15 (2 H, m, 5-H); $\nu_{max.}$(CH_2Cl_2) 3 405 and 1 665 cm^{-1}; *m/z* 176 (M^+, 100%). Similarly, the dihydropyridazinone (**36**) gave 5-*phenyltetrahydropyridazin*-3(2H)-*one* (**46**) (85%), m.p. 168—171 °C (from EtOH) (Found: C, 68.0; H, 6.9; N, 16.0%), *m/z* 176 (M^+, 100%).

Product (**49**).—Treatment of the 5-(2-allyloxyphenyl)dihydropyridazinone (**42o**) (1.4 g) by procedure H gave material which was dissolved in Bu^tNH_2 (20 ml)–PhMe (90 ml). The solution was boiled under reflux for 3 days, poured into 1M-H_2SO_4, and washed with Et_2O. Basification with aqueous NaOH and extraction with EtOAc gave an oil (1.3 g), which was dissolved in 0.1M-HCl. The solution was washed with Et_2O and evaporated at 80 °C/15 mmHg to give 4,5-*dihydro*-5-[2-(2-*hydroxy*-3-t-*butylaminopropoxy*)*phenyl*]*pyridazin*-3(2H)-*one hydrochloride* (**49**) (1.3 g), m.p. 265—267 °C (decomp.) (from EtOH–water) (Found: C, 57.6; H, 6.8; Cl, 9.8; N, 11.7. $C_{17}H_{24}ClN_3O_3$ requires C, 57.7; H, 6.8; Cl, 10.0; N, 11.9%); $\nu_{max.}$(Nujol) 3 385 and 1 668 cm^{-1}; $\lambda_{max.}$(H_2O) 280 nm (ε 6 400); *m/z* 318 [($M^+ - 35$), 2%] and 86 (100).

Reactions involving Phenyl-lithium.—A solution of PhLi in C_6H_6–Et_2O (1.7M; 7 ml) was added to a solution of phthalazin-1(2*H*)-one (**50**)[17] (1.5 g) in THF (60 ml) which was stirred at 3 °C under N_2. A white precipitate was formed. An aliquot (10 ml) was withdrawn and added to water (30 ml). Extraction with EtOAc gave phthalazin-1(2*H*)-one (0.19 g), m.p. and mixed m.p. 182—183 °C. More PhLi solution (7 ml) was added to the remaining mixture. The precipitate dissolved, giving an orange solution. Work-up gave material which was then dissolved in MeOH. The solution was boiled under reflux for 30 min, concentrated, and cooled to give 4-phenylphthalazin-1(2*H*)-one (**51**) (0.68 g), m.p. 240—241 °C (lit.,[17] 235 °C).

Solutions of the dihydrophenylpyridazinones (**16**) and (**36**) (0.5 g in each case) were treated with a solution of PhLi (1.7M; 1.75 ml and then 3.5 ml) as in the foregoing experiment. White precipitates were formed during the first addition; these dissolved, giving brown solutions, during the second addition. Work-up after the first and the second additions gave the starting materials (**16**) and (**36**) in recoveries of 75—80%.

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