87. *Reactions of Methazonic Acid. Part I. The Preparation of 3-Nitrolepidines and 3-Nitro-4-arylquinolines.*

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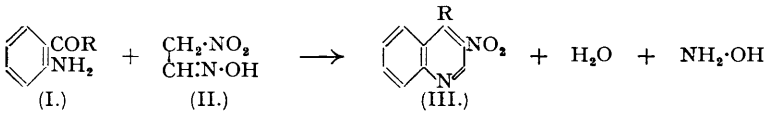
The course of the reaction between methazonic acid and substituted 2-aminoacetophenones depends on the nature of the substituent. In dilute mineral acid the initial product is a *o*-(2-nitroethylideneamino)acetophenone, or in some cases the oxime of this derivative. *o*-(2-Nitroethylideneamino)acetophenones undergo cyclisation to 3-nitrolepidines and hydrolysis to the parent amines in varying degrees when treated with dilute sodium hydroxide solution. Both they and their oximes are quantitatively cyclised by activated alumina, except in a few special cases. Derivatives of *o*-aminobenzophenone behave similarly, leading finally to 3-nitro-4-arylquinolines. 3-*Nitro*-4-2′-*pyridylquinoline* is described.

3-Nitroquinoline and its derivatives have been little studied, probably on account of their inaccessibility. Few synthetic routes to these compounds are known. Only eight cases of direct nitration at the 3-position have been described, and these concern either hydroxy- or amino-quinolines; they are 4-hydroxyquinaldine (Conrad and Limpach, *Ber.*, 1887, **20**, 950; 1888, **21**, 1981; Kermack and Weatherhead, *J.*, 1939, 563), 2 : 4-dihydroxyquinoline (Gabriel, *Ber.*, 1918, **51**, 1500; Ashley, Perkin, and Robinson, *J.*, 1930, 382), *N*-oxides of 4-hydroxyquinaldine and 4-hydroxy-2-phenylquinoline (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, 1613), 2-hydroxy-4 : 6-dimethylquinoline (Balaban, *J.*, 1930, 2346), 4 : 6-diaminoquinoline and derivatives (F.P. 779,092; G.P. 613,065; U.S.P. 2,066,730), 7-chloro-4-hydroxyquinoline (Breslow *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1232), and 4-hydroxyquinoline (Schofield and Swain, *J.*, 1949, 1367). Again, apart from the possible preparation of 3-nitrocarbostyril (Friedländer and Lazarus, *Annalen*, 1885, **229**, 243; Decker, *J. pr. Chem.*, 1901, **64**, 101) by a

method of limited utility, only two synthetic routes to 3-nitroquinolines are available. The more recent of these (Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 76; Morley and Simpson, *J.*, 1948, 2024) depends on the reaction of an aromatic amine with nitromalonaldehyde, and is limited to 3-nitroquinolines unsubstituted at $C_{(4)}$. The earlier known synthesis utilises the reaction between methazonic acid (II) and an *o*-aminoarylaldehyde or ketone (I; R = H or alkyl), an isatin derivative (I; R = CO_2H), or an anthranilic acid (I; R = OH) (G.P. 335,197, 347,375; Friedländer, **13**, 818; **14**, 521), in dilute mineral acid solution.

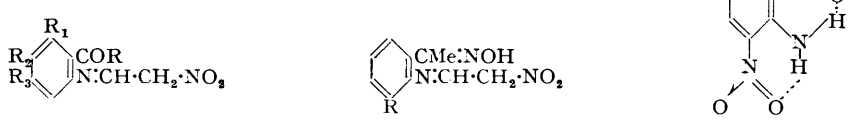


(I.) (II.) (III.)

The methazonic acid synthesis has received little attention, except for the preparation of individual compounds, no systematic study having been reported. Bargellini and Settimj (*Gazzetta*, 1923, **53**, 601) repeated the preparation, described in a patent, of 3-nitroquinoline, Renshaw and Friedman (*J. Amer. Chem. Soc.*, 1939, **61**, 3320; cf. Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 709) reported a yield of 22% in the same instance, and Clemo and Swan raised this to 48% by carrying out the reaction in alcohol containing concentrated hydrochloric acid (*J.*, 1945, 867). Clemo and Swan (*loc. cit.*) also reported successful application of the reaction, though with mediocre yields, to 6-aminopiperonal and 6-aminoveratraldehyde, but Ruggli and Frey (*Helv. Chim. Acta*, 1939, **22**, 1413) obtained only a complex product from 4 : 6-diamino*iso*phthalaldehyde. Several workers have prepared 3-nitro-4-hydroxyquinolines from variously substituted anthranilic acids (Colonna, *Gazzetta*, 1937, **67**, 46; 1939, **69**, 684; Musajo, *ibid.*, 1937, **67**, 222; Bachman *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 365; Breslow *et al.*, *loc. cit.*; Albert, Brown, and Duewell, *J.*, 1948, 1284). It is relevant that these reactions with anthranilic acids always proceed through the intermediate formation of a 2-nitroethylideneamino-compound (IV; R = OH), the cyclisation of which (always in mediocre yield) has only been achieved by sodium acetate in acetic anhydride solution. Applications of the reaction involving isatins will be described in a subsequent paper.

With regard to 2-aminoarylaldehydes and ketones, the original patent describes the use of *o*-aminobenzaldehyde and *o*-aminoacetophenone, and a similar reaction procedure was said to be applicable to various unspecified (including halogeno-)2-aminobenzaldehydes, and to aldehydes and ketones of the naphthalene or anthracene series. Although 2-aminobenzaldehydes are difficult to obtain, many 2-aminoacetophenones are now available, and this fact, coupled with our interest in the possible products and substances to be obtained from them, prompted the present investigation of the scope of the reaction between 2-aminoarylketones and methazonic acid, as a source of 3-nitroquinoline derivatives.

Before examining substituted 2-aminoketones we re-investigated the method described in the patent for preparation of 3-nitrolepidine itself, which consists in treating *o*-aminoacetophenone, in dilute hydrochloric acid solution, with aqueous sodium methazonate, and subsequently acidifying the solution with an unspecified quantity of hydrochloric acid. The yellow precipitate formed at room temperature, said to be a mixture of 3-nitrolepidine and *o*-aminoacetophenone oxime, is stated to be readily freed from the latter by dilute sodium hydroxide solution. We noticed, however, that the initial reaction product dissolved completely in cold dilute alkali, and only after some seconds was the quinoline derivative precipitated. Clearly, 3-nitrolepidine could not have been formed in the original condensation, since it is insoluble in alkali, and it therefore seemed likely that the reaction, like that with anthranilic acids, proceeds in two stages. Recrystallisation of the initial condensation product led to the isolation of o-(2-*nitroethyl-*



(IV.) (V.) (VI.)

ideneamino)acetophenone (IV; R = Me, $R_1 = R_2 = R_3 = H$). Cyclisation of the pure nitroethylideneamino-compound by cold dilute alkali was quantitative, and its facility is in

great contrast to the case of the analogous derivatives of anthranilic acids (IV; R = OH), mentioned above. Recovery of 3-nitrolepidine by the method described in the patent never exceeded 14%, based on the amino-ketone. A small improvement (25%) was obtained by careful adjustment of the amount of dilute mineral acid, and by using solid methazonic acid. The obvious discrepancy between the fact that (IV; R = Me, $R_1 = R_2 = R_3 = H$) is quantitatively cyclised to (III; R = Me) by dilute alkali, and the small overall yield of 3-nitrolepidine from the reaction between *o*-aminoacetophenone and methazonic acid under the conditions employed led us to a closer examination of them. This particular reaction has in fact proved to be complex, and further discussion of it is reserved for a later publication.

The more convenient procedure using solid methazonic acid was adopted in all subsequent work with other amino-ketones, and in most cases it also proved necessary to include an organic solvent, usually acetone, in order to ensure homogeneous reaction media. The 4-, 5-, and 6-monosubstituted and 4 : 5-disubstituted 2-aminoacetophenones examined invariably gave compounds of type (IV), always in higher yield than in the case of *o*-aminoacetophenone itself (Table I). Apart from a general tendency for electronegative substituents, particularly *para* to the amino-group, to facilitate the condensation, the results are not entirely clear-cut from the electronic standpoint. One reason for this may lie in the differing solubilities of the products in the varying reaction media, but it may also be that in some cases various side-reactions occur, similar to those shown to a pronounced degree by *o*-aminoacetophenone, though this possibility was not investigated.

Several 3-substituted 2-aminoacetophenones were examined, and in each case the reaction proved in some way unusual. 3-Chloro-, 3-bromo-, and 3-*iodo*-2-*aminoacetophenone* (see below) each reacted with methazonic acid in acetone–dilute hydrochloric acid to give paler products than the normal condensation derivatives (IV). These gave no reaction for a free amino-group, but appeared to be amphoteric since they did not separate from the acid reaction mixture before dilution (in contrast to IV), and also dissolved easily in dilute alkali without cyclising to a quinoline derivative. At present we regard these substances as the oximes (V; R = Cl, Br, or I) of the related 2-nitroethylideneamino-compounds (Table II). After melting with effervescence, they soldified and remelted at a higher temperature. Although the point was not directly proved, it is probable that the second m. p. is that of the corresponding 3-nitrolepidine (see below), formed by elimination of hydroxylamine. Available knowledge of oxime–ketone hydrolysis equilibria (see, *e.g.*, Conant and Bartlett, *J. Amer. Chem. Soc.*, 1932, **54**, 2881) does not make clear why in these cases oxime formation of the acetophenone should be favoured, in contrast to the apparently similar cases of 5-halogeno-2-aminoacetophenones mentioned above. 2-Amino-3-methylacetophenone with an electron-releasing substituent was expected to provide a useful comparison, but in fact it constituted another variation on the normal course of reaction, since 3-*nitro*-4 : 8-*dimethylquinoline* resulted directly in this case. 3-Nitro-2-aminoacetophenone failed to react with methazonic acid in acetone–hydrochloric acid, either at room temperature or at 95°. In view of the relative steric effectiveness of halogen, methyl, and nitro-groups, *e.g.*, in restricting free rotation in the diphenyl series (Gilman, " Organic Chemistry, An advanced Treatise," 1943, p. 362), this failure is probably not due to steric hindrance, and we attribute it to hydrogen bonding in the structure of 3-nitro-2-aminoacetophenone (VI; R = Me).

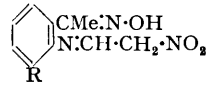
The second stage of the synthesis of 3-nitrolepidines, the cyclisation of compounds (IV), showed interesting variations. In effecting this step with dilute alkali, besides cyclisation, hydrolysis to the original amine may occur. The ease of these competing reactions varied considerably. Thus 5-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_3 =$ H, $R_2 = NO_2$) was converted into 3 : 6-*dinitrolepidine* during attempted crystallisation from aqueous acetone, and 4-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_2 =$ H, $R_3 = NO_2$) was partly cyclised to 3 : 7-*dinitrolepidine* by hot acetone. However, 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = NO_2$, $R_2 = R_3 =$ H) were all completely hydrolysed to the parent amines by dilute alkali. Although this great ease of alkaline hydrolysis was confined to the *Bz*-nitro-compounds, some degree of hydrolysis did occur with most other compounds of type (IV), as manifested in the diminished yields of 3-nitrolepidines (Table III). The results do not at first sight appear to indicate a consistent effect, depending on the electronic character of the substituent, upon the behaviour of these Schiff's bases towards dilute alkali, but it must be remembered that the two competing reactions of alkaline hydrolysis and cyclisation are each affected in a complicated way by the character of substituents. Depending on its position, a substituent may exert its chief effect on the ketone group, increasing or decreasing its electrophilic nature, upon the azomethine linkage, increasing or decreasing its ease of hydrolysis, or upon the nitroethylideneamino-group, augmenting or

TABLE I.

	R.	R_1.	R_2.	R_3.	Yield, %.[1]	M. p. (decomp.).	Form.	Solvent.[2]	Formula.	Analysis, %. Found. C.	Found. H.	Calc. C.	Calc. H.
(1)	CH_3	H	H	H	27	124—125°	Bright yellow leaflets	b	$C_{10}H_{10}O_3N_2$	58·1	5·2	58·25	4·85
(2)	,,	NO_2	H	H	80	187—188	Yellow leaflets	c	$C_{10}H_9O_5N_3$	48·2	3·8	47·8	3·6
(3)	,,	H	NO_2	H	85	214—216	Yellow needles	a [3]	,,	47·8	3·6	47·8	3·6
(4)	,,	H	H	NO_2	55	207—208	Yellow leaflets	Not recryst.[4]	,,	46·7	3·6	47·8	3·6
(5)	,,	H	Cl	H	75	190—191	Yellow cubes	a	$C_{10}H_9O_3N_2Cl$	49·9	3·7	49·9	3·7
(6)	,,	H	H	Cl	50	199—200	Pale yellow solid	c	,,	50·0	3·6	49·9	3·7
(7)	,,	H	CH_3	H	54	192—193	Yellow prisms	a	$C_{11}H_{12}O_3N_2$	60·0	5·8	60·0	5·5
(8)	,,	H	CH_3	CH_3	49	214—215	Pale yellow solid	a	$C_{12}H_{14}O_3N_2$	62·0	6·7	61·5	6·0
(9)	,,	H	CH_3O	CH_3O	59	192—193	Orange microneedles	a	$C_{12}H_{14}O_5N_2$	54·3	5·0	54·1	5·3
(10)	,,	H	$-[CH_2]_3-$		44	221—222	Yellow needles	a	$C_{13}H_{14}O_3N_2$	63·0	5·7	63·4	5·7
(11)	,,	H	$-[CH_2]_4-$		79	212—213	Yellow needles	a	$C_{14}H_{16}O_3N_2$	64·1	6·2	64·6	6·2
(12)	Ph	H	H	H	78	135—136	Yellow needles	b	$C_{15}H_{12}O_3N_2$	66·75	4·3	67·2	4·5
(13)	,,	NO_2	H	H	66	163—164	Pale yellow needles	d	$C_{15}H_{11}O_5N_3$	57·6	3·6	57·5	3·5
(14)	,,	H	NO_2	H	71	187—188	Yellow needles	a	,,	57·9	3·8	57·5	3·5
(15)	,,	H	H	NO_2	65	175—176	Yellow microneedles	a	,,	57·5	3·75	57·5	3·5
(16)	p-C_6H_4·OMe	H	H	H	79	164—165	Pale yellow needles	b	$C_{16}H_{14}O_4N_2$	64·0	5·0	64·4	4·7

[1] Uncrystallised product—usually substantially pure.
[2] a = Acetone; b = alcohol; c = aqueous acetone; d = acetone–alcohol.
[3] Repeated crystallisation from aqueous acetone caused cyclisation.
[4] Attempted crystallisation from acetone caused cyclisation.

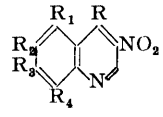
TABLE II.



	R.	Yield, %.[1]	M. p.	Form.	Solvent.	Formula.	Analysis, %. Found. C.	Found. H.	Found. N.	Calc. C.	Calc. H.	Calc. N.
(17)	Cl	46	170° (218—219°)	Pale yellow leaflets	Acetone	$C_{10}H_{10}O_3N_3Cl$	46·5	4·0	16·0	47·0	3·9	16·4
(18)	Br	35	170 (207—208)	Pale yellow cubes	Acetone	$C_{10}H_{10}O_3N_3Br$	39·8	3·5	13·5	40·0	3·4	14·0
(19)	I [2]	38	140 (183—184)	Pale yellow prisms	Acetone	$C_{10}H_{10}O_3N_3I,\frac{1}{2}H_2O$	33·9	2·7	—	33·7	3·1	—

[1] Yield of crude product.
[2] Insufficient of the compound was available for cyclisation.

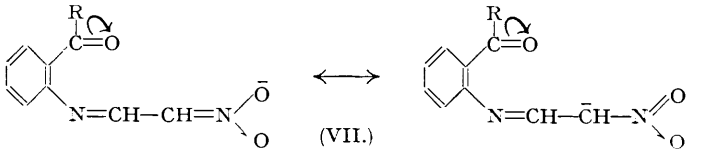
TABLE III.



R.	R_1.	R_2.	R_3.	R_4.	Yield, %.[1] A.	Yield, %.[1] B.	M. p.	Form.	Solvent.[2]	Formula.	Analysis, %. Found. C.	Found. H.	Calc. C.	Calc. H.
CH_3	H	H	H	H	92	Q	117—118°	Colourless needles	a	$C_{10}H_8O_2N$	63·3	3·8	63·8	4·25
,,	NO_2	H	H	H	0	75	131—132	Pale pink needles	b	$C_{10}H_7O_4N_3$	50·9	3·2	51·5	3·0
,,	H	NO_2	H	H	0	Q	168—169	Pale pink needles	c	$C_{10}H_7O_4N_3$	51·0	3·25	51·5	3·0
,,	H	H	NO_2	H	0	Q	182—183	Pale yellow needles	c	$C_{10}H_7O_4N_3$	51·95	3·0	51·5	3·0
,,	H	Cl	H	H	86	Q	149—150	Fawn needles	a	$C_{10}H_7O_2N_2Cl$	53·6	3·3	53·9	3·15
,,	H	H	Cl	H	60	Q	137—138	Colourless needles	b	$C_{10}H_7O_2N_2Cl$	54·1	3·5	53·9	3·15
,,	H	H	H	Cl	—[3]	Q	218—219	Colourless needles	b	$C_{10}H_7O_2N_2Cl$	54·55	3·4	53·9	3·15
,,	H	H	H	Br	—[3]	Q	200—201	Fawn needles	b	$C_{10}H_7O_2N_2Br$	45·3	2·3	44·95	2·6
,,	H	CH_3	H	H	44	Q	128—129	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·3	5·0	65·3	5·0
,,	H	H	H	CH_3[3]	—	—	116—117	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·25	4·9	65·3	5·0
,,	H	CH_3	CH_3	H	55	Q	152—153	Cream microneedles	b	$C_{12}H_{12}O_2N_2$	67·6	6·0	66·65	5·6
,,	H	CH_3O	CH_3O	H	32	Q	207—208	Cream microneedles	b	$C_{12}H_{12}O_4N_2$	58·2	5·3	58·1	4·9
,,	H	$-[CH_2]_3-$		H	76	Q	115—116	Colourless needles	a	$C_{13}H_{12}O_2N_2$	68·45	5·3	68·4	5·3
,,	H	$-[CH_2]_4-$		H	96	Q	135—136	Cream leaflets	b	$C_{14}H_{14}O_2N_2$	69·2	5·85	69·4	5·8
,,	H	H	Ac	H[3]	—	—	150—151	Colourless needles	a	$C_{12}H_{10}O_3N_2$	63·0	4·5	62·6	4·35
Ph	H	H	H	H	64	Q	109—110	Colourless needles	a	$C_{15}H_{10}O_2N_2$	71·4	4·1	72·0	4·0
,,	NO_2	H	H	H	0	?	175—176	Colourless needles	a	$C_{15}H_9O_4N_3$	61·5	2·7	61·0	3·1
,,	H	NO_2	H	H	0	Q	174—175	Buff needles	a	$C_{15}H_9O_4N_3$	61·1	3·15	61·0	3·1
,,	H	H	NO_2	H	0	Q	171—172	Pale yellow flakes	d	$C_{15}H_9O_4N_3$	60·8	3·0	61·0	3·1
p-C_6H_4·OMe	H	H	H	H	51	Q	128—129	Pale yellow plates	a	$C_{16}H_{12}O_3N_2$	68·0	4·4	68·6	4·3
2-C_5H_4N	H	H	H	H[3]	—	—	113—114	Pale yellow flakes	b	$C_{14}H_9O_2N_3$	67·0	4·0	66·9	3·6
											N, 17·3		N, 16·7	

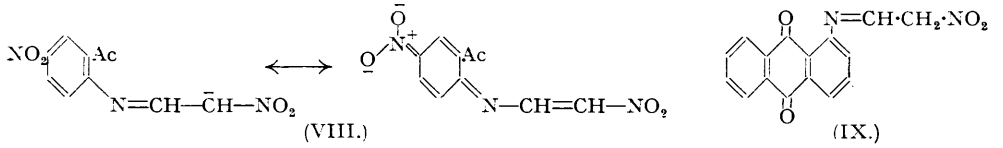
[1] A, dilute NaOH; B, activated alumina; Q, quantitative.
[2] a = Alcohol; *b* = aqueous alcohol; *c* = aqueous acetone; *d* = alcohol–acetone.
[3] See description on p. 403.

detracting from its strength as a pseudo-acid. The importance of the last effect is seen when it is remembered that this mode of cyclisation may involve the anion (VII) of the *aci*-form of (IV). Thus the 5-nitro-group will to a small extent increase the electrophilic nature



(VII.)

of the carbonyl group, and will greatly strengthen the pseudo-acid by increasing the stability of the anion through resonance (VIII), thus facilitating cyclisation. The 4-nitro-group, whilst having a smaller effect on the strength of the pseudo-acid [cf. the dissociation constants (10^5 K) of benzoic acid (6·27), *p*-nitrobenzoic acid (37·6), and *m*-nitrobenzoic acid (32·1); Watson,



(VIII.) (IX.)

" Modern Theories of Organic Chemistry," 1941, p. 27], will, on the other hand, exert its main influence by increasing the electrophilic character of the ketone group. In either case, under the faintly alkaline conditions represented by aqueous-acetone solution, cyclisation could be encouraged without serious interference from hydrolysis. With compounds of type (IV), however, electronegative substituents clearly facilitate hydrolysis, so much so that with the *Bz*-nitro-compounds the reaction is so rapid in cold alkali as to forestall cyclisation. In other cases, *e.g.*, that of 2-(2-*nitroethylideneamino*)-5-*methylacetophenone* (IV; R = Me, $R_1 = R_3 = H$, R_2 = Me), whilst hydrolysis would be slower, the strength of the pseudo-acid will be decreased, as will the electrophilic activity of the ketone group, so that the yield of 3-*nitro*-4 : 6-*dimethylquinoline* actually realised represents only the unpredictable balance of these complicated factors.

Clearly, the most satisfactory type of cyclising agent for use with compounds (IV) would be one which allowed the conversion of the side chain into the ionised *aci*-form, or alternatively was able to cyclise (IV) without ionisation, and in either case did not allow hydroxylic attack at the azomethine linkage. During experiments on the reaction between methazonic acid and *o*-aminoacetophenone it was noticed that quantitative ring-closure of (IV; R = Me, $R_1 = R_2 = R_3 = H$) to 3-nitrolepidine occurred in aqueous acetone in the presence of activated alumina. This procedure proved applicable, with equal success, in the case of substituted *o*-(2-nitroethylideneamino)acetophenones. Recovery of the substantially pure quinoline derivatives approached the theoretical, even in the cases of (IV; R = Me, $R_1 = H$, $R_2 = H$ or NO_2, $R_3 = NO_2$ or H). The only instance among acetophenone derivatives in which a concomitant degree of hydrolysis occurred under this treatment was that of 6-nitro-2-(2-nitroethylideneamino)acetophenone (IV; R = Me, $R_1 = NO_2$, $R_2 = R_3 = H$), the yield of 3 : 5-*dinitrolepidine* being 75%. This we attribute to steric hindrance between the nitro- and the acetyl group (see below).

The compounds (V), arising from 3-halogeno-2-aminoacetophenones, were also capable of cyclisation to 8-*halogeno*-3-*nitrolepidines* by treatment with alumina. As indicated above, the m. p. of the quinoline corresponded in each case to the second m. p. of the related compound (V).

The ambiguous wording of the original specification (G.P. 335,197) led Hollins (" The Synthesis of Nitrogen Ring Compounds," London, 1924, p. 285) to state that *o*-aminobenzophenone had been utilised in a quinoline synthesis with methazonic acid, but in fact this reaction was not mentioned, and 3-nitro-4-arylquinolines have not been described. Since compounds of the latter type promised to be interesting in several connections, we describe here the reaction of some 2-aminobenzophenones with methazonic acid, reserving for a later paper a description of some reactions of the products obtained.

o-Aminobenzophenone reacted with methazonic acid in acetone–hydrochloric acid to give a high yield of o-(2-*nitroethylideneamino*)*benzophenone*. 2-(2-*Nitroethylideneamino*)-4′-*methoxybenzophenone* was obtained similarly. The nitro-2-aminobenzophenones presented a further interesting parallel to the nitro-2-aminoacetophenones. Thus 3-nitro-2-aminobenzophenone failed to react with methazonic acid, presumably because of hydrogen bonding (VI; R = Ph).

The other isomers provided good yields (Table I) of 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)-*benzophenone*, which, as expected, proved to be much less labile than their acetophenone counterparts, surviving crystallisation without becoming cyclised.

(IV; R = Ph, $R_1 = R_2 = R_3 = H$) and (IV; R = *p*-C_6H_4·OMe, $R_1 = R_2 = R_3 = H$), on dissolution in dilute alkali, were quickly converted into 3-*nitro*-4-*phenyl*- and 3-*nitro*-4-*p*-*methoxyphenyl-quinoline*, respectively, some hydrolysis also occurring. On the other hand, the nitro-compounds were again completely hydrolysed in these circumstances. Once again, activated alumina proved a valuable cyclisation reagent, and by its aid 4- and 5-nitro-2-(2-nitroethylideneamino)benzophenone, as well as the derivatives of *o*-aminobenzophenone and 2-amino-4′-methoxybenzophenone, were cyclised quantitatively. The poor yield of 3 : 5-*dinitro*-4-*phenylquinoline* arising by alumina cyclisation we again attribute to the steric effect of the nitro-group.

It is interesting that 2-2′-aminobenzoylpyridine reacted with methazonic acid in dilute hydrochloric acid to give 3-*nitro*-4-2′-*pyridylquinoline* directly, presumably because of the increased electrophilic activity of the carbonyl group caused by protonisation of the pyridyl nitrogen atom in acid solution. In contrast 1-aminoanthraquinone provided 1-(2-*nitroethylideneamino*)*anthraquinone* (IX), but no method of cyclising this compound has yet been found; both caustic alkali and alumina effected complete hydrolysis, whilst sodium acetate–acetic anhydride left it unchanged.

Various reactions, absorption spectra, etc., of the products described above will be described in the future, as will be the reaction of methazonic acid with some aniline derivatives.

3-*Iodo*-2-*aminoacetophenone*, used in the present work, was obtained by reducing 3-*iodo*-2-*nitroacetophenone*, prepared by a Sandmeyer reaction on 2-nitro-3-aminoacetophenone. It was characterised by conversion into 8-*iodo*-4-*hydroxycinnoline* on diazotisation.

Experimental.

(M. p.s are uncorrected.)

Materials.—The ketones were obtained by known methods as follows: *o*-Aminoacetophenone, 3-, 4-, 5-, and 6-nitro-2-aminoacetophenone, 5-chloro-, 3-chloro-, and 3-bromo-2-aminoacetophenone (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405; Schofield and Theobald, *J.*, 1949, 796). 2-Nitro-3-aminoacetophenone (Leonard and Boyd, *loc. cit.*; cf. Schofield and Swain, *J.*, 1949, 1367). 4-Chloro-2-aminoacetophenone (Atkinson and Simpson, *J.*, 1947, 232). 2-Amino-3-methylacetophenone (Simpson, unpublished). 2-Amino-5-methyl-, 2-amino-4 : 5-dimethyl-, 2-amino-4 : 5-*cyclo*penteno-, and 2-amino-4 : 5-*cyclo*hexeno-acetophenone (Schofield, Swain, and Theobald, *J.*, 1949, 2399). 2-Amino-1 : 4-diacetylbenzene (Schofield and Theobald, *ibid.*, p. 2404). 6-Aminoacetoveratrone (Simpson, *J.*, 1946, 94). *o*-Aminobenzophenone (Hewett *et al.*, *J.*, 1948, 292). 2-Amino-4′-methoxybenzophenone (Simpson *et al.*, *loc. cit.*). 2-, 3-, 4-, 5-, and 6-Nitro-2-aminobenzophenone (Schofield and Theobald, unpublished). 2-2′-Aminobenzoylpyridine (Schofield, *J.*, 1949, 2408).

Methazonic acid was prepared as described by Steinkopf (*Ber.*, 1909, **42**, 2031), and the product freed from sodium chloride by extraction with ether.

2-(2-*Nitroethylideneamino*)*aryl Ketones.*—In each case the amino-ketone and methazonic acid were dissolved in water, concentrated hydrochloric acid, and, in some cases, acetone, the solution left overnight, and the product collected and crystallised. The following table, in conjunction with Table I, summarises

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
1	5·0	—	200	15	2·34	109—120°
2	0·2	5	5	1	0·22	180—182
3	2·0	150	25	25	2·17 [a]	204—206
4	0·5	10	5	5	0·38	207—208
5	1·0	25	25	10	0·9	187—188
6	0·5	10	5	5	0·35	194—196
7	0·2	—	5	1	0·16	188—191
8	0·2	5	5	2	0·14	196—201
9	0·2	—	5	1	0·16	175—180
10	1·0	100	—	20	0·61	216—218
11	1·0	150	5	5	1·09	212—213
12	1·0	20	10	10	1·05	130—133
13	1·0	20	5	10	0·85 [a]	156—158
14	1·0	30	5	10	0·92	168—170
15	0·5	50	5	5	0·42	175—176
16	1·0	50	50	15	1·04	162—163

[a] Slight concentration of the solution was effected in isolating the product.

the essential data. Weights of methazonic acid are omitted since in all cases 1 equiv. of this compound, with respect to the amino-ketone, was used. The products are, in general, yellow, highly crystalline

substances. Acetone is usually the best solvent for crystallisation, the compounds being but moderately soluble in alcohol, benzene, or chloroform, and almost insoluble in ether or water.

2-(2-*Nitroethylideneamino*)*acetophenone Oximes*.—In these cases the 3-halogeno-2-aminoacetophenones were dissolved in acetone, water, and hydrochloric acid, again with 1 equiv. of methazonic acid, and left for 24 hours. The product (see following table) only separated after dilution with water, or removal of acetone followed by dilution (see Table II).

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Vol. of water added (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
17	0·5	10	5	2	20	0·35	171—176°
18	0·2	5	2	1	10	0·10	176—178
19	0·5	5	1	1	10	0·26	138—140

Quinoline Derivatives.—(*a*) The nitroethylideneamino-compounds were stirred with 2N-sodium hydroxide solution, sometimes with gentle warming. In a few cases the substance dissolved, giving a yellow solution which rapidly deposited the quinoline derivative, or more usually deposition began before dissolution was complete. The products were collected and washed with water, whereupon in most cases substantially pure compounds were obtained. For analysis, crystallisation from acetone, aqueous acetone, alcohol, or aqueous alcohol was effected (Table III). Such alkaline treatment of *Bz*-nitro-2-(2-nitroethylideneamino)-compounds led only to recovery of the parent amine. In other cases, partial hydrolysis was indicated by acidification of the reaction liquor, followed by diazotisation and coupling with alkaline β-naphthol. The 3-halogeno-2-(2-nitroethylideneamino)acetophenone oximes dissolved readily in dilute alkali but no precipitate appeared subsequently, and the acidified solution gave no test for a primary amine.

(*b*) An acetone solution of the nitroethylideneamino-compound was treated with 10 parts of activated alumina, and left overnight. Usually the solution lightened in colour during the cyclisation. Filtration from alumina and removal of acetone usually gave the substantially pure product; occasionally slight stickiness was removed by trituration with a little cold ether. In the cases of 6-nitro-2-(2-nitroethylideneamino)acetophenone and the analogous benzophenone, the products, after removal of the acetone, were oily, and the pure quinoline was only isolated with some difficulty, especially in the second case where the parent amine and derived quinoline showed similar solubilities.

3-*Nitro*-7-*acetyl-lepidine*.—A solution of 2-amino-1 : 4-diacetylbenzene (1 g.) and methazonic acid (0·59 g.) in water (50 c.c.) and concentrated hydrochloric acid (10 c.c.) was left for 24 hours, and the precipitate collected, washed, and stirred with dilute alkali. Crude 3-nitro-7-acetyl-lepidine (0·50 g.) separated, and crystallised from alcohol in colourless needles, m. p. 150—151°.

3-*Nitro*-4-2′-*pyridylquinoline*.—A solution of 2-2′-aminobenzoylpyridine (1 g.) and methazonic acid (0·55 g.) in water (10 c.c.) and concentrated hydrochloric acid (5 c.c.) was left overnight, neutralised with sodium acetate, and extracted with chloroform. The dried (Na_2SO_4) extract yielded a sticky solid, crystallising in pale yellow flakes of 3-nitro-4-2′-pyridylquinoline (0·87 g.), m. p. 113—114°.

3-*Nitro*-4 : 8-*dimethylquinoline*.—A solution of 2-amino-3-methylacetophenone (0·1 g.) and methazonic acid (0·07 g.), in acetone (5 c.c.), water (5 c.c.), and concentrated hydrochloric acid (2 c.c.), was left for 24 hours. Removal of the acetone and addition of water precipitated the crude product (0·09 g., m. p. 103—105°), which separated from dilute ethanol in colourless microneedles, m. p. 116—117°.

3-*Iodo*-2-*nitroacetophenone*.—2-Nitro-3-aminoacetophenone (3 g.) in hydrochloric acid (30 c.c. of *ca*. 10N.) was diazotised at 0° with aqueous sodium nitrite (20%). Excess of nitrous acid was destroyed with urea, potassium iodide (3·4 g. in 10 c.c. of water) added, and the product collected after 1 hour. Trituration with a little ether, and crystallisation from benzene–ligroin (b. p. 60—80°), gave the substantially pure product (2·2 g.). 3-*Iodo*-2-*nitroacetophenone* formed buff leaflets, m. p. 97—98° (Found : C, 33·77; H, 2·46. $C_8H_6O_3NI$ requires C, 33·01; H, 2·08%).

3-*Iodo*-2-*aminoacetophenone*.—The above compound (2 g.) in acetic acid (10 c.c.) at 95° was treated with iron powder (1·5 g. added during 1 hour), additions of water (5 × 2 c.c.) being made at 10-minute intervals. After 1 hour more at 95° the mixture, after dilution, yielded to ether the practically pure product (1·51 g.). 3-*Iodo*-2-*aminoacetophenone* formed golden-yellow prisms, m. p. 57—58° (Found : C, 36·41; H, 4·11. C_8H_8ONI requires C, 36·80; H, 3·09%), when crystallised from ether–ligroin (b. p. 40—60°).

8-*Iodo*-4-*hydroxycinnoline*.—The hydrochloride suspension formed from the above amine (0·2 g.) and concentrated hydrochloric acid (5 c.c.) was diazotised at 0° with aqueous sodium nitrite (10%), and the solution left at room temperature for 5 days. The mixture was heated for a short time at 95°, and the precipitate collected (0·04 g.). 8-*Iodo*-4-*hydroxycinnoline* formed pale yellow leaflets, m. p. 261—262° (Found : C, 35·74; H, 1·88. $C_8H_5ON_2I$ requires C, 35·30; H, 1·85%), from ethanol.

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