Pyridazines. Part IV.[1] Action of Grignard Reagents on 6-Methyl- and 4,5-Dihydro-6-α-styryl-pyridazin-3(2*H*)-ones

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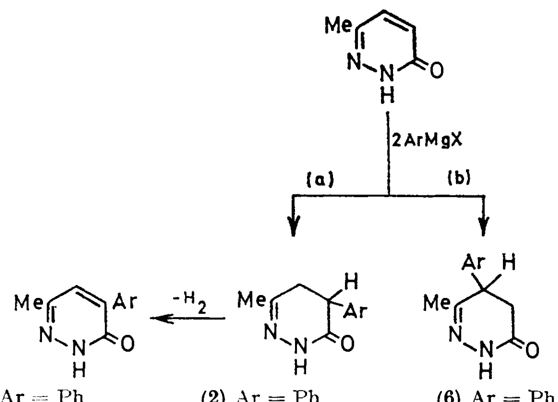
6-Methylpyridazin-3(2*H*)-one reacts with phenyl- and *p*-methoxyphenyl-magnesium bromide (4 mol. equiv.) in 1 : 1 ether-tetrahydrofuran to give a mixture of the corresponding 4- and 5-aryl-4,5-dihydro-6-methylpyridazin-3(2*H*)-ones. With *p*-tolyl- and α-naphthyl-magnesium bromide, only the corresponding 4-aryl-4,5-dihydro-pyridazin-3(2*H*)-ones are obtained. When the reaction is carried out in tetrahydrofuran, 4-aryl-6-methylpyridazin-3(2*H*)-ones are obtained.

4,5-Dihydro-6-α-styrylpyridazin-3(2*H*)-one reacts with *p*-anisyl-, *p*-tolyl-, and α-naphthyl-magnesium bromide (3 or 4 mol. equiv.) in tetrahydrofuran or ether–tetrahydrofuran to give 3-aryl-4,5-dihydro-6-α-styrylpyridazines and/or 3-aryl-6-α-styrylpyridazines. Use of phenylmagnesium bromide, however, gives 3,4-diphenyl-6-α-styrylpyridazine.

It has been reported [2] that 6-aryl-4,5-dihydropyridazin-3(2*H*)-ones react with phenyl- and *p*-methoxyphenyl-magnesium bromide to give 3,6-diarylpyridazines, and that 6-arylpyridazin-3(2*H*)-ones react with arylmagnesium bromides to give 4,6-diaryl-4,5-dihydropyridazin-3(2*H*)-ones.

In the present investigation, 6-methylpyridazin-3(2*H*)-one (1) was treated with *p*-tolyl- and α-naphthyl-magnesium bromide (3 or 4 mol. equiv.) in ether–tetrahydrofuran to give the corresponding 4-aryl-4,5-dihydro-6-methylpyridazin-3(2*H*)-ones (4) and (5). However, with phenyl- (3 or 4 mol. equiv.) and *p*-methoxyphenyl- (4 mol. equiv.) magnesium bromides, the product was a mixture of 4-aryl- [(2) and (3) (predominant)] and 5-aryl- [(6) and (7)] 4,5-dihydro-6-methylpyridazin-3(2*H*)-ones, indicating that 1,4-addition takes place to the –C=C–C=N– (a) and –C=C–C=O– (b) systems, respectively (Scheme 1). When 6-methylpyridazin-3(2*H*)-one reacted with phenyl-, *p*-methoxyphenyl-, *p*-tolyl-, or α-naphthyl-magnesium bromide (4 mol. equiv.) in tetrahydrofuran, the corresponding 4-arylpyridazin-3(2*H*)-ones (8)—(11) were obtained.



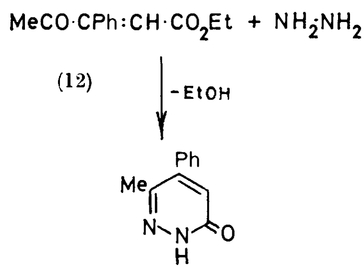
(8) Ar = Ph (9) Ar = *p*-MeO·C_6H_4 (10) Ar = *p*-MeC_6H_4 (11) Ar = α-$C_{10}H_7$
(2) Ar = Ph (3) Ar = *p*-MeO·C_6H_4 (4) Ar = *p*-MeC_6H_4 (5) Ar = α-$C_{10}H_7$
(6) Ar = Ph (7) Ar = *p*-MeO·C_6H_4

SCHEME 1

The i.r. spectra of the products (2)—(5) showed strong bands between 1640 and 1680 cm^{-1} (C=O) and two sharp bands in the 3 μm region (NH) (Table 2), characteristic of 4,5-dihydropyridazin-3(2*H*)-ones.[1,2] The u.v. spectra (in ethanol) were identical; maxima occurred at shorter wavelength than in the case of the corresponding unsaturated derivatives (8)—(11) (Table 2). The structures of compounds (2) and (4) were supported by their n.m.r. spectra (see Experimental section). Compound (2) was identical with an authentic specimen.

Compounds (6) and (7) were identified from their i.r. spectra (Table 2; *cf.* refs. 1 and 2), from the n.m.r. spectrum of compound (6) (see Experimental section), and by comparison of compound (6) with an authentic specimen prepared by heating ethyl 3-phenyl-levulinate [3] with hydrazine hydrate.

Dehydrogenation of compound (6) with bromine in glacial acetic acid gave compound (13), which was identical with an authentic specimen prepared by heating ethyl 4-oxo-3-phenylpent-2-enoate [4] (12) with hydrazine hydrate.



The i.r. spectra of the products (8)—(11) showed strong bands between 1640 and 1650 cm^{-1}, and one broad band in the 3 μm region (Table 2). The structures assigned were substantiated by the n.m.r. spectrum of (8) (see Experimental section). Thus the reaction has

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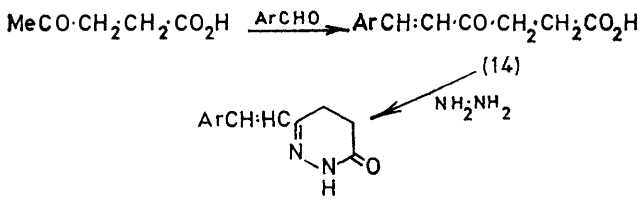
taken place by 1,4-addition to an αβ-unsaturated C=N or C=O group, to give a 4-aryl- or 5-aryl-4,5-dihydropyridazin-3(2*H*)-one derivative, respectively, which is apparently dehydrogenated to the corresponding unsaturated system. The similarity of the u.v. spectra of these compounds (in ethanol) (Table 2) indicated that they had similar structures. That they were 4-aryl rather than 5-aryl derivatives was shown by comparison of compound (8) with an authentic specimen prepared by heating 2-phenyl-levulinic acid[5] with hydrazine hydrate followed by dehydrogenation of the product with bromine in glacial acetic acid.

Thus in the reaction of 6-methylpyridazin-3(2*H*)-one with arylmagnesium halides the nature of the products depends on the solvent used and the ratio of Grignard reagent to substrate. Dehydrogenation [*e.g.* (2) ⟶ (8)] appears to take place under the influence of the Grignard reagent in a high-boiling solvent: this could only be effected by refluxing compound (2) with phenylmagnesium bromide in tetrahydrofuran, but not in ether–tetrahydrofuran.

Synthesis of 4,5-*Dihydro*-6-α-*styrylpyridazin*-3(2H)-*ones* (15)—(17).—These compounds were prepared by condensing the appropriate aldehyde with levulinic acid in the presence of sodium hydroxide catalyst to give the corresponding δ-arylmethylenelevulinic acids (14), followed by treatment with hydrazine hydrate in glacial acetic acid. The structure of compounds (14) was established by oxidation with alkaline potassium permanganate to give succinic acid, which would not be obtained from β-arylmethylenelevulinic acids.

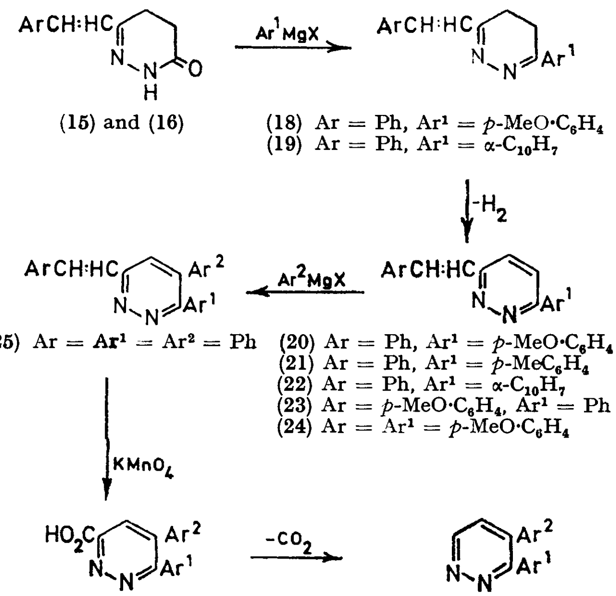


(15) Ar = Ph
(16) Ar = p-MeO·C_6H_4
(17) Ar = p-MeC_6H_4

Compounds (15)—(17) have similar u.v. spectra (Table 1). Their i.r. spectra (Table 1) show two sharp bands in the 3 μm region in agreement with their 4,5-dihydropyridazin-3(2*H*)-one structure.[2] Compound (15) is readily hydrolysed by concentrated hydrochloric acid to give δ-benzylidenelevulinic acid. Pyridazin-3(2*H*)-ones are not cleaved under these conditions.[2]

Attempts to convert compound (15) into the corresponding pyridazin-3(2*H*)-one, by treatment with bromine in glacial acetic acid, gave 6-(1,2-dibromo-2-phenylethyl)-4,5-dihydropyridazin-3(2*H*)-one, identified from its analytical data and its i.r. spectrum [$\nu_{max.}$ 3250 and 3100 cm^{-1} (both sharp) (NH), characteristic of 4,5-dihydropyridazin-3(2*H*)-ones [1,2]].

Action of Grignard Reagents on the Styrylpyridazinones (15) *and* (16).—Phenylmagnesium bromide (3 or 4 mol. equiv.) reacted with the styrylpyridazinone (15) in tetrahydrofuran or in ether–tetrahydrofuran to give 3,4-diphenyl-6-α-styrylpyridazine (25), probably by the mechanism shown in Scheme 2.



(15) and (16)
(18) Ar = Ph, Ar¹ = p-MeO·C_6H_4
(19) Ar = Ph, Ar¹ = α-$C_{10}H_7$
(25) Ar = Ar¹ = Ar² = Ph
(20) Ar = Ph, Ar¹ = p-MeO·C_6H_4
(21) Ar = Ph, Ar¹ = p-MeC_6H_4
(22) Ar = Ph, Ar¹ = α-$C_{10}H_7$
(23) Ar = p-MeO·C_6H_4, Ar¹ = Ph
(24) Ar = Ar¹ = p-MeO·C_6H_4
(26) Ar¹ = Ar² = Ph
(27) Ar¹ = Ar² = Ph

SCHEME 2

The structure of compound (25) was deduced from the observations that (i) its i.r. spectrum showed no bands in the 3 and 6 μm regions, (ii) ozonolysis gave rise to benzaldehyde, indicating that the styryl group was still intact, (iii) its n.m.r. spectrum showed signals at τ 2·15—2·65 (15H, m, ArH), 2·03 (1H, s), and 1·61 (2 × d, CH=CH),[6] and (iv) oxidation with alkaline potassium permanganate afforded the corresponding carboxylic acid (26), which on decarboxylation with copper bronze, gave 3,4-diphenylpyridazine (27), identical with an authentic specimen.[7]

However, reactions of compound (15) with p-methoxyphenyl- and α-naphthyl-magnesium bromide in tetrahydrofuran or ether–tetrahydrofuran in the molar ratio 1 : 3 or 1 : 4 gave in both cases a mixture [of compounds (18) and (20), and (19) and (22), respectively]. With p-tolylmagnesium bromide, however, the dehydrogenated product (21) was only obtained.

The i.r. spectra of compounds (18)—(22) show no bands in the 3 or 6 μm region, indicating that the reaction has taken place by 1,2-addition to the carbonyl group. These products give benzaldehyde on ozonolysis, indicating the presence of the styryl group. The u.v. spectra (in ethanol; Table 3) of compounds (20)—(22) show absorption at longer wavelength than (18) and (19) and resemble that of 4-methoxy-*trans*-stilbene.[8]

When compounds (18) and (19) were refluxed with ethanol, they were readily dehydrogenated to (20) and (22), respectively.

Structure (20) was substantiated by its n.m.r. spec-

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TABLE 1

Dihydrostyrylpyridazinones

Compound	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	ν_{NH}/cm^{-1} (KBr)	ν_{CO}/cm^{-1}	$\lambda_{max.}$/nm	ε
(15)	168—169	73	72·0	5·9	14·0	$C_{12}H_{12}N_2O$	72·0	6·0	14·0	3100, 3220 †	1675	224	11,370
												314	44,170
(16)	187—188	92	67·4	6·3	12·7	$C_{13}H_{14}N_2O_2$	67·8	6·1	12·2	3090, 3220 †	1695	224	9470
												326	38,720
(17)	208—209	77	72·6	6·5	13·5	$C_{13}H_{14}N_2O$	72·9	6·6	13·1	3090, 3220 †	1675	224	11,500
												317	37,600

† Sharp.

TABLE 2

Pyridazinones (2)—(11)

Compound	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	ν_{NH}/cm^{-1} (KBr) *	ν_{CO}/cm^{-1}	$\lambda_{max.}$/nm	ε
(2)	125	22	70·05	6·8	14·5	$C_{11}H_{12}N_2O$	70·2	6·4	14·9	3080, 3200 *	1640—1680	245	7110
(3)	138	35	65·7	6·6	12·7	$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	3100, 3226 *	1670	227	12,290
												250	6730
(4)	145	28	71·3	6·9	13·9	$C_{12}H_{14}N_2O$	71·3	7·0	13·9	3040, 3150 *	1680	245	7170
(5)	175	16	75·7	5·9	11·3	$C_{15}H_{14}N_2O$	75·6	5·9	11·8	3100, 3226 *	1670	223	43,140
												260	7840
												270	8100
												280	7840
(6)	154	11	70·4	6·4	14·8	$C_{11}H_{12}N_2O$	70·2	6·4	14·9	3140 *	1650	245	5970
(7)	118	3·5	66·5	6·6	11·9	$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	3110, 3215 *	1645, 1680	230	14,150
												250	12,990
(8)	170	45	71·2	5·5	15·2	$C_{11}H_{10}N_2O$	71·0	5·4	15·1	3020—3120 †	1650	270 ‡	5110
												305	6630
												315	6860
(9)	205	33	67·1	5·8	13·0	$C_{12}H_{12}N_2O_2$	66·7	5·6	13·0	2860—3000 †	1640	327	15,280
(10)	191 §	40	72·4	6·1	13·8	$C_{12}N_{12}N_2O$	72·0	6·0	14·0	3050—3100 †¶	1650	320	10,340
(11)	248	30	75·9	5·4	11·9	$C_{15}H_{12}N_2O$	76·3	5·1	11·9	3020—3140 †	1650	221	72,100
												280	6230
												307	6880

* Sharp. † Broad. ‡ In ethanol with a few drops of conc. sulphuric acid: $\lambda_{max.}$ 270 and 315 nm (ε 5290 and 7900). § From ethanol; all the others from benzene. ¶ In Nujol.

TABLE 3

Styrylpyridazines (18)—(24)

Compound	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	$\lambda_{max.}$/nm	ε
(18)	149 *	9	78·4	6·5	10·2	$C_{19}H_{18}N_2O$	78·6	6·2	9·7	287	15,950
(19)	156 †	11	84·9	5·8	8·8	$C_{22}H_{18}N_2$	85·1	5·9	9·0	221	53,700
										285	12,850
(20)	191 ‡	35	79·3	5·7	9·2	$C_{19}H_{16}N_2O$	79·1	5·6	9·7	316	28,230
(21)	206 ‡	45	83·4	6·0	9·9	$C_{19}H_{16}N_2$	83·8	5·9	10·3	306	27,540
(22)	177 ‡	39	85·7	5·3	9·0	$C_{22}H_{16}N_2$	85·7	5·2	9·1	220	56,270
										315	23,760
(23)	185 ‡	41	78·7	5·8	9·6	$C_{19}H_{16}N_2O$	79·1	5·6	9·7	332	19,730
										370	6640
(24)	226 *	49	75·2	5·2	8·9	$C_{20}H_{18}N_2O_2$	75·5	5·7	8·8	335	28,560
										375	4020
4-Methoxy-*trans*-stilbene §										305	31,620
										318	31,620
										335	19,950

* From benzene. † From methanol. ‡ From ethanol. § Ref. 8.

trum, which shows two unsymmetrical signals at τ 1·9 (1H) and 2·01 (1H), which appear to be distorted doublets corresponding to the two protons in the heterocyclic ring. It also shows a multiplet at τ 2·6 (9H, ArH),[6] two unsymmetrical singlets at τ 2·9 (1H) and 3·1 (1H) (*trans*-CH:CH), and a sharp singlet at τ 6·14 (OMe).

Phenyl- and *p*-methoxyphenyl-magnesium bromide (4 mol. equiv.) reacted with compound (16) in tetrahydrofuran to give 3-aryl-6-α-*p*-methoxystyrylpyridazines (23) and (24), respectively. The i.r. spectra of these compounds show no bands characteristic of OH, NH, and CO groups, which indicates that the reaction has taken place by 1,2-addition to the carbonyl group followed by elimination of water. Structures (23) and (24) are supported by their u.v. spectra (Table 3) and by ozonolysis of compound (23) to give *p*-anisaldehyde.

EXPERIMENTAL

I.r. spectra were measured with Perkin-Elmer Infracord model 137 and Unicam SP 1200 instruments. U.v. spectra were measured with a Zeiss spectrophotometer type PAQ 11, and n.m.r. spectra with a Varian 60A instrument.

4-Oxo-6-p-tolylhex-5-enoic Acid (14; Ar = *p*-MeC_6H_4).—A solution of levulinic acid (5·8 g) in water (100 ml) was added to a mixture of *p*-tolualdehyde (6 g) in ethanol (50 ml) and aqueous 5% sodium hydroxide (80 ml). The mixture was refluxed for 0·5 h, cooled, and neutralised with concentrated hydrochloric acid. The precipitate yielded *4-oxo-6-p-tolylhex-5-enoic acid* (46%), m.p. 129—130° (from water) Found: C, 71·3; H, 6·6. $C_{13}H_{14}O_3$ requires C, 71·55; H, 6·4%).

4,5-Dihydro-6-α-styrylpyridazin-3(2H)-ones (15)—(17).—A solution of the 6-aryl-4-oxohex-5-enoic acid (14) (0·015 mol) was refluxed for 2 h with hydrazine hydrate (0·015 mol) in glacial acetic acid (50 ml). The mixture was diluted with water, and the precipitate was filtered off and crystallised from ethanol (Table 1).

4-Benzyl-6-methylpyridazin-3(2H)-one.—A solution of 2-benzylidene-4-methylbut-3-en-4-olide (18·6 g) in ethanol (100 ml) was treated with hydrazine hydrate (4 ml), refluxed for 2 h, cooled, and diluted with water. The precipitate (from water) gave *4-benzyl-6-methylpyridazin-3(2H)-one* (56%), m.p. 165—166° (Found: C, 71·5; H, 6·1; N, 13·6. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%).

Action of Grignard Reagents on 6-Methylpyridazin-3(2H)-one.—(i) A solution of 6-methylpyridazin-3(2*H*)-one (0·033 mol) in tetrahydrofuran (50 ml) was added in portions to a solution of the arylmagnesium bromide [from aryl bromide (0·132 mol) and magnesium (0·132 g atom)] in dry ether (50 ml). The mixture was refluxed for 5 h on a boiling water-bath, then decomposed with saturated aqueous ammonium chloride. The organic layer was separated, washed with water, and dried (Na_2SO_4). On removal of the solvent *in vacuo* a semi-solid separated. After trituration several times with n-hexane, the products were found to be a mixture of compounds (2) and (6), and compounds (3) and (7) in the case of phenyl- and *p*-methoxyphenyl-magnesium bromide, respectively, whereas in the case of *p*-tolyl- and α-naphthyl-magnesium bromides, they were compounds (4) and (5), respectively (Table 2).

(ii) In similar reactions with 6-methylpyridazin-3(2*H*)-one (0·025 mol) and arylmagnesium bromide (0·075 mol) in dry tetrahydrofuran the products were *4-aryl-4,5-dihydro-6-methylpyridazin-3(2H)-ones*, except in the case of phenylmagnesium bromide, where a mixture of 4- (2) and *5-aryl-4,5-dihydro-6-methylpyridazin-3(2H)-ones* (6) was obtained.

(iii) Repeating procedure (ii) with 4 mol. equiv. of arylmagnesium bromide instead of 3 gave 4-aryl-6-methylpyridazin-3(2*H*)-ones (8)—(11) (Table 2).

Compound (2) showed n.m.r. signals at τ 2·6 (5H, m, ArH), 6·33 (t, CH), 7·2 (d, CH_2), and 7·92 (s, MeC:N); compound (4) showed signals at τ 2·9 (4H, m, ArH), 6·35 (t, CH), 7·15 (d, CH_2), 7·65 (s, ArMe), and 7·94 (MeC:N); compound (6) showed signals at τ 2·7 (5H, m, ArH), 4·6 (d, CH_2), 6·4 (t, CH), and 7·6 (s, MeC:N); compound (8) showed signals at τ 1·8 (s, CH=C), 2·5(d) and 2·8(d) (4H, ArH), 5·96 (s, OMe), and 6·9 (MeC:N).

Action of Arylmagnesium Bromides on 4,5-Dihydro-6-α-styryl- (15) and 6-α-p-methoxystyryl- (16) pyridazin-3(2H)-ones.—The pyridazin-3-one (15) (0·025 mol) in dry tetrahydrofuran (50 ml) was added slowly to a solution of phenylmagnesium bromide [from bromobenzene (0·1 mol) and magnesium (0·1 g atom)] in dry ether (50 ml). After 5 h under reflux decomposition of the Grignard complex gave *3,4-diphenyl-6-α-styrylpyridazine* (25) as yellow crystals (40%), m.p. 185—186° (from benzene) (Found: C, 85·7; H, 5·7; N, 9·1. $C_{24}H_{18}N_2$ requires C, 86·2; H, 5·4; N, 8·4%), $\lambda_{max.}$ 316 and 370 nm (ε 54,290 and 450).

Similar treatment of compound (15) (0·025 mol) with *p*-methoxyphenyl- and α-naphthyl-magnesium bromides (0·1 mol) gave mixtures of compounds (18) and (20), and compounds (19) and (22), respectively. However, with *p*-tolylmagnesium bromide, (21) was the only product obtained. Similarly compound (16) gave the pyridazines (23) and (24) on treatment with phenyl- and *p*-methoxyphenyl-magnesium bromide, respectively (Table 3).

Oxidation of 3,4-Diphenyl-6-α-styrylpyridazine with Potassium Permanganate.—3,4-Diphenyl-6-α-styrylpyridazine (3·34 g) suspended in water (50 ml) was treated with aqueous 10% potassium hydroxide (2 drops). The mixture was warmed on a steam-bath and potassium permanganate (3·5 g) was added in portions until the colour persisted. The excess of permanganate was destroyed with hydrogen peroxide and the mixture was treated with ethanol (30 ml) to coagulate the colloidal manganese dioxide. The clear alkaline filtrate was carefully neutralised with conc. hydrochloric acid and extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the acid obtained was decarboxylated by heating with copper bronze to give 3,4-diphenylpyridazine, m.p. and mixed m.p. 106—108°.

Ozonolysis of 3-Aryl-6-α-styrylpyridazines.—The pyridazines (20)—(24) (2 g) in chloroform (50 ml) were ozonised (3 h). After removal of the solvent *in vacuo* the ozonide was decomposed with zinc dust and dilute acetic acid, extracted with ether, and then steam distilled. The aldehyde produced was identified as its 2,4-dinitrophenylhydrazone (m.p. and mixed m.p.).

Bromination of 4,5-Dihydro-6-α-styrylpyridazin-3(2H)-one.—The pyridazin-3-one (15) (0·01 mol) was dissolved in glacial acetic acid (50 ml) and slowly treated with bromine (0·01 mol) in glacial acetic acid (5 ml). The separated solid crystallised from ethanol to give *6-(1,2-dibromo-2-phenylethyl)-4,5-dihydropyridazin-3(2H)-one* (53%), m.p. 144—145° (Found: C, 39·95; H, 3·6; Br, 44·6; N, 7·5. $C_{12}H_{12}Br_2N_2O$ requires C, 40·0; H, 3·3; Br, 44·4; N, 7·4%).

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