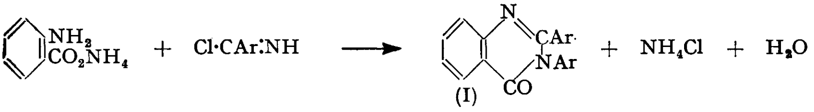
205. *Syntheses in the Quinazolone Series. Part I. Synthesis of 2 : 3-Diaryl-4-quinazolones.*

By Paul R. Levy and Henry Stephen.

2 : 3-Diaryl-4-quinazolones may be prepared in good yields (i) by condensation of *N*-arylbenzimidoyl chloride with ammonium anthranilate or methyl anthranilate, and (ii) by reduction of *N*-aroyl-*o*-nitrobenzamides.

Mumm and Hesse[1] obtained 2 : 3-diphenyl-4-quinazolone by treating a solution of *N*-phenylbenzimidoyl chloride in ether with aqueous sodium anthranilate. The method is unsuitable for general application, since the imidoyl chlorides are rapidly hydrolysed by water, giving quinazolones in low yield. The procedure was modified by condensing ammonium anthranilate with an *N*-arylbenzimidoyl chloride in acetone, in which both reactants are soluble, the progress of the reaction being indicated by the deposition of ammonium chloride. The weight of the latter did not correspond with the following reaction and the yield of diaryl-4-quinazolone did not exceed 35%.



(I)

A mixture of the quinazolone (I) with 30% of an *o*-aroylamino-*N*-arylbenzamide (V) was obtained in every case investigated, and in addition some *NN'*-diarylbenzamidine and a primary aromatic amine. The formation of the various compounds indicates

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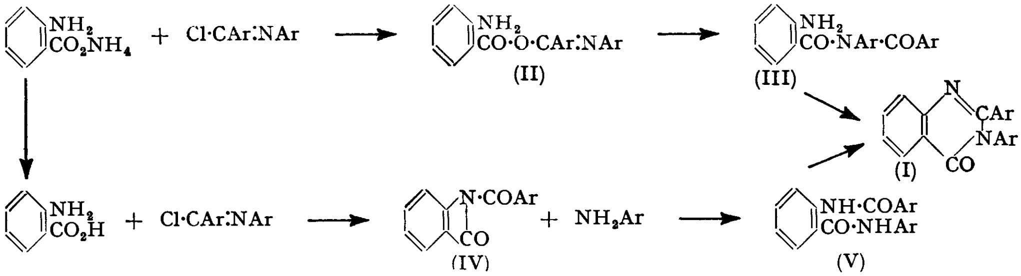
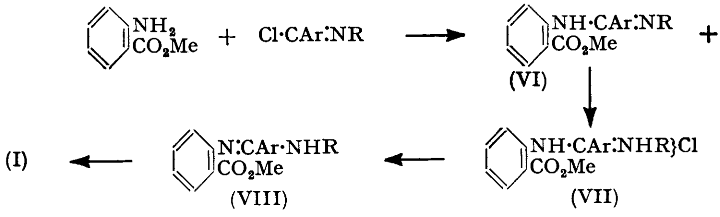
[1] Mumm and Hesse, *Ber.*, 1910, **43**, 2508.

that two reactions are taking place: condensation of benzimidoyl chloride with ammonium anthranilate to give the quinazolone (I), and with anthranilic acid to give the diamide (V). The second reaction is due to formation of anthranilic acid through the dissociation of ammonium anthranilate, which is appreciable in dry acetone even at 0°, and at higher temperatures the salt is almost completely dissociated.



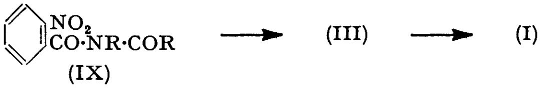
The formation of the diacylamine (III) by isomeric change of compounds of the type (II) has been established by Mumm and Hesse,[1] and the present investigation has shown that the condensation of the diacylamine (III) to give the quinazolone (I) takes place rapidly in acetone. The reaction between anthranilic acid and *N*-phenylbenzimidoyl chloride was also investigated by Mumm and Hesse,[1] who obtained benzoylanthranil (IV), aniline, and diphenylbenzamidine. The formation of *o*-benzamido-*N*-phenylbenzamide (V) by the action of aniline on benzoylanthranil at 170° is known.[2] The present investigation, however, has shown that diamides (V) and similar compounds are readily formed by the addition of primary aromatic amines to benzoylanthranil in acetone at 50°. The formation of the diamide (V) can be obviated by adding solid ammonium anthranilate to a solution of benzimidoyl chloride in dry acetone. The dissociation of ammonium anthranilate is minimised and a 70% yield of quinazolone is obtained.

N-Arylbenzimidoyl chlorides (1 mol.) condense with methyl anthranilate (2 mol.) in acetone rapidly at room temperature, yielding 80—90% of the 2 : 3-diarylquinazolone (the additional mol. of methyl anthranilate is used to combine with hydrogen chloride liberated). Less than 2 mol. of methyl anthranilate give a low yield of the quinazolone. It is assumed that the amidine (VI) is first formed and undergoes the well-known tautomeric



change to (VIII), the structure of which is now suitable for ring formation by elimination of methyl alcohol to give the quinazolone (I). The interconversion (VI) ⟶ (VIII) takes place by electromerisation of the cation of the salt (VII). This part of the investigation is being extended.

N-Aroyl-*o*-nitrobenzamides (IX) are readily prepared in good yields by condensing sodium *o*-nitrobenzoate with an arylimidoyl chloride in dry acetone. They are smoothly reduced by sodium dithionite in alcohol, to the diarylamines (III) which undergo immediate ring closure to the quinazolones (I).



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[2] (*a*) Anschütz, Schmidt, and Greiffenberg, *Ber.*, 1902, **35**, 3480; (*b*) Bogert *et al.*, *J. Amer. Chem. Soc.*, 1905, **27**, 6561; 1911, **33**, 949.

EXPERIMENTAL

The following imidoyl chlorides were obtained by the action of phosphorus pentachloride [3] or thionyl chloride [4] on the aroylamine: N-o-*methoxyphenylbenzimidoyl chloride*, b. p. 188—190°/6 mm. (90% yield) (Found: Cl, 14·2. $C_{14}H_{12}ONCl$ requires Cl, 14·5%); N-*phenyl*-α-*naphthimidoyl chloride* (81% yield), needles (from benzene), m. p. 95° (Found: Cl, 13·6. $C_{17}H_{12}NCl$ requires Cl, 13·4%); N-*phenyl*-o-*toluimidoyl chloride*, b. p. 174—177°/10 mm. (90% yield) (Found: Cl, 15·3. $C_{14}H_{12}NCl$ requires Cl, 15·45%).

Preparation of N-*Aroyl*-o-*nitrobenzamides*.—The imidoyl chloride (1 mol.) in twice its weight of dry acetone was mixed with sodium *o*-nitrobenzoate (1·1 mol.) in five times its weight of acetone. Precipitation of sodium chloride occurred immediately and after 1 hr. at room temperature the acetone was removed by distillation. The residue was extracted with boiling water to remove sodium chloride and excess of sodium *o*-nitrobenzoate, and the insoluble portion crystallised from an appropriate solvent. Yields of 90—95% (based on imidoyl chloride used) were obtained for the *compounds* listed in Table 1.

TABLE 1. N-*Aroyl*-o-*nitrobenzamides*, *o*-$NO_2 \cdot C_6H_4 \cdot CO \cdot NAr \cdot COAr'$.

					Found (%) :			Rqd. (%) :	
Ar	Ar′	M. p.	Form	Solvent	C	H	Formula	C	H
Ph	Ph	173—174° [a]	Needles	Aq. AcOH	69·2	4·0	$C_{20}H_{14}O_4N_2$	69·4	4·05
o-C_6H_4Me	Ph	131—132	Plates	EtOH	70·0	4·5	$C_{21}H_{16}O_4N_2$	70·0	4·4
m-C_6H_4Me	Ph	141—142	,,	AcOH	69·6	4·3 [b]			
p-C_6H_4Me	Ph	175—177	Needles	AcOH	69·9	4·6			
o-$C_6H_4 \cdot OMe$	Ph	122—123	,,	EtOH	66·9	4·2	$C_{21}H_{16}O_5N_2$	67·0	4·25
p-$C_6H_4 \cdot OMe$	Ph	114—115	,,	EtOH	67·1	4·25			
β-$C_{10}H_7$	Ph	176	Plates	AcOH	72·6	4·1	$C_{24}H_{16}O_4N_2$	72·7	4·0
Ph	α-$C_{10}H_7$	—	Needles	Aq. AcOH	72·5	4·1			
2 : 4-$C_6H_3Me_2$	Ph	113	Plates	EtOH	70·2	4·6	$C_{22}H_{18}O_4N_2$	70·6	4·8
Ph	*o*-C_6H_4Me	122—123	Needles	EtOH	69·8	4·5	$C_{21}H_{16}O_4N_2$	70·0	4·4
Ph	*p*-C_6H_4Cl	150—151	Flakes	AcOH	[c]	—	$C_{20}H_{13}O_4N_2Cl$	—	—

[a] Obtained also from *o*-nitrobenzimidoyl chloride and sodium benzoate. [b] Found: N, 7·7. Reqd.: N, 7·8%. [c] Found: Cl, 7·3. Reqd.: Cl, 7·4%.

Preparation of 2 : 3-*Diaryl*-4-*quinazolones*.—(1) Solutions of the arylimidoyl chloride (1 mol.) and ammonium anthranilate (1·5 mol.) in acetone at room temperature were mixed and after 2 hr. the precipitate of ammonium chloride was filtered off. Water was added to incipient crystallisation, and the mixture set aside for 12 hr. This crystalline deposit (A) was filtered off and washed with acetone. The washings and filtrate, on evaporation, gave further crystals (B). Examination of (A) from condensations of ammonium anthranilate with *N*-phenyl-, *N*-*m*-tolyl-, *N*-*p*-methoxyphenyl-, and *N*-β-naphthyl-benzimidoyl chloride proved that (A) was in each case an *o*-aroylamino-*N*-arylbenzamide, which when heated above the m. p. gave the corresponding 2 : 3-diaryl-4-quinazolone. For comparison the *o*-arylamino-*N*-arylbenzamides were prepared in good yields from benzoylanthranil (1 mol.) and the appropriate primary aromatic amine (1 mol.) either by heating them [2a] at 180° or by refluxing them in acetone for 1 hr., water being then added dropwise to the boiling solution until a precipitate formed. After cooling, the precipitate was filtered off and crystallised.

o-Benzamidobenzanilide crystallises from ethyl benzoate in needles, m. p. 277° (Found: C, 75·8; H, 5·0. Calc. for $C_{20}H_{16}O_2N_2$: C, 75·9; H, 5·1%), *o*-benzamidobenzo-*m*-toluidide from acetic acid in needles, m. p. 224° (Found: C, 76·1; H, 5·6. Calc. for $C_{21}H_{18}O_2N_2$: C, 76·3; H, 5·5%), o-*benzamidobenzo*-p-*anisidide* from chlorobenzene in needles, m. p. 228° (Found: C, 73·0; H, 5·1. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2%), and *o*-benzamidobenzo-β-naphthalide from ethyl benzoate in needles, m. p. 258° (lit.,[5] 258°).

Benzoylanthranil was obtained by heating a mixture of anthranilic acid (25 g.) with benzoyl chloride (60 g.) at 150° for 1½ hr. After removal of benzoic acid and excess of benzoyl chloride at 5 mm., the residue of benzoylanthranil [2a] was crystallised from acetic anhydride (28 g.; m. p. 123°). It was also prepared by treating benzoylanthranilic acid (10 g., 1 mol.) with a large excess (20 g.) of thionyl chloride: when reaction had ceased, the excess of thionyl chloride was removed and the residual benzoylanthranil distilled at 189—192°/8 mm. (yield 9·5 g., 97%; m. p. 123°).

Crystals (B) were basic and readily soluble in 2N-hydrochloric acid, and after filtration of the

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[3] Wallach, *Annalen*, 1877, **184**, 1.

[4] Von Braun and Pinkernelle, *Ber.*, 1934, **67**, 1218.

[5] de Diesbach, Jacobi, and Taddei, *Helv. Chim. Acta*, 1942, **23**, 469.

acidic solution addition of aqueous ammonia gave a copious precipitate of 2 : 3-diaryl-4-quinazolone.

An alternative procedure, which eliminated the formation of *o*-aroylamino-*N*-arylbenzamides and gave good yields of the quinazolones, was to add, for example, finely powdered ammonium anthranilate (1·7 g., 1·1 mol.) to a solution of *N*-phenylbenzimidoyl chloride (2·15 g., 1 mol.) in acetone (15 c.c.) with shaking. After 1 hr. at room temp. the solution was poured into cold water (500 c.c.), and the precipitated base filtered off. Two crystallisations from dilute alcohol gave 2 : 3-diphenyl-4-quinazolone (70%, 2 g.), m. p. and mixed m. p. 158—159°.

(2) The arylimidoyl chloride (1 mol.), dissolved in approx. twice its weight of dry acetone, was added slowly with shaking to a solution of methyl anthranilate (2 mol.) in ten times its volume of acetone at 0°. After 12 hr. at room temperature the acetone was removed and the gummy residue extracted with warm concentrated hydrochloric acid, then filtered off, and the filtrate was poured into a large excess of cold concentrated aqueous ammonia. Unchanged methyl anthranilate was removed in a current of steam, and the residue filtered off and crystallised. The yields of 2 : 3-diaryl-4-quinazolones varied from 75 to 85%.

TABLE 2. 2 : 3-*Disubstituted quinazolones.*

2-Subst.	3-Subst.	Method (yield)	M. p.	Form	Solvent	Found (%) : C	Found (%) : H	Formula	Reqd. (%) : C	Reqd. (%) : H
Ph [a]	Ph	1, 2, 3	158°	Needles	EtOH	—		—	—	—
Ph	*o*-C_6H_4Me	3 (75%)	142—143	Plates	Aq. EtOH	80·8	5·1 [b]	$C_{21}H_{16}ON_2$	80·7	5·2
Ph [c]	*m*-C_6H_4Me	1, 2, 3 (80%)	144—145	Needles	Aq. EtOH	80·55	5·3			
Ph	*p*-C_6H_4Me	3 (90%)	180—181	Plates	EtOH	80·7	5·05 [d]			
Ph	*o*-C_6H_4·OMe	2, 3 (80%)	159—160	Needles	Aq. EtOH	76·8	5·0 [e]	$C_{21}H_{16}O_2N_2$	76·8	4·9
Ph	*p*-C_6H_4·OMe	1, 2, 3 (90%)	197	Leaflets	EtOH	76·8	4·9			
Ph	β-$C_{10}H_7$	,,	182—183	Needles	Aq. EtOH	82·6	4·6	$C_{24}H_{16}ON_2$	82·8	4·6
Ph [f]	2 : 4-$C_6H_3Me_2$	2, 3 (75%)	135—136	Plates	—	80·9	5·4 [g]	$C_{22}H_{18}ON_2$	81·0	5·5
p-C_6H_4Cl	Ph	2, 3 (80%)	175—176	Needles	Aq. EtOH	[h]		$C_{20}H_{13}ON_2Cl$	—	—
o-C_6H_4Me	Ph	3 (80%)	152	Plates	EtOH	80·6	5·2 [i]	$C_{21}H_{16}ON_2$	80·7	6·2
α-$C_{10}H_7$	Ph	2, 3 (90%)	180	Prisms	Aq. EtOH	82·5	4·3	$C_{24}H_{16}ON_2$	82·8	4·6

[a] Hirwe and Kulkarni [6] give m. p. 186°. Mumm *et al.*[1] and de Diesbach *et al.*[5] give 158°. [b] Found : N, 9·1. Reqd. : N, 9·0%. [c] Hirwe *et al.*[6] give m. p. 145°, de Diesbach *et al.*[5] give 139°. [d] Found : N, 9·0. Reqd. : N, 9·0%. [e] Found : N, 8·8. Reqd. : N, 8·5%. [f] de Diesbach *et al.*[5] give m. p. 130°. [g] Found : N, 8·4. Reqd. : N, 8·6%. [h] Found : N, 8·4. Calc. : N, 8·6%. [i] Found : N, 8·8. Reqd.: N, 9·0%.

(3) Sodium dithionite (hydrosulphite) (10 mol.) in the minimum volume of cold water was added dropwise to a boiling ethanolic solution of the nitro-compound (1 mol.). Any material which separated was brought into solution by addition of solvent. The alcohol was removed by distillation and the residual liquid poured into a large volume of cold water. The precipitated material was filtered off, washed repeatedly with boiling water to remove inorganic matter and extracted with warm concentrated hydrochloric acid to dissolve the quinazolone. An insoluble residue of unchanged nitro-compound was filtered off, the filtrate poured into a large excess of aqueous ammonia, and the precipitated base crystallised. The yields of quinazolones were of the order of 90% after allowance for the nitro-compound recovered. Attempts to reduce the nitro-compounds with tin and hydrochloric acid gave small yields (15%) of quinazolones; better yields (40%) were obtained by using alcohol to dissolve the nitro-compound. Quinazolones prepared are reported in Table 2.

3-m-*Nitrophenyl*-2-*phenyl*-4-*quinazolone*. The best yield (60%) was obtained by heating a mixture of *m*-nitroaniline (2·8 g., 1 mol.) and benzoylanthranil (4·5 g., 1 mol.) at 300° for 1 hr. After cooling, the melt was extracted with acetic acid (50%) (charcoal); the solution deposited yellow needles of the *quinazolone*, m. p. 199° (Found : C, 70·1; H, 3·8; N, 12·2. $C_{20}H_{13}O_3N_3$ requires C, 70·0; H, 3·8; N, 12·25%). Methods 1 and 2 gave 15% yields.

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[6] Hirwe and Kulkarni, *Proc. Indian Acad. Sci.*, 1942, **16**, *A*, 296.