

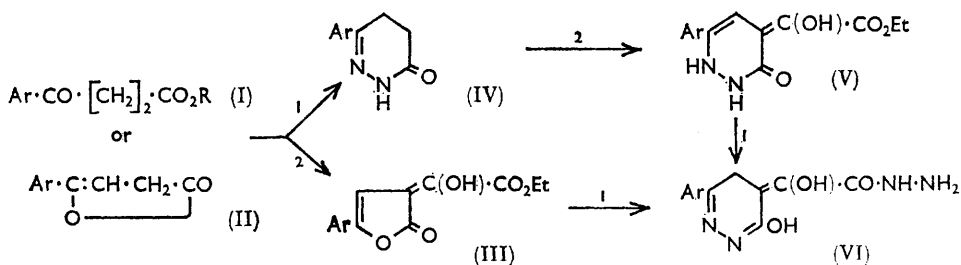
**1015. Pyridazines. Part I. The Synthesis of 6-Aryl-4,5-dihydro-3-hydroxy-4-pyridazinylidenglycolohydrazides.**

By T. ABDEL NOUR, F. G. BADDAR, and A. FATEEN.

The title compounds are prepared by warming ethyl 5-aryl-2,3-dihydro-2-oxo-3-furylidene-glycollates with hydrazine hydrate. Their structure is established by a study of their ultraviolet, infrared, and nuclear magnetic resonance spectra, and by comparison with authentic specimens prepared by treating the corresponding 4-ethoxalyipyridazines with hydrazine hydrate.

ETHYL 5-ARYL-2,3-DIHYDRO-2-OXO-3-FURYLIDENEGLYCOLLATES (III), prepared by condensation of  $\beta$ -aroylpropionic esters (I; R = Me or Et) or 4-aryl-4-hydroxybut-3-enoic acid lactones (II) with ethyl oxalate,<sup>1</sup> react quantitatively with hydrazine hydrate to give 6-aryl-4,5-dihydro-3-hydroxy-4-pyridazinylidenglycolohydrazides (VI).

The structure of the 6-*p*-tolyl- (VIb) and the 6-*p*-methoxyphenyl derivatives (VIc) were established by their identity with authentic specimens prepared according to the following scheme.



Reagents: 1,  $\text{NH}_2\cdot\text{NH}_2$ ; 2,  $(\text{CO}_2\text{Et})_2$ .  
 a: Ar = Ph; b: Ar = *p*- $\text{C}_6\text{H}_4\cdot\text{Me}$ ; c: Ar = *p*- $\text{C}_6\text{H}_4\cdot\text{OMe}$ ; d: Ar = *p*- $\text{C}_6\text{H}_4\cdot\text{Cl}$ .

2,3,4,5-Tetrahydro-3-oxo-6-*p*-tolyl- (IVb) and -6-*p*-methoxyphenyl-pyridazine (IVc), prepared by heating the corresponding esters (Ib and c) or lactones (IIb and c) with hydrazine hydrate in *n*-butanol, were condensed with ethyl oxalate in the presence of potassium ethoxide to give the esters (Vb and c). These were converted into the glycolohydrazides (VIb and c) by heating with hydrazine hydrate in *n*-butanol. However, when the esters (Va and d) were similarly treated, they were cleaved to a mixture of the dihydrazide of oxalic acid and the pyridazines (IVa and d). The higher stability of compounds (Vb and c) towards hydrazine hydrate may be due to the presence of an electron-releasing substituent in the aryl group, which increases the electron density on the  $\alpha$ -carbon atom, and thus decreases its susceptibility to attack by nucleophilic reagents.

The infrared spectra of the lactones (III) show the characteristic bands reported in

<sup>1</sup> Baddar and Sherif, *J.*, 1961, 707.

TABLE 1.  
Infrared absorptions (cm.<sup>-1</sup>) of the lactones (III).

Compound	Carbonyl bands			Enolic OH	
	Enolic <sup>2a</sup>	Unsaturated $\alpha$ -keto-ester <sup>2b</sup>	Unsaturated $\gamma$ -lactone <sup>2b</sup>	KBr disc	Soln.
(IIIa)	1640	1670	1740	3080—2940w, br	
(IIIb)	1630	1667	1735	3200—2950w, br	3480w (CCl <sub>4</sub> )
(IIIc)	1640	1680	1740	3125—2940w, br	
(IIId)	1630	1670	1735	3175—3070w, br	No change (CHCl <sub>3</sub> )

Table 1. The reduction in frequencies, as compared to those reported <sup>2c</sup> for similar groups, may be attributed to conjugation. The existence of these compounds in the enol form is inferred from the weak broad bands at 3200—2940 cm.<sup>-1</sup>. This chelated enol form is also supported by the nuclear magnetic resonance (n.m.r.) spectrum of compound (IIIc), which shows a signal at 10.94  $\tau$  (627 c./sec. on the 1000 c./sec. scale), characteristic of an enolic proton as a hydrogen bridge. This is also confirmed by a sharp signal at 6.72  $\tau$  (404 c./sec. on the 500 c./sec. scale), which can only be due to an olefinic proton in conjugation with another double bond.

The ultraviolet spectra (in ethanol) of the 6-aryl-2,3,4,5-tetrahydro-3-oxypyridazines (IVa, b, and c) (Table 2) show that these compounds absorb at a longer wavelength than the methyl analogue (IV; Me for Ar). This indicates the presence of a conjugated system, and could be taken as evidence for the partial existence of these compounds in solution in the lactim form.<sup>3</sup> This has been supported by their infrared spectra (Table 2), which

TABLE 2.  
Infrared (cm.<sup>-1</sup>) and ultraviolet spectra (m $\mu$ ) of the pyridazines (IV).

Compound	Secondary NH *	NH and OH †	Cyclic amide C:O *	$\lambda_{\max}$ .	$\epsilon$	$\lambda_{\min}$ .	$\epsilon$
(IVa)	3260, 3125	—	1660	286	15,870	235	3360
(IVb)	3260, 3125	3510, 3333	1660	288	18,310	236	1790
(IVc)	3280, 3125	—	1666	294	19,460	240	1845
(IVd)	3250, 3125	3550, 3333	1670	—	—	—	—
2,3,4,5-Tetrahydro-3-oxo-5,6-diphenylpyridazine				288	15,940	240	4060

\* KBr disc. † CHCl<sub>3</sub> solution.

show, in the case of compounds (IVb and d), strong sharp bands at 3510 and 3550 cm.<sup>-1</sup> (in CHCl<sub>3</sub>), respectively, characteristic of an intermolecularly bonded OH.<sup>2d</sup> The bands at 1660—1670 cm.<sup>-1</sup> are characteristic of the stretching frequency of the carbonyl group of cyclic amides.<sup>2e</sup>

The ultraviolet spectrum of the 5,6-diphenyl derivative (Table 2) is very similar to that of compound (IVa), which indicates that the phenyl group in position 5 does not exert any steric influence on the conjugation of the 6-phenyl group with the pyridazinone nucleus.

The infrared spectra of the ethyl 6-aryl-1,2,3,4-tetrahydro-3-oxo-4-pyridazinylidene-glycollates (V) (Table 3) showed broad bands in the region 3225—2980 cm.<sup>-1</sup>, which persisted even when the spectra were run in chloroform, and which indicate that these compounds exist in the chelated enol form. The n.m.r. spectra of the 6-phenyl, 6-*p*-methoxyphenyl, and 6-*p*-chlorophenyl derivatives (Va, c, and d) gave the expected signal for the aromatic region and the O—CH<sub>2</sub>—CH<sub>3</sub> group. No signals, however, were observed for the —CH<sub>2</sub>—CH< group; instead a very sharp signal (503—508 c./sec.) due to one single proton (H-5) was detected. Both the 6-*p*-methoxyphenyl (Vc) and the 6-*p*-chlorophenyl derivative (Vd) showed a very broad signal (350 c./sec.), arising from one NH proton (H-2) and the same, but much sharper, signal was found in the 6-phenyl derivative (Va). These observations indicate that the compounds probably exist in the keto-form (V).

<sup>2</sup> Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1961, (a) p. 132; (b) p. 179; (c) p. 181; (d) p. 96; (e) p. 205.

<sup>3</sup> Cf. Overend, Turton, and Wiggins, *J.*, 1950, 3505.

TABLE 3.  
Infrared absorptions (cm.<sup>-1</sup>) of the esters (V).

Compound	NH <sup>2e</sup> and OH <sup>2d</sup>	Carbonyl bands			Medium
		$\alpha$ -Keto-ester <sup>2b</sup>	Cyclic amide <sup>2e</sup>	Enolic <sup>2a</sup>	
Va)	{ 3510—3480 3030—2980	1750s	1667s	1613s	KBr
	{ 3570m, 3450m 3225—3125				
(Vb)	{ 3570m 3125—2985	1754	1666	1613	KBr
(Vc)	{ 3570w, 3470m 3280—3125	1754	1670	1615	CHCl <sub>3</sub>
(Vd)	{ 3333—3125	1735	1650	1600	KBr
	{ 3570w, 3450m 3225—3030				

The structure assigned to the hydrazides (VI) by comparison with authentic specimens was further supported by a study of the n.m.r. spectrum of compound (VIc), which shows a sharp signal at 4.37  $\tau$  due to the two identical protons of the CH<sub>2</sub> group. The existence of this compound in the completely enolised form is inferred from the lack of splitting and absence of signal for the proton  $\alpha$  to the two carbonyl groups. The infrared spectrum (KBr) of compound (VIb) shows three main bands, 1725, 1666, and 1620 cm.<sup>-1</sup>, characteristic of the carbonyl stretching frequency of acid hydrazides, cyclic amides,<sup>2e</sup> and enolic carbonyl groups,<sup>2a</sup> respectively. The broad band at 3200—2980 cm.<sup>-1</sup> is indicative of a strongly chelated OH group.

The ultraviolet spectra (in n-butanol) of hydrazides (VIb and c) are very similar;  $\lambda_{\max}$  283 and 353 m $\mu$  ( $\epsilon$  11,370 and 5690),  $\lambda_{\min}$  330 m $\mu$  ( $\epsilon$  5170) for compound (VIb), and  $\lambda_{\max}$  263 and 356.5 m $\mu$  ( $\epsilon$  14,030 and 9410),  $\lambda_{\min}$  286 m $\mu$  ( $\epsilon$  6120) for compound (VIc). The absorption of these compounds at a long wavelength is indicative of the presence of a highly conjugated system. This may be taken as evidence that they exist in the dienol form (VI), which is stabilised by chelation.

#### EXPERIMENTAL

The ultraviolet and infrared spectra were run on Spectracord model 4000A and Infracord model 137 Spectrophotometers, respectively.

*Ethyl 5-Aryl-2,3-dihydro-2-oxo-3-furylidene-glycollates* (III).—A stirred suspension of potassium ethoxide [from powdered potassium (1.89 g.) and ethanol (4.5 ml.)] in dry ether, was treated with dry ethyl oxalate (10.5 g., 1.5 mol.), and left for 1 hr. The ethyl  $\beta$ -aroylpropionate (1 mol.) was added, the mixture left overnight, refluxed for 7 hr., and worked up as usual.<sup>1</sup> The semi-solid product was triturated with light petroleum (b. p. 40—60°) and crystallised from benzene to give the *ester* (Table 4).

TABLE 4.  
Ethyl 5-aryl-2,3-dihydro-2-oxo-3-furylidene-glycollates (III).

Reactant	Product	Yield (%)	M. p.	Found (%)			Formula	Required (%)		
				C	H	Cl		C	H	Cl
(Ia; R = Et)	(IIIa)	80	132°	64.4	4.7	—	C <sub>14</sub> H <sub>12</sub> O <sub>5</sub>	64.6	4.6	—
(Ia; R = Me)	(IIIa)	66		64.65	4.8	—	"	"	"	—
(Ib; R = Et)	(IIIb)	80	140—142	65.8	5.2	—	C <sub>15</sub> H <sub>14</sub> O <sub>5</sub>	65.7	5.1	—
(Ib)	(IIIb)	63		(OEt, 16.3)				(OEt, 16.4)		
(Ic; R = Et)	(IIIc)	81	150—152	62.6	4.85	—	C <sub>15</sub> H <sub>14</sub> O <sub>5</sub>	62.1	4.9	—
(Ic)	(IIIc)	65								
(Id; R = Et)	(IIId)	66	154—155	57.3	3.85	11.7	C <sub>14</sub> H <sub>11</sub> ClO <sub>5</sub>	57.0	3.7	12.05
(Id; R = Me)	(IIId)	61								

The same products were obtained from methyl  $\beta$ -aroylpropionates and from 4-aryl-4-hydroxybut-3-enoic acid lactones.

6-Aryl-2,3,4,5-tetrahydro-3-oxopyridazines (IV).—The solution of the acid (I) or the lactone (II) (2 g.) in n-butanol (10 ml.) was refluxed with hydrazine hydrate (2 ml.; 95–100%) for

TABLE 5.

6-Aryl-2,3,4,5-tetrahydro-3-oxopyridazines (IV).

Reactant	Product	Yield (%)	M. p.	Found (%)				Formula	Required (%)			
				C	H	Cl	N		C	H	Cl	N
(Ia; R = H)	(IVa)	79	150°*	68.9	5.9	—	16.2	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O	68.95	5.8	—	16.1†
(Ib; R = H)	(IVb)	95	157–158	70.3	6.3	—	15.0	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O	70.2	6.4	—	14.9
(IIb)	(IVb)	84		70.3	6.25	—	14.8					
(Ic; R = H)	(IVc)	81	150–151	64.4	5.8	—	15.1	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	64.7	5.9	—	13.7
(IIc)	(IVc)	86		64.7	5.8	—	13.9					
(Id; R = H)	(IVd)	78	178‡	57.8	4.5	16.95	15.75	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O	57.55	4.3	17.0	13.4†

\* Skraup and Schwamberger (*Annalen*, 1928, **462**, 147) give m. p. 153°. † Calc. ‡ Steck, Brundage, and Fletcher (*J. Amer. Chem. Soc.*, 1953, **75**, 1117) give m. p. 179–179.5°.

3 hr. The product precipitated on cooling was crystallised from benzene to give the *pyridazine* (Table 5). In certain cases a small amount of a high-melting by-product was obtained, but its structure was not established.

2,3,4,5-Tetrahydro-3-oxo-5,6-diphenylpyridazine was similarly prepared from  $\beta$ -benzoyl- $\beta$ -phenylpropionic acid or 3,4-diphenyl-4-hydroxybut-3-enoic acid lactone in 88 and 66% yield, respectively, and had m. p. 222–223° (from benzene) (lit.,<sup>4</sup> 217–218°) (Found: C, 76.2; H, 5.7; N, 11.3. Calc. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O: C, 76.8; H, 5.6; N, 11.2%).

Ethyl 6-Aryl-1,2,3,4-tetrahydro-3-oxo-4-pyridazinylideneglycollates (V).—A mechanically stirred suspension of potassium ethoxide [from powdered potassium (2.75 g.) and absolute ethanol (6.5 ml.)] in dry ether (100 ml.) was treated with freshly distilled ethyl oxalate (15.75 g., 1.5 mol.) and left for 1 hr. Powdered 6-aryl-2,3,4,5-tetrahydro-3-oxopyridazine (IV) (1 mol.) was added and the mixture was kept overnight, gently refluxed for 7 hr., and worked up as usual. The product was extracted with ether and the soluble fraction was triturated with light petroleum (b. p. 40–60°), then crystallised from a suitable solvent to give the *glycollate* (Table 6). The fraction insoluble in ether was crystallised from toluene, but its structure is not yet established.

TABLE 6.

Ethyl 6-aryl-1,2,3,4-tetrahydro-3-oxo-4-pyridazinylideneglycollates (V).

Product	Yield (%)	M. p.	Found (%)				Formula	Required (%)			
			C	H	Cl	N		C	H	Cl	N
(Va)	63	175°*	61.6	5.2	—	10.1	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	61.3	5.15	—	10.2
(Vb)	33	187–188*	62.1	5.6	—	9.75	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	62.5	5.6	—	9.7
(Vc)	74	179–180*	60.2	5.4	—	9.1	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>5</sub>	59.2	5.3	—	9.2
(Vd)	70	183†	54.5	4.45	11.7	19.5	C <sub>14</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>4</sub>	54.5	4.2	11.5	9.1

\* From benzene. † From ethyl acetate–light petroleum (b. p. 40–60°).

6-Aryl-4,5-dihydro-3-hydroxy-4-pyridazinylideneglycolohydrazides (VI).—(a) A solution of the pyridazine (V) (2 g.) in n-butanol (10 ml.) was treated portionwise with hydrazine hydrate (2 ml.). The mixture was refluxed for a few minutes and the precipitated *product* (Table 7) crystallised from a suitable solvent. In the case of compounds (Va and d), the precipitated products proved to be oxalic acid dihydrazide, whereas the residues left after evaporation of the mother-liquors under reduced pressure were compounds (IVa and d), respectively.

(b) The reaction was carried out as in (a), using the lactones (III) instead of the pyridazines (V). The identity of the products obtained by the two methods was established by m. p.s, mixed m. p.s, and infrared spectra.

Conversion of Ethyl  $\beta$ -Benzoyl- $\beta$ -phenylpropionate into 4-Hydroxy-3,4-diphenylbut-3-enoic Acid Lactone.—A stirred suspension of potassium ethoxide [from potassium (0.23 g.)] in dry ether

<sup>4</sup> Almstrom, *Annalen*, 1913, **400**, 137.

TABLE 7.

Reactant (Va)	Product (CONH·NH <sub>2</sub> ) <sub>2</sub> + (IVa)	Yield (%)	M. p.	Found (%)				Formula	Required (%)			
				C	H	Cl	N		C	H	Cl	N
(IIIa)	(VIa)	100	310° *	55.4	4.65	—	21.5	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub>	55.4	4.6	—	21.0
(Vb)	(VIb)	94	305 †	56.4	5.2	—	18.0	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>	56.9	5.15	—	20.0
(IIIb)	(VIb)	85										
(Vc)	(VIc)	94	300 †	53.9	4.55	—	17.1	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub>	53.9	4.9	—	19.3
(IIIc)	(VIc)	88										
(Vd)	(CONH·NH <sub>2</sub> ) <sub>2</sub> + (IVd)	100	313 †	49.0	3.8	11.8	19.0	C <sub>12</sub> H <sub>11</sub> ClN <sub>4</sub> O <sub>3</sub>	48.9	3.7	12.05	19.0

\* From n-butanol. † From acetic acid.

was treated with ethyl  $\beta$ -benzoyl- $\beta$ -phenylpropionate (1.7 g.), kept overnight, and worked up as usual.<sup>1</sup> The product was triturated with light petroleum (b. p. 40–60°) and crystallised from ethanol to give the lactone (60%), m. p. and mixed<sup>5</sup> m. p. 157°.

The authors thank Dr. Attelio Malera of Varian Co., Zurich, for the n.m.r. spectra and for their interpretation.

FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY,  
ABBASSIA, CAIRO, U.A.R.

[Received, January 21st, 1964.]

<sup>5</sup> Baddar and Sherif, *l.*, 1960, 2309.