931. *The Synthesis of Ethyl 4-Aryl-5,6,7,8-tetrahydro-5-oxoquinoline-3-carboxylates and their Derivatives.*

By H. Antaki.

In an extension of the Hantzsch collidine synthesis, cyclohexane-1,3-dione reacts with aromatic aldehydes and ethyl β-aminocrotonate to give ethyl 4-aryl-1,4,5,6,7,8-hexahydro-2-methyl-5-oxoquinoline-3-carboxylates (I). With chromium trioxide these give the 5,6,7,8-tetrahydro-esters (II), cleavage of the pyridine ring of which by sulphuric acid at 100° leads to 9-aryloctahydro-1,8-dioxoxanthens (III). Condensation of aromatic aldehydes with cyclohexane-1,3-dione in the presence of ammonium acetate gives 9-aryldecahydro-1,8-dioxoacridines (IV).

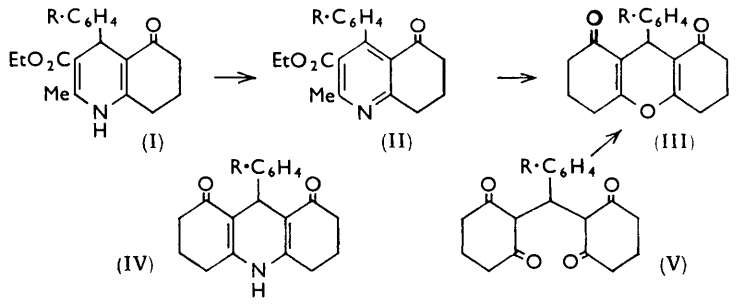
5,6,7,8-Tetrahydro-5-oxoquinolines were required for other work, but the few routes reported for the synthesis of *Bz*-tetrahydroquinolines [1] were not adaptable for preparation of these derivatives. The Hantzsch collidine synthesis [2] was applied to 1,3-diketones by Knoevenagel and Ruschhaupt.[3] We have now found that, although cyclohexane-1,3-dione reacts with benzaldehyde or *p*-nitrobenzaldehyde in alcohol to give 2,2′-benzylidene- and 2,2′-*p*-nitrobenzylidene-biscyclohexane-1,3-dione, yet the monocyclic diketone condenses smoothly with aromatic aldehydes and ethyl β-aminocrotonate in alcoholic acetic acid

[1] Braun, Petzold, and Seeman, *Ber.*, 1922, **55**, 3779; Braun, Gmelin, and Schulthein, *Ber.*, 1923, **56**, 1338; Huzise and Tiba, *Bull. Chem. Soc. Japan*, 1939, **14**, 478; Basu, *Annalen*, 1934, **512**, 131; Dornow and Neuse, *Arch. Pharm.*, 1955, **288**, 174; Stobbe and Volland, *Ber.*, 1902, **35**, 3973; Allen and Sallans, *Canad. J. Res.*, 1933, **9**, 574.

[2] Hantzsch, *Ber.*, 1884, **17**, 2910.

[3] Knoevenagel and Ruschhaupt, *Ber.*, 1898, **31**, 1025.

to give ethyl 4-aryl-1,4,5,6,7,8-hexahydro-2-methyl-5-oxoquinoline-3-carboxylates (I). These products are smoothly oxidised by chromium trioxide in dilute acetic acid to the tetrahydroquinolines (II) and these, when heated in concentrated sulphuric acid, slowly pass into the xanthen derivatives (III) by fission of the pyridine ring and re-cyclisation.



The tetrahydro-ketones (II) have a reactive carbonyl group (phenylhydrazones), and the methyl group is also reactive as a 2-4′-nitrostyryl derivative was obtained by condensation with *p*-nitrobenzaldehyde.

The structure of the xanthens (III) was proved by independent synthesis of one of them: *p*-nitrobenzaldehyde and cyclohexane-1,3-dione in alcohol gave 2,2′-*p*-nitrobenzylidenebiscyclohexane-1,3-dione (V; R = NO_2) which cyclised to the xanthen (III; R = NO_2) in 70% acetic acid.

Replacement of ethyl β-aminocrotonate in the original condensation by ammonium acetate led to the acridine derivatives (IV). The phenyl member of this series has been prepared before [4] but by a route involving a tedious preparation.

The compounds prepared in this work are listed in the Tables.

Experimental

Ethyl 1,4,5,6,7,8-*Hexahydro*-2-*methyl*-4-p-*nitrophenyl*-5-*oxoquinoline*-3-*carboxylate* (I; R = NO_2).—*p*-Nitrobenzaldehyde (30·2 g., 1 mol.), ethyl β-aminocrotonate (26 g., 1 mol.), and cyclohexane-1,3-dione (22·4 g., 1 mol.) were heated under reflux in ethyl alcohol (180 c.c.) and glacial acetic acid (60 c.c.) for 1 hr. Part of the solvent was removed by distillation and the residue diluted with water until a faint turbidity resulted. The *product* crystallised on cooling and was recrystallised from alcohol.

Ethyl 5,6,7,8-*Tetrahydro*-2-*methyl*-4-p-*nitrophenyl*-5-*oxoquinoline*-3-*carboxylate* (II; R = NO_2.)—The foregoing compound (35 g., 1 mol.) was dissolved in hot acetic acid (140 c.c.) and water (60 c.c.). Chromium trioxide (6·6 g., 0·6 mol.) in 70% acetic acid (60 c.c.) was added to this solution at 70°, with stirring. When the solution became pale brown it was diluted with water until a slight turbidity persisted and was then kept overnight at 0°. The *product* that separated was filtered off, washed free from chromium salts, and crystallised from alcohol. The *phenylhydrazone* separated from aqueous alcohol in yellow needles, m. p. 220° (decomp.) (Found: C, 67·1; H, 5·3; N, 12·3. $C_{25}H_{24}N_4O_4$ requires C, 67·5; H, 5·4; N, 12·6). Ethanolic hydrochloric acid converted this hydrazone into ethyl 5,6-dihydro-3-methyl-1-*p*-nitrophenylindolo[2,3-*f*]quinoline-2-carboxylate,[5] golden plates (from alcohol), m. p. 217° (Found: C, 69·6; H, 5·0; O, 15·7; N, 10·3. Calc. for $C_{25}H_{21}N_3O_4$: C, 70·2; H 4·9; O, 14·9; N, 9·8%).

This product (1·7 g., 1 mol.) and *p*-nitrobenzaldehyde (1·5 g., 2 mol.) in acetic anhydride (80 c.c.) were refluxed for several hours. Alcohol was added and the solvents were removed by distillation. The residual solution was diluted with water and the separated solids repeatedly triturated with hot alcohol. The residual 2-4′-*nitrostyryl derivative* was twice crystallised from alcohol–acetic acid, forming small yellow plates, m. p. 250° (Found: C, 63·6; H, 4·2; N, 8·7. $C_{33}H_{24}N_4O_9$ requires C, 63·8; H, 3·9; N, 9·0%).

[4] Vorländer, *Annalen*, 1899, **309**, 379.
[5] Cookson and Mann, *J.*, 1949, 67; Mann, *J.*, 1949, 2817; Braunholtz and Mann, *J.*, 1955, 393.

TABLE 1.

Ethyl 4-aryl-1,4,5,6,7,8-hexahydro- (I) and 4-aryl-5,6,7,8-tetrahydro-2-methyl-5-oxoquinoline-3-carboxylates (II).

				Found (%)					Required (%)			
	R	M. p.	Form *	C	H	O	N	Formula	C	H	O	N
(I)	*p*-NO_2	240°	Prisms	64·0	5·8	22·3	7·7	$C_{19}H_{20}N_2O_5$	64·0	5·6	22·4	7·8
(II)	*p*-NO_2	168	Plates	65·0	5·3	22·5	7·4	$C_{19}H_{18}N_2O_5$	64·4	5·0	22·5	7·9
(I)	*p*-OMe	229	Needles †	70·3	7·1	18·6	4·0	$C_{20}H_{23}NO_4$	70·3	6·7	18·7	4·1
(II)	*p*-OMe	153	Prisms	70·6	6·5	18·8	4·5	$C_{20}H_{21}NO_4$	70·7	6·2	18·8	4·1
(I)	3,4-(OMe)	203	Plates	67·7	6·8	21·7	3·8	$C_{21}H_{25}NO_5$	67·9	6·8	21·5	3·8
(II)	3,4-(OMe)	154	,,	68·3	6·6	21·4	3·7	$C_{21}H_{23}NO_5$	68·2	6·2	21·6	3·8
(I)	*p*-NMe_2 ...	256 ‡	Needles	71·1	7·3	14·0	7·8	$C_{21}H_{26}N_2O_3$	71·2	7·4	13·5	7·9
(I)	*p*-Cl	244	Prisms	65·9	5·6	13·2	4·4	$C_{19}H_{18}ClNO_3$ §	65·2	5·8	13·9	4·0
(I)	*o*-NO_2	>300	,,	63·8	5·7	22·6	7·5	$C_{19}H_{20}N_2O_5$	64·0	5·6	22·4	7·8

* Yellow, unless otherwise stated. † White. ‡ With decomp. § Found: Cl, 10·2. Reqd.: Cl, 10·2%.

TABLE 2.

9-Aryl-1,2,3,4,5,6,7,8-octahydro-1,8-dioxoxanthens (III) and 9-aryl-1,2,3,4,5,6,7,8,9,10-decahydro-1,8-dioxoacridines (IV).

				Found (%)					Required (%)			
	R	M. p.	Form *	C	H	O	N	Formula	C	H	O	N
(III)	*p*-NO_2 ...	263° ‡	Plates	67·2	5·2	23·5	4·0	$C_{19}H_{17}NO_5$	67·2	5·0	23·5	4·1
(III)	*o*-NO_2 ...	251 ‡	,,	67·2	5·0	23·5	4·1	,,	,,	,,	,,	,,
(IV)	*o*-NO_2 ...	>300	Needles	67·1	5·3	18·9	8·2	$C_{19}H_{18}N_2O_4$	67·4	5·4	18·9	8·3
(IV)	*o*-NO_2 ...	>300	Plates	67·3	5·4	19·5	8·0	,,	,,	,,	,,	,,
(III)	*p*-NH_2 ...	290 ‡	,,	73·1	6·2	16·3	4·6	$C_{19}H_{19}NO_3$	73·7	6·1	15·5	4·5
(III)	*o*-Cl	261 ‡	,, †	69·3	5·1	15·0	—	$C_{19}H_{17}ClO_3$ §	69·6	4·8	14·6	—
(IV)	*p*-NMe_2	282	,,	74·6	7·3	9·7	8·5	$C_{21}H_{24}N_2O_2$	75·0	7·1	9·5	8·3
(IV)	*p*-MeO ...	298	,,	74·4	6·7	15·4	4·0	$C_{20}H_{21}NO_3$	74·3	6·5	14·8	4·3

*†‡ As in Table 1. § Found: Cl, 10·9. Reqd.: Cl, 10·8%.

1,2,3,4,5,6,7,8-*Octahydro*-9-p-*nitrophenyl*-1,8-*dioxoxanthen* (III; R = NO_2).—The quinoline derivative (II; R = NO_2) (8 g.) was dissolved in hot concentrated sulphuric acid (80 c.c.) and kept at 100° for 6 hr. After cooling, the solution was poured in an excess of water, and the *xanthen* was filtered off, washed with water, and crystallised from alcohol. The 10-*anilinoacridine* formed yellow prisms, m. p. 273° (decomp.) (Found: C, 70·3; H, 5·7; O, 14·2; N, 10·2. $C_{25}H_{24}O_4N_3$ requires C, 69·7; H, 5·5; O, 14·8; N, 9·7%).

9-o-*Chlorophenyl*-1,2,3,4,5,6,7,8-*octahydro*-1,8-*dioxoxanthen*.—Cyclohexane-1,3-dione (2·3 g., 2 mol.) and *p*-chlorobenzaldehyde (1·4 g., 1 mol.) were heated under reflux in alcohol (25 c.c.) for 0·5 hr. The solution was concentrated and diluted with water. 2,2′-p-*Chlorobenzylidene-biscyclohexane*-1,3-*dione* (V; R = Cl) crystallised on cooling in pale lemon-yellow plates, m. p. 237° (Found: C, 65·8; H, 5·4; O, 18·1; Cl, 10·5. $C_{19}H_{19}ClO_4$ requires C, 65·8; H, 5·4; O, 18·4; Cl, 10·2). The product was cyclised by refluxing it in 70% acetic acid for a short time followed by dilution with water; the xanthen crystallised on cooling. Its 10-*anilinoacridine* separated from alcohol in yellow prisms, m. p. 295° (decomp.) (Found: C, 71·5; H, 5·5; O, 8·3; N, 6·9; Cl, 9·0. $C_{25}H_{24}O_2N_2Cl$ requires C, 71·5; H, 5·7; O, 7·6; N, 6·6; Cl, 8·4%). 2,2′-p-*Nitro-benzylidenebiscyclohexane*-1,3-*dione*, similarly prepared, formed white plates, m. p. 226° (Found: C, 63·5; H, 5·2; N, 3·8. $C_{19}H_{19}NO_6$ requires C, 63·8; H, 5·3; N, 3·9), and on cyclisation as above gave the xanthen.

1,2,3,4,5,6,7,8,9,10-*Decahydro*-9-p-*nitrophenyl*-1,8-*dioxoacridine*.—Cyclohexane-1,3-dione (2·4 g., 2 mol.) and *p*-nitrobenzaldehyde (1·6 g., 1 mol.) were heated in alcohol (25 c.c.) and acetic acid (10 c.c.) with ammonium acetate (5 g.) under reflux for 0·5 hr. Part of the solvent was boiled off and the residual solution diluted with water. After cooling the solid *acridine* was collected, washed with water, and crystallised from alcohol.

RESEARCH INSTITUTE FOR TROPICAL MEDICINE,
CAIRO, EGYPT.

[*Received, August 29th,* 1962.]