4-Oxo-1,2,3,4-tetrahydroquinazolines. I. Syntheses and Pharmacological Properties of 2-Methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines and Their 1-Acyl Derivatives

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Reduction of 2-methyl-3-aryl-4(3H)-quinazolinone hydrochloride (VIII, Ar = C_6H_5, 2-$CH_3C_6H_4$, and 2,3-$(CH_3)_2C_6H_3$) with $NaBH_4$ gave the corresponding 2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (IX) in high yield. 2-Ethylaminobenzanilide was prepared by $NaBH_4$ reduction of 2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IV). Acetylation of IX gave the 1-acetyl derivative (X), and 1-(N,N-disubstituted aminoacetyl) derivatives (XII) were synthesized from IX through 1-chloroacetyl derivatives (XI). In pharmacological test, compounds **10** and **13** showed analgetic activity as potent as aminopyrine. With compounds **6** and **9** antiinflammatory activity was observed.

Since Gujral and co-workers[1] have reported that 2-methyl-3-(2-tolyl)-4(3H)-quinazolinones have hypnotic properties, detailed synthetic and biological studies on 3-aryl-4(3H)-quinazolinone derivatives have been made,[2-4] but the synthesis and biological properties of 2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazoline, reduced at the C=N bond in the 2-methyl-4(3H)-quinazolinone ring, have not been described. In this paper, the syntheses of 2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (Ar = C_6H_5, 2-$CH_3C_6H_4$, and 2,3-$(CH_3)_2C_6H_3$) and of their 1-acyl derivatives (Table I) are described for a study of their pharmacological properties. 4-Oxo-1,2,3,4-tetrahydroquinazolines have been synthesized from the reaction of anthranilamide with aromatic aldehyde or ketones under acidic or basic conditions.[3-9] However, there are several methods describing the reduction of 4(3H)-quinazolinones to 4-oxo-1,2,3,4-tetrahydroquinazoline. According to Mirza, 3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline was prepared by reduction of 3-methyl-4(3H)-quinazolinone with $LiAlH_4$ in benzene.[10] Cohen and Vaughan[11] mentioned that 6-sulfamyl-7-chloro-4(3H)-quinazolinone was reduced to the corresponding 4-oxo-1,2,3,4-tetrahydroquinazoline by $NaBH_4$ in the presence of aluminum chloride.

The reduction of 2-methyl-3-phenyl-4(3H)-quinazoline (I) with $NaBH_4$ in solvents such as alcohol, tetrahydrofuran, or dioxane could not be effected at 10–100°, unchanged I being recovered. However, using diglyme at 100° the reduction gave a crystalline product (mp 118–199°), which was identified as 2-ethylaminobenzanilide (II),[12] prepared for comparison from 2-ethylaminobenzoic acid (III) (Scheme I).

The reduction of I·HCl (1 mole) with $NaBH_4$ (1.2 moles) in tetrahydrofuran–diglyme afforded 2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline in 88% yield. 3-(2-Tolyl) and 3-(2,3-xylyl) derivatives were reduced to the corresponding tetrahydro derivatives (IX) under the same condition. This method could be used for a general synthesis of the 4-oxo-1,2,3,4-tetrahydroquinazoline nucleus.

Reduction of IV with $NaBH_4$ gave II in good yield. Wilson showed that the =NCH(CH$_3$)N= bonds in hexahydropyrimidine and imidazoline derivatives were readily cleaved with $NaBH_4$.[13] Biressi and co-workers found that the reduction of 2-aryl-4-oxo-1,2,3,4-tetrahydroquinazoline derivatives with trimethylamineboron afforded 2-(N-substituted amino)benzamide derivatives but with $NaBH_4$ gave unchanged starting material.[14] When IV was treated with HCl in methanol, 2-aminobenzanilide (V) was obtained by ring opening of quinazolinone. IV was treated with 37% formaldehyde and hydrogenated with Pd–C catalyst to give the N-methyl derivative (VII). This compound was also obtained by reduction of 1,2-dimethyl-3-phenyl-4-oxo-dihydroquinazolinium iodide (VI) prepared by Bogert's method.[15]

The oxidation of IV with potassium permanganate in acetone gave I in good yield. Acetylation of 2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (IX) afforded the 1-acetyl derivatives (X). Reaction of VIII with chloroacetyl chloride gave the 1-chloroacetyl derivatives (XI) which were converted to the 1-(N,N-disubstituted aminoacetyl) derivatives (XII) by reaction with secondary amines (Scheme II).

Results

Results are summarized in Table II. From these data it appeared that the analgetic activity of our series of quinazolinones was affected by the relation between substituents at positions 1 and 3. In **1**–**6** with smaller substituents at position 1, analgetic activity was scarcely observed. However, methylation of phenyl at position 3 resulted in increase of activity.

(1) M. L. Gujral, R. M. Saxena, and R. S. Tiwari, *Indian J. Med. Res.*, **43**, 637 (1955).

(2) G. B. Jackmann, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.*, **12**, 529 (1960); J. Klosa, *J. Prakt. Chem.*, **14**, 84 (1961).

(3) (a) K. H. Boltze, H. D. Hell, D. Lurenz, and M. Rübery-Schwer, *Arzneimittel-Forsch.*, **13**, 688 (1963); (b) C. H. Boehringer and Sohn, French Patent M2588 (1964); *Chem. Abstr.*, **61**, 16075*h* (1964); C. H. Boehringer and Sohn, Netherlands Application 302,479 (1965); *Chem. Abstr.*, **64**, 9743 (1966).

(4) S. Toyoshima, K. Shimada, S. Hamano, and T. Ogo, *Yakugaku Zasshi*, **85**, 502 (1965); *Chem. Abstr.*, **63**, 7009*e* (1965).

(5) J. R. Fehlman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(6) H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

(7) T. A. K. Smith and H. Stephen, *Tetrahedron*, **1**, 38 (1957).

(8) H. Böhme and H. Böing, *Arch. Pharm.*, **293**, 1011 (1960).

(9) H. Gurien and B. B. Brown, *J. Pharm. Sci.*, **52**, 1102 (1963).

(10) R. Mirza, *Sci. Cult.* (Calcutta), **17**, 530 (1952).

(11) E. Cohen and J. R. Vaughan, Jr., U. S. Patent 2,976,289 (1961); *Chem. Abstr.*, **55**, 17663 (1961).

(12) G. Lockemann and W. Neumann [*Chem. Ber.*, **80**, 310 (1947)] reported that this compound melted at 176–171°, but our authentic sample melted at 118–119°.

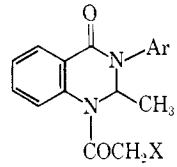
(13) E. M. Wilson, *Tetrahedron*, **21**, 2561 (1965).

(14) M. G. Biressi, M. Carissimi, and F. Ravenna, *Tetrahedron Letters*, 3919 (1966).

(15) M. T. Bogert and G. A. Geiger, *J. Am. Chem. Soc.*, **34**, 683 (1912).

Table I

1-Acyl-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines



No.	Ar	X	Yield, %	Salt	Mp, °C	Recrystn solvent[d]	Formula[e]
1	C_6H_5	H	77.5	...	125–127	A	$C_{17}H_{16}N_2O_2$
2	2-$CH_3C_6H_4$	H	74.3	...	166–169	A	$C_{18}H_{18}N_2O_2$
3	2,3-$(CH_3)_2C_6H_3$	H	76.4	...	150–151	B	$C_{19}H_{20}N_2O_2$
4	C_6H_5	Cl	77.1	...	174–176	A	$C_{17}H_{15}ClN_2O_2$
5	2-$CH_3C_6H_4$	Cl	87.0	...	168–170	A	$C_{18}H_{17}ClN_2O_2$
6	2,3-$(CH_3)_2C_6H_3$	Cl	61.1	...	172–173	A	$C_{19}H_{19}ClN_2O_2$
7	C_6H_5	$N(CH_3)_2$	91.4	HCl	225–226[c]	C	$C_{19}H_{22}ClN_3O_2$
8	2-$(CH_3C_6H_4$	$N(CH_3)_2$	85.7	*a*	120–121	B	$C_{20}H_{23}N_3O_2$
9	2,3-$(CH_3)_2C_6H_3$	$N(CH_3)_2$	84.5	*a*	157–158	B	$C_{21}H_{25}N_3O_2$
10	C_6H_5	$N(C_2H_5)_2$	83.3	HCl	148–150[c]	D	$C_{21}H_{26}ClN_3O_2 \cdot H_2O$
11	2-$CH_3C_6H_4$	$N(C_2H_5)_2$	91.0	*a*	114–115	B	$C_{22}H_{27}N_3O_2$
12	2,3-$(CH_3)_2C_6H_3$	$N(C_2H_5)_2$	79.5	*a*	146–147	B	$C_{23}H_{29}N_3O_2$
13	C_6H_5		80.2	HCl	243–245[c]	C	$C_{22}H_{26}ClN_3O_2 \cdot H_2O$
14	2-$CH_3C_6H_4$		78.1	*a*	114–115	B	$C_{23}H_{27}N_3O_2$
15	2,3-$(CH_3)_2C_6H_3$		70.0	HCl[b]	248–249	C	$C_{24}H_{30}ClN_3O_2$

[a] Free base. [b] Free base, mp 124–126°. [c] Decomposition. [d] Recrystallized from A, EtOH; B, benzene–hexane; C, EtOH–Et_2O D, Me_2CO. [e] All compounds were analyzed for C, H, N.

Compounds **7–15** with aminoalkyl substituents at position 1 exhibited comparatively potent activity. Methylation of phenyl at position 3 decreased the potency. Higher analgetic activity like that of aminopyrine was observed in **10** and **13**. However, the duration of the activity was shorter than that of aminopyrine. In a carrageenin-induced edema, test compounds **6**, **9**, **13**, and **14** were almost as active as phenylbutazone and more active than aminopyrine. Antihistamic effects of these compounds were very weak, but methylation of phenyl at position 3 resulted in increased efficiency. Prolongation of thiopental sleeping time was observed in **7–15**, **10** showing the highest potency. At maximum tolerated doses, many compounds produced sedation, decrease of spontaneous activity, and muscle relaxation. In **11**, **12**, and **14**, however, increases of spontaneous activity and tremor were observed. Compounds **6**, **10**, and **13**, which showed potent analgetic activity or inflammatory activity, did not produce any behavioral change in animals.

Experimental Section

Pharmacology Methods. (1) **Analgetic Activity.**—Analgetic effects were estimated by the intraperitoneal or oral administration of samples dissolved in saline or suspended in 0.5% carboxymethylcellulose (CMC) solution so that each dose could be given in 0.1 ml/10 g in mice. At the same time morphine was applied subcutaneously at 1 mg/kg. Analgetic activity was determined by the tail-pinch method.[16] The base of the tail was pressed by the 500-g pressure of an artery clip. In mice exhibiting "complete analgesia," the effectiveness was determined and the ED_{50} was calculated.[17]

(2) **Antiinflammatory Effect.**—Male Wister rats (about 150 g) received an oral administration of samples dissolved in saline. One hour later, 0.1 ml of 1% carrageenin saline solution was injected into the tissue of the planter surface of the hind paw of the rats as a phlogistic agent. The volume of the foot was estimated before injection of the phlogistic agent and after 0.5, 1, 2, 3, 4, and 5 hr. Foot volume was measured by immersion of the foot in the side-armed vessel filled with water to an ink mark at the level of the lateral malleolus. The volume of water overflow was measured by pipet.

(3) **Antihistamic Activity.**—Guinea pig intestine was isolated and suspended in a bath containing 20 ml of aerated Tyrode's solution maintained at 37 ± 0.5° according to Magnus. The samples were added to the Magnus bath at 10^{-5} g/ml 3 min prior to addition of histamine (5×10^{-8} g/ml).

(4) **Potentiation on the Anesthetic Effect of Barbiturates.**—A group of five mice was injected with test compounds intraperitoneally at 100 mg/kg 30 min prior to an intravenous injection of thiopental sodium (25 mg/kg). Prolongation of the sleeping time was compared with that of control animals. Room temperature was maintained at 24 ± 0.5° throughout the experiment.

(5) **Acute Toxicity and Behavioral Observation.**—Adult male dd strain mice weighing 20 ± 1 g were used. The animals used for the oral toxicity test were fasted 14 hr before dosing. Samples to be tested were dissolved in saline or suspended in 0.5% CMC solution so that each dose could be delivered in 0.1 ml/10 g of body weight, and were injected intraperitoneally or given orally by stomach tube. The animals were observed for behavioral changes and mortality for 4 days after administration of the test drugs. LD_{50} values were calculated by the Weil method[17] based on the number of dead animals on day 4.

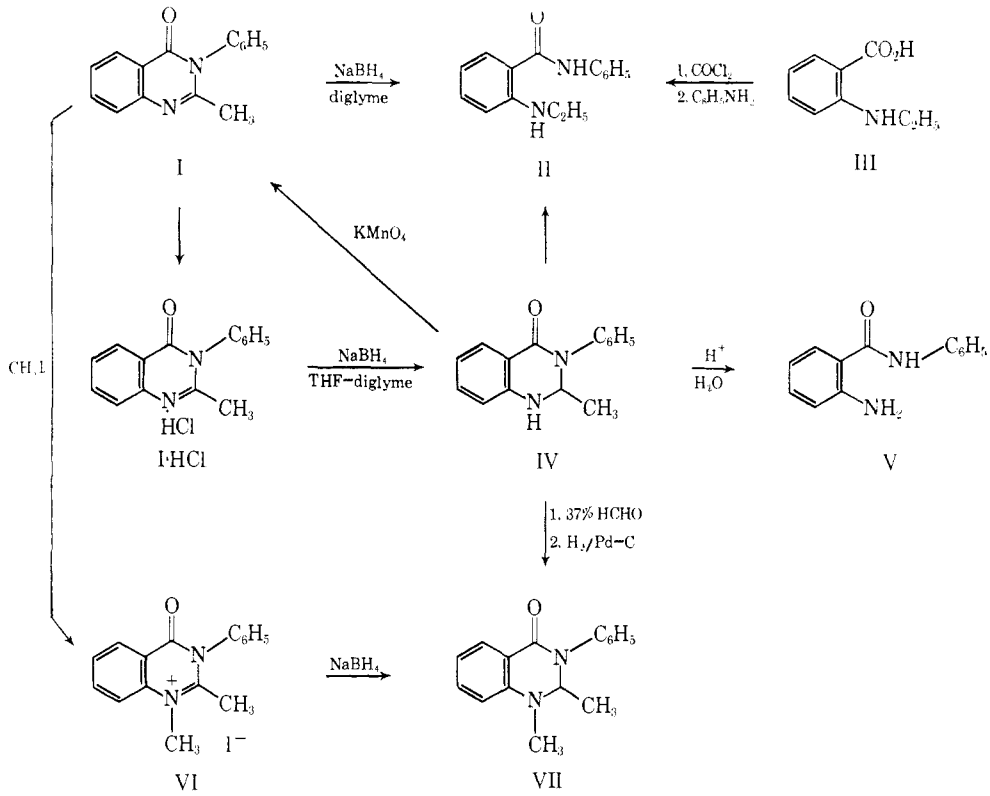
Chemical Methods.[18] **2-Ethylaminobenzanilide (III). A. From 2-ethylaminobenzoic Acid (III).**—To a stirred solution of III (17.6 g) in 5% HCl (148 ml) was passed gaseous $COCl_2$ at a rate of about 3 bubbles/sec for 2 hr at 30–35°. Separation of a crystalline product began soon after the stream of $COCl_2$ was started. The solid was collected, washed with cold H_2O, and dried; mp 121–122°, yield 9.9 g. A mixture of this product (9.9 g) and aniline (5.3 g) was heated on a boiling-water bath for 2 hr. The reaction mixture turned into a clear solution with evolution of CO_2 and then solidified. The crystalline product was

(16) H. Takagi, T. Inukai, and M. Nakama, *Japan. J. Pharmacol.*, **16**, 287 (1966).

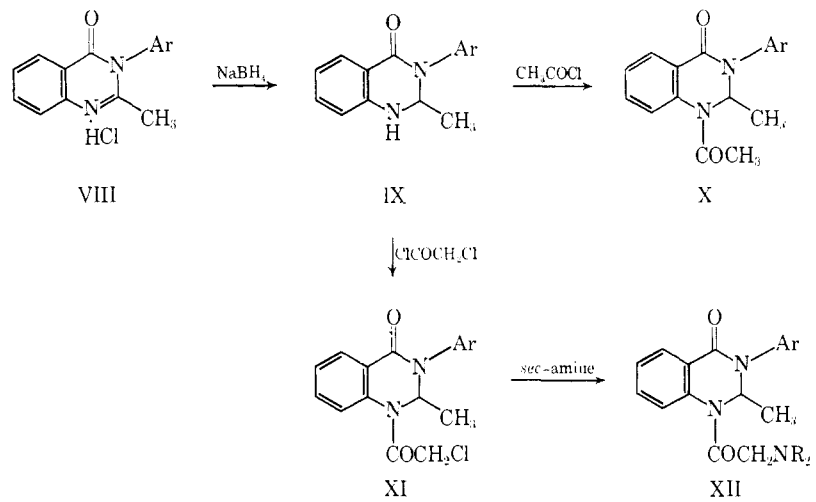
(17) C. S. Weil, *J. Biometric Soc.*, **8**, 249 (1952).

(18) Melting points are uncorrected and were determined in open capillaries in a bath. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

SCHEME I



SCHEME II



Ar = C_6H_5, 2-$CH_3C_6H_4$, 2,3-$(CH_3)_2C_6H_3$

NR_2 = $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N$⬡

recrystallized from EtOH to give colorless prisms, mp 118–119°, yield 10.7 g. *Anal.* ($C_{15}H_{16}N_2O$) C, H, N.

B. From 2-Methyl-3-phenyl-4(3H)-quinazoline (I).[19]—To a solution of I (2.36 g) in diglyme (50 ml) was added $NaBH_4$ (0.38 g) and the mixture was heated for 5 hr at 95–100°. The reaction mixture was concentrated under reduced pressure. The residue was treated with H_2O and a few drops of AcOH to decompose excess $NaBH_4$, made alkaline with K_2CO_3, and extracted (C_6H_6). The dried extract was evaporated to give a colorless residue which was crystallized by adding hexane. Recrystallization from EtOH gave colorless prisms, mp 118–119°, yield 1.5 g (63%). The ir spectrum of the product agreed with that of a sample obtained by method A.

2-Methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (IV and IX). (**a**) **Ar = C_6H_5 (IV).**—To a stirred suspension of 2-methyl-3-phenyl-4(3H)-quinazoline hydrochloride (I·HCl) in dry THF (40 ml) was added a solution of $NaBH_4$ (0.46 g) in diglyme (15 ml) during 45 min at 5–10°. The mixture was stirred for 3 hr at the same temperature. H_2O was added to the reaction mixture until H_2 evolution ceased and the solvent was removed under reduced pressure. The residue was treated with H_2O to give a crystalline product. Recrystallization from EtOH gave colorless prisms, mp 167–169°, yield 2.1 g (88%). *Anal.* ($C_{15}H_{14}N_2O$) C, H, N.

(**b**) **Ar = 2-$CH_3C_6H_4$ (IX).**—A solution of $NaBH_4$ (1.8 g) in diglyme (60 ml) was added to a stirred suspension of 2-methyl-3-(2-tolyl)-4(3H)-quinazolinone hydrochloride[20] (11.5 g) in dry

(19) R. Anschütz, O. Schmidt, and A. Greiffenberg, *Ber.*, **35**, 3480 (1902).

(20) J. K. Kacker and S. P. Zaheer, *J. Indian Chem. Soc.*, **28**, 344 (1951).

Table II
Summary of Pharmacological Observations

No.	Max tolerated dose, mg/kg *po*	Max tolerated dose, mg/kg ip	Behavior in max tolerated dose (*po*)[a]	Analgetic effect: Effective (%) at 66 mg/kg ip	Analgetic effect: Effective (%) at 100 mg/kg ip	Analgetic effect: ED_{50}, mg/kg	% prolongation of sleeping time by barbiturate, 100 mg/kg ip	Antiinflam, % inhib of carrageenin abscess, 100 mg/kg *po*	Antihistamic effect, % inhib of histamine spasm, 10^{-5} g/ml	LD_{50}, mg/kg
1	>400	400	a, i	0	20	...	33	..	*b*	...
2	>400	400	a, c	20	20	...	33	..	*b*	...
3	400	200	Unchanged	20	40	...	33	12	*b*	...
4	>400	400	Unchanged	0	20	...	40	..	15	...
5	400	200	Unchanged	0	20	...	30	10	15	...
6	400	200	Unchanged	40	40	...	40	24	35	...
7	>200	100	a, c	40	40	...	100	..	20	...
8	>400	200	Unchanged	20	40	...	...	10	16	...
9	>400	200	a, c	20	40	...	38	22	40	...
10	>400	200	Unchanged	40	80	74.7 (45.1–123.9) ip[c]	312	18	15	254.1 (216.1–298.8) ip[d]
11	200	100	h, d, g, i, f, j	0	20	...	256	16	20	...
12	200	100	b, n, o, i, d, l	0	20	...	200	16	15	...
13	400	100	Unchanged	40	60	85.6 (53.4–149.1) ip[e]	150	20	60	215.6 (170.5–267.2) ip[f]
14	200	100	b, h, i, k	0	20	...	250	20	60	...
15	200	100	a, m, k, e	0	20	...	299	15	45	...
Aminopyrine	>400	100	a, m	40	100	77.9 (57.1–106.3) ip[g]	...	13	...	315.6 (241.1–413.2) ip[h]
Chlorphenylamine	100	50	a, m	..	..	...	...	..	100	...
Diphenhydramine	100	50	a	..	...	...	...	..	100	...
Phenylbutazone	>400	200	Unchanged	..	...	...	...	20	...	...

[a] Behavior: a, spontaneous activity ↓; b, spontaneous activity ↑; c, respiration ↓; d, respiration ↑; e, palpebral size ↓; f, palpebral size ↑; g, exophthalmos; h, tremor; i, clonic convulsion; , tonic convulsion; k, loss of righting reflex; l, staggering gate; m, muscle relaxation; n, Straub reaction; o, shivering. [b] Insoluble in Tyrode solution. [c] 162.4 (104.8–251.8) *po*. [d] 864.2 (708.5–1059.0) *po*. [e] 162.4 (102.1–260.8) *po*. [f] 740.4 (595.0–903.8) *po*. [g] 356.4 (246.1–491.1) *po*. [h] 1505.8 (1087.8–1816.8) *po*.

THF (150 ml) as above. Recrystallization from EtOH gave colorless prisms, mp 196–198°, lit.[3a] mp 192–193°, yield 8.6 g (85%). *Anal.* ($C_{16}H_{16}N_2O$) C, H, N.

(c) **Ar = 2,3-$(CH_3)_2C_6H_3$ (IX).**—2-Methyl-3-(2,3-xylyl)-4(3H)-quinazolinone hydrochloride[2] (15 g) was reduced with $NaBH_4$ (2.3 g), as under a, yielding colorless needles (from EtOH), mp 245–246°, yield 10.5 g (80%). *Anal.* ($C_{17}H_{18}N_2O$) C, H, N.

Oxidation of IV with $KMnO_4$.—To a stirred solution of IV (238 mg) in dry Me_2CO (10 ml) was added a solution of $KMnO_4$ (158 mg) in dry Me_2CO (15 ml) during 2 hr at room temperature, and stirring was continued for 30 min. Excess $KMnO_4$ was removed by addition of solid $NaHSO_3$ and the mixture was filtered. The solvent was evaporated to give a crystalline residue. Recrystallization from EtOH gave I (190 mg) as colorless prisms, mp 144–146°. The product was identified with an authentic sample of I (mixture melting point and ir).

Reduction of IV with $NaBH_4$.—To a stirred solution of IV (1.2 g) in THF (20 ml) was added a solution of $NaBH_4$ (0.23 g) in diglyme (5 ml) for 1 hr at 20°. The reaction mixture became dem yellow and stirring was continued for 5 hr. H_2O (2 ml) and AcOH (2 drops) were added to the mixture to decompose excess $NaBH_4$ and the solvent was distilled under reduced pressure. To the residue was added H_2O to give a crystalline product. Recrystallization from EtOH gave colorless prisms, mp 116–118°, yield 1.0 g. Admixture with II did not depress its melting point, and ir spectra of the product and II agreed.

Decomposition of IV with HCl.—To a solution of IV (500 mg) in 95% MeOH (20 ml) was added concentrated HCl (1 ml) and stirring was continued for 2 hr at room temperature. The solvent was distilled under reduced pressure. The residue was dissolved in H_2O and made alkaline with K_2CO_3, and the crystalline product was filtered and recrystallized from EtOH–hexane; colorless needles (370 g), mp 116–117°. The product was identified as 2-aminobenzanilide (V)[21,22] from its ir spectrum which was identical with that of V.

1,2-Dimethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (VII). A.—IV in EtOH (70 ml) was treated with 37% HCHO (1.0 g) and warmed at 50–60° for 1 hr. The mixture was hydrogenated under atmospheric pressure with 10% Pd–C (0.5 g), the theoretical volume of H_2 being absorbed in 5 hr at room temperature. The catalyst was removed and the solvent was distilled. The residue was dissolved in Et_2O and washed with H_2O, the dried extract was evaporated, and the oily residue was distilled under reduced pressure to give a colorless oil, bp 187–190° (0.5 mm), yield 1.8 g (75%). *Anal.* ($C_{16}H_{16}N_2O$) C, H, N.

B.—1,2-Dimethyl-3-phenyl-4-oxodihydroquinazolinium iodide (VI) was prepared by a modification of the procedure of Bogert.[14] A mixture of I (3.6 g), CH_3I (8.5 g), and dry C_6H_6 (4 ml) was heated in a sealed tube at 110–112° for 7.5 hr and cooled. The separated crystalline product was filtered and recrystallized from MeOH to give VI as colorless needless, mp 241–242° dec, yield 3.9 g (69%), lit.[14] mp 243° dec. To a stirred suspension of VI (1.9 g) in absolute EtOH (20 ml) was added a solution of $NaBH_4$ (0.23 g) in absolute EtOH (25 ml) for 30 min. The temperature was maintained at 3–5° during the addition and stirring was continued for 2.5 hr at room temperature. The solvent was distilled under reduced pressure, and the residue was treated with H_2O and extracted with Et_2O. The dried extract was evaporated and distilled at 186–190° (0.5 mm) to give a colorless oil (1.1 g, 87%). Ir spectra of the product and of the sample obtained from a were superimposable.

1-Acetyl-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazoline (X). General Procedure.—A solution of AcCl (0.009 mole) in dry Me_2CO (5 ml) was added to a stirred mixture of IX (0.006 mole) and powdered anhydrous K_2CO_3 (0.01 mole) in dry Me_2CO (100 ml) at 0–5°. Stirring was continued for 3 hr at room temperature and for 2 hr at 40–45°. The solvent was distilled, and the residue was treated with H_2O to give a crystalline product which was recrystallized from suitable solvent. The products are listed in Table I (1–3).

1-Chloroacetyl-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (XI, Ar = C_6H_5).—To a stirred suspension of IV (IX, Ar = C_6H_5) (4.0 g) in dry C_6H_6 (300 ml) was added a solution of $ClCH_2COCl$ (3.0 g) in dry C_6H_6 (10 ml) at 5–10°. The mixture was stirred for 1.5 hr at room temperature and refluxed for 5 hr. Inorganic compounds were removed and the solvent was distilled to give a residue which was crystallized on addition of H_2O. Recrystallization from EtOH gave colorless prisms, mp 174–176°, yield 4.3 g (Table I, 4). The derivatives (**5**, **6**) in Table I were prepared similarly.

1-(N,N-Disubstituted Aminoacetyl)-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (XII).—In the general procedure, the 1-chloroacetyl derivatives XI (2.0 g) were dissolved in 30 ml of a 20% solution of *sec*-amine in C_6H_6. The mixture was stirred for 4 hr at room temperature, washed (H_2O), and dried (K_2CO_3). Evaporation of the solvent gave a crystalline residue (for Table I, **8**, **9**, **11**, **12**, **14**) or an oily residue (Table I, **7**, **10**, **13**, **15**). The oily residues were dissolved in Et_2O and treated with HCl–MeOH to give crystalline hydrochlorides. The products (**7**–**15**) are listed in Table I.

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(21) R. C. Shah, *J. Indian Chem. Soc.*, **7**, 205 (1921); *Chem. Abstr.*, **19**, 615 (1925).

(22) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 55 (1944).