Preparation and Reactions of Ethyl 4-Bromo-2,3-dioxobutyrate 2-Arylhydrazones and 4-Bromo-2,3-dioxo-1-phenylbutanal 2-Arylhydrazones

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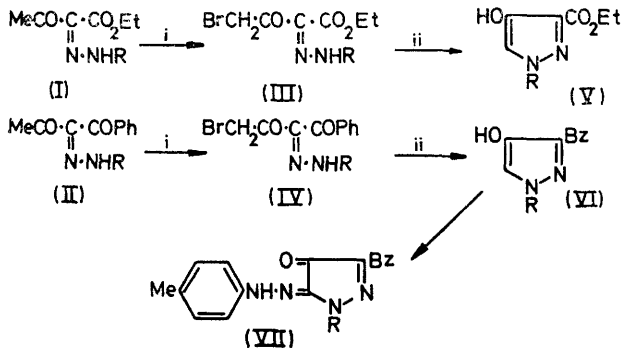
Ethyl 2,3-dioxobutyrate 2-arylhydrazones and 2,3-dioxo-1-phenylbutanal 2-arylhydrazones react with bromine in ether to give the corresponding 4-bromo-derivatives. Some ethyl 1-aryl-4-hydroxypyrazole-3-carboxylates and 1-aryl-3-benzoyl-4-hydroxypyrazoles have been synthesised by refluxing these 4-bromo-compounds in ethanol containing sodium acetate. 1-Aryl-3-benzoyl-4-hydroxypyrazoles react with toluene-*p*-diazonium salts to give 1-aryl-3-benzoyl-5-(*p*-tolylhydrazono)-2-pyrazolin-4-ones.

DURING studies of ethyl 2,3-dioxobutyrate 2-arylhydrazones (I),[1] pentane-2,3,4-trione-3-arylhydrazones,[2] and 2,3-dioxo-1-phenylbutanal 2-arylhydrazones (II),[3] precursors of a new class of potential antidiabetic pyrazole derivatives,[1-3] their reaction with bromine was investigated.

Earlier attempts to prepare ethyl 4-bromo-2,3-dioxobutyrate 2-arylhydrazones (III) and 4-bromo-2,3-dioxo-1-phenyl (or methyl) butanal 2-arylhydrazones [*e.g.* (IV)] were discouraging. Under various conditions, replacement of acetyl groups by bromine, disubstitution of the acetyl group, and nuclear substitution in the arylhydrazone group occurred.[4-6] However, the 4-bromo-derivatives (III) and (IV) were eventually obtained in good yields by the reaction of hydrazones (I) and (II) in ether with an equimolar quantity of

[1] H. G. Garg and P. P. Singh, *J. Medicin. Chem.*, 1968, **11**, 1104.
[2] H. G. Garg and P. P. Singh, *J. Medicin. Chem.*, 1968, **11**, 1103.
[3] H. G. Garg and P. P. Singh, *J. Chem. Soc.*, 1969, 1141.
[4] F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 1931, 786; *J. Amer. Chem. Soc.*, 1932, **54**, 263.
[5] F. D. Chattaway and R. J. Lye, *J. Chem. Soc.*, 1933, 480.
[6] F. D. Chattaway and D. R. Ashworth, *J. Chem. Soc.*, 1933, 1624.

bromine in sunlight at room temperature. The identity of the products was confirmed by treatment with acidified potassium iodide [7] to give the original hydrazones.[8]



Reagents: i, Br_2–Et_2O; ii, NaOAc–EtOH.

Ethyl 4-bromo 2,3-dioxobutyrate 2-arylhydrazones (III), when refluxed in ethanol containing sodium acetate, gave crystalline ethyl 1-aryl-4-hydroxypyrazole-3-carboxylates (V) (*cf.* ref. 9). The 4-bromo-derivatives (IV) behaved analogously, giving 1-aryl-3-benzoyl-4-hydroxypyrazoles (VI), which yielded crystalline 2,4-dinitrophenylhydrazone derivatives. The pyrazoles (VI) on treatment with toluene-*p*-diazonium chloride yielded 1-aryl-3-benzoyl-5-(*p*-tolylhydrazono)-2-pyrazolin-4-ones (VII).

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus.

Ethyl 2,3-dioxobutyrate 2-arylhydrazones and 2,3-dioxo-1-phenylbutanal 2-arylhydrazones were prepared by coupling diazotised anilines with acetoacetic ester and 3-oxo-1-phenylbutanal, respectively.[8]

Ethyl 4-Bromo-2,3-dioxobutyrate 2-(o-Nitrophenyl)hydrazone (III; R = *o*-$O_2N{\cdot}C_6H_4$).—Ethyl 2,3-dioxobutyrate 2-(*o*-nitrophenyl)hydrazone (0·83 g., 0·003 mole) suspended in dry ether (20 ml.) was treated with bromine (0·48 g., 0·003 mole) in ether (5 ml.), in sunlight. The suspended material went into solution with evolution of hydrogen bromide. After 1—2 hr., the ether was evaporated off, and the product was washed with water to remove hydrobromic acid and dried. It gave pale yellow crystals, m.p. 120—122° (from ethanol) (Found: Br, 22·0. $C_{12}H_{12}BrN_3O_5$ requires Br, 22·35%). The other similarly prepared ethyl 4-bromo-2,3-dioxobutyrate 2-arylhydrazones are listed in Table 1.

Ethyl-4-Hydroxy-1-(o-nitrophenyl)pyrazole-3-carboxylate (V; R = *o*-$O_2N{\cdot}C_6H_4$).—To the 4-bromo-derivatives (III; R = *o*-$O_2N{\cdot}C_6H_4$) (1·17 g., 0·003 mole) dissolved in ethanol (30 ml.) was added sodium acetate (1·5 g.) in water (10 ml.). The mixture was refluxed for 2 hr. then cooled. The crystals which separated (0·4 g., 50%) gave yellow *plates*, m.p. 85° (from ethanol) (Found: C, 51·5; H, 3·7; N, 15·3. $C_{12}H_{11}N_3O_5$ requires C, 51·9; H, 3·9; N, 15·1%). The other 1-aryl-4-hydroxypyrazole-3-carboxylates similarly prepared are listed in Table 2.

4-Bromo-2,3-dioxo-1-phenylbutanal 2-Phenylhydrazone (IV; R = Ph).—To 2,3-dioxo-1-phenylbutanal 2-phenylhydrazone (1·33 g., 0·005 mole) suspended in dry ether (15 ml.), bromine (0·8 g., 0·005 mole) in ether was gradually added in sunlight. The suspended material went into solution and hydrogen bromide was evolved. After 1 hr. the ether was evaporated off and the product was washed with water to remove hydrobromic acid and dried (1·4 g., 80%); m.p. 72—73° (from ethanol) (Found: Br, 22·9.

TABLE 1

Ethyl 4-bromo-2,3-dioxobutyrate 2-arylhydrazones (III)

			Found (%)			Required (%)	
R	M.p.	Colour	N	Br	Formula	N	Br
3-Nitrophenyl	96—97°	Light yellow	11·6	22·0	$C_{12}H_{12}BrN_3O_5$	11·7	22·3
4-Nitrophenyl	129—130	Light yellow	11·2	21·8	$C_{12}H_{13}BrN_3O_5$	11·7	22·3
4-Chlorophenyl	75—77	Pale yellow	7·6	33·0 *	$C_{12}H_{12}Br_2ClN_3O$	8·1	33·2 *
2-Ethoxyphenyl	64—65	Yellow	7·8	22·3	$C_{14}H_{17}BrN_2O_4$	7·9	22·4
4-Ethoxyphenyl	76	Yellow	7·5	22·0	$C_{14}H_{17}BrN_2O_4$	7·9	22·4
p-Tolyl	78—79	Pale yellow	8·6	24·5	$C_{13}H_{15}BrN_2O_3$	8·5	24·4
4-Sulphamoylphenyl	120—121	Yellow	10·8	20·2	$C_{12}H_{14}BrN_3O_5S$	10·7	20·4
2-Methoxyphenyl	90—91	Yellow (needles)	8·0	23·0	$C_{13}H_{15}BrN_2O_4$	8·1	23·3
2,4-Dimethylphenyl	87—88	Yellow (needles)	8·4	23·6	$C_{14}H_{17}BrN_2O_3$	8·2	23·4
2,5-Dichlorophenyl	122	Yellow (needles)	7·0	39·6 *	$C_{12}H_{11}BrCl_2N_2O_3$	7·3	39·5 *
o-Tolyl	103	Pale yellow	8·2	24·7	$C_{13}H_{15}BrN_2O_3$	8·5	24·4

* Br + Cl.

TABLE 2

Ethyl 1-aryl-4-hydroxypyrazole-3-carboxylates (V)

R	M.p.	Colour	Found (%)	Formula	Required (%)
3-Nitrophenyl	191—192°	Light yellow (needles)	N, 15·0	$C_{12}H_{11}N_3O_5$	N, 15·1
4-Nitrophenyl	209—210	Yellow (needles)	N, 14·7	$C_{12}H_{11}N_3O_5$	N, 15·1
4-Chlorophenyl	80	Pale yellow (needles)	Cl, 13·4	$C_{12}H_{11}ClN_2O_3$	Cl, 13·3
2-Ethoxyphenyl	125—126	Yellow	N, 9·6	$C_{14}H_{16}N_2O_4$	N, 10·1
4-Ethoxyphenyl	80—82	Yellow (needles)	N, 9·7	$C_{14}H_{16}N_2O_4$	N, 10·1
p-Tolyl	98—99	Yellow (plates)	N, 11·1	$C_{13}H_{14}N_2O_3$	N, 11·3
4-Sulphamoylphenyl	125—126	Orange (needles)	S, 10·0	$C_{12}H_{13}N_3O_5S$	S, 10·3
2-Methoxyphenyl	97—98	Yellow (needles)	N, 10·4	$C_{13}H_{14}N_2O_4$	N, 10·7

[7] H. G. Garg and M. M. Bokadia, *J. Indian Chem. Soc.*, 1957, **34**, 286, and the references cited therein.

[8] H. G. Garg and S. S. Joshi, *J. Indian Chem. Soc.*, 1960, **37**, 626.

[9] F. D. Chattaway and R. J. Lye, *Proc. Roy. Soc.*, 1932, *A* **135**, 282.

$C_{16}H_{13}BrN_2O_2$ requires Br, 23·2%). Other 4-bromo-derivatives (IV) are listed in Table 3.

3-Benzoyl-4-hydroxy-1-phenylpyrazole (VI; R = Ph).—To a solution of the 4-bromo-derivative (IV; R = Ph) (1·03 g., 0·003 mole) in ethanol (25 ml.) was added sodium acetate (1·5 g.) in water (10 ml.). The mixture was refluxed for 2 hr., then cooled. The crystals which separated yielded pale yellow *needles* (0·7 g., 85%), m.p. 85—86° (from aqueous ethanol) (Found: C, 72·4; H, 4·3; N, 10·3. $C_{16}H_{12}N_2O_2$ requires C, 72·7; H, 4·5; N, 10·7%). The 2,4-dinitrophenylhydrazone had m.p. 270° (decomp.). Other 4-hydroxypyrazoles prepared are listed in Table 4.

3-Benzoyl-1-phenyl-5-(p-tolylhydrazono)-2-pyrazolin-4-one (VII; R = Ph).—A solution containing diazotised *p*-toluidine (0·27 g., 0·0025 mole) in hydrochloric acid (12N; 2 ml.) was filtered into a cooled, stirred mixture of 3-benzoyl-4-hydroxy-1-phenylpyrazole (0·66 g., 0·0025 mole) in ethanol (20 ml.) and sodium hydroxide (2 g.) in water (10 ml.). After 3 hr. the precipitate was filtered off and washed with water; it formed brown *crystals*, m.p. 75° (decomp.) (from ethanol) (Found: N, 14·4. $C_{23}H_{18}N_4O_2$ requires N, 14·7%).

TABLE 3

4-Bromo-2,3-dioxo-1-phenylbutanal 2-arylhydrazones (IV)

			Found (%)			Required (%)	
R	M.p.	Colour	N	Br	Formula	N	Br
2-Nitrophenyl	140—142°	Pale yellow	10·5	20·3	$C_{16}H_{12}BrN_3O_4$	10·7	20·5
3-Nitrophenyl	120—121	Pale yellow	10·8	20·1	$C_{16}H_{12}BrN_3O_4$	10·7	20·5
o-Tolyl	110—112	Pale yellow	7·4	22·0	$C_{17}H_{15}BrN_2O_2$	7·8	22·3
4-Chlorophenyl	121—122	Pale yellow	7·0	30·0 *	$C_{16}H_{12}ClBrN_2O_2$	7·1	30·4 *
4-Bromophenyl	130—132	Pale yellow	6·7	37·4	$C_{16}H_{12}Br_2N_2O_2$	6·6	37·7
3-Methoxyphenyl	143—144	Brown	7·2	21·0	$C_{17}H_{15}BrN_2O_3$	7·4	21·3
2-Ethoxyphenyl	105—106	Yellow	7·0	20·3	$C_{18}H_{17}BrN_2O_3$	7·1	20·5
4-Ethoxyphenyl	44—46	Red	6·8	20·2	$C_{18}H_{17}BrN_2O_3$	7·1	20·5
4-Sulphamoylphenyl	115 (decomp.)	Light yellow	9·7	18·6	$C_{16}H_{14}BrN_3O_4S$	9·9	18·9
2,5-Dichlorophenyl	193 (decomp.)	Yellow	6·6	36·0 *	$C_{16}H_{11}Cl_2BrN_2O_2$	6·7	36·4 *
2,5-Dimethylphenyl	134—136	Yellow	7·4	21·2	$C_{16}H_{17}BrN_2O_2$	7·5	21·4
2,6-Dimethylphenyl	66—67	Yellow	7·3	21·0	$C_{18}H_{17}BrN_2O_2$	7·5	21·4
2-Chlory-6-methylphenyl	70—71	Pale yellow	7·2	28·8 *	$C_{17}H_{14}ClBrN_2O_2$	7·1	29·3 *

* Br + Cl.

TABLE 4

1-Aryl-3-benzoyl-4-hydroxypyrazoles (VI)

R	M.p.	Colour	Found (%)	Formula	Required (%)
2-Nitrophenyl	88—89°	Light yellow	N, 13·3	$C_{16}H_{11}N_3O_4$	N, 13·6
3-Nitrophenyl	154—155	Yellowish (needles)	N, 13·2	$C_{16}H_{11}N_3O_4$	N, 13·6
o-Tolyl	163	Light yellow (needles)	N, 9·8	$C_{17}H_{14}N_2O_2$	N, 10·1
4-Chlorophenyl	159—160	Light yellow	Cl, 11·4	$C_{16}H_{11}ClN_2O_2$	Cl, 11·8
4-Bromophenyl	170	Light yellow (needles)	Br, 23·0	$C_{16}H_{11}BrN_2O_2$	Br, 23·3
3-Methoxyphenyl	168—169	Yellowish	N, 9·3	$C_{17}H_{14}N_2O_3$	N, 9·5
2-Ethoxyphenyl	153	Brown (needles)	N, 8·7	$C_{18}H_{16}N_2O_3$	N, 9·1
4-Sulphamoylphenyl	220	Pale yellow (needles)	S, 8·8	$C_{16}H_{13}N_3O_4S$	S, 9·3
2,5-Dichlorophenyl	117—119	Light yellow	Cl, 20·9	$C_{16}H_{10}Cl_2N_2O_2$	Cl, 21·3
2,5-Dimethylphenyl	156—158	Light yellow	N, 9·3	$C_{18}H_{16}N_2O_2$	N, 9·6
2-Chloro-6-methylphenyl	88—89	Light yellow (needles)	Cl, 11·1	$C_{17}H_{13}ClN_2O_2$	Cl, 11·3

TABLE 5

1-Aryl-3-benzoyl-5-(*p*-tolylhydrazone)-2-pyrazolin-4-ones (VII)

R	M.p.	Colour	Found N (%)	Formula	Required N (%)
3-Nitrophenyl	207—209°	Brown	16·1	$C_{23}H_{17}N_5O_4$	16·4
2-Methylphenyl	140—142	Dark brown	13·8	$C_{24}H_{20}N_4O_3$	14·1
4-Chlorophenyl	124—125	Reddish brown	13·0	$C_{23}H_{17}ClN_4O_2$	13·4
4-Bromophenyl	99—100	Dark brown	11·7	$C_{23}H_{17}BrN_4O_3$	12·1
3-Methoxyphenyl	125 (decomp.)	Light brown	13·3	$C_{24}H_{20}N_4O_3$	13·6
2-Ethoxyphenyl	106—108	Dark brown	12·9	$C_{25}H_{22}N_4O_3$	13·1
2,5-Dichlorophenyl	113—114	Brown	12·1	$C_{23}H_{13}Cl_2N_4O_2$	12·4
2,5-Dimethylphenyl	136—138	Dark brown	13·4	$C_{25}H_{22}N_4O_2$	13·7
2-Chloro-6-methylphenyl	75—77	Brown	16·6	$C_{24}H_{19}ClN_4O_2$	16·9

The other derivatives similarly prepared are listed in Table 5.

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