[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

CONDENSATIONS OF AROMATIC AMINES WITH FORMALDEHYDE IN MEDIA CONTAINING ACID. VI. THE USE OF FORMIC ACID IN THE PREPARATION OF 3,6-DISUBSTITUTED DIHYDROQUINAZOLINES FROM PARA-SUBSTITUTED AMINES, AND FROM THEIR BIS(ARYLAMINO)-METHANES AND SCHIFF BASES

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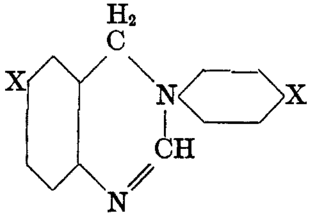
Quinazolines of the type shown (I) have been obtained from para-substituted arylamines by condensation with formaldehyde in aqueous acid solution[1], and by treatment of *N*-(2-aminobenzyl)-arylamines with formic acid or ethyl orthoformate[2]. The first procedure gives small yields of dihydroquinazoline as one of several products whose separation may be troublesome and wasteful. The second method, involving a familiar ring-closure, appears to be dependable but presents the disadvantage that the required aminobenzylarylamines are obtainable only by a slow and cumbersome method[3]. These considerations, and others discussed below, made it appear that a satisfactory method for the preparation of dihydroquinazolines (I) might be based upon a combination of the two methods, *i.e.*, by starting with the amine and formaldehyde, or with other precursors of the aminobenzylarylamine and by operating under conditions favorable to formation of the aminobenzylarylamine, and in presence of formic acid to ensure the final ring-closure. This paper



I

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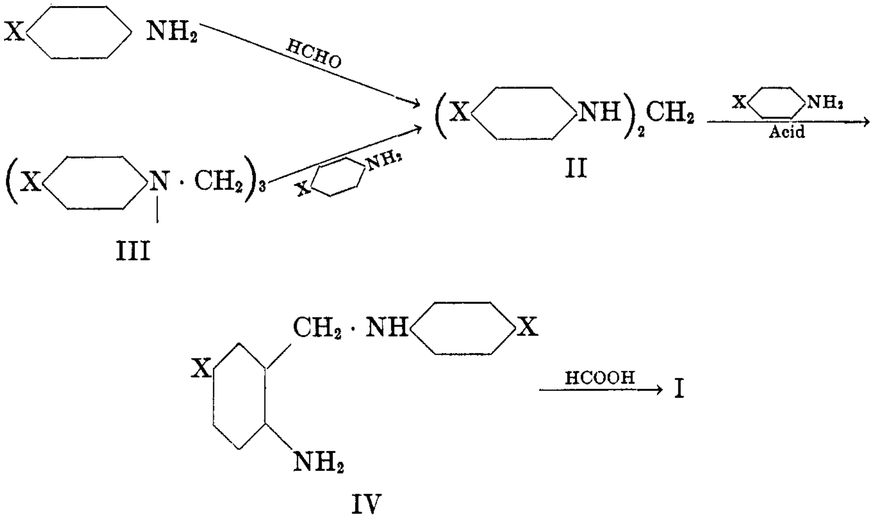
[1] See the preceding paper of this series [WAGNER AND EISNER, *J. Am. Chem. Soc.*, **59**, 879 (1937)] for recent work and literature.

[2] v. WALTHER AND BAMBERG, *J. prakt. Chem.*, [2], **73**, 209 (1906).

[3] *Ger. Pat.*, **105**, 797; *Friedl.* **5**, 84.

describes experiments in which this possibility was tested, and which showed that dihydroquinazolines may be obtained conveniently from para-substituted arylamines, their methylenebisarylamines or their trimeric Schiff bases, as shown in the reaction scheme.



II

III

IV

The compounds used as starting materials were *p*-toluidine, *p*-anisidine, *p*-phenetidine, *p*-chloroaniline, and *p*-bromoaniline, and corresponding methylenediarylamines (II) and Schiff bases (III). The final step has been realized independently for the bases (IV) obtained from *p*-toluidine[2], *p*-chloroaniline, and *p*-bromoaniline[1].

1. Dihydroquinazolines from para-substituted amines.—With the amine and formaldehyde as initial reactants, yielding first the methylenebisarylamine (II), conversion of the last-named to the aminobenzylarylamine (IV) requires acid and amine, usually provided as amine hydrochloride. It was found that the formic acid added to effect ring-closure with IV would serve also as the acid needed for formation of the latter from II; the needed amine was supplied presumably by hydrolysis of some II by the aqueous acid. After the reaction considerable amine was present as the formyl derivative, and it is likely that this or other formyl derivative was instrumental in the ring-closure[4].

Interaction of amine, formaldehyde and formic acid at water-bath temperature yielded in each case the expected dihydroquinazoline, present in the residue left after the reaction mixture was made strongly alkaline

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[4] See *e.g.*, PAAL AND BUSCH, *Ber.*, **22**, 2686 (1889); *Ger. Pat.* **51**, 712, *Friedl.* **2**, 125; NIEMENTOWSKI, *J. prakt. Chem.*, [2] **51**, 564 (1895); KULISCH, *Chem. Zentr.* **1899**, I, 847.

(to decompose formylamine) and steam-distilled. Yields averaged 20 to 30 per cent., except in the case of *p*-bromoaniline, which gave a 10 per cent. yield. Results appear in Table I.

The steam-volatile material was found, in the cases examined, to consist of the original amine and its methyl and dimethyl derivatives. Methylation is to be expected in such reactions[5], but in these experiments was due in part to the reducing action of formic acid[6], as shown by the characteristic effervescence and by the extent of the methylation.

2. Dihydroquinazolines from methylenediarylamines.—Cairncross and Bogert[7] reported a single trial of this method, using the ethyl ester of methylene-N,N′-bis(*p*-aminobenzoic acid), but under strongly hydrolyzing conditions, and obtained a 9 per cent. yield of the corresponding dihydroquinazoline. In the present study the procedure used by Cairncross and Bogert was not tested with other methylenebisarylamines, for a consideration of the reactions involved indicated the advisability of different conditions.

TABLE I

Preparation of Dihydroquinazolines from Para-substituted Amines, Formaldehyde, and Formic Acid

AMINE	AMINE, G.	HCOOH, EQUIV.[a]	HCHO, EQUIV.	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE G.	DIHYDROQUINAZOLINE %[b]
p-Toluidine	25	2.1	0.5	12.7	5.7	20.6
	25[c]	2.1	1.0	6.0	7.2	26.3
	25	3.4	0.5	11.8	6.3	22.8
	25	1.3 + 1.7	0.5	9.6	6.8	24.7
p-Anisidine	12.3[d]	1 + 2	0.6	0.7	3.0	22.0
p-Phenetidine	10	2.1	0.6	4.0	2.4	22.2
	10	2.1	1.1	3.9	3.3	30.5
p-Chloroaniline	10.6	1 + 2	0.5	5.1	2.4	20.9
p-Bromoaniline	17.2	1 + 2	1.0	6.8	1.9[e]	10.4

[a] When two quantities are given the formic acid was added in two stages.

[b] Yields are calculated on ratio 2 amine: 1 quinazoline.

[c] Average of 4 experiments.

[d] Average of 2 experiments.

[e] Product was isolated through the recrystallized hydrochloride, probably with considerable loss. This experiment, gave also 1.5 g. of the base of m.p. 134–5° previously reported (Ref. 1) as one product of the condensation of *p*-bromoaniline and formaldehyde in dilute hydrochloric acid solution.

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[5] Maffei *et al.*, Ref. I; Eisner and Wagner, *J. Am. Chem. Soc.*, **56**, 1938 (1934).

[6] Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933); *cf.* Eisner and Wagner, *ibid.*, **56**, 1941 (1934); footnote.

[7] Cairncross and Bogert, *Coll. Czechoslovak. Chem. Comm.*, **7**, 57 (1936).

The intermediate formation of the aminobenzylarylamine (IV) from the methylenebisarylamine (II) requires amine, amine-salt and conditions not strongly hydrolytic. In preliminary experiments methylenebis(*p*-toluidine) and *p*-toluidine, with formic acid somewhat more than equivalent to the latter, were warmed together to promote formation of *o*-amino-*m*-xylyl-*p*-toluidine (IV); a moderate excess of formic acid was added and the heating was continued. Yields of dihydroquinazoline averaged 21.7 per cent.

At this stage of the work there became available the results of Simons' study[8] of the reactions in the system including methylenebisarylamine and amine salt, found to yield the dihydroquinazoline and also its precursors (IV and the tetrahydroquinazoline), as well as free amine, either split out during the reactions or left residually. All the other compounds present are convertible to dihydroquinazoline: aminobenzylarylamine by formic acid, free amine by joint action of formaldehyde and formic acid, and (as shown in the experimental part) tetrahydroquinazoline by action of formic acid. The procedure developed to take advantage of these apparent possibilities for obtaining the dihydroquinazoline involved heating methylenebisarylamine and amine hydrochloride in the molecular ratio of five to one for an hour on the water-bath, addition of some formaldehyde and a moderate excess of formic acid, and continuation of the heating. Yields of the dihydroquinazolines ranged from 27 to 38 per cent. Results are presented in Table II.

TABLE II

PREPARATION OF DIHYDROQUINAZOLINES FROM METHYLENEBISARYLAMINES

METHYLENEBISARYLAMINE	AMINE, G.	AMINE-HCL, EQUIV.	HCHO, EQUIV.	HCOOH, EQUIV.	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE	
						G.	%[a]
$(CH_3C_6H_4NH)_2CH_2$	11.3	0.2	0.12	4	0.5	3.5	27.0
	11.3	0.2	0.5	4	2.3	3.9	30.0
$(CH_3OC_6H_4NH)_2CH_2$	5.20[b]	0.3	1.2	8	1.2	2.29	36.7
$(C_2H_5OC_6H_4NH)_2CH_2$	5.70	0.3	1.2	8	1.5	2.31	33.7
$(ClC_6H_4NH)_2CH_2$	1.00	0.65	1.7	10	0.17	0.52	37.6
$(BrC_6H_4NH)_2CH_2$	4.00	0.65	2.2	14	0.67	1.72	31.6

[a] Yields are calculated on the assumption that methylenediarylamine and amine hydrochloride are both convertible to dihydroquinazoline.

[b] Average of 2 experiments.

3. Dihydroquinazolines from trimeric Schiff bases.—The method used was based on the preceding, and on consideration of the fact that the

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[8] SIMONS, *J. Am. Chem. Soc.*, **59**, 518 (1937).

initial step is the formation of the methylenediamine, a change which requires presence of free amine:

$$\frac{1}{3}\,(Ar\cdot N\cdot CH_2)_3 + ArNH_2 = ArNH\cdot CH_2\cdot NHAr.$$

For the first stage of the reaction there was heated a mixture of the Schiff base and free amine in a molar ratio of about one to three, and in presence of amine hydrochloride in amounts well above the minimum found effective by Simons[8]. There were then added formaldehyde and formic acid, and the heating was continued. By this procedure the yields of dihydroquinazolines varied from 22 to 39 per cent. Results appear in Table III.

Methods 2 and 3 gave better yields and less resinous material than the first method, and a smaller proportion of methylated products. The methylenediamines and Schiff bases are readily obtained as starting materials and may be used without careful purification.

TABLE III

PREPARATION OF DIHYDROQUINAZOLINES FROM TRIMERIC SCHIFF BASES

SCHIFF BASE	BASE, G.	AMINE-HCL, EQUIV.[a]	AMIEN, EQUIV.[a]	HCHO, EQUIV.[a]	HCOOH, EQUIV.[a]	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE	
							G.	%[b]
$(CH_3C_6H_4NCH_2)_3$	1.80	1.4	3	5	30	0.48	1.44	32.6
$(CH_3OC_6H_4NCH_2)_3$	4.50	0.56	3	1.1	18	0.20	2.50	25.4
$(C_2H_5OC_6H_4NCH_2)_3$	5.00	0.58	3.4	2.2	17.6		3.42	29.2
$(ClC_6H_4NCH_2)_3$	5.00	0.51	3.3	2.1	16.3		2.43	21.6
$(BrC_6H_4NCH_2)_3$	2.10	1.3	3.9	6.5	40		2.20	39.1

[a] The equivalencies given are calculated with reference to the trimeric Schiff base, and do not properly suggest the reaction relationships.

[b] Calculations of percentage yields are based on the assumption that all starting materials (Schiff base, amine and amine-HCl) are convertible to dihydroquinazoline.

EXPERIMENTAL

Methylenebisarylamines.—These starting compounds were made from amine and formaldehyde (0.5 equivalent) in presence of ethyl alcohol and potassium hydroxide.[11] The reaction mixture was heated on the water bath for several hours, and was then cooled and saturated with carbon dioxide. Alcohol was added to dissolve the product, which was obtained in several crops by chilling and progressive dilution with water. Methylenebis(*p*-anisidine) could not be recrystallized from either dilute alcohol or ether, as it was recoverable only as trimeric methylene-*p*-anisidine. The exceptional instability of this diamine was mentioned by Bischoff and Reinfeld[9]. The other compounds were crystallizable, though with considerable loss. Methylenebis(*p*-toluidine) and methylenebis(*p*-anisidine) have been characterized satisfactorily[11]. Methylenebis(*p*-chloroaniline) was obtained from ligroïn as a nearly

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[9] BISCHOFF, *Ber.*, **31**, 3244 (1898); BISCHOFF AND REINFELD, *ibid.*, **36**, 41 (1903); LEPETIT, *Atti. accad. Lincei*, [5], **26**, I, 172 (1917).

white crystal meal of m.p. 59–60°. Bischoff and Reinfeld[12] reported acceptable analytical results for this compound, but no molecular weight, so this was determined. Calculated for $C_{13}H_{12}N_2Cl_2$: mol. wt., 267. Found: mol. wt. (benzene), 252, 257.

Methylene-N,N′-*bis*(*p-phenetidine*).—White crystal meal from dilute alcohol or from ligroïn; m.p. 75° obs.

Anal. Calc'd for $C_{17}H_{22}N_2O_2$: C, 71.33; H, 7.76; N, 9.78; mol.wt., 286.

Found: C, 71.55; H, 7.94; N, 9.73, 9.72; mol.wt. (benzene), 293, 297. In molten camphor there were obtained the molecular weight values 218 and 228, indicating fission at 175°.

It appears that the compound of m.p. 89° previously reported by Bischoff[9] to be this diamine was the trimeric Schiff base described below. Bischoff's analytical values for carbon, hydrogen and nitrogen represent a total deficiency of 1.26% and do not well support the diamine formula; the values for hydrogen and nitrogen would be acceptable for the Schiff base. Bischoff reported no molecular-weight determination.

Methylene-N,N′-*bis*(p-*bromoaniline*).—This compound was obtained in white crystalline clumps from dilute alcohol. The yield was 80%, and the m.p. 92° obs.

Anal. Calc'd for $C_{13}H_{12}Br_2N_2$: C, 43.84; H, 3.37; N, 7.86; Br, 44.91; mol. wt., 356.

Found: C, 43.88, 43.93; H, 3.39, 3.50; N, 7.42, 7.51, 7.51; Br, 44.61, 44.76; mol. wt. (benzene), 366, 343. In molten camphor the indicated molecular weight values were 306 and 318, indicating instability at 175°.

Houben and Arnold[10] designated as methylenebis(*p*-bromoaniline) a base of m.p. 181° (decomp.) obtained from *p*-bromoaniline and methyl chloromethyl sulfate. Their complete analysis appears to be unexceptionable, but they report no molecular weight, and the melting point seems to be entirely too high for the compound named. As shown in a previous paper[1] the trimeric Schiff base melts at 169° (turbid), but the possibility that this is the base described by Houben and Arnold appears to be excluded by their analytical values for carbon and bromine.

That the base of m.p. 92° described above is methylenebis(*p*-bromoaniline) may be inferred from the fact that it was obtained in 80% yield from *p*-bromoaniline and 0.5 equivalent of formaldehyde. The identification is supported by the analytical values given, and by the results of the two chemical tests of structure which follow.

(*1*) *Cleavage by reduction.*—Cleavage of diamines by strong reduction[13] yields primary and secondary amines as principal products, with not more than a small amount of tertiary amine, the last obtained no doubt as a result of incidental methylation by some formaldehyde formed from the diamine by hydrolysis. The base of m.p. 92°, when split by reduction, gave the results just stated. Three grams of the compound was ground with 6 g. of zinc dust, and the mixture was added in small portions to 40 cc. of concentrated hydrochloric acid kept at 0°. After about an hour the excess zinc was dissolved by gentle warming, and the clear solution was made alkaline and steam-distilled. The steam-volatile oil was examined by the Hinsberg-Kessler procedure. There were obtained 2.05 g. of *N*-(*p*-bromophenyl)benzene-

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[10] Houben and Arnold, *Ber.*, **41**, 1565 (1908).

[11] Eberhardt and Welter, *ibid.*, **27**, 1804 (1894); Bischoff, Ref. 9; Bischoff and Reinfeld, Ref. 9.

[12] Bischoff and Reinfeld, *Ber.*, **36**, 46 (1903).

[13] Miller and Wagner, *J. Am. Chem. Soc.*, **54**, 3698 (1932), and unpublished results.

sulfonamide (m.p. 135° obs.), equivalent to 1.13 g. of *p*-bromoaniline; 0.80 g. of the secondary amine derivative (m.p. 74–75° obs.), equivalent to 0.46 g. of methyl-*p*-bromoaniline; 0.15 g. of dimethyl-*p*-bromoaniline picrate (m.p. 138° obs.), equivalent to 0.07 g. of the tertiary amine.

(2) Conversion to trimeric Schiff base by formaldehyde.—Treatment of diamines with excess formaldehyde converts them into Schiff bases[14]. The base of m.p. 92° (1.78 g.) was dissolved in alcohol and treated with formaldehyde (5 cc. of 37% formalin). The mixture was allowed to stand for some hours, and water was added to incipient turbidity. The mixture on further standing deposited an amorphous material, viscous at first but later solid which was separated and crystallized from dilute alcohol. The product (0.68 g.) was crystallized from ligroïn. It melted at 166° (turbid); a mixture with trimeric methylene-*p*-bromoaniline melted at 165.5° obs. (turbid).

The foregoing evidence establishes the base of m.p. 92° as methylenebis(*p*-bromoaniline).

*Methylene-*p*-phenetidine.*—This Schiff base was made by the general method[13]. The yield was 88% crude, and 69% after crystallization from ligroïn. Like the corresponding compound from *p*-bromoaniline[1], this base crystallized in long flexible needles, much matted; m.p. 90° obs.

Anal. Calc'd for $(C_9H_{11}NO)_3$: C, 72.48; H, 7.38; N, 9.39; mol. wt., 450.

Found: C, 72.64, 72.48; H, 7.51, 7.29; N, 9.23, 9.31; mol. wt. (benzene), 435, 450. In molten camphor there were obtained molecular weight values of 291 and 288, indicating partial depolymerization at 175°.

The designation of this compound as cyclic trimeric methylene-*p*-phenetidine was supported by the results of cleavage[15]. Reduction of 2.00 g. of the base by zinc dust and cold concentrated hydrochloric acid gave 1.40 g. of steam-volatile oil, which by the Hinsberg procedure yielded derivatives of primary and secondary amines, and 0.19 g. of a tertiary amine of m.p. 35°. This was found by mixture melting point test to be identical with dimethyl-*p*-bromoaniline (m.p. 35°) made by methylation of *p*-bromoaniline with methyl sulfate. The picrates (m.p. 141° obs.) likewise were shown to be identical.

Preparation of Dihydroquinazolines

Isolation procedure.—The manner in which the reaction mixtures were worked up was fairly uniform for all the experiments. When the heating period was at an end the mixture was made strongly alkaline with sodium hydroxide and was submitted to steam-distillation. The basic products in the distillate were in some experiments taken up in ether, and the extract was dried with sodium sulfate, was filtered into a tared beaker, and the mixture of bases was weighed after evaporation of the ether. In some cases the mixture was examined by the Hinsberg-Kessler procedure to obtain evidence of methylation.

The residue not volatile with steam was generally yellow and liquid or soft while hot, but became solid on cooling. It was removed, air-dried, and then extracted with ether to remove the sticky, resinous material which made unsatisfactory the direct crystallization of the dihydroquinazoline after dissolving the mass in alcohol or ligroïn. The dihydroquinazolines considered in this paper are very slightly soluble in cold ether. The simpler extraction procedure was to cover the solid with ether in a small beaker and to press and disintegrate the mass by manipulation with

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[14] Ingold and Piggott, *J. Chem. Soc.*, **123**, 2745 (1923).

[15] Wagner, *J. Am. Chem. Soc.*, **54**, 660 (1932); Miller and Wagner, Ref. 13.

a glass rod with flattened end. As the resins dissolved the dihydroquinazoline remained as a finely granular residue. After chilling of the beaker in ice, the solid was collected in a small Buchner funnel, and beaker and product were washed with small portions of chilled ether. Alternatively the crude residue from the steam distillation was extracted with ether in a Soxhlet apparatus. Extraction of the dihydroquinazoline was slow, but the product crystallized out in large part in the flask. The operation was checked at a time when nearly all the ether was in the extraction chamber, with only enough in the flask to hold the resins in solution. The crystals were filtered off and washed sparingly with chilled ether. The first procedure was much the more rapid. The crude dihydroquinazolines isolated in these ways were in many experiments white or nearly so, and practically pure. They were recrystallized from hot alcohol suitably diluted.

The quantity of resinous material was greatest in experiments in which amine was taken as starting material, and in some cases represented a large part of the original amine. The resins were examined for isolable compounds in several experiments, but with little success. They appeared to be mixtures of bases, some of moderate molecular weights and others gluey and intractable. The resins dissolved in hot dilute hydrochloric acid, and on chilling the solution or on adding excess of concentrated hydrochloric acid precipitates of hydrochlorides were obtained. In alcohol solutions of the resins picric acid produced heavy precipitates of picrate mixtures of indefinite melting points. In several experiments with *p*-toluidine various treatments of the resinous material yielded three distinct picrates, of m.p. 210°, 203° and 187° obs., not identified. The last was not identical with the picrates of *p*-toluidine or Tröger's base, both of which melt near 187°.

1. Dihydroquinazolines from amines, formaldehyde, and formic acid.—The amine was treated with 0.5 to 1 equivalent of 37% formalin, and about 2 equivalents of 90% formic acid was added while the mixture was cooled under the tap. The deep red solution was heated for several hours on the water-bath. A more or less brisk effervescence, indicative of methylation[6] was sustained for a time. In some experiments the amine was first treated with 1 equivalent of formic acid and 0.5 to 1 equivalent of formaldehyde, and the mixture was heated, this procedure being designed to favor formation of the diamine and then the aminobenzylarylamine. There were then added more formaldehyde and an excess of formic acid, and the heating was continued. This procedure showed no superiority over the first. Results of trials by these methods appear in Table I.

2. Dihydroquinazolines from methylenebisarylamines.—The methylenebisarylamine was mixed with one-fifth equivalent or more of amine hydrochloride and the mixture was heated on the water bath for an hour. A quantity of formaldehyde nearly equivalent to the amine and amine salt taken initially was added, followed by formic acid in excess, and the mixture was heated further for about two hours. Results of the trials are given in Table II.

3. Dihydroquinazolines from trimeric Schiff bases.—A mixture of the methylenearylamine with 3 equivalents of the corresponding amine and one-half equivalent or more of the amine hydrochloride was heated for an hour on the water bath. The preparation was completed as in the preceding method, by addition of formaldehyde and formic acid, followed by further heating. Results by this method appear in Table III.

3-(p-Anisyl)-6-methoxy-3,4-dihydroquinazoline.—This compound, not previously described, was obtained in colorless plates of m.p. 136° obs., or 138° corr.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44; CH_3O, 23.1; mol. wt. 268.
Found: C, 71.68, 71.69; H, 5.83, 6.04: N, 10.42, 10.49; CH_3O, 22.9; mol. wt. (camphor), 265, 271.

Picrate.—An alcohol solution of 0.50 g. of the base was mixed with a saturated solution of 0.90 g. of picric acid in cold alcohol (0.86 g. is two equivalents). The picrate weighed 0.94 g., a theoretical yield of the 1:1 picrate. Crystallization from alcohol gave 0.77 g. of pure picrate, of m.p. 209° obs., or 214° corr.

*3-(*p*-Anisyl)-6-methoxy-1,2,3,4-tetrahydroquinazoline.*—This compound was prepared from the dihydroquinazoline by hydrogenation using sodium and alcohol: 2.04 g. of dihydroquinazoline gave 1.18 g. (58%) of tetrahydroquinazoline. After recrystallization from dilute alcohol the compound melted at 133° obs., or 135° corr. This is close to the melting-point of the dihydroquinazoline, but a mixture of the two melted around 122°.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.37. Found: N, 10.34, 10.30, 10.26.

*Picrate of 3-(*p*-phenetyl)-6-ethoxy-3,4-dihydroquinazoline.*—This derivative was made as outlined for the anisyl compound: 0.25 g. of the dihydroquinazoline and 0.43 g. of picric acid (more than 2 equivalents) were separately dissolved in the least possible alcohol, and the solutions were mixed. The picrate weighed 0.44 g., a 99.2% yield of the 1:1 picrate. After crystallization from alcohol the compound melted at 182° obs., or 185.7° corr.

*Conversion of 3-(*p*-tolyl)-6-methyl-1,2,3,4-tetrahydroquinazoline to the dihydroquinazoline by action of formic acid.*—The tetrahydroquinazoline (3.5 g.) and formic acid (5.5 cc. of 90%) were sealed in a tube, and the mixture was heated for two hours at 150°. After suitable treatment there was isolated 2.7 g. (79%) of 3-(*p*-tolyl)-6-methyl-3,4-dihydroquinazoline; m.p. 156–7°, identified by mixture melting point test. By action of formic acid at water-bath temperature the tetrahydroquinazoline was less extensively attacked, only a small amount of the dihydroquinazoline being obtained as picrate.

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SUMMARY

Methods are described for preparation of 3,6-disubstituted dihydroquinazolines from para-substituted amines, and from their methylenebisarylamines and trimeric Schiff bases, with the aid of formic acid. Preparation from the amines gave in general smaller yields, more resinous material, and a higher proportion of methylated products, than by the other two methods. With the methylenebisarylamines or trimeric Schiff bases as starting materials the yields ranged from 25 to 39 per cent., calculated on the assumption that all bases taken were available for formation of

dihydroquinazoline. By proper selection of the starting compound and of experimental conditions yields of over 30 per cent. of the dihydroquinazolines can be assured.

Compounds not previously reported which are described in the experimental section are methylenebis(*p*-phenetidine) (m.p. 75°; the compound hitherto designated as methylenebis(*p*-phenetidine)[9] was found to be the trimeric Schiff base, m.p. 90°), methylene-*N*,*N*′-bis(*p*-bromoaniline) (m.p. 92°; this name was incorrectly assigned by Houben and Arnold[10] to a compound of m.p. 181°), trimeric methylene-*p*-phenetidine (m.p. 90°), 3-(*p*-anisyl)-6-methoxy-3,4-dihydroquinazoline (m.p. 138°), and its picrate (m.p. 214°), 3-(*p*-anisyl)-6-methoxyl-1,2,3,4-tetrahydroquinazoline (m.p. 135°), and the picrate of 2-(*p*-phenetyl)-6-ethoxy-3,4-dihydroquinazoline (m.p. 185.7°).