4-Oxo-1,2,3,4-tetrahydroquinazolines. II.[1] Synthesis of 1-Alkyl- and 1-[2-(Disubstituted amino)ethyl]-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines

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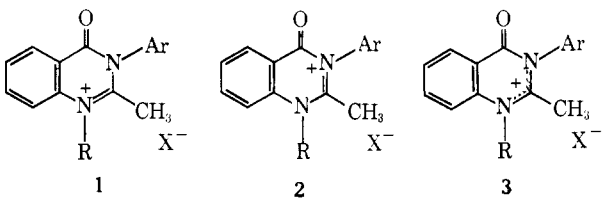
Reaction of 2-(N-ethylacetamido)benzanilide with HI in EtOH afforded 1-ethyl-2-methyl-3-phenyl-4-oxodihydroquinazolinium iodide in quantitative yield. This conversion was reversible under mild alkaline conditions. 1-Ethyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline was obtained by $NaBH_4$ reduction of the salt in good yield. Nine derivatives of 1-[2-(disubstituted amino)ethyl]-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines were synthesized from N-substituted anthranilic acid derivatives *via* 1-[2-(disubstituted amino)ethyl]-2-methyl-3-aryl-4-oxodihydroquinazolinium compounds.

According to Hauptmann,[2] 1-dialkylaminoalkyl-2-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines were synthesized, and the pharmacological studies of these compounds were reported by Muačević and co-workers.[3] In a previous paper,[1] we had found that the reduction of 2-methyl-3-aryl-4(3H)-quinazolinone hydrochloride with $NaBH_4$ afforded the corresponding 4-oxo-1,2,3,4-tetrahydroquinazolines in good yield, and also reported the synthesis of the 1-acyl derivatives. This paper describes the synthesis and some pharmacological properties of 1-alkyl- and 1-[2-(disubstituted amino)-ethyl]-2-methyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (XIV).

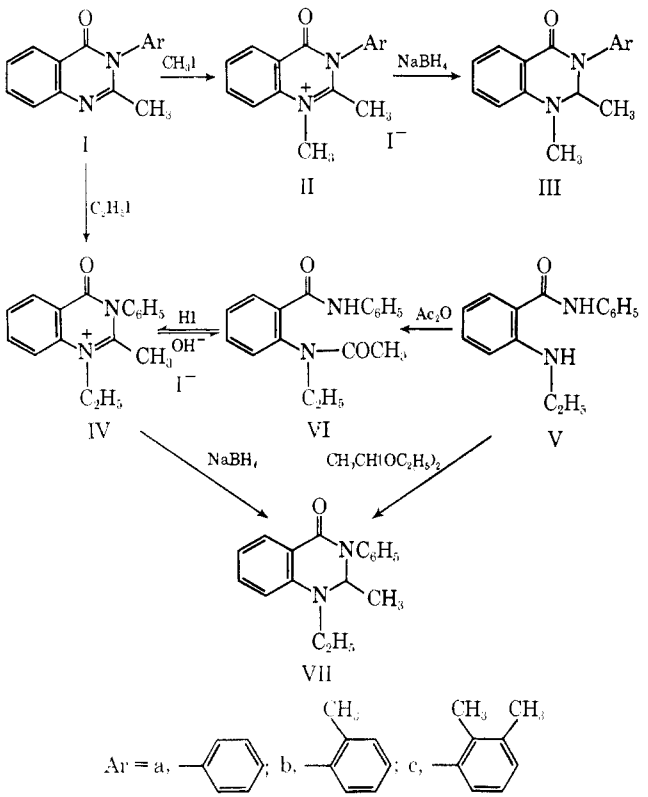
Methylation of 2-methyl-3-aryl-4(3H)-quinazolinone [I, Ar = C_6H_5, 2-$CH_3C_6H_4$, and 2,3-$(CH_3)_2C_6H_3$] with methyl iodide was carried out by a modified Bogert[4] procedure to give 1,2-dimethyl-3-aryl-4-oxodihydroquinazolinium iodide (II),[5] which was converted



1 2 3

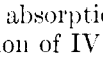
to 1,2-dimethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (III) by $NaBH_4$ reduction in good yield. However reaction of I (Ar = C_6H_5) with EtI in a sealed tube to 1-ethyl-2-methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium iodide (IV) did not go too well. A more possible approach to IV appeared to be the sequence V → VI → IV as shown in Scheme I. Acetylation of 2-ethylaminobenzanilide (V) gave the N-acetyl derivatives (VI), and reaction of VI with HI in ethanol gave IV in quantitative yield. This new type of cyclization is a useful method of synthesis of 1-substituted 2-methyl-3-aryl-4-oxodihydroquinazolinium compounds. IV readily cleaved to VI under mild alkaline condition. This conversion was found to be reversible. The 4-oxo-

SCHEME I



dihydroquinazolinium iodides (II and IV) showed typical absorption bands at 1725, 1620, 1560 cm^{-1}. Reduction of IV with $NaBH_4$ gave 1-ethyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (VII) in excellent yield.

The structure of VII was confirmed by an independent synthesis. Reaction of V with acetaldehyde diethyl acetal in the presence of sulfuric acid gave an oily mixture, from which VII was isolated in about 33% yield from chromatography over alumina.

The new cyclization of 2-acetamidobenzanilide derivatives was applied to a synthesis of 1-[2-(disubstituted amino)ethyl]-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines (XIV, $N(R)_2$ = $N(CH_3)_2$, $N(C_2H_5)_2$, $-N$ ). N-Substituted anthranilic acid derivatives (IX) were prepared from 2-chlorobenzoic acid (VIII) by a procedure modified from that of Hauptmann.[2] Acetylation of IX gave the N-acetyl

(1) Part I: K. Okumura, T. Oine, Y. Yamada, G. Hayashi, and M. Nakama, *J. Med. Chem.*, **11**, 348 (1968).

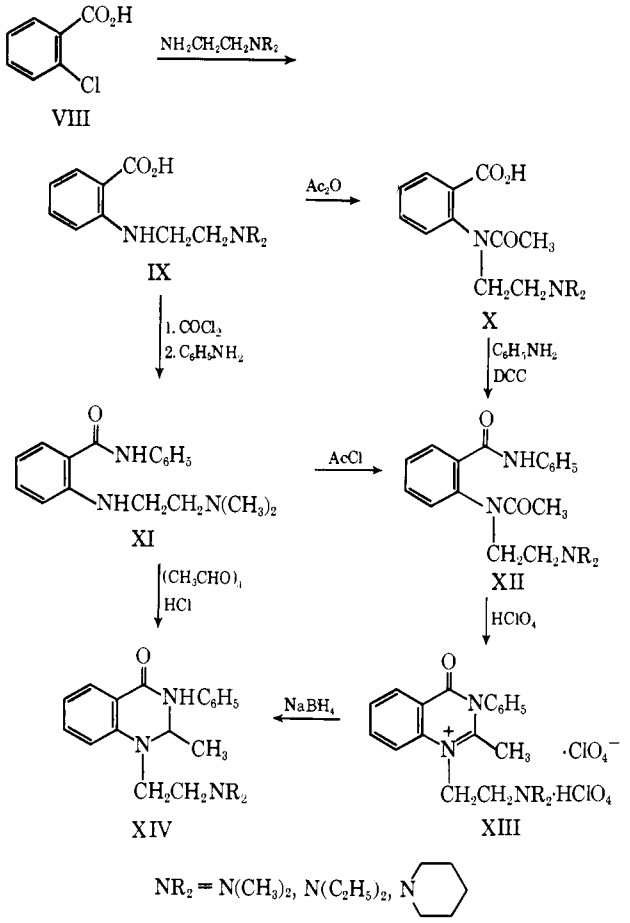
(2) K. H. Hauptmann, *Arzneimittel-Forsch.*, **15**, 610 (1965).

(3) G. Muačević, H. Sötzer, and H. Wick, *ibid.*, **15**, 613 (1965).

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

(5) It is not clear whether 4-oxodihydroquinazolinium compounds possess the 3,4-dihydro structure (**1**), the 1,4-dihydro structure (**2**), or the resonance structure (**3**). However in this paper, **1** is expediently used for the 4-oxodihydroquinazolinium compounds.

Scheme II



derivatives X. Condensation of X and aniline by the use of N,N′-dicyclohexylcarbodiimide afforded the oily anilides XII, which were converted to 4-oxodihydroquinazolinium compounds (XIII) by the addition of excess 66% aqueous perchloric acid (Scheme II). The ir spectra of XIII agreed with that of II and IV at 1500–1800 cm^{-1}. Reduction of XIII with $NaBH_4$ gave expected XIV in good yield. The other derivatives shown in Tables I and II were prepared similarly. XIV [$R_2 = (CH_3)_2$] was synthesized by the following method. The anilide derivative XI was obtained from IX [$R_2 = (CH_3)_2$] in an unsatisfactory yield through the isatoic anhydride derivative. Reaction of XI and paraldehyde in the presence of dry HCl in EtOH afforded an oily mixture, from which XIV [$R_2 = (CH_3)_2$] was isolated by distillation after chromatography over alumina (yield 32%). The ir spectra of this product and a sample obtained by $NaBH_4$ reduction of XIII [$R_2 = (CH_3)_2$] were superimposable.

Results

Results of pharmacological observations are summarized in Table III. It was previously mentioned[1] that the analgetic activities of these derivatives were affected by the relation between substituents at positions 1 and 3 of the quinazoline. The analgetic activities of **17** and **18** which have a diethylaminoethyl substituent at position 1 were almost as potent as that of aminopyrine intraperitoneally and twice as active as that of aminopyrine orally. However, by intraperitoneal injection, the activities of **17** and **18** were not resolvable, since the ED_{50} values were about $^1/_{2.2}$ of the LD_{50} values.

The other compounds which have methyl, dimethylaminoethyl, and piperidinoethyl substituents at position 1 showed rather weak analgetic activity. Prolongation of thiopental sleeping time was found in all test compounds. In **21** the highest potency was observed in a carrageenin-induced edema test; **12**, **14**, and **18** showed higher antiinflammatory activity. In particular, the activities in **14** and **21** were higher than that of phenylbutazone. Antihistaminic effects in these compounds were very weak. At the maximum tolerated dose, many compounds produced a slight increase of spontaneous activity.

Experimental Section[6]

Pharmacological Methods. (1) **Analgetic Activity.**—Analgetic activities were estimated by the tail pinch method in mice.[7] ED_{50}[8] values were determined by the number of mice that responsed analgetically in each dose.

(2) **Potentiation of the Anesthetic Effect of Barbiturates.**—The test compounds were injected intraperitoneally at 100 mg/kg. Thirty minutes later, thiopental sodium was injected intravenously in a dose of 25 mg/kg. Prolongation of the sleeping time was compared with that of control animals.

(3) **Antiinflammatory Effect.**—Male Wistar rats (about 150 g) were used. Antiinflammatory effects were determined by the inhibition of the test compounds on the carrageenin-induced edema.[9]

(4) **Antihistaminic Activity.**—Guinea pig intestine was isolated. Antihistamic activities were assayed according to Magnus. The test compounds were added to the Magnus bath at 10^{-5} g/ml 3 min prior to addition of histamine (5×10^{-8} g/ml).

(5) **Acute Toxicity and Behavioral Observation.**—Adult male dd strain mice weighing 20 ± 1 g were used. The test compounds were dissolved in saline or suspended in 0.5% CMC solution and administered intraperitoneally or orally. The behavioral changes of the animals were observed and LD_{50} values were calculated by the Weil method[8] according to the number of dead animals on day 4.

Chemical Methods. 1,2-Dimethyl-3-aryl-4-oxodihydroquinazolinium iodides (II) were prepared by a modification of the procedure of Bogert.[3]

a, Ar = 2-$CH_3C_6H_4$.—A mixture of 2-methyl-3-(2-tolyl)-4(3H)-quinazolinone (I, Ar = 2-$CH_3C_6H_4$) (1.25 g), MeI (2.1 g), and dry C_6H_6 (2 ml) was heated in a sealed tube at 110–120° for 7 hr and cooled. The separated crystalline product was collected. Recrystallization from MeOH gave pale yellow needles, mp 228–229° dec, yield 0.9 g (45%). *Anal.* ($C_{17}H_{17}IN_2O$) C, H, N.

b, Ar = 2,3-$(CH_3)_2C_6H_3$.—Methylation of I [Ar = 2,3-$(CH_3)_2$-C_6H_3] (5.3 g) was carried out as above, giving colorless needles from MeOH, mp 240–241° dec, yield 4.8 g (59%). *Anal.* (C_{18}-$H_{19}IN_2O$) C, H, N.

1,2-Dimethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (III). a, Ar = 2-$CH_3C_6H_4$.—A solution of $NaBH_4$ (0.23 g) in EtOH (25 ml) was added to a stirred suspension of II (Ar = 2-$CH_3C_6H_4$) (1.95 g) in EtOH (20 ml) during 30 min in an ice bath. The mixture became clear and stirring was continued for 2.5 hr at room temperature. The solvent was distilled under reduced pressure. To the residue was added H_2O and the separated oil was extracted with Et_2O. The dried extract was evaporated to give a crystalline residue, which was recrystallized from EtOH–hexane to give colorless prisms, mp 106–107°, yield 1.2 g (90%) (Table II, **11**).

b, Ar = 2,3-$(CH_3)_2C_6H_3$.—Compound II [Ar = 2,3-$(CH_3)_2C_6H_3$] (3.0 g) was reduced with $NaBH_4$ (0.34 g) as above, yielding 2.0 g (95%), mp 137–138° (Table II, **12**).

(6) Melting points were uncorrected and were determined in open capillaries in an oil 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.

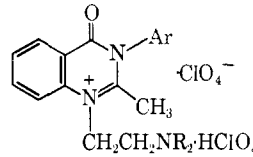
(7) H. Takagi, T. Inukai, and M. Nakama, *Japan. J. Pharmacol.*, **16**, 287 (1966).

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

(9) K. Shimamoto and O. Kanemitsu, *Folia Pharmacol. Japon.*, **56**, 575 (1960).

TABLE I

1-[2-(DISUBSTITUTED AMINO)ETHYL]-2-METHYL-3-ARYL-4-OXODIHYDROQUINAZOLINIUM COMPOUNDS

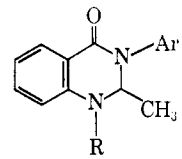


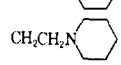
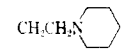
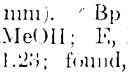
No.	Ar	$-NR_2$	Yield, %, from X	Mp, °C dec	Recrystn solvent[a]	Formula[b]
1	C_6H_5	$-N(CH_3)_2$	85	255–256	A	$C_{19}H_{23}Cl_2N_3O_5$
2	$2\text{-}CH_3C_6H_4$	$-N(CH_3)_2$	51	259–260	B	$C_{20}H_{25}Cl_2N_3O_5$
3	$2,3\text{-}(CH_3)_2C_6H_3$	$-N(CH_3)_2$	58	258–260	C	$C_{21}H_{27}Cl_2N_3O_5$
4	C_6H_5	$-N(C_2H_5)_2$	53	248–249	C	$C_{21}H_{27}Cl_2N_3O_5$
5	$2\text{-}CH_3C_6H_4$	$-N(C_2H_5)_2$	50	193–195	D	$C_{22}H_{29}Cl_2N_3O_5 \cdot H_2O$
6	$2,3\text{-}(CH_3)_2C_6H_3$	$-N(C_2H_5)_2$	38	220–222	D	$C_{23}H_{31}Cl_2N_3O_5$
7	C_6H_5		58	249–250	A	$C_{22}H_{27}Cl_2N_3O_5$
8	$2\text{-}CH_3C_6H_4$		30	253–255	A	$C_{23}H_{29}Cl_2N_3O_5$[c]
9	$2,3\text{-}(CH_3)_2C_6H_3$		54	233–235	A	$C_{24}H_{31}Cl_2N_3O_5$[d]

[a] A, DMF–EtOH; B, Me_2CO–Et_2O; C, DMF–Me_2CO–Et_2O; D, MeOH. [b] All compounds were analyzed for C, H, N. [c] C: calcd, 49.11; found, 49.85. [d] C: calcd, 50.00; found, 50.69.

TABLE II

1-SUBSTITUTED 2-METHYL-3-ARYL-4-OXO-1,2,3,4-TETRAHYDROQUINAZOLINES



No.	Ar	R	Yield, %	Salt	Mp, °C	Recrystn solvent[f]	Formula[g]
10	C_6H_5	CH_3	87	*a*	*b*	...	$C_{16}H_{16}N_2O$
11	$2\text{-}CH_3C_6H_4$	CH_3	90	*a*	106–107	A	$C_{17}H_{18}N_2O$
12	$2,3\text{-}(CH_3)_2C_6H_3$	CH_3	95	*a*	137–138	A	$C_{18}H_{24}N_2O$
13	C_6H_5	C_2H_5	87	*a*	77–78	B	$C_{17}H_{18}N_2O$
14	C_6H_5	$CH_2CH_2N(CH_3)_2$	66	*a*	*c*	...	$C_{19}H_{23}N_3O$[h]
15	$2\text{-}CH_3C_6H_4$	$CH_2CH_2N(CH_3)_2$	96	Picrolonate	209–210[d]	A	$C_{34}H_{33}N_7O_6$[i]
16	$2,3\text{-}(CH_3)_2C_6H_3$	$CH_2CH_2N(CH_3)_2$	65	*a*	102–103	E	$C_{21}H_{25}N_3O$
17	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	87	$(COOH)_2$	182–183[d]	D	$C_{23}H_{29}N_3O_5$
18	$2\text{-}CH_3C_6H_4$	$CH_2CH_2N(C_2H_5)_2$	79	Picrate	158–160[d]	D	$C_{28}H_{32}N_6O_8$
19	$2,3\text{-}(CH_3)_2C_6H_3$	$CH_2CH_2N(C_2H_5)_2$	76	*a*	110–111	E	$C_{23}H_{31}N_3O$
20	C_6H_5		68	HCl	242–244[e]	A	$C_{22}H_{28}ClN_3O$
21	$2\text{-}CH_3C_6H_4$		61	HCl	264–266[d]	D	$C_{23}H_{31}ClN_3O$
22	$2,3\text{-}(CH_3)_2C_6H_3$		64	HCl	250–252[d,e]	F	$C_{24}H_{32}ClN_3O$

[a] Free base. [b] Bp 186–190° (0.5 mm). [c] Bp 250–255° (0.2 mm). [d] Decomposition. [e] Free base melts at 130–131°. [f] A, EtOH; B, hexane–Et_2O; C, Me_2CO; D, MeOH; E, hexane; F, EtOH–Et_2O. [g] All compounds were analyzed for C, H, N. [h] C: calcd, 73.75; found, 73.29. [i] C: calcd, 61.23; found, 61.72.

2-(N-Ethylacetamido)benzanilide (VI).—A mixture of 2-ethylaminobenzanilide (V)[1] (2.0 g) and Ac_2O (6 g) was stirred for 2 hr at room temperature and for an additional 30 min at 60°. Excess Ac_2O was distilled under reduced pressure. The residue was treated with H_2O, extracted with $CHCl_3$, and washed with 10% Na_2CO_3. Distillation of the dried extract gave a crystalline residue, which was recrystallized from C_6H_6 to give colorless prisms, mp 146–148°, yield 2.3 g (98%). *Anal.* ($C_{17}H_{18}N_2O_2$) C, H, N.

1-Ethyl-2-methyl-3-phenyl-4-oxodihydroquinazolinium Iodide (IV). A.—A mixture of I (Ar = C_6H_5) (4.8 g), EtI (12.5 g), and C_6H_6 (5 ml) was heated in a sealed tube at 115–125° for 20 hr and cooled. The separated crystalline product was collected by filtration. Recrystallization from MeOH (150 ml) gave IV as colorless needles, mp 236–239° dec, yield 0.9 g (12%). An analytical sample was recrystallized twice from MeOH; mp 241–242° (dec); ir, ν_{max}^{Nujol} (cm^{-1}) 1720, 1620, 1552. *Anal.* ($C_{17}H_{17}IN_2O$) C, H, N.

I·HI (1.7 g) was obtained from the mother liquor of recrystallization: mp 218–220° dec; ir, ν_{max}^{Nujol} (cm^{-1}) 1730, 1652, 1575, 1545. I (Ar = C_6H_5) (1.9 g, 40%) was recovered from the mother liquor of the reaction mixture.

B.—To a solution of VI (1.2 g) in EtOH (10 ml) was added 57% HI (1.2 g). A crystalline product appeared soon after the addition. The mixture was allowed to stand for 3 hr at room temperature. The crystalline product was filtered and recrystallized from MeOH to give pale yellow needles, mp 241–242° dec, yield 1.6 g (96%). Ir spectra of the product and a sample obtained by method A were superimposable.

Reaction of IV with Aqueous Alkaline.—To a suspension of IV (0.2 g) in a mixture of H_2O (10 ml) and C_6H_6 (20 ml) was added 10% K_2CO_3 (1.5 ml), and the mixture was shaken until the crystals disappeared. The C_6H_6 layer was separated, dried (Na_2SO_4), and evaporated to give a crystalline residue (130 mg), mp 139–142°. Recrystallization from C_6H_6 afforded colorless prisms, mp 146–147°, yield 0.11 g (76.5%). The product

Table III

Summary of Pharmacological Observations

Compd	Salt	Max tolerated dose, mg/kg po	Max tolerated dose, mg/kg ip	Behavior in max tolerated po dose[a]	Analgetic effect: Eff % 66 mg/kg ip	Analgetic effect: Eff % 100 mg/kg ip	Analgetic effect: ED_{50}, mg/kg	Prolonged % of sleeping time by barbiturate 100 mg/kg ip	Anti-inflam act., % inhib of carrageenin abscess 100 mg/kg po	Anti-histamic effect, % inhib of histamine spasm 10^{-5} g/ml	LD_{50}, mg/kg
11	Free	400	400	a	...	...	...	119	...	*b*	...
12	Free	400	200	Unchanged	20	40	...	120	20	*b*	...
14	HCl	400	200	a, c, d	20	40	...	83	22	70	...
15	Free	400	200	a, c	...	...	...	50	...	*b*	...
16	HCl	400	200	c, d	0	20	...	90	5	60	...
17	Oxalate	400	100	b, c	40	80	80.3 (57.5–134.0) ip 195.0 (145.0–256.3) *po*	70	10	65	180.0 (157.2–221.0) ip 677.6 (524.3–857.7) *po*
18	Oxalate	400	100	b, c	40	80	70.6 (41.9–118.5) ip 168.1 (42.7–334.9) *po*	140	20	80	155.5 (127.3–180.4) ip 620.4 (520.5–750.7) *po*
19	Oxalate	200	100	b, c	0	20	...	126	10	80	...
20	HCl	400	200	b	0	20	...	105	5	95	...
21	HCl	400	200	Unchanged	0	0	...	140	27	50	...
22	HCl	200	100	b, d	0	0	...	300	7	50	...
Aminopyrine	...	400	100	a, e	...	...	77.9 (57.1–106.3) ip 356.4 (246.1–491.1) *po*	...	13	...	315.6 (241.1–413.2) ip 1505.8 (1087.8–1816.8) *po*
Chlorphenylamine	...	100	50	a, e	...	...	...	...	...	100	...
Diphenhydramin	...	100	50	a	...	...	...	...	...	100	...
Phenylbutazone	...	400	200	Unchanged	...	...	...	...	20	...	...

[a] Behavior: a, decreased spontaneous activity; b, increased spontaneous activity; c, tremors; d, staggering gate; e, muscle relaxation. [b] Insoluble in Tyrode solution.

was comfirmed to be identical with VI (melting point and ir spectra).

1-Ethyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (VII). A.—Compound IV (1.0 g) was reduced with $NaBH_4$ (0.11 g) in EtOH. Recrystallization from Et_2O–hexane (1:2) afforded colorless prisms, mp 77–78°, yield 0.59 g (87%). Analytical data are listed in Table II (**4**).

B.—A mixture of V (3.0 g), acetaldehyde diethyl acetal (2.5 g), concentrated H_2SO_4 (1 drop), and absolute EtOH (30 ml) was refluxed for 4.5 hr. The solvent was evaporated and the residue was dissolved in Et_2O and washed (5% $NaHCO_3$, saturated NaCl). The dried ethereal solution was distilled to give a colorless oil (3.3 g). The residue was dissolved in absolute hexane and chromatographed over Al_2O_3. The eluate with hexane–C_6H_6 (3:2) gave a colorless oil (1.3 g), which crystallized after standing in a refrigerator. Recrystallization from Et_2O–hexane (1:2) gave colorless prisms, mp 75–77°, yield 1.1 g (33%). Admixture with a sample obtained by method A did not depress its melting point.

N-[2-(Disubstituted aminoethyl]anthranilic acids (IX) were prepared by a modification of Hauptmann's method.[2]

a, R_2 = $(CH_3)_2$.—2-Chlorobenzoic acid (35.5 g) was dissolved in a solution of KOH (13 g) in H_2O (23 ml), and 1,1-dimethylethylenediamine (22 g), K_2CO_3 (15.8 g), and Cu powder (5 g) were added. The mixture was refluxed for 72 hr, cooled, and acidified with 10% HCl (170 ml). The separated semisolid was extracted with Et_2O, and the acidic aqueous layer was placed on a column of Amberlite IR-120 (1000 ml of acid form). The column was washed with H_2O and eluted with 5% NH_4OH (5 l.). The eluate was evaporated to dryness under reduced pressure. The residue was crystallized by trituration in MeOH and recrystallization from MeOH to give IX [R_2 = $(CH_3)_2$] as colorless needles, mp 180–182° dec, yield 15.4 g (33%). *Anal.* ($C_{11}H_{16}N_2O_2$) C, H, N.

b, R_2 = $(C_2H_5)_2$.—VIII (108.6 g) and 1,1-diethylethylenediamine (88.5 g) were worked up as for a. Recrystallization from 96% EtOH gave colorless prisms, mp 161–163° dec, yield 57.8 g (31%). *Anal.* ($C_{13}H_{20}N_2O_2$) C, H, N.

c, $-NR_2$ = $-N$⟨⬡⟩ was similarly prepared from VIII (108.6 g) and N-(2-aminoethyl)piperidine (87.6 g). Recrystallization from 96% EtOH afforded prisms, mp 195–197° dec, yield 51 g (30%). *Anal.* ($C_{14}H_{20}N_2O_2$) C, H, N.

N-Acetyl-N-[2-(disubstituted amino)ethyl]anthranilic Acids (X). a, R_2 = $(CH_3)_2$.—A mixture of IX [R_2 = $(CH_3)_2$] (3.0 g) and Ac_2O (30 g) was stirred for 4 hr at room temperature. Excess Ac_2O and AcOH were distilled under reduced pressure. The residue was crystallized by the addition of Et_2O–Me_2CO. Recrystallization from Me_2CO afforded colorless needles of hydrated X [R_2 = $(CH_3)_2$], mp 95–97°, yield 25.1 g (65%). *Anal.* ($C_{13}H_{18}N_2O_3 \cdot H_2O$) C, H, N.

b, R_2 = $(C_2H_5)_2$.—Acetylation of IX [R_2 = $(C_2H_5)_2$] (25 g) was similarly worked up. Recrystallization from Me_2CO gave acetyl derivative of X [R_2 = $(C_2H_5)_2$] as colorless prisms, mp 102–103°, yield 32.3 g (90%). *Anal.* ($C_{15}H_{22}N_2O_3 \cdot AcOH$) C, H, N.

c, $-N(R)_2$ = $-N$⟨⬡⟩.—Compound IX [$-NR_2$ = $-N$⟨⬡⟩] (30 g) was acetylated with Ac_2O (60 g) as above. The product was recrystallized from THF to give colorless prisms, mp 150–152°, yield 29.5 g (84%). *Anal.* ($C_{16}H_{22}N_2O_3$) C, H, N.

2-(2-Dimethylaminoethyl)aminobenzanilide (XI).—A stirred solution of IX [R_2 = $(CH_3)_2$] (6.2 g) in H_2O (60 ml) was treated with $COCl_2$ at 15–20°. Gelationous precipitates separated from the mixture. After 1 hr, a solution of $NaOAc \cdot 3H_2O$ (8.4 g) in H_2O (10 ml) was added to the mixture and the treatment with $COCl_2$ continued for an additional 4 hr. The mixture was evaporated to dryness under reduced pressure at room temperature. Aniline (10 g) was added to the residue and the mixture was heated at 95–100° for 2 hr and cooled. The brown reaction mixture dissolved in H_2O (20 ml) and was made alkaline with K_2CO_3, and the separated oil was extracted with Et_2O. The dried extract was evaporated to give a brown oil, from which excess aniline was distilled off under reduced pressure. The residue was crystallized by the addition of hexane. Recrystallization from C_6H_6–hexane (1:3) afforded colorless plates, mp 116–118°, yield 1.75 g (21%). *Anal.* ($C_{17}H_{21}N_3O$) C, H, N.

1-(2-Dimethylaminoethyl)-2-methyl-3-phenyl-4-oxodihydroquinazolinium Diperchlorate [XIII, R_2 = $(CH_3)_2$]. A.—To a solution of X [R_2 = $(CH_3)_2$] (5.0 g) and aniline (2.5 g) in dry THF was added N,N′-dicyclohexylcarbodiimide (9.0 g). The mixture was stirred for 20 hr at room temperature and filtered to separate colorless precipitates. The filtrate was evaporated to give an oily residue. The residue was dissolved in 10% HCl and filtered, and the acidic filtrate was washed with Et_2O to remove unreacted materials. The aqueous layer was made alkaline with K_2CO_3 and the separated oil was extracted with $CHCl_3$. Distillation of the dried extract afforded an oily residue (*ca.* 6 g). A solution of the residue (0.5 g) in Et_2O (20 ml) was adjusted at pH 6.4–6.6 by the addition of 60% $HClO_4$ to give a gummy precipitate, which was crystallized by treating with Me_2CO. Recrystallization from EtOH gave perchlorate of 2-N-(2-dimethylaminoethyl)acetamidobenzanilide [XII, R_2 = $(CH_3)_2$] as colorless needles: mp 175–179° dec; ir, ν_{max}^{Nujol} (cm^{-1}) 3300, 3100, 1675, 1650, 1600, 1540. *Anal.* ($C_{19}H_{24}ClN_3O_6$) C, H, N.

The remaining residue (*ca.* 5.5 g) was dissolved in absolute EtOH (40 ml) and treated with excess 60% $HClO_4$ to give a crystalline product, which was very insoluble in organic solvents.

Recrystallization from DMF–EtOH afforded XIII [$R_2 = (CH_3)_2$] as colorless needles: mp 255–256° dec; yield 7.4 g (85%); ir, ν_{max}^{Nujol} (cm^{-1}) 3130, 1720, 1625, 1555. Analytical data are listed in Table I.

1-[2-(Disubstituted amino)ethyl]-2-methyl-3-aryl-4-oxodihydroquinazolinium diperchlorates were prepared in a similar way, without isolation of XII. The products are shown in Table I (**2–9**).

B.—AcCl (0.15 g) was added to a mixture of XIII (0.28 g), powdered K_2CO_3 (0.2 g), and dry C_6H_6 (3 ml). The mixture was stirred overnight at room temperature, treated with H_2O (5 ml), and made alkaline with 10% K_2CO_3. The benzene layer was separated, washed with H_2O, and dried (K_2CO_3). Distillation of the solvent gave an oily residue (0.3 g), which was dissolved in Et_2O and treated with excess 60% $HClO_4$. The crude crystalline product and EtOH (3 ml) were refluxed for 10 min and cooled. The separated crystals were collected, mp 255–256° dec, yield 0.35 g. Ir spectra of the product and a sample obtained by method A were superimposable.

1-(2-Dimethylaminoethyl)-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline [XIV, $R_2 = (CH_3)_2$]. **A.**—To a stirred suspension of XII [$R_2 = (CH_3)_2$] (5.0 g) in EtOH (50 ml) was added a solution of $NaBH_4$ (0.8 g) in EtOH (90 ml) at −5 to −2° over a period of 3 hr. The mixture became clear after the addition and the solvent was distilled under reduced pressure. To the residue was added H_2O and separated oil was extracted with Et_2O. The dried extract was evaporated and the residue was distilled at 250–255° (0.2 mm) to give a viscous oil, yield 2.0 g (66%). *Anal.* ($C_{19}H_{23}N_3O$) H, N; C: calcd, 73.75; found, 73.29.

The **oxalate** yielded colorless plates (from Me_2CO), mp 86–89° dec. Analytical data are listed in Table II (**14**).

1-[2-(Disubstituted amino)ethyl]-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines were prepared by the same way as above. The products are shown in Table II (**15–22**).

B.—A solution of XIII (1.4 g) and paraldehyde (0.66 g) in absolute EtOH (20 ml) was saturated with dry HCl at 0–5° and the mixture was allowed to stand at room temperature overnight. The solvent was distilled under reduced pressure. The residue was made alkaline with concentrated NH_4OH and the separated oil was extracted with Et_2O. Distillation of the extract gave an oily residue (1.5 g), which was dissolved in dry C_6H_6 and chromatographed over Al_2O_3. The C_6H_6–MeOH (98:2) eluate afforded a colorless viscous oil, which was distilled, bp 280° (bath temperature) (0.2 mm), yield 0.5 g (32%). Ir spectra of the product and a sample obtained by method A were superimposable.

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Derivatives of 3-Piperidinol as Central Stimulants

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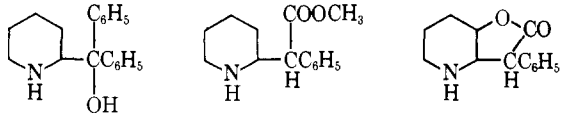
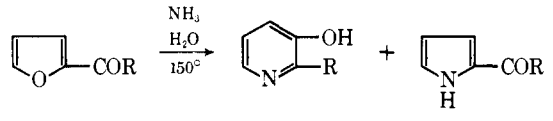
A number of 2-aralkyl-3-pyridinols, prepared by the ammonolysis of aralkyl 2-furyl ketones, were hydrogenated to 3-piperidinols. Several of these latter compounds and their N-substituted derivatives were potent central stimulants. Two of the most active compounds were resolved and the activity was found predominantly in one optical isomer in each case.

The clinical usefulness of pipradrol (III) and methylphenidate (IV) as central stimulants prompted the preparation of the 2-aralkyl-3-piperidinols I (Table I). These compounds were obtained by hydrogenating the corresponding 3-pyridinols II (Table II), followed by alkylation or acylation where necessary. The 3-pyridinols II (Table II), where X = H, were prepared by the ammonolysis and concomitant ring closure of 2-furyl ketones to a mixture of the desired II and an aralkyl 2-pyrryl ketone VI.



III IV V



VII VI

Ammonia or ammonium salts in various solvent combinations have been used for this reaction,[1] but in the present study ammonia in aqueous methanol gave the best yields. In some instances the reaction failed. For example, 2-furoylphenylacetonitrile cleaved to furamide; 2-furyl 9-fluorenyl ketone gave fluorene quantitatively, and 2-furyl 9-xanthenyl ketone gave xanthene and a small amount of the desired 3-pyridinol. A 5-methyl group in the furan ring reduced the yield of pyridinol to less than 5%. No effort was made to isolate the by-product 2-pyrryl ketones.

The diarylmethyl 2-furyl ketones (Table III) were obtained in good yield from ethyl furoate and a diphenylmethane with $NaNH_2$ or KNH_2 in liquid ammonia. Several attempts to acylate furan with diphenylacetyl chloride and stannic chloride gave only traces of ketone, although this method[2] has been used successfully for similar compounds.

The hydrogenation of the 3-pyridinols to the 3-piperidinols was difficult. With Pt hydrogenation of the bases in acetic acid or the hydrochloride salts in ethanol gave complex mixtures containing most of the possible combinations of phenyl, cyclohexyl, pyridine,

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