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NOVEL METHODS FOR THE SYNTHESIS OF SOME PYRIDAZINO-, FURO-, AND POLYSUBSTITUTED PYRIDAZINES

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ABSTRACT

3,4-Diethoxycarbonyl-5,6-diphenylpyridazine **1** reacted with hydrazine hydrate to form tetrahydropyridazino [4,5-c]pyridazine **2**, which reacted with ethyl bromoacetate to give 6,7-diethoxycarbonylmethyl-3,4-diphenyl-5,8-dioxopyridazino [4,5-c]pyridazine **3**. However, acetylation of **2** with acetyl chloride gave three different pyridazino[4,5-c]pyridazines **4–6**. The reaction of the starting diester **1** with different amounts of phenylmagnesium bromide gave different products **7–10**. The structure of product **8** was elucidated by alkaline hydrolysis and hydrazinolysis to afford **11** and **13**, respectively. Treatment of **13** with benzaldehyde in piperidine yielded the starting Grignard product **8** and benzalazine **17**.

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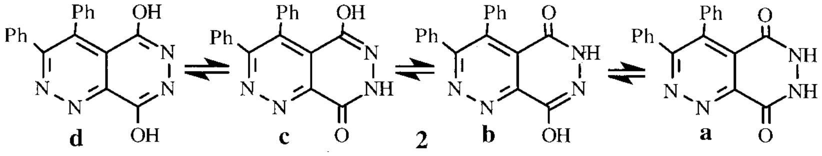
In continuation of our previous work on the synthesis of condensed pyridazine derivatives [1], we reported in this work a new synthesis for preparing 3,4,5,8-dioxo-5,6,7,8-tetrahydropyridazino[4,5-c]pyridazine **2** starting with 3,4-diethoxycarbonyl-5,6-diphenyl-pyridazine **1** [2] and hydrazine hydrate (Scheme 1). The structure of the product **2** has been verified by analytical data, infrared, mass, and electronic spectra. The electronic spectrum of compound **2** carried out at different pH values (2–11) in a universal buffer exhibited three isosbestic points; indicating that compound **2** must be present in four tautomeric structures **2a–d**. The mass spectrum of compound **2** showed the molecular ion peak $[\mathrm{M}^{\overset{\bullet}{+}} = 316]$ is that of the base peak.

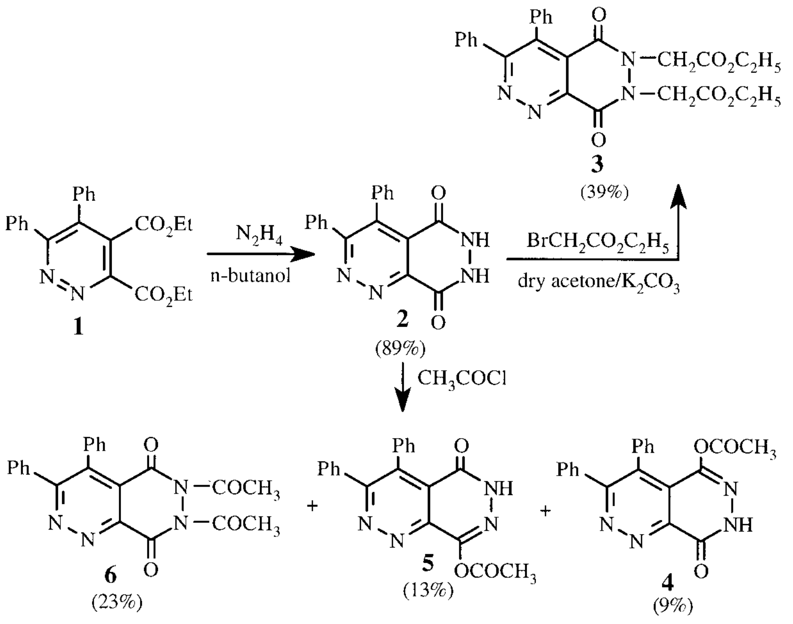


The structure **2** was also confirmed by its reaction with ethyl bromoacetate in the presence of anhydrous potassium carbonate in dry acetone to give 6,7-diethoxycarbonylmethyl-3,4-diphenyl-5,8-dioxopyridazino[4,5-c]pyridazine **3** (Scheme 1).

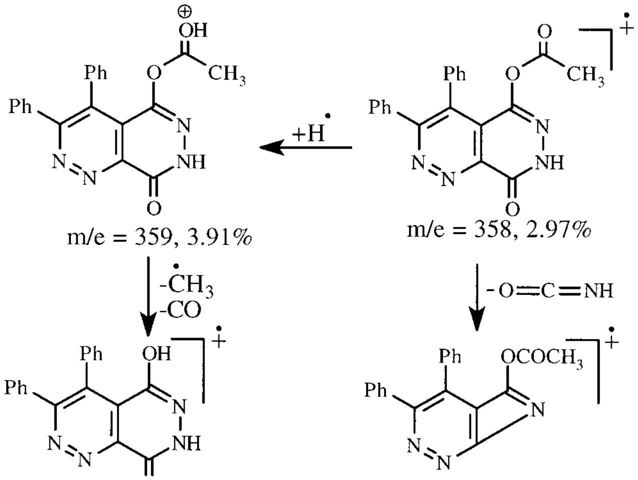
The analytical data of **3** indicate that two moles of ethyl bromoacetate were consumed by each mol of compound **2**. Its IR spectrum showed absorption bands for CO (ester) and CO (cyclic amide) at 1757 and 1684 cm^{-1}, respectively, indicating that the reaction has taken place at -CO-NH- system rather than $-\underset{\mathrm{OH}}{\underset{|}{\mathrm{C}}}{=}\mathrm{N}-$. The mass spectrum of **3** showed the molecular ion peak $[\mathrm{M}^{\overset{\bullet}{+}} = 488]$. The principal fragmentation route involves splitting of ethylene oxide followed by ethylene or carbon monoxide giving rise to the base peak at $[\mathrm{M}^{\overset{\bullet}{+}} = 316]$.

When the pyridazino[4,5-c]pyridazine derivative **2** was allowed to react with acetyl chloride it gave three products namely; 6,7-diphenyl-3-oxo-(2H)-pyridazino[4,5-c]pyridazinyl-8-acetate **4**, 6,7-diphenyl-8-oxo-(1H)-pyridazino[4,5-c]pyridazinyl-3-acetate **5** and 1,2-diacetyl-6,7-diphenyl-3,8-dioxopyridazino[4,5-c]pyridazine **6**. The structures of the products **4–6** were verified by their IR spectra and their mass spectra.

The reaction of 3,4-diethoxy-5,6-diphenylpyridazine **1** with nucleophile derived from Grignard reagent was studied using one to four moles of phenylmagnesium bromide in diethyl ether and dry benzene (1:1) mixture as a solvent medium. (Scheme 4).



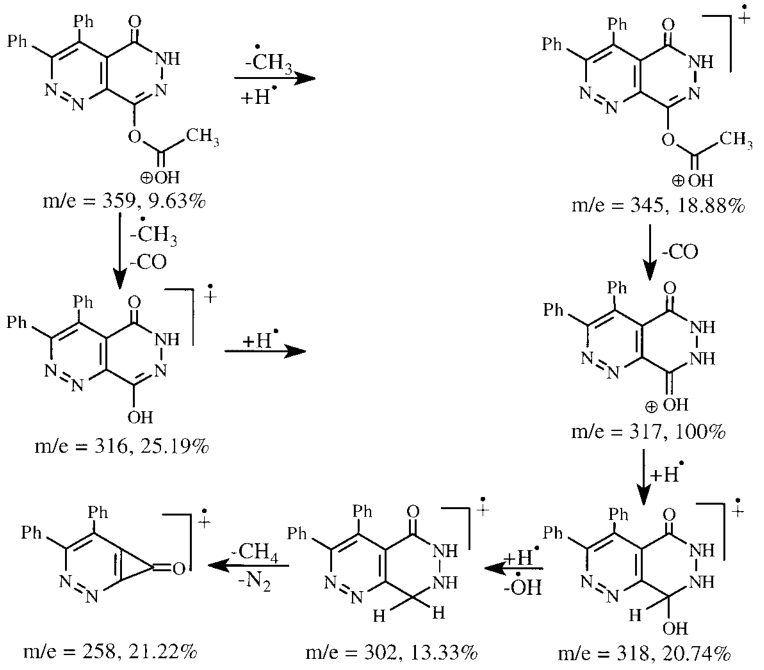
Scheme 1.



Scheme 2.

(A) **With one mol:** When the diester **1** was allowed to react with one mol of phenylmagnesium bromide, the reaction afforded the diketone **7**, whose structure was deduced from its analytical and spectral data. Its IR spectrum revealed a sharp band at 1688 cm^{-1} characteristic for the carbonyl stretching frequency of α,β-unsaturated ketone. Its mass spectrum showed the molecular ion $[M^{+\bullet} = 440, 0.02]$ and the base peak corresponding to the fragment dibenzoyl radical $[M^{+\bullet} = 105]$. The ^{1}H-NMR spectrum exhibited only a multiplet for 20 protons of the four phenyl groups.

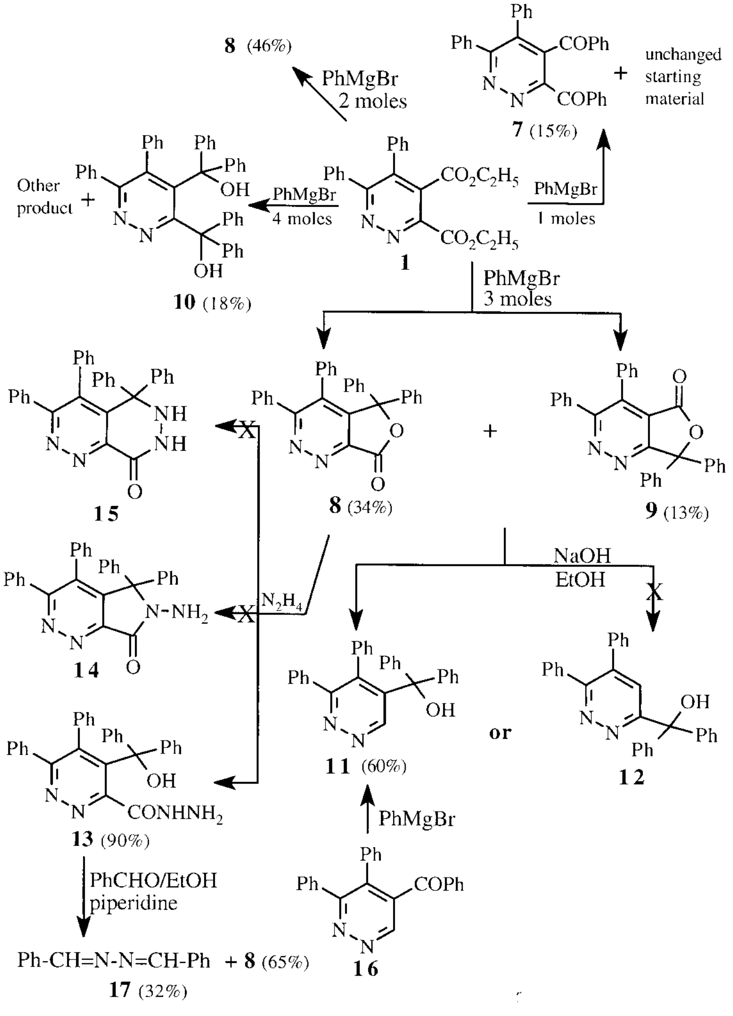
(B) **With two moles:** The diester reacted with two moles of phenylmagnesium bromide to give only one product, which from elemental analysis, IR and mass spectrum, the structure of the product might be the lactone structure **8** or **9**. Alkaline hydrolysis of the product with 5% ethanolic NaOH solution afforded a white crystalline product, and its IR spectrum exhibited the OH stretching frequency at 3416 cm^{-1}, but lacked any band for carbonyl group. This reaction might proceed via cleavage of the proposed lactone ring followed by decarboxylation. The differentiation between these two possible lactone structures **8** or **9** was only attained by comparison of the hydrolysed product **11** or **12** with an authentic sample



Scheme 3.

prepared by the action of phenylmagnesium bromide on 5-benzoyl-3,4-diphenylpyridazine **16** [2]. The product carbinol **11** was found to be identical (by m.p. and spectral data) with that obtained by the alkaline hydrolysis of the initially formed lactone. So, the resulting lactone must be 3,4,5,5-tetraphenyl-7- oxofuro[3,4-c]pyridazine **8** not **9**.

When the ethanolic solution of the lactone **8** was allowed to react with hydrazine hydrate on cold, one product could be isolated from the reaction



Scheme 4.

mixture, which might be either hydrazide **13** or pyridazine **14** or **15**. The structure of the product was verified by its IR spectrum and showed a sharp band at 1657 cm^{-1}, characteristic for the carbonyl stretching frequency of amide, and a broad band in the 3170–3506 cm^{-1} region due to NH and OH stretching frequencies. The presence of such absorption has been considered compelling evidence for structure **13** or **15** and eliminate *N*-aminopyrrolo structure **14**. The instability of the product was shown during crystallization, since it converted to the original lactone **8** by merely heating in polar solvent. This fact is compatible with structure **13**, i.e., open-chain structure. When compound **13** was allowed to react with ethanolic benzaldehyde solution in the presence of piperidine, the reaction gave two products. The first product was found to be identical with the original lactone **8**, while the second product **17** melted at 91–93°C, and its elemental analysis contained only C, H, and N. Its IR spectrum lacked any band characteristic for the NH group, but is retained C=N band at 1626 cm^{-1}. The mass spectrum of this product showed the peak of the molecular ion is that of the base peak $[\mathrm{M}^{\overset{\bullet}{+}} = 208]$. All these facts indicated that product **17** must be benzalazine (lit. m.p. 92–93°C); also no m.p. depression was observed when mixed with an authentic sample prepared by the addition of hydrazine hydrate to benzaldehyde on cold.

(C) **With three moles:** The reaction of the diester **1** with three moles of phenylmagnesium bromide afforded two products having exactly the same elemental analysis but different IR and mass spectral data. One of the two isolated products was found to be identical (m.m.p and IR) with compound **8**. The structure of the second product **9** was deduced from the following facts: its IR spectrum exhibited the absorption band for the carbonyl group of γ-lactone at 1788 cm^{-1}, i.e., at a slightly longer wavelength than the carbonyl group of the first product **8**. The mass spectrum of compound **8** showing the peak due to the molecular ion is that of the base peak $[\mathrm{M}^{\overset{\bullet}{+}} = 440, 100\%]$ and the main fragment is formed by the splitting of $\mathrm{CO_2}$ (Scheme 6). However, the mass spectrum of compound **9** showed the peak due to the molecular ion $[\mathrm{M}^{\overset{\bullet}{+}} = 440, < 1\%]$. The principal fragmentation route involved splitting the benzyne molecule $[\mathrm{M}^{\overset{\bullet}{+}} = 364, 100\%]$ which is responsible for the proposed structure.

(D) **With four moles:** The reaction of the diester **1** with phenylmagnesium bromide (four moles) gave two products. The structure of **10** was elucidated and established by its elemental analysis, its IR spectrum exhibited the stretching frequency of OH group at 3207 cm^{-1} and lack of any band characteristic for carbonyl group. The mass spectrum of compound **10** showed the molecular ion peak $[\mathrm{M}^{\overset{\bullet}{+}} = 596, 0.19\%]$. The principal fragmentation route involved splitting of phenyl radical and benzene molecule giving rise to the base peak $[\mathrm{M}^{\overset{\bullet}{+}} = 441, 100\%]$. All the aforementioned facts indicate that the product is 3,4-(diphenylhydroxy-methyl)-5,6-diphenylpyridazine **10**. The structure of the second product is still under investigation.

EXPERIMENTAL

All melting points taken on the Griffin and Georg melting point apparatus are uncorrected. IR absorption spectra were taken with a Moltson-1000 series FTIR spectrometer. ^{1}H-NMR spectra were determined on Brucker, DRX500, or Brucker, AC-200. The mass spectra were determined using a AMD 604 spectrophotometer, SHIMADZU single focusing mass spectrometer at a beam energy 70 ev, or Finnigan SSQ 7000. Elemental analyses were carried out at the Microanalytical unit, Faculty of Science, Ain Shams University by using the Perkin-Elmer 2400CHN Elemental Analyzer.

Synthesis of 3,4-Diphenyl-5,8-dioxo-5,6,7,8-tetrahydropyridazino-[4,5-c]pyridazine 2

Reaction of 3,4-diethoxycarbonyl-5,6-diphenylpyridazine 1 with hydrazine hydrate: A mixture of compound **1** (4 g) and excess hydrazine (~3 ml) was refluxed in *n*-butanol (20 ml) for 2 h. The reaction mixture was left to cool. The precipitate formed was separated by filtration and recrystallized from n-butanol to give red crystals of **2** (89% yield). Compound **2** had m.p. 315°C (*n*-butanol); IR: cm^{-1} 3354 (broad, OH), 3285 (broad, NH), 1689 (CO) and 1561 (C=N); exact mass measurement: Calcd for $C_{18}H_{12}N_4O_2$: 316.49. Found: 316 (100%).

Anal. calcd for $C_{18}H_{12}N_4O_2$; C, 68.36; H, 3.82; N, 17.7%. Found: C, 68.59; H, 4.04; N, 17.43.

Reaction of 3,4-Diphenyl-5,8-dioxo-5,6,7,8-tetrahydropyridazino-[4,5-c]pyridazine 2 with Ethyl Bromoacetate

Synthesis of 6,7-diethoxycarbonylmethyl-3,4-diphenyl-5,8-dioxo-5,6,7,-8-tetrahydropyridazino[4,5-c]pyridazine 3: A mixture of compound **2** (0.5 g, 0.0015 mol), ethyl bromoacetate (0.5 ml, 0.003 mol), anhydrous potassium carbonate (0.34 g) and dry acetone (50 ml) was refluxed for 27 h. The organic layer was separated and evaporated to give **3** as yellow crystals. Compound **3** had m.p. 125°C (petroleum–ether 80–100°C) (39% yield); IR: cm^{-1} 2991

(C-H aliphatic), 1727 (CO of ester) and 1684 (CO amide); exact mass measurement: Calcd for $C_{26}H_{24}N_4O_6$: 488.220. Found: 489 [M + 1] (100%).

Anal. calcd for $C_{26}H_{24}N_4O_6$: C, 63.94; H, 4.95; N, 11.47. Found: C, 64.24; H, 5.03; N, 11.39.

Reaction of 3,4-Diphenyl-5,8-dioxo-5,6,7,8-tetrahydropyridazino-[4,5-c]pyridazine 2 with Acetyl Chloride

Synthesis of 6,7-diphenyl-3-oxo(2H)pyridazino[4,5-c]pyridazinyl-8-acetate 4; 6,7-diphenyl-8-oxo(1H)pyridazino[4,5-c]pyridazinyl-3-acetate 5 and 1,2-diacetyle-6,7-diphenyl-3,8-dioxopyridazino[4,5-c]pyridazine 6: Compound **2** (1 g, 0.0032 mol) was refluxed with excess acetyl chloride (5 ml) for 3 h, pour into cold water and neutralized with sodium hydroxide solution (10%), and the resulting yellow solid was filtered off and washed with water. TLC for the crude product showed that there are four products. Fractional crystallization gave compound **4** m.p. 285°C (benzene) (9% yield), compound **5**, m.p. 308°C (methanol) (13% yield), and compound **6** m.p. 326°C (acetic acid) (23% yield). Compound **4**; IR: cm^{-1} 3500 (broad, OH), 3200 (broad, NH), 3061 (CH ar.), 2907 (CH aliphatic), 1777 (CO ester), 1672 (CO amide); exact mass measurement: Calcd for $C_{20}H_{14}N_4O_3$: 358.148. Found: 359 (2.97%) [M + 1]. Compound **5**; IR: cm^{-1} 3467 (broad, OH), 3173 (broad, NH), 3084 (CH ar.), 2895 (CH aliphatic), 1777 (CO ester), 1672 (CO amide); exact mass measurement: Calcd for $C_{20}H_{14}N_4O_3$: 358.148. Found: 359 (9.6%) [M + 1]. Compound **6**; IR: 3060 (CH ar.), 2960 (CH aliphatic), 1660 (CO amide).

Anal. calcd for compound **4**; $C_{20}H_{24}N_4O_6$: C, 67.02; H, 3.94; N, 15.64. Found: C, 66.98; H, 3.85; N, 15.56.

Anal. calcd for compound **5**; $C_{20}H_{24}N_4O_6$: C, 67.02; H, 3.94; N, 15.64. Found: C, 67.14; H, 3.81; N, 15.82.

Anal. calcd for compound **6**; $C_{22}H_{16}N_4O_4$: C, 65.98; H, 4.03; N, 14.00. Found: C, 65.75; H, 3.98; N, 13.95.

Action of Grignard Reagents on 3,4-Diethoxycarbonyl-5,6-diphenylpyridazine 1

A: One Mol of Phenylmagnesium Bromide

Synthesis of 3,4-dibenzoyl-5,6-diphenylpyridazine 7: A solution of phenylmagnesium bromide [prepared from 0.008 mol bromobenzene and magnesium (0.008 g-atom)] in dry ether (50 ml) was added to a solution of diester **1** (3 g; 0.008 mol) in dry benzene (50 ml). The mixture was refluxed for 5 h on water-bath, left overnight at room temperature, then decomposed with a saturated solution of ammonium chloride. The ethereal layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give compound **7**. Compound **7** was obtained as yellow crystals, had m.p. 196–197°C (pet. ether 80–100°C) (15% yield); IR: cm^{-1} 1688 (CO of α,β-unsaturated ketone); exact mass measurement: Calcd for $C_{30}H_{20}N_2O_2$: 440.496. Found: 440 (0.02%), 311 (4.37%), 230 (0.02%), 178 (2.00%), 105 (100%) and 77 (44.43%). ^1H-NMR ($CDCl_3$): 7.98–7.22 (m, 20H, $4 \times C_6H_5$).

Anal. calcd for $C_{30}H_{20}N_2O_2$: C, 81.79; H, 4.58; N, 6.37%. Found: C, 81.52; H, 4.54; N, 6.24.

B: Two Moles of Phenylmagnesium Bromide

Synthesis of 3,4,5,5-tetraphenyl-7-oxofuro[3,4-]pyridazine 8: A solution of the phenylmagnesium bromide [prepared from 0.016 mol bromobenzene and magnesium (0.016 g.-atom)] in dry ether (50 ml) was added to a solution of diester **1** (3 g, 0.008 mol) in dry benzene (50 ml). The mixture was refluxed for 5 h on a boiling water-bath, left overnight at room temperature, then decomposed with a saturated solution of ammonium chloride. The ethereal layer was separated, filtered, dried, and concentrated under reduced pressure to give furo[3,4-c] pyridazine **8**. Compound **8** was obtained as yellow crystals, had m.p. 190°C (ethanol) (46% yield); IR: cm^{-1} 1792 (CO of cyclic lactone); exact mass measurement: Calcd for $C_{30}H_{20}N_2O_2$: 440.496. Found: 440.

Anal. calcd for $C_{30}H_{20}N_2O_2$: C, 81.79; H, 4.58; N, 6.37%. Found: C, 81.64; H, 4.68; N, 6.08.

C: Three Moles of Phenylmagnesium Bromide

Synthesis of 3,4,5,5-tetraphenyl-7-oxofuro[3,4-c]pyridazine 8 and 3,4,7,7-tetraphenyl-5-oxofuro[3,4-c]pyridazine 9: A solution of phenylmagnesium bromide [0.024 mol of bromobenzene and magnesium (0.024 g-atom)] in dry ether (75 ml) was added to a solution of diester **1** (3 g, 0.008 mol) in dry benzene (50 ml). The reaction mixture was refluxed for 5 h on a boiling water bath, left overnight at room temperature, then decomposed with a saturated solution of ammonium chloride. The ethereal layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Fractional crystallization of the solid obtained from ethanol gave two products **8** and **9**. Compound **8** (34% yield) had the same m.p., elemental analysis and spectral data as the product already separated from two moles of Grignard regent with diester **1**. Compound **9** was obtained as yellow crystals, m.p. 230°C (ethanol) 13% yield); IR: cm^{-1} 1788 (CO for cylic lactone); ms: 440(< 1%).

Anal. calcd for $C_{30}H_{20}N_2O_2$: C, 81.79; H, 4.58; N, 6.37%. Found: C, 82.10; H, 4.74; N, 6.12.

D: Four Moles of Phenylmagnesium Bromide

Synthesis of 3,4-(diphenylhydroxymethyl)-5,6-diphenylpyridazine 10: A solution of phenylmagnesium bromide [0.032 mol of bromobenzene and magnesium (0.032 g-atom)] in dry ether (75 ml) was added to a solution of diester **1** (3 g, 0.008 mol) in dry benzene (50 ml). The reaction mixture was refluxed for 5 h on a boiling water-bath, left overnight at room temperature, then decomposed with a saturated solution of ammonium chloride. The ethereal layer was separated, dried, and evaporated under reduced pressure. Fractional crystallization **10** was obtained as white crystals, had m.p. 136–138°C (methanol) (18% yield); IR: cm^{-1} 3204 (broad, OH), 3061 (–CH ar.); exact mass measurement: Calcd for $C_{42}H_{22}N_2O_2$: 596.7. Found 596 (0.19%), 519 (24.47%), 518 (67.68%), 517 (29.29%), 442 (6.85%), 441 (100%).

Anal. calcd for $C_{42}H_{22}N_2O_2$: C, 84.53; H, 5.41; N, 4.70. Found: C, 84.32; H, 5.48; N, 4.93.

Alkaline Hydrolysis of 3,4,5,5-Tetraphenyl-7-oxofuro-[3,4-c]pyridazine 8

Synthesis of 5(3,4-diphenylpyridazinyl)diphenylcarbinol 11: Compound **8** (0.5 g) was refluxed for 2 h with 10 ml. (5%) alcoholic sodium hydroxide solution. On cooling, colourless crystals of **11** were formed (60% yield). Compound **11** had m.p. 230°C; IR: cm^{-1} 3416 (OH), 3060 (CH ar.).

Anal. Calcd for $C_{29}H_{22}N_2O$: C, 84.02; H, 5.31; N, 6,76. Found: C, 84.30; H, 5.22; N, 6.95.

The Action of Phenylmagnesium Bromide on 5-Benzoyl-3,4-diphenylpyridazine 16

Synthesis of 5(3,4-diphenylpyridazinyl)diphenycarbinol 11: A solution of phenylmagnesium bromide (0.012 mol bromobenzene and magnesium

(0.012 g,-atom)) in dry ether (50 ml) was added to a solution of compound **16** (2 g, 0.006 mol) in dry benzene (50 ml). The mixture was heated under reflux for 5 h, left overnight at room temperature, then decomposed with a saturated solution of ammonium chloride. The ethereal layer was separated, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The resulting solid product was collected by filtration and the recrystallized from ethanol. The product obtained was found to be identical with compound **11** which was obtained from alkaline hydrolysis of compound **8** (m.m.p. and spectral data).

Hydrazinolysis of 3,4,5,5-Tetraphenyl-7-oxofuro[3,4-c]pyridazine 8

Synthesis of 3,4-diphenyl-5-(diphenylhydroxymethyl)pyridazine-6-acid hydrazide 13: Compound **8** (0.2 g) was allowed to react with excess hydrazine hydrate in ethanol (15 ml) at room temperature for 2 h. A white product **13** was precipitated and separated by filtration and dried under vacuum; IR: cm^{-1} 1675 (CO amide).

Reaction of 3,4-diphenyl-5-(diphenylhydroxymethyl)pyridazine-6-acid hydrazide 13 with benzaldehyde: Compound **13** (0.16 g) in 15 ml ethanol was allowed to react with benzaldehyde (0.5 ml) in the presence of piperidine, for 24 h on cold. The yellow precipitate was collected by filtration and recrystallized from ethanol to give the original lactone **8** (m.mp. and superimpossable of spectral data). The slow evaporation of the filtrate gave yellow crystals, which upon crystallization from petroleum–ether 60/80°C, yields benzalazine **17**, m.p. 90–91°C; IR: cm^{-1} 1626 (C=N); exact mass measurement: Calcd for $C_{14}H_{12}N_2$: 208.24. Found: 208.

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