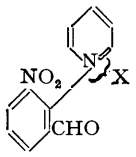
177. *A Novel Synthesis of Some Quinoline Derivatives.*

By Douglas Allan and James D. Loudon.

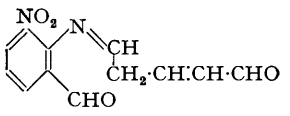
Derivatives of benzaldehyde or benzophenone, which carry a sufficiently reactive chloro- or toluene-*p*-sulphonyloxy-substituent in the ortho-position, are converted into derivatives of β-3-quinolylacraldehyde *via* pyridinium salts of type (I). A note on the nitration of *o*-hydroxyacetophenone is appended.

During the preparation of the *toluene*-p-*sulphonyl* derivative of 3-nitrosalicylaldehyde, using pyridine as solvent, it was observed that the ester readily reacted even with the cold solvent to

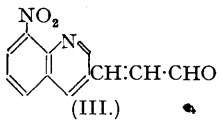
form a pyridinium salt. The salt was difficult to isolate in solid form but was conveniently prepared in aqueous solution. The *toluene*-p-*sulphonyl* derivative of 5-nitrosalicylaldehyde, although less reactive towards pyridine, yielded a crystalline pyridinium salt when its solution in pyridine was heated under reflux. The addition of alkali to aqueous solutions of these salts initiates a remarkably rapid series of changes resulting in the precipitation of compounds which are considered to be β-3-(8-*nitroquinolyl*)- and β-3-(6-*nitroquinolyl*)-*acraldehyde* respectively (cf. III). The structures assigned to these compounds are based on analogy with the well-known opening of the pyridine ring in 2 : 4-dinitrophenylpyridinium chloride (Zincke, *Annalen*, 1904, **330**, 361; **333**, 296; 1905, **338**, 107; **341**, 365) whereby in the present cases an intermediate such as (II) is made available for cyclisation to the quinoline (III).



(I.)



(II.)



(III.)

Extensive confirmation of the structure of these products has been obtained from a study of the compounds themselves and may be illustrated with reference to the product (III) derived from pyridine and 3-nitrosalicylaldehyde. (*a*) Oxidation with nitric acid removed two carbon atoms with formation of a *carboxylic acid*, which lost carbon dioxide when heated at its melting point and gave 8-nitroquinoline, identified by direct comparison with an authentic specimen. Accordingly, the presence of the quinoline ring with a side-chain in the heterocyclic nucleus may be inferred. (*b*) The compound was a feeble base which reacted with carbonyl reagents : a *phenylhydrazone* rather than a pyrazoline derivative appeared to be formed in reaction with phenylhydrazine. (*c*) By the action of acetic anhydride and a trace of sulphuric acid there was produced a *diacetate* from which the parent compound was regenerated by hydrolysis with dilute acid. This behaviour, together with the reducing properties of the compound, indicates the presence of an aldehydic group, but attempts to prepare the corresponding acid by mild oxidation have not been successful. (*d*) Addition of bromine resulted in formation of an unstable, pale yellow *dibromide* which, by shaking with cold aqueous sodium carbonate, readily eliminated hydrogen bromide to give a *monobromo-substitution* product. The latter retained the power of forming a *diacetate* and, on oxidation, yielded the nitroquinolinecarboxylic acid already obtained from (III). The production in this way of α-bromo-β-3-(8-nitroquinolyl)acraldehyde from the dibromide of (III) is a normal consequence of the structural features of the acraldehyde side-chain although it affords an interesting contrast to the regeneration of β-2-quinolylacrylic acid from the corresponding dibromide under similar conditions (Alberts and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 1284).

The scope of the reaction as a synthesis of hitherto inaccessible derivatives of quinoline is obviously conditioned by the availability of salts of type (I). In practice, the actual isolation of these salts is unnecessary, and in most of the cases examined an aqueous extract of the pyridine reaction products was directly employed for conversion into the quinoline. Depending on the reactivity of the toluene-*p*-sulphonic esters, these extracts were prepared either in one stage by the interaction of the sulphonyl chloride and the phenolic aldehyde in pyridine or by heating the pre-formed ester with pyridine. Appropriately substituted halogenobenzenes may also be used ; for example, 2-chloro-5-nitrobenzaldehyde when heated with pyridine afforded an aqueous extract from which β-3-(6-nitroquinolyl)acraldehyde was obtained. Salt formation is facilitated by the second nitro-group in 3 : 5-dinitrosalicylaldehyde from which β-3-(6 : 8-*dinitroquinolyl*)*acraldehyde* was readily prepared. On the other hand, replacement of the aldehydic by a ketonic function in the starting material is unfavourable to the reaction, for although β-3-(6 : 8-*dinitro*-4-*phenylquinolyl*)*acraldehyde* was readily obtained from 2-chloro- or 2-hydroxy-3 : 5-dinitrobenzophenone, yet little or no reaction occurred with 2-chloro-5-nitrobenzophenone. Again, from the *toluene*-p-*sulphonyl* derivatives of 3-nitro- and 5-nitro-2-hydroxyacetophenone—materials which contain potentialities for the ultimate synthesis of phenanthridines—only traces of compounds, apparently of a different type, were obtained. In no case was it possible to isolate crystalline products when α-picoline was used in place of pyridine in these reactions.

Note on the Nitration of o-*Hydroxyacetophenone.*—There appears to be some confusion in the literature regarding the 3- and 5-nitro-2-hydroxyacetophenones which were required for the

above investigation. By direct nitration of 2-hydroxyacetophenone in acetic acid, Wittig (*Annalen*, 1925, **446**, 181) isolated in small yield a steam-volatile nitro-ketone of m. p. 98·5—99·5° which he described as 3-nitro-2-hydroxyacetophenone, presumably because 3-nitrosalicylic acid was also isolated as a by-product. Lindemann and Romanoff (*J. pr. Chem.*, 1929, **122**, 214), who state that the phenolic ketone is destroyed by direct nitration, nitrated the oxime and, after separation and hydrolysis, obtained as main product a nitro-ketone (A) of m. p. 111—112° (oxime, m. p. 231°) together with a small quantity of a nitro-ketone (B) of m. p. 89—90° (oxime, m. p. 182°). Since the oxime of (A) afforded the known 5-nitro-3-methylbenz*iso*oxazole, (A) was oriented as 5-nitro-2-hydroxyacetophenone and, by exclusion, (B) was 3-nitro-2-hydroxyacetophenone. Repetition of Lindemann and Romanoff's work gave nitrated oximes of the recorded m. p.s but on hydrolysis (A) was obtained having m. p. 98—99°. It was identical with a steam-volatile nitro-ketone obtained by modifying Wittig's method of direct nitration and its orientation as the 5-nitro-isomer was confirmed by oxidation to 5-nitrosalicylic acid. The 3-nitro-isomer, obtained as subsidiary product both from the direct and from the indirect method of nitration, had m. p. 83°. All attempts to dinitrate *o*-hydroxyacetophenone either directly or stepwise failed, the only product isolated being picric acid.

Experimental.

Toluene-p-*sulphonate of* 3-*Nitrosalicylaldehyde.*—Sodium carbonate (0·32 g.) was added to a suspension of the aldehyde (0·5 g.) and toluene-*p*-sulphonyl chloride (0·6 g.) in hot water (25 c.c.) and the mixture was heated under reflux for one hour. The *ester* formed colourless crystals, m. p. 131° from benzene (Found : C, 52·5; H, 3·5. $C_{14}H_{11}O_6NS$ requires C, 52·3; H, 3·4%).

β-3-(8-*Nitroquinolyl*)*acraldehyde.*—(*a*) 3-Nitrosalicylaldehyde (5 g.), dissolved in cold, anhydrous pyridine (15 c.c.), was treated with toluene-*p*-sulphonyl chloride (6 g.) added portionwise so that the temperature remained below 27°. After 12 hours at room temperature the mixture was poured into dilute hydrochloric acid and ice, whereupon the above toluene-*p*-sulphonate separated (3·3 g., m. p. and mixed m. p. 130—131°). The clear yellow filtrate was neutralised by dropwise addition of dilute sodium hydroxide until a transient red colour just persisted. The quinolylacraldehyde which separated formed colourless needles (2·3 g.), m. p. 201—202°, from acetic acid (charcoal).

(*b*) When the pyridine reaction mixture was gently warmed (40°) for a few minutes and then allowed to cool before being worked up, the yield of the ester was diminished and a correspondingly greater, but less pure quantity of the *quinoline* derivative was obtained (Found : C, 63·2; H, 3·8; N,12·1. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·5; N, 12·3%). It gave an *oxime*, golden-yellow plates, m. p. 250° (decomp.), from acetic acid, when heated (4 hours) with hydroxylamine in ethanol–dioxan (Found : C, 59·1; H, 4·2; N, 17·2. $C_{12}H_9O_3N_3$ requires C, 59·3; H, 3·7; N, 17·3%); a *phenylhydrazone*, orange crystals, m. p. 205°, from acetic acid, for which Raiford and Petersen's pyrazoline-test (*J. Org. Chem.*, 1937, **1**, 544) was negative (Found : N, 17·7. $C_{18}H_{14}O_2N_4$ requires N, 17·4%); and a *diacetate*, colourless needles, m. p. 136—137°, formed when a small drop of concentrated sulphuric acid was added to a suspension of the acraldehyde in cold acetic anhydride and the whole, after 12 hours, was poured into water (Found : C, 58·45; H, 4·2. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·2%). The parent acraldehyde was regenerated when a solution of the diacetate in cold concentrated hydrochloric acid was allowed to stand for 1 hour and was then poured into water.

αβ-Dibromo-β-3-(8-*nitroquinolyl*)*propaldehyde* was obtained as yellow needles, m. p. 220° (decomp.), from warm (not boiling) acetic acid, when a solution containing molar proportions of the components in acetic acid was heated (10 minutes) at 100° and allowed to cool (Found : C, 37·1; H, 2·1. $C_{12}H_8O_3N_2Br_2$ requires C, 37·1; H, 2·1%).

α-Bromo-β-3-(8-*nitroquinolyl*)*acraldehyde* was obtained when the above dibromide was shaken with aqueous sodium carbonate or was subjected to prolonged heating in acetic acid. It formed colourless needles, m. p. 183° from dilute acetic acid (Found : C, 46·55; H, 2·2. $C_{12}H_7O_3N_2Br$ requires C, 46·9; H, 2·3%); it yielded a *diacetate*, m. p. 150—151° (Found : C, 47·1; H, 3·2. $C_{16}H_{13}O_6N_2Br$ requires C, 46·95; H, 3·2%), and when oxidised with concentrated nitric acid yielded the following acid.

8-*Nitroquinoline*-3-*carboxylic Acid.*—A solution of *β*-3-(8-nitroquinolyl)acraldehyde in nitric acid (*d* 1·42) was carefully heated on the water-bath and the vigorous reaction which ensued was controlled by occasional cooling. Heating was continued for 1 hour, water was added, and after most of the nitric acid had been distilled off, the *acid* separated on cooling and formed slender needles, m. p. 285° (with gas evolution) from ethanol (Found : C, 54·85; H, 3·0; N, 12·7. $C_{10}H_6O_4N_2$ requires C, 55·0; H, 2·75; N, 12·8%). When sublimed at its m. p. it yielded a mixture of unchanged acid, extracted in dilute alkali, and 8-nitroquinoline, identified by m. p. and mixed m. p. 88—89° with an authentic specimen.

Toluene-p-*sulphonate of* 5-*Nitrosalicylaldehyde.*—(*a*) The aldehyde (2 g.), toluene-*p*-sulphonyl chloride (2·4 g.), and dimethylaniline (10 c.c.) were heated at 100° for 1 hour. The solid *ester* obtained on pouring into dilute hydrochloric acid was crystallised from acetic acid (charcoal) and had m. p. 97—98° (Found : C, 52·4; H, 3·6. $C_{14}H_{11}O_8NS$ requires C, 52·3; H, 3·4%). (*b*) The sulphonyl chloride (30 g.) was added to a warm solution of the aldehyde (25 g.) in pyridine (25 c.c.) and, after being heated at 100° for a few minutes, the mixture was left at room temperature for 12 hours and was then poured into dilute hydrochloric acid. The purified ester weighed 32 g. (67%) and the aqueous filtrate yielded some *β*-3-(6-nitroquinolyl)acraldehyde (below).

(4-*Nitro*-2-*formylphenyl*)*pyridinium Toluene*-p-*sulphonate.*—A solution of the preceding ester (4 g.) in anhydrous pyridine (4 c.c.) and benzene (3 c.c.) was heated under reflux for 2 hours. After cooling, the crystalline *salt* was collected, washed with dry ether, and recrystallised from a very little warm

(not boiling) water. It formed colourless needles, m. p. 215—216° (Found : C, 56·8; H, 4·1; N, 6·8. $C_{19}H_{16}O_6N_2S$ requires C, 57·0; H, 4·0; N, 7·0%).

β-3-(6-Nitroquinolyl)acraldehyde.—The aqueous solution (clarified if necessary by charcoal) obtained (*a*) as filtrate from the above ester of 5-nitrosalicylaldehyde, (*b*) by dissolving the above pyridinium salt in water, or (*c*) by heating either 2-chloro-5-nitrosalicylaldehyde or the above ester of 5-nitrosalicylaldehyde with pyridine at 100° for 2 hours and adding them to cold dilute hydrochloric acid, was treated dropwise with 10% sodium hydroxide solution until no further change of colour occurred. After standing for 30 minutes, the mixture was again made slightly acid to coagulate the solid, which was then collected and crystallised from acetic acid. The *acraldehyde*, small pale yellow clusters of m. p. 247° (Found : C, 63·1; H, 3·2; N, 12·3. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·5; N, 12·3%), gave a *phenylhydrazone*, orange-red needles, m. p. 226—228° (decomp.) (Found : C, 67·9; H, 4·4; N, 17·6. $C_{18}H_{14}O_2N_4$ requires C, 68·1; H, 4·3; N, 17·4%), and a colourless diacetate, m. p. 188°, for which persistently high values for carbon were obtained on analysis.

6-Nitroquinoline-3-carboxylic acid, m. p. 300° (decomp.), from ethanol–acetic acid, was prepared by oxidising *β*-3-(6-nitroquinolyl)acraldehyde as in the case of its isomer (Found : C, 55·3; H, 3·1; N, 12·8. $C_{10}H_6O_4N_2$ requires C, 55·0; H, 2·75; N, 12·8%), and yielded 6-nitroquinoline, m. p. and mixed m. p. 150—151°, on sublimation at 300—310°.

β-3-(6 : 8-Dinitroquinolyl)acraldehyde.—Toluene-*p*-sulphonyl chloride (1 g.) was added at 0° to the suspension resulting from mixing 3 : 5-dinitrosalicylaldehyde (1 g.) and pyridine (10 c.c.), and the whole, after being vigorously shaken at room temperature for 30 minutes, was kept for several hours and then poured into dilute hydrochloric acid. The resulting aqueous solution was made alkaline with sodium carbonate, warmed to 60°, and the collected precipitate was crystallised first from acetic acid and then from benzene. The *aldehyde* formed fine colourless needles, m. p. 241° (Found : C, 52·9; H, 2·4; N, 15·2. $C_{12}H_7O_5N_3$ requires C, 52·7; H, 2·6; N, 15·0%), and gave a *phenylhydrazone*, dark red crystals, m. p. 245° (decomp.) from benzene (Found : C, 59·7; H, 3·8; N, 19·3. $C_{18}H_{13}O_4N_5$ requires C, 59·5; H, 3·6; N, 19·3%), and a *diacetate*, colourless needles, m. p. 177—178° from benzene (Found : C, 51·4; H, 3·5. $C_{16}H_{13}O_8N_3$ requires C, 51·2; H, 3·5%).

α-Bromo-β-3-(6 : 8-dinitroquinolyl)acraldehyde.—A solution of the preceding aldehyde (1 g.) in acetic acid was treated with the calculated quantity of bromine and heated at 100° for a few minutes. The dibromide, bright yellow needles, m. p. 225° (decomp.), which separated on cooling, was rather unstable and was converted into the corresponding *α-bromo-acraldehyde* by shaking with cold dilute sodium carbonate solution. The latter compound formed fine colourless needles, m. p. 238° (decomp.) from acetic acid (Found : C, 41·4; H, 1·6. $C_{12}H_6O_5N_3Br$ requires C, 40·9; H, 1·7%).

6 : 8-Dinitroquinoline-3-carboxylic acid, pale yellow crystals of m. p. 301—302° (decomp.), was obtained by oxidising the corresponding acraldehyde with nitric acid (Found : C, 44·0; H, 2·0. $C_{10}H_5O_6N_3,\frac{1}{2}H_2O$ requires C, 44·1; H, 2·2%), and yielded 6 : 8-dinitroquinoline, m. p. 151° from benzene, on decarboxylation by sublimation.

β-3-(6 : 8-Dinitro-4-phenylquinolyl)acraldehyde.—(*a*) A solution of 2-chloro-3 : 5-dinitrobenzophenone (5 g.) in dry pyridine (15 c.c.) was heated at 100° for 30 minutes. After being cooled, added to dilute hydrochloric acid, and clarified with charcoal, the resulting aqueous solution was slowly treated with dilute sodium hydroxide until no further colour change occurred. After 1 hour the precipitate was collected and formed straw-coloured plates, m. p. 243—244°, from acetic acid (Found : C, 62·0; H, 3·2; N, 12·2. $C_{18}H_{11}O_5N_3$ requires C, 61·9; H, 3·15; N, 12·0%). (*b*) The same compound, m. p. and mixed m. p. 242—243°, was also obtained from the aqueous extract, prepared in the usual way, from the interaction of toluene-*p*-sulphonyl chloride (0·37 g.) and 3 : 5-dinitro-2-hydroxybenzophenone (0·6 g.) in anhydrous pyridine (5 c.c.).

Nitration of o-Hydroxyacetophenone.—Nitric acid (30 g.; *d*, 1·52) was slowly added to a stirred solution of the ketone (20 g.) in acetic acid (100 c.c.) kept below 12°. The temperature of the resulting mixture was then allowed to rise spontaneously to 50—55° (caution) whereupon the mixture was quickly poured into crushed ice. The solidified oil was collected and, together with material recovered from a benzene extract of the aqueous mother-liquor, was distilled in steam. The first runnings, which contained some oil, were discarded, and the solid which separated from the later distillate (*ca.* 6 l.) yielded 5-nitro-2-hydroxyacetophenone as colourless needles (4—5 g.), m. p. 98—99° from ethanol (Found : C, 53·3; H, 4·0; N, 7·9. Calc. for $C_8H_7O_4N$: C, 53·05; H, 3·9; N, 7·75%), identical with a specimen prepared by acid-hydrolysis of the oxime of m. p. 131° (Lindemann and Romanoff, *loc. cit.*) and oxidised (0·1 g.) by boiling (30 minutes) with dilute nitric acid (10 c.c.) to 5-nitrosalicylic acid, m. p. and mixed m. p. 228—229°. The residue in the steam-distillation flask afforded 3-nitro-2-hydroxyacetophenone, which was dissolved out in benzene and recovered from an alkaline extract of the solution. This compound formed pale yellow needles (0·5 g.) from ethanol, m. p. 82—83° (Found : C, 53·2; H, 3·9; N, 7·7%), and was identical with a specimen prepared from the oxime of m. p. 182° (*loc. cit.*). A mixture of the 3- and the 5-nitro-isomer (4 g., m. p. 60—65°) was recovered in benzene from the aqueous portion of the steam-distillate and was partly separated by renewed distillation in steam. Attempts to convert it directly into 3 : 5-dinitro-2-hydroxyacetophenone were unsuccessful.

Toluene-p-sulphonate of 3-Nitro-2-hydroxyacetophenone.—Toluene-*p*-sulphonyl chloride (0·2 g.) was added to a solution of the nitro-ketone in pyridine at 0°. After 24 hours at room temperature, the mixture was poured into dilute hydrochloric acid, and the solidified *ester*, m. p. 98—99° from ethanol, was collected (Found : C, 53·8; H, 3·7. $C_{15}H_{13}O_6NS$ requires C, 53·7; H, 3·9%). The filtrate, treated with dilute sodium hydroxide until the red colour was just permanent, gave a felted mass of purplish crystals, m. p. 113—115° from benzene–petroleum (Found : C, 64·6; H, 3·85; N, 11·45. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·1; N, 11·6%). This *compound*, which differed from the others of the present series in the intensity of its colour (almost black), was very sparingly soluble in dilute acids but was obtained in such small quantity that further investigation was not possible.

Toluene-p-sulphonate of 5-Nitro-2-hydroxyacetophenone.—This *ester*, m. p. 93—94° from ethanol, was obtained from its components as in the previous experiment (Found : C, 54·0; H, 3·9%), and the water-soluble product of the reaction, after the usual treatment and attempted purification on alumina, gave

only traces of a crystalline material. Equally unpromising results were obtained, both here and in the previous case, from experiments in which the pre-formed esters were heated in pyridine.

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