100. *Pyranoquinolines. Part I. Application of the Kostanecki–Robinson Reaction to Derivatives of 3-Acetyl-4-hydroxyquinoline.*

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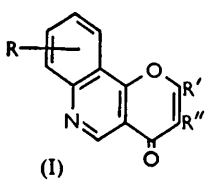
The synthesis and some reactions of certain pyranoquinolines are described.

We have found that Snyder and Jones's method [1] for the synthesis of substituted ethyl α-acetyl-β-anilinoacrylates leads to the simultaneous formation of the corresponding acrylanilides which have not previously been recorded. Thermal cyclisation of the anilinoacrylates in an inert solvent [1,2] yielded derivatives of 3-acetyl-4-hydroxyquinoline which were heated with various acid anhydrides and the sodium salts of the corresponding acid (Kostanecki–Robinson reaction [3]). It was not possible to isolate any products from these reactions, but substitution of triethylamine [4] for the sodium salts led to a series of 4′-oxopyrano(3′ : 2′-3 : 4)quinolines (I). Interaction of benzoic anhydride and 3-acetyl-4-hydroxy-6-, -7-, or -8-nitroquinoline gave in each case a mixture of the nitro-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline (I; R = NO_2, R′ = Ph, R″ = H) and the 5′-benzoyl derivative (I; R = NO_2, R′ = Ph, R″ = Bz). A mixture of the phenylpyranoquinoline (I; R = Cl, R′ = Ph, R″ = H) and 3-acetyl-4-benzoyloxy-7-chloroquinoline was obtained on reaction of 3-acetyl-7-chloro-4-hydroxyquinoline with benzoic anhydride, whereas 3-acetyl-6-bromo-4-hydroxyquinoline yielded only the phenylpyranoquinoline (I; R = Br, R′ = Ph, R″ = H). Furoic anhydride with the above-mentioned nitro-, chloro-, and bromo-compounds gave only the 5′-furoyl derivatives of the furylpyranoquinolines (I; R = NO_2, Cl, or Br, R′ = C_4H_3, R″ = C_4H_3·CO) in all cases. Cinnamic anhydride also gave the 5′-cinnamoyl derivatives of the styrylpyranoquinolines (I; R = NO_2, Cl, or Br, R′ = Ph·CH=CH, R″ = Ph·CH=CH·CO) except that 3-acetyl-4-hydroxy-7-nitroquinoline gave only the 6′-styryl derivative (I; R = NO_2, R′ = Ph·CH=CH, R″ = H).



(I)

All the pyranoquinolines described gave characteristic colours with concentrated sulphuric acid, pale yellow in the phenyl, orange in the furyl, and deep red in the styryl series. No colours were obtained with ferric chloride in alcohol. The carbonyl group is less reactive than in the flavones and attempts to prepare oximes or 2 : 4-dinitrophenylhydrazones were unsuccessful.

[1] Snyder and Jones, *J. Amer. Chem. Soc.*, 1946, **68**, 1253.
[2] Hapara and Desai, *J. Indian Chem. Soc.*, 1954, **31**, 951—956.
[3] Allan and Robinson, *J.*, 1924, **125**, 2192.
[4] Kuhn and Law, *Ber.*, 1944, **77**, 196.

Experimental

α-Acetyl-β-p-bromoanilino-N-p-bromophenylacrylamide and Ethyl α-Acetyl-β-p-bromoanilinoacrylate.—Equimolecular quantities of ethyl orthoformate, ethyl acetoacetate, and *p*-bromoaniline were heated at 160—165° (oil-bath) in an apparatus for fractional distillation. After the theoretical amount of ethyl alcohol had distilled, the cooled solidified residue was boiled with methyl alcohol, and the insoluble material was collected from the hot mixture and crystallised from toluene, to give *α-acetyl-β-p-bromoanilino-N-p-bromophenylacrylamide* (39·8 g.) as needles, m. p. 188—189° (Found: C, 46·8; H, 3·3; N, 6·3. $C_{17}H_{14}O_2N_2Br_2$ requires C, 46·6; H, 3·2; N, 6·4%).

Further material was collected from the cooled filtrate and recrystallised from methyl alcohol, to give *ethyl α-acetyl-β-p-bromoanilinoacrylate* (135 g.) as needles, m. p. 89—91° (Found: C, 50·0; H, 4·5; N, 4·5. $C_{13}H_{14}O_3NBr$ requires C, 50·1; H, 4·4; N, 4·7%).

Similarly, *o*-nitroaniline gave *ethyl α-acetyl-β-o-nitroanilinoacrylate*, m. p. 107—109° (Found: C, 56·5; H, 5·0; N, 10·5. $C_{13}H_{14}O_5N_2$ requires C, 56·0; H, 5·0; N, 10·1%), and *α-acetyl-β-o-nitroanilino-N-o-nitrophenylacrylamide*, needles, m. p. 233—235° (Found: C, 55·6; H, 3·9; N, 15·6. $C_{17}H_{14}O_6N_4$ requires C, 55·2; H, 3·9; N, 15·1%).

The following new acrylanilides were also isolated: *α-acetyl-β-m-chloroanilino-N-m-chlorophenyl-*, m. p. 151—152° (Found: C, 59·0; H, 4·2; N, 7·9. $C_{17}H_{14}O_2N_2Cl_2$ requires C, 58·5; H, 4·0; N, 8·0%), *α-acetyl-β-m-nitroanilino-N-m-nitrophenyl-*, m. p. 188—190° (Found: C, 54·9; H, 3·6%), and *α-acetyl-β-p-nitroanilino-N-p-nitrophenyl-acrylamide*, m. p. 245—246° (Found: C, 54·9; H, 4·0; N, 15·0%).

3-Acetyl-6-bromo-4-hydroxyquinoline.—To stirred diphenyl ether (50 c.c.) at the b. p. but no longer heated, ethyl α-acetyl-β-*p*-bromoanilinoacrylate (10 g.) was added portionwise. The whole was heated under reflux for 30 min. The cooled mixture was diluted with an equal volume of ether, and the insoluble material collected and dissolved in one equivalent of dilute sodium hydroxide solution. Acidification gave *3-acetyl-6-bromo-4-hydroxyquinoline* (4·25 g.), m. p. >300° (Found: C, 49·6; H, 3·1; N, 5·5. $C_{11}H_8O_2NBr$ requires C, 49·6; H, 3·0; N, 5·3%).

6-Bromo-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline.—3-Acetyl-6-bromo-4-hydroxyquinoline (2·66 g.) was refluxed with triethylamine (6·06 g.) and benzoic anhydride (11·3 g.) at 170—180° for 3 hr., the cooled mixture extracted with ether (4 × 50 c.c.), and the insoluble material (2·2 g.) crystallised from acetic acid, to give *6-bromo-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline* (2·5 g.), needles, m. p. 228—229° (Found: C, 61·2; H, 3·0; N, 4·3. $C_{18}H_{10}O_2NBr$ requires C, 61·4; H, 2·8; N, 4·0%). The *picrate* had m. p. 260—261° (Found: N, 9·6. $C_{24}H_{13}O_9N_4Br$ requires N, 9·6%).

7-Chloro-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline.—3-Acetyl-7-chloro-4-hydroxyquinoline (3·5 g.) was refluxed with benzoic anhydride (18·0 g.) and triethylamine (9·6 g.) at 170—180° for 4·25 hr., the cooled mixture extracted with ether (4 × 50 c.c.), and the insoluble material (4·3 g.) boiled with ethyl alcohol (300 c.c.) for 15 min. The residue (0·8 g.) crystallised from glacial acetic acid, giving *3-acetyl-4-benzoyloxy-7-chloroquinoline*, needles, m. p. 245—246° (Found: C, 65·9; H, 3·8; N, 3·8. $C_{18}H_{12}O_3NCl$ requires C, 66·4; H, 3·7; N, 4·3%).

The alcoholic filtrate was concentrated, to give *7-chloro-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)-quinoline* (3·3 g.), needles, m. p. 203—204° (Found: C, 70·8; H, 3·3; N, 4·0. $C_{18}H_{10}O_2NCl$ requires C, 70·3; H, 3·3; N, 4·5%).

Similarly, 3-acetyl-4-hydroxy-6-nitroquinoline at 150—160° (3·5 hr.), and the corresponding -7- and -8-nitroquinolines at 170—180° (3·0 and 2·0 hr., respectively), gave mixtures of the following ether-insoluble pyranoquinolines: *5′-benzoyl-6-nitro-*, prisms (from acetic acid), m. p. 249—250° (decomp.) (Found: C, 70·9; H, 3·4; N, 6·8. $C_{25}H_{14}O_5N_2$ requires C, 71·1; H, 3·3; N, 6·6%), *6-nitro-*, prisms (from) ethyl alcohol), m. p. 268—270° decomp.) (Found: C, 67·4; H, 3·2; N, 8·8. $C_{18}H_{10}O_4N_2$ requires C, 67·9; H, 3·2; N, 8·8%) [methiodide, m. p. 188° (decomp.) (Found: N, 5·8. $C_{19}H_{13}O_4N_2I$ requires N, 6·1%) (separated from the 5′-benzoyl derivative by extraction with hot alcohol), *5′-benzoyl-7-nitro-*, prisms (from acetone), m. p. 282° (decomp.) (Found: C, 70·8; H, 3·4; N, 6·8%), *7-nitro-*, prisms (from nitrobenzene), m. p. 285—287° (decomp.) (Found: C, 67·7; H, 2·8; N, 9·2%) (separated from the 5′-benzoyl derivative by extraction with hot methyl alcohol), *5′-benzoyl-8-nitro-*, prisms (from *n*-propyl alcohol), m. p. 192° (Found: C, 70·4; H, 3·2; N, 6·6%), and *8-nitro-*, prisms [from 1 : 1 ethyl acetate–light

petroleum (b. p. 40—60°)], m. p. 222—225° (decomp.) (Found: C, 68·2; H, 3·3; N, 8·8%) (separated from the 5′-benzoyl derivative by extraction with hot toluene) *4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline.*

6-Bromo-5′-furoyl-6′-furyl-4′-oxopyrano(3′ : 2′-3 : 4)quinoline.—3-Acetyl-6-bromo-4-hydroxyquinoline (2·66 g.), triethylamine (11·1 g.), and furoic anhydride (10·3 g.) were refluxed at 170—180° for 3·5 hr. Extraction of the resultant black oil with acetone gave *6-bromo-5′-furoyl-6′-furyl-4-oxopyrano(3′ : 2′-3 : 4)quinoline* (3·2 g.), needles (from nitrobenzene), m. p. >300° (Found: C, 57·6; H, 2·5; N, 3·8. $C_{21}H_{10}O_5NBr$ requires C, 57·8; H, 2·3; N, 3·2%).

Similarly, 3-acetyl-7-chloro-4-hydroxyquinoline, 3-acetyl-4-hydroxy-6-, -7-, and -8-nitroquinoline gave: the *7-chloro-* (prepared at 160—170°; 2·5 hr.), needles (from nitrobenzene), m. p. >300° (Found: C, 64·3; H, 2·4; N, 3·9. $C_{21}H_{10}O_5NCl$ requires C, 64·4; H, 2·6; N, 3·6%), *6-nitro-* (prepared at 170—180°; 2 hr.), prisms (from nitrobenzene), m. p. 228° (decomp.) (Found: C, 62·2; H, 2·7; N, 7·3. $C_{21}H_{10}O_7N_2$ requires C, 62·7; H, 2·5; N, 7·0%), *-7-nitro-* (prepared at 150—160°; 2·5 hr.), prisms (from nitrobenzene), m. p. >300° (Found: C, 62·9; H, 2·5; N, 7·3%), and *8-nitro-derivative* (prepared at 160—170°; 2·5 hr.), needles (from nitrobenzene), m. p. >300° (Found: C, 63·1; H, 2·7; N, 7·5%), of *5′-furoyl-6′-furyl-4′-oxopyrano(3′ : 2′-3 : 4)quinoline.*

6-Bromo-5′-cinnamoyl-4′-oxo-6′-styrylpyrano(3′ : 2′-3 : 4)quinoline.—3-Acetyl-6-bromo-4-hydroxyquinoline (2·66 g.) was refluxed with cinnamic anhydride (13·9 g.) and triethylamine (6·06 g.) at 170—180° for 3·25 hr. The resultant black oil was kept at room temperature for 2 days, then diluted with acetone (25 c.c.), and the insoluble material crystallized from dioxan to give *6-bromo-5′-cinnamoyl-4′-oxo-6′-styrylpyrano(3′ : 2′-3 : 4)quinoline* as needles, m. p. 271—273° (decomp.) (Found: C, 68·2; H, 3·7; N, 3·3. $C_{29}H_{18}O_3NBr$ requires C, 68·5; H, 3·6; N, 2·8%).

Similarly were prepared *7-chloro-5′-cinnamoyl-* (at 170—180°; 3·5 hr.), prisms (from *n*-butyl alcohol), m. p. 250° (Found: C, 74·7; H, 4·3; N, 2·3. $C_{29}H_{18}O_3NCl$ requires C, 75·1; H, 3·9; N, 2·9%), *5′-cinnamoyl-6-nitro-* (160—170°; 3·0 hr.), needles (from nitrobenzene), m. p. 250° (decomp.) (Found: C, 72·7; H, 4·0; N, 6·2. $C_{29}H_{18}O_5N_2$ requires C, 73·4; H, 3·8; N, 5·9%), *7-nitro-* (160—170°; 2 hr.), prisms (from nitrobenzene), m. p. 288° (decomp.) (Found: C, 70·0; H, 3·8; N, 6·9. $C_{20}H_{12}O_4N_2$ requires C, 69·8; H, 3·5; N, 7·1%), and *5′-cinnamoyl-8-nitro-4′-oxo-6′-styrylpyrano(3′ : 2′-3 : 4)quinoline* (160—170°; 2·5 hr.), prisms (from acetic acid), m. p. 236° (decomp.) (Found: C, 73·5; H, 3·8; N, 5·7%).

Alkaline Hydrolysis of 6-Bromo- and 8-Nitro-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline.—6-Bromo-4′-oxo-6′-phenylpyrano(3′ : 2′-3 : 4)quinoline (0·2 g.) was refluxed in 0·1N-sodium hydroxide (10 c.c.) and ethyl alcohol (2 c.c.) for 1·5 hr. The cooled mixture, on extraction with ether (10 c.c.), gave acetophenone (0·05 g.) (2 : 4-dinitrophenylhydrazone, m. p. 238—240°). Acidification of the aqueous phase afforded *3-bromo-4-hydroxyquinoline-3-carboxylic acid* (0·13 g.), m. p. 276° (decomp.) (Found: N, 5·2. $C_{10}H_6O_3NBr$ requires N, 5·2%).

Similarly the nitro-compound (0·2 g.) gave acetophenone (0·05 g.) and *8-nitroquinoline-3-carboxylic acid* (0·25 g.), m. p. 264° (Found: N, 11·6. $C_{10}H_8O_5N_2$ requires N, 12·0%).

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