

1293. *Pyridazines. Part III.*¹ *Synthesis of 6-Aryl-2,3,4,5-tetrahydro- and -2,3-dihydro-pyridazin-3-ones and 3,6-Diarylpyridazines*

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6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones have been prepared by the action of hydrazine hydrate on γ -substituted γ -oxobutyric acids. They react with arylmagnesium halides to give the corresponding 3,6-diarylpyridazines. Dehydrogenation of the 2,3,4,5-tetrahydropyridazin-3-ones (IIa—c) by bromine in acetic acid affords the corresponding 2,3-dihydropyridazin-3-ones. The structures assigned to the products are supported by infrared and ultraviolet spectra.

γ -ARYL- γ -OXOBUTYRIC acids react with hydrazine hydrate in boiling n-butanol to give the 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (II). Thus, from γ -3,4-dimethylphenyl- (Ia), γ -2,4-dimethylphenyl- (Ib), γ -2,5-dimethylphenyl- (Ic), γ -2-xanthenyl- (Ig), and γ -2-fluorenyl- γ -oxobutyric (Ih) acids, the pyridazin-3-ones (IIa—c, g, h) were obtained in good yield.

The ultraviolet spectra of (IIa—c) (Table 1) are very similar to those of the analogous pyridazin-3-ones described in a previous Paper.² The hypsochromic shift in the absorption of (IIb) and (IIc) compared with that of (IIa) is attributed to the inhibition of resonance of the phenyl group with the C=N by the bulky *o*-methyl group. The spectra of (IIg) and (IIh) show the characteristic bands of xanthen and fluorene, respectively.

The infrared spectra of (IIa—c) (Table 2) show two sharp bands in the $3\ \mu$ region and a strong band in the $6\ \mu$ region characteristic of the stretching frequencies of the NH and CO groups, respectively, of cyclic amides.¹⁻³

Dehydrogenation of (IIa—c) by bromine in acetic acid afforded the corresponding 6-aryl-2,3-dihydropyridazin-3-ones (Va—c). Their infrared spectra (Table 2) show a broad band in the $3\ \mu$ region.¹ The carbonyl doublet at $6\ \mu$ and the band at $855\text{--}860\ \text{cm.}^{-1}$ are characteristic of cyclic $\alpha\beta$ -unsaturated ketones having an α -H atom. The doublet

¹ Part II, F. G. Baddar, A. El-Habashi, and A. K. Fateen, *J.*, 1965, 3342.

² T. Abdel-Nour, F. G. Baddar, and A. K. Fateen, *J.*, 1964, 5302.

³ J. L. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1961, p. 205.

TABLE 1

Ultraviolet spectra of 2,3,4,5-tetrahydro- and 2,3-dihydro-pyridazin-3-ones *

Compound	$\lambda_{\max.}$ (m μ)	ϵ	$\lambda_{\min.}$ (m μ)	ϵ
(IIa)	287	18,340	238—239	2410
(IIb)	270	14,470	234	5190
(IIc)	266	12,740	234—236	6420
(IIg)	298	22,030	245	5650
(IIh)	320.5	36,250	241—242	10,020
(Va)	258	27,820	226	7980
(Vb)	254	21,670	224	10,030
(Vc)	248	18,830	226	10,100

* S. Dixon, H. Gregory, and L. F. Wiggins, *J.*, 1949, 2139, give, for 2,3,4,5-tetrahydro-6-phenylpyridazin-3-one and 2,3-dihydro-6-phenylpyridazin-3-one, $\lambda_{\max.}$ 284 m μ (ϵ 9500) and 251.5 m μ (ϵ 10,000), respectively.

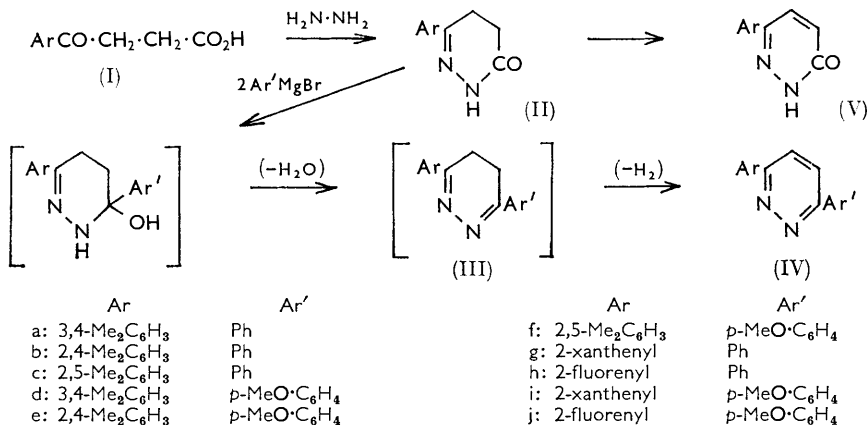


TABLE 2

Infrared spectra of 2,3,4,5-tetrahydro- and 2,3-dihydropyridazin-3-ones

Compound	NH bands (cm. ⁻¹)		CO band of cyclic amides
	Solid (KBr)	Solution (CHCl ₃)	
(IIa)	3205, 3086sh	3425, 3247sh	1680
(IIb)	3300, 3145	3448, 3226	1680
(IIc)	3289, 3145	3448, 3226	1690
(IIg)	3205	3497, 3333	1695
(IIh)	3226, 3096	3425	1680
(Va) *	2941—2857br	3390	1670, 1690
(Vb) *	3030—2857br	—	1665, 1685
(Vc) *	3030—2857br	—	1670, 1690

* The spectra of these compounds show a band at 855—860 cm.⁻¹.

arises from the coupling of the C=O vibration with the overtone of the α -H bending vibration, whereas the band at 860 cm.⁻¹ stands for the bending frequency of the α -C-H bond in $\alpha\beta$ -unsaturated carbonyl compounds.⁴ Their ultraviolet spectra [cf. (Va—c) in Table 1] reveal that they absorb at a shorter wavelength than the corresponding pyridazin-3-ones.

Attempts to prepare the 2,3-dihydro-compounds (Va—c) by condensing the corresponding β -aroylacrylic acids with hydrazine hydrate in boiling n-butanol were not successful. The acrylic acids required were readily prepared by condensing the appropriate hydrocarbon with maleic anhydride in presence of aluminium chloride. In the case of *o*- and *p*-xylene, when these were used as solvents in the Friedel-Craft's reaction, the corresponding β -aroyl- α -arypropionic acids were obtained. This is apparently due to the addition of the hydrocarbon to the initially formed acrylic acid. The structure of these two acids was based

⁴ P. Yates and L. L. Williams, *J. Amer. Chem. Soc.*, 1958, **80**, 5896.

on analogy,⁵ and was supported by the formation of a red precipitate of the pyrylium salt when dry hydrogen chloride was passed into their alcoholic solutions with salicylaldehyde. This reaction is characteristic of β -aroyl- α -arylpropionic acids.^{6,7}

Condensation of xanthen with maleic anhydride in presence of aluminium chloride in acetylene tetrachloride gave rise to a mixture of *cis*- and *trans*- β -2-xanthenoylacrylic acid. After successive crystallisations, a yellow acid, which is probably the *trans*-acid,⁸ was obtained pure. It gave, on reduction, γ -oxo- γ -2-xanthenylbutyric acid,⁹ and, on oxidation with alkaline potassium permanganate, xanthone-2-carboxylic acid.⁹ The colourless *cis*-acid, which could not be obtained free from the *trans*-isomer, gave, on oxidation with potassium permanganate, xanthone-2-carboxylic acid.

Action of Grignard Reagents on 6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones.—Phenyl- and *p*-anisyl-magnesium bromide reacted with 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (II) to give the corresponding 3,6-diarylpyridazines (IV). It is believed that the reaction takes place through the intermediate formation of 3,6-diaryl-4,5-dihydropyridazines (III), which are spontaneously dehydrogenated to 3,6-diarylpyridazines (IV).¹

The ease of dehydrogenation of the 3,6-diaryl-4,5-dihydropyridazines to the corresponding 3,6-diarylpyridazines has also been reported by Campbell and Khanna.¹⁰

The structures of the 3,6-diarylpyridazines obtained were supported, besides analytical data, by their absorption spectra. Thus, their infrared spectra do not show the characteristic OH, NH, or CO stretching bands. The ultraviolet spectra of (IVa—f) (Table 3) are very close to those of the analogous 3,6-diarylpyridazines previously reported.¹

EXPERIMENTAL

Ultraviolet (in ethanol) and infrared (KBr disc) spectra were measured on Perkin-Elmer Spectracord 4000A and Infracord 137 spectrophotometers, respectively.

TABLE 3
Ultraviolet spectral data

Compound	$\lambda_{\max.}$ (m μ)	ϵ	$\lambda_{\min.}$ (m μ)	ϵ
(IVa)	285	29,510	237—238	6780
(IVb)	270	26,310	232	9810
(IVc)	264.5	23,800	228	10,000
(IVd)	301	37,030	245	6940
(IVe)	289	26,420	241	4180
(IVf)	289	26,150	242	5700
(IVg)	308—309	27,970	245.5	12,010
(IVh)	316—319	43,250	248—252	9930
(IVi)	313	45,280	250—252	8530
(IVj)	323	49,670	255	5260

Preparation of 6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (II).—To a solution of the γ -substituted- γ -oxobutyric acid (0.10 mole) in *n*-butanol (10 ml.), hydrazine hydrate (98—100%) (2 ml.) was added, and the mixture was refluxed for 3 hr., then left to cool. The product, which crystallised out, was filtered off, washed with ether, and recrystallised from a suitable solvent, to give the 6-aryl-2,3,4,5-tetrahydropyridazin-3-one (Table 4).

Preparation of 6-Aryl-2,3-dihydropyridazin-3-ones (Va—c).—To a stirred solution of the 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (IIa—c) (0.01 mole), in glacial acetic acid (10 ml.), bromine (0.015 mole) was added slowly, and the mixture heated at 65—70° for 2 hr. The product was precipitated by the addition of water, filtered off, and washed with cold ethyl acetate. It was then triturated with ammonia solution, filtered off, and washed with cold water. On recrystallisation from a suitable solvent, 6-aryl-2,3-dihydropyridazin-3-ones (Va—c) were obtained (Table 5).

⁵ Adams, *Org. Reactions*, 1949, **5**, 251.

⁶ M. C. Mitter and L. K. De, *J. Indian Chem. Soc.*, 1939, **16**, 199; R. D. Desai and M. A. Wali, *Proc. Indian Acad. Sci.*, 1937, **6A**, 135.

⁷ F. G. Baddar, H. A. Fahim, and A. M. Fleifel, *J.*, 1955, 2199.

⁸ Cf. A. E. Kretov and V. V. Litvinov, *Zhur. obshchei Khim.*, 1961, **31**, 2880.

⁹ F. G. Baddar, A. M. El Abbady, and S. Ayoub, *J.*, 1960, 2556.

¹⁰ N. Campbell and N. M. Khanna, *J.*, 1949, S33.

TABLE 4
 6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (II)

Cmpd.	M. p.	Yield (%)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(IIa)	152—154° (EtOH)	89	71.0	6.6	14.3	C ₁₂ H ₁₄ N ₂ O	71.3	7.0	13.85
(IIb)	118—119 (EtOH)	59	71.65	6.6	13.7	C ₁₂ H ₁₄ N ₂ O	71.3	7.0	13.85
(IIc)	104—106 (C ₆ H ₁₂)	49	71.4	7.0	14.05	C ₁₂ H ₁₄ N ₂ O	71.3	7.0	13.85
(IIf)	206—207 (Me ₂ CO)	95	73.7	5.3	10.0	C ₁₇ H ₁₄ N ₂ O ₂	73.4	5.1	10.1
(IIh)	244 (Me ₂ CO)	95	77.8	5.4	10.7	C ₁₇ H ₁₄ N ₂ O	77.8	5.4	10.6

 TABLE 5
 6-Aryl-2,3-dihydropyridazin-3-ones (V)

Cmpd.	M. p.	Yield (%)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(Va)	251—252° (EtOH)	90	71.8	6.0	14.0	C ₁₂ H ₁₂ N ₂ O	72.0	6.0	14.0
(Vb)	137—138 (C ₆ H ₆)	90	72.0	5.9	13.85	C ₁₂ H ₁₂ N ₂ O	72.0	6.0	14.0
(Vc)	176—178 (Me ₂ CO)	80	72.3	5.9	13.7	C ₁₂ H ₁₂ N ₂ O	72.0	6.0	14.0

cis- and trans-β-2-Xanthenoylacrylic Acid.—Aluminium chloride (2.66 g.) (2 mol.) was added slowly to a stirred mixture of xanthene (1.8 g., 1 mol.) and maleic anhydride (1 g., 1 mol.) in *s*-tetrachloroethane (20 ml.), and stirring was continued for 6 hr. The reaction mixture was left overnight, then worked up as usual. The product was crystallised from ethyl acetate–benzene, to give the colourless *cis*-acid contaminated with the yellow *trans*-isomer, m. p. 204° with previous darkening. Concentration of the mother-liquor gave a yellow crystalline product, which was recrystallised from the same solvent, to give *trans-β-xanthenoylacrylic acid* as yellow crystals, m. p. 204° (Found: C, 73.9; H, 4.7. C₁₇H₁₂O₄ requires C, 72.85; H, 4.3%).

Preparation of β-Aroyl-α-arylpropionic Acids.—(a) Powdered aluminium chloride (4 g.) was added slowly to a stirred mixture of β-3,4-dimethylbenzoyl- or β-2,5-dimethylbenzoylacrylic acid (2 g.) in *o*- or *p*-xylene (*ca.* 40 ml.), respectively. Stirring was continued for 6 hr., and the reaction mixture was left overnight, then worked up as usual. Recrystallisation from benzene gave β-3,4-dimethylbenzoyl-α-(3,4-dimethylphenyl)propionic acid, m. p. 213—214° (Found: C, 77.4; H, 7.2. C₂₀H₂₂O₃ requires C, 77.4; H, 7.1%), and β-2,5-dimethylbenzoyl-α-(2,5-dimethylphenyl)propionic acid, m. p. 119—121° (Found: C, 77.3; H, 7.15%).

(b) Powdered aluminium chloride (2.7 g., 2 mol.) was added portionwise to a stirred suspension of maleic anhydride (1 g., 1 mol.) in *o*- or *p*-xylene (*ca.* 20 ml.), and the reaction carried out as above. The products were recrystallised from benzene, to give the above acids (2.75 g.) 87%).

Action of Grignard Reagents on 6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones.—The powdered pyridazin-3-one (0.01 mole) was added to a solution of the arylmagnesium bromide (0.04 mole) in ether (50 ml.), and the mixture was refluxed for 8 hr., cooled, decomposed with ice and hydrochloric acid, and worked up as usual. The products were recrystallised from suitable solvents, to give 3,6-diarylpyridazines (IV) (Table 6).

 TABLE 6
 3,6-Diarylpyridazines (IV)

Cmpd.	M. p.	Yield (%)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(IVa)	148—150° (Et ₂ O)	40	83.1	6.3	10.6	C ₁₈ H ₁₆ N ₂	83.1	6.15	10.80
(IVb)	120 (40—60° pet)	46	83.6	6.3	10.4	C ₁₈ H ₁₆ N ₂	83.1	6.15	10.80
(IVc)	143 (MeOH)	42	83.1	6.3	10.8	C ₁₈ H ₁₆ N ₂	83.1	6.15	10.80
(IVd)	170—172 (C ₆ H ₆)	41	78.6	6.1	9.5	C ₁₅ H ₁₈ N ₂ O	78.6	6.25	9.65
(IVe)	134—136 (EtOH)	55	78.4	6.4	9.7	C ₁₅ H ₁₈ N ₂ O	78.6	6.25	9.65
(IVf)	136—137 (Et ₂ O)	41	78.85	6.45	9.4	C ₁₅ H ₁₈ N ₂ O	78.6	6.25	9.65
(IVg)	218—220 (C ₆ H ₆)	50	82.0	5.1	8.4	C ₂₃ H ₁₆ N ₂ O	82.1	4.8	8.30
(IVh)	226—228 (CCl ₄)	50	86.2	5.3	8.6	C ₂₃ H ₁₆ N ₂ O	86.25	5.0	8.75
(IVi)	224—225 (C ₆ H ₆)	50	78.7	5.0	7.7	C ₂₄ H ₁₈ N ₂ O ₂	78.7	4.95	7.65
(IVj)	254—256 (C ₆ H ₆)	63	82.1	5.3	7.8	C ₂₄ H ₁₈ N ₂ O	82.3	5.2	8.00