pyridinium bromide (XIb).[30] Work-up in a manner similar to that for IIIb gave an oil from which no crystalline material could be obtained. Distillation provided 6.2 g of viscous yellow oil, bp 210–245° (0.06–1.0 mm), subsequently chromatographed on neutral alumina using benzene as eluent and redistilled to give 1.4 g (9%) of viscous yellow oil [bp 198–202 (0.03 mm); uv λ_{max}^{MeOH} 267.5 nm, 353, 427] shown by nmr spectroscopy to be 21% of the 1,2-dihydropyridine IIi and 79% of the 1,6-dihydropyridine IIIi: nmr δ 3.47 (IIi, OCH_3, s), 3.66 (IIIi, OCH_3, s), 4.05 (IIIi, NCH_2, s), 4.30 (IIi, NCH_2, s), 7.53 (IIIi, C-2, s), and other multiplets to be expected from this mixture.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.66; H, 6.45; N, 4.69.

1-(2,6-Dichlorobenzyl)-3-cyano-6-(1,1-dicarbethoxypropyl)-1,6-dihydropyridine (XIII).—Diethyl ethylmalonate, 1.87 ml, was added dropwise to a stirred suspension of 0.50 g of a 49.7% dispersion of sodium hydride in mineral oil in 20 ml of THF. The resulting solution was added dropwise to a stirred suspension of 3.0 g (0.010 mol) of 1-(2,6-dichlorophenyl)-3-cyanopyridinium chloride (XII)[26] in 20 ml of THF. The mixture was stirred for 0.5 hr, was filtered, and was concentrated. The residual oil was dissolved in ether and treated with charcoal. The solvent was removed and the residue crystallized on trituration with petroleum ether. Recrystallization from benzene–petroleum ether gave 0.8 g (18%) of crude XIII: mp 117–122° dec; uv λ_{max}^{MeOH} 363 nm, 310, 242 (sh). The nmr was consistent with the structure XIII. The triplets for two nonequivalent methyls of the ester and the methyl of the C-ethyl appear at about 1 ppm. The diastereotopic protons of the methylene of the C-ethyl give a multiplet at 2.0 ppm. The methylene protons of the ester groups appear at 4.1 ppm. The benzylmethylene appears at 4.64 ppm. The ring protons appear at 4.95 (C-5, d of d, J = 8.0, 4.5 Hz), 6.3 (C-4, d of d, J = 8.0, 1.5 Hz), 6.88 (C-2, d, J = 1.5 Hz). Recrystallization from 2-propanol and ether improved the melting point, 130.5–132.5°, but the nmr did not change.

Anal. Calcd for $C_{22}H_{24}Cl_2N_2O_4$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.28; H, 4.72; N, 6.25.

(30) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966).

Registry No.—IIa, 27531-36-8; IIg, 27531-37-9; IIi, 27531-38-0; IIIa, 27531-39-1; IIIb, 27531-40-4; IIIc, 27531-41-5; IIId, 27531-42-6; IIIe, 27531-43-7; IIIe (2-deuterio), 27531-44-8; IIIf, 27531-45-9; IIIg, 27531-46-0; IIIh, 27531-47-1; IIIi, 27531-48-2; V, 27531-49-3; VIII, 27531-54-0; XIII, 27531-55-1; methylmagnesium bromide, 75-16-1; *tert*-butylmagnesium chloride, 677-22-5; phenylmagnesium bromide, 100-58-3.

Quinazolines and 1,4-Benzodiazepines. XLVIII. Ring Enlargement of Some Chloromethylquinazolin-4-ones[1]

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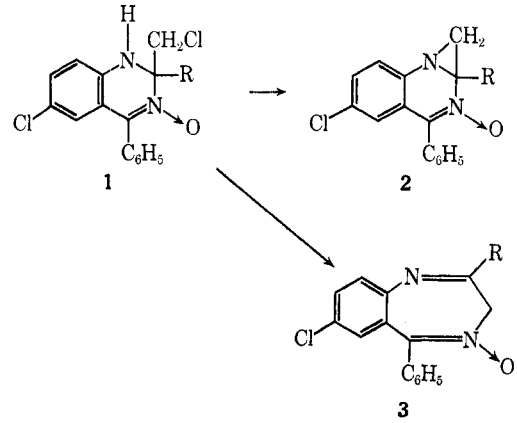
Treatment of 2-chloromethyl-1,2,3,4-tetrahydroquinazolin-4-ones with bases gives 1,4-benzodiazepin-5-ones. Aziridines are implicated as intermediates.

Reaction of 2-chloromethylquinazoline 3-oxide derivatives, such as **1**, with strong bases leads to ring expansion with formation of two types of compounds, benzodiazepines **3** and their structural isomers **2**.[2] One can consider this reaction to be an internal alkylation in which the chloromethyl group alkylates either the 1 nitrogen to produce **2** or the 3 nitrogen to produce ultimately **3**. Obviously, this reaction should be extendable to the synthesis of other heterocycles containing a seven-membered ring. However, since a change of the substituent R from hydrogen to methyl is enough to change the product from one type to the other, one might expect that other changes would also affect this delicate balance.[2] It therefore seemed of interest to study additional examples of this reaction.



We now report that 1,2,3,4-tetrahydro-4-oxoquinazolines,[3] *e.g.*, **5**, give only products derived by alkylation of the 1 nitrogen. The starting materials, **5**, **12**, and **17**, are easily prepared by the acid-catalyzed condensation of an anthranilamide with chloroacetone with azeotropic removal of the water formed. Treatment of **5** with potassium *tert*-butoxide in tetrahydrofuran, conditions which in the case discussed above favor formation of the aziridines **2**, yielded the benzodiazepinone **7**.

The nmr spectrum of **7** showed a singlet at δ 2.17 ppm for the methyl group, a band at δ 4.16 ppm for the methylene group, and a band at δ 8.5 for the NH. It absorbed 1 mol of hydrogen on hydrogenation over platinum to give the tetrahydrobenzodiazepinone **9**.[4] The structure of **7** was confirmed by its hydrolysis to an acetonyl anthranilamide (**8**) which on treatment with base gave 2-acetylindoxyl (**10**).[5] Alkylation of anthranilamide with chloroacetone in the presence of calcium carbonate also gave **8** (Scheme I).

Reaction of **5** with potassium methoxide in methanol, conditions which in the quinazoline 3-oxide series favor

(1) (a) Presented in part at the Middle Atlantic Regional Meeting of the American Chemical Society, New York, N. Y., Feb 1966. (b) Paper XLVII: R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **35**, 2243 (1970).

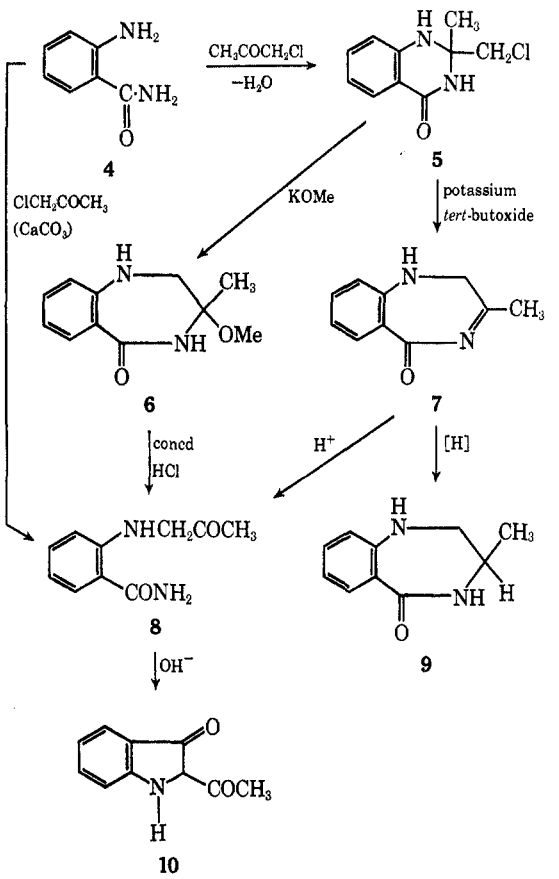
(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **89**, 332 (1967).

(3) H. Boehme and H. Boeing, *Arch. Pharm. (Weinheim)*, **293**, 1011 (1960); W. L. F. Armarego in "Fused Pyrimidines: Part I, Quinazolines," D. J. Brown, Ed., Interscience, New York, N. Y., 1967, pp 392–394.

(4) Similar compounds have been prepared by A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **31**, 4268 (1966).

(5) H. C. F. Su and K. C. Tsou, *J. Amer. Chem. Soc.*, **82**, 1187 (1960).

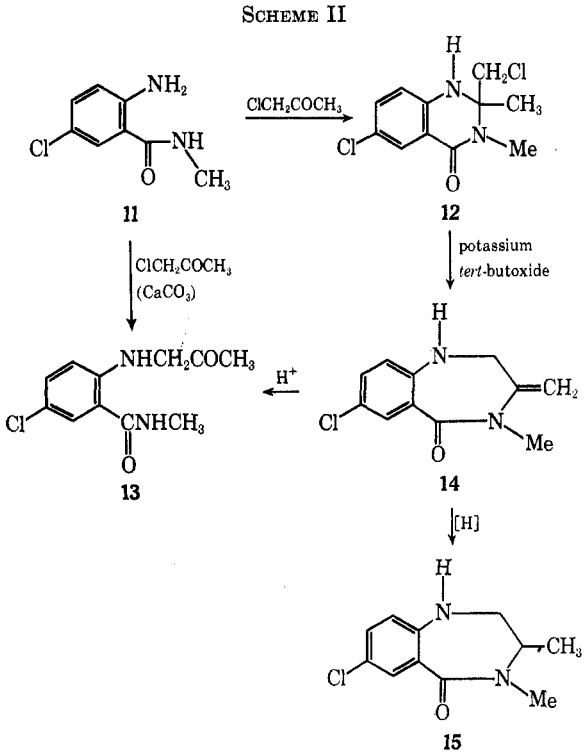
SCHEME I



alkylation at the 3 nitrogen to give products of structure **3**,[2] gave the methoxy derivative **6**, which also gave **8** on hydrolysis. Therefore, in both solvents, nitrogen 1 is alkylated.

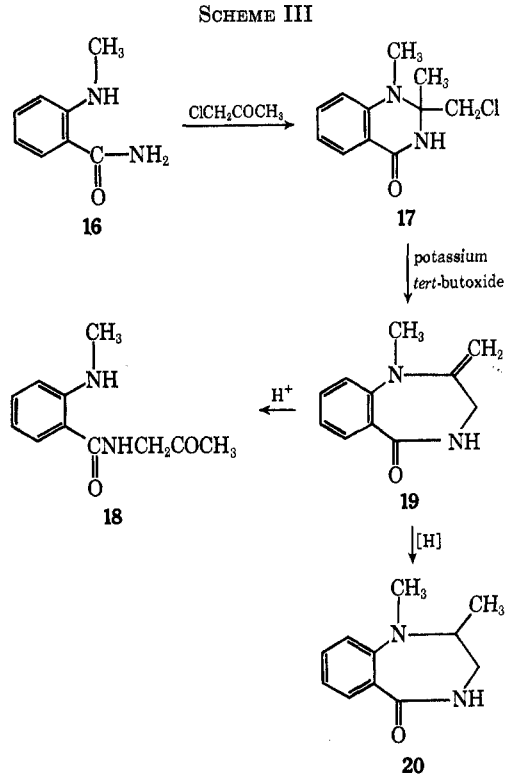
The *N*-methyl derivatives of **5** were also prepared and ring expanded. Reaction of **12** with potassium *tert*-butoxide in tetrahydrofuran gave a product to which structure **14** was assigned on the basis of the nmr spectrum. The double bond could be reduced to give **15**. As with **7**, acid hydrolysis gave an acetonyl compound **13** which was also obtained by alkylation of **11** with chloroacetone (Scheme II).

SCHEME II



Reaction of the 1-methylquinazolinone **17** with potassium *tert*-butoxide in tetrahydrofuran gave a product to which structure **19** was assigned on the basis of the nmr spectrum. Hydrolysis gave the acetonyl compound **18**. Catalytic hydrogenation gave the tetrahydrobenzodiazepinone **20** whose nmr spectrum showed a doublet (J = 6 Hz) at δ 1.0 ppm for the *C*-methyl group (Scheme III).

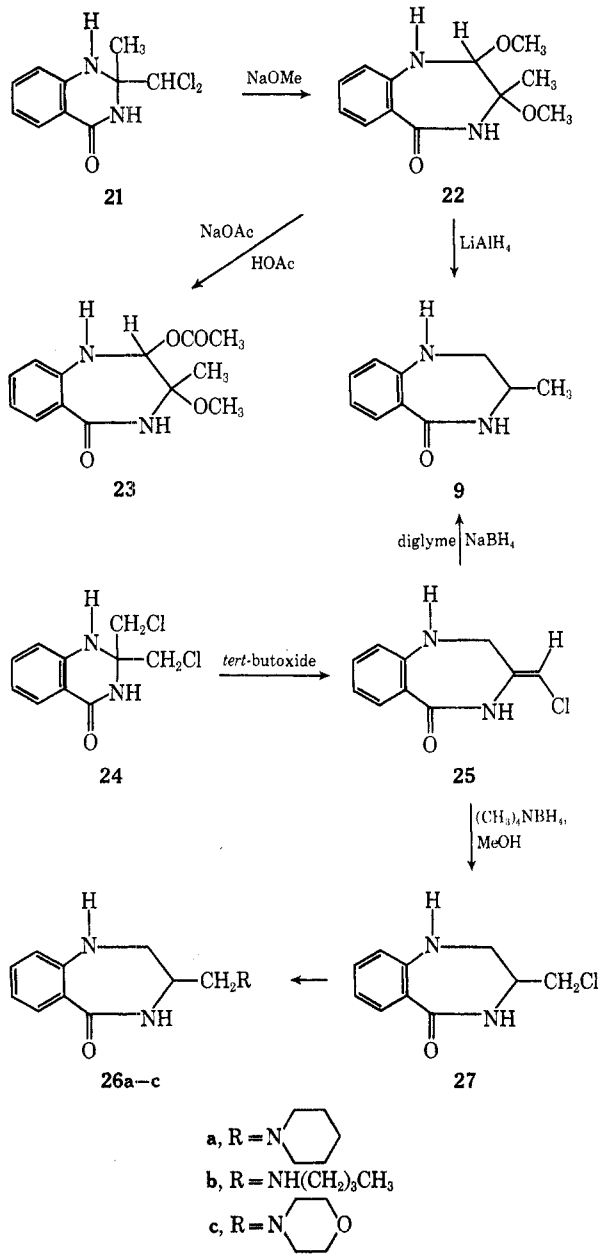
SCHEME III



The quinazolines **21** and **24** derived from symmetrical and unsymmetrical dichloroacetone were also studied. The dichloromethyl derivative **21** gave **22** with sodium methoxide in methanol. Reduction of **22** with lithium aluminum hydride gave **9** which confirms the presence of the benzodiazepine ring system. The disposition of the methoxy groups is shown by the nmr spectrum which contains a singlet at δ 1.47 ppm for the *C*-methyl and doublet at δ 4.23 ppm for the C-2 hydrogen which collapses to a singlet on exchange with D_2O. On treatment with sodium acetate in acetic acid, the 2-methoxy group is exchanged for acetate to give **23**, demonstrating the nonequivalence of the two methoxy groups. The nmr spectrum of **23** shows that it is the 2-methoxy rather than the 3-methoxy which has been displaced, since the methine proton at C-2 shifts from δ 4.23 to 5.58 ppm.

Treatment of the bischloromethyl compound **24** with 1 equiv of potassium *tert*-butoxide caused the loss of 1 mol of hydrogen chloride and formation of **25**. The gross structure of **25** was confirmed by reduction with sodium borohydride in diglyme to **9**. The position of the double bond was shown by the nmr spectrum. The

SCHEME IV



methylene group at C-2 gives rise to a doublet (J = 4 Hz) at δ 3.85 (2 H). The vinyl hydrogen gave a singlet at δ 5.67 ppm, and the two exchangeable protons attached to the nitrogens are at δ 7.0 and 8.51 ppm. The presence of a chlorine atom apparently stabilizes the double bond in the exocyclic position. Reduction of **25** with tetramethylammonium borohydride in methanol gave the chloromethylbenzodiazepine **27**. This compound, on displacement of the chlorine with primary or secondary amines, gave the aminomethyl derivatives **26** (Scheme IV).

Discussion

Since there are two ionizable protons in **5**, there are two possible pathways by which the benzodiazepinones **6** and **7** could be formed. The products obtained from the *N*-methyl derivatives show that the N-1 proton is abstracted by the base to give the anion A as the first step to the reaction. The next step is ring closure to the aziridine B, which then isomerizes to the benzodiazepine **7**. This conclusion follows since the 3-methyl derivative, **12**, gave a similar product, **14**, while the 1-methyl derivative **17** gives a different type of product. If an alternative path through ions C and D was followed, the 1-methyl derivative **17** would have given a product similar to that of the original compound **5**, and the 3-methyl derivative **12** would have given the other type of product. (See Scheme V.)

This situation is much simpler than the case of the 1,2-dihydroquinazoline 3-oxides **1** which were studied previously.[2] Here only the path leading to the formation of aziridines is followed. There is no evidence for the formation of any intermediates in which the heterocyclic ring has opened.

Experimental Section[6]

2-Chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (5).—A mixture of 2-aminobenzamide **4** (136.0 g, 1.0 mol), 2-chloropropanone (170 ml, 2.1 mol), and benzene (2.5 l.) was stirred under reflux for 4 hr; the water produced was collected with a Dean-Stark trap. The reaction mixture was cooled to 20°, and the precipitated crystals were filtered to give tan plates, mp 159–163° (198.1 g, 94%). An analytical sample was obtained as colorless plates after three recrystallizations from ethyl acetate: mp 165–168°; ir ($CHCl_3$) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{11}ClN_2O$: C, 57.01; H, 5.26. Found: C, 57.19; H, 5.02.

1,2,3,4-Tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (6).—A solution of 4.2 g (20 mmol) of 2-chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (**5**) and 2.24 g (20 mmol) of potassium *tert*-butoxide in 150 ml of methanol was stirred at room temperature for 4 hr. The precipitated inorganic material was removed by filtration through Celite, and the filtrate concentrated *in vacuo* to give 4.0 g of crude product, mp 168–172° dec. Two recrystallizations from methanol gave colorless prisms: mp 165–168° dec; ir ($CHCl_3$) 1635 cm^{-1} (CO); uv max 223 (ϵ 29,000), 255 (8500), and 340 (5000).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.01; H, 6.67.

1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (7).—Potassium *tert*-butoxide (22.4 g, 0.2 mol) was added to a cooled (10–15°) solution of 2-chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (**5**) (42.1 g, 0.2 mol) in tetrahydrofuran (500 ml) with stirring. The reaction mixture was stirred at room temperature overnight and filtered through a bed of Celite, and the clear filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from methylene chloride and the solids were filtered to give off-white plates, mp 143–149° (15.0–21.6 g, 43–63%). An analytical sample was obtained as off-white plates after four recrystallizations from ethanol: mp 156–159°; ir ($CHCl_3$) 1660 cm^{-1} (CO); uv max 215 mμ (ϵ 23,000), 255 (9000), and 341 (4050); nmr (DMSO) δ 2.17 (s, 3, CH_3), 4.16 (m, 2, CH_2), and 8.5 ppm (m, 1, NH).

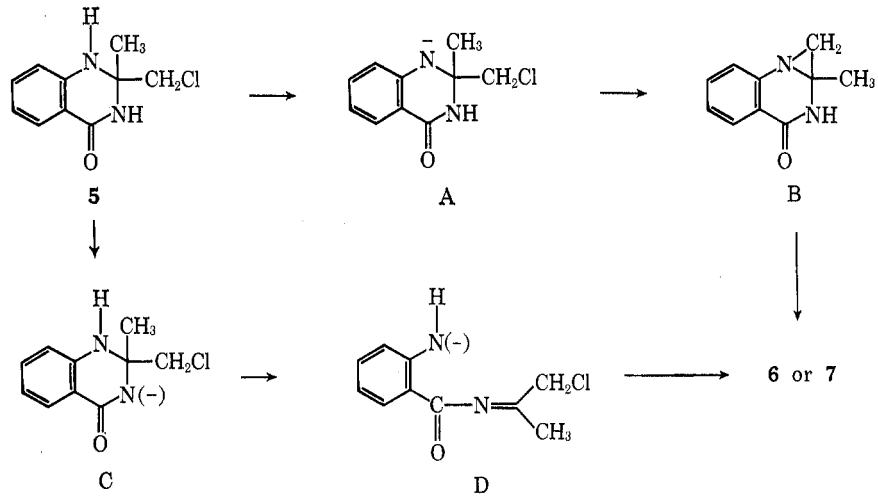
Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 69.05; H, 5.79.

2-Acetonylaminobenzamide (8). A. From 7.—1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (**7**) (20.0 g, 0.115 mol) was dissolved in concentrated hydrochloric acid (300 ml) and stored at room temperature overnight. The solution was neutralized with 50% aqueous sodium hydroxide, diluted with water, and extracted with methylene chloride in five portions. The methylene chloride extracts were combined, dried over sodium sulfate, filtered, and concentrated to dryness. The solid residue was collected by filtration to give tan needles, mp 140–150° (15 g, 68.1%). An analytical sample was obtained as colorless needles after two recrystallizations from ethanol: mp 162–163.5°; ir (KBr) 3470 (NH), 3360 and 3310 (NH_2), 1780 (CO), 1640 and 1615 cm^{-1} (amide CO); nmr (DMSO) δ 2.14 (s, 3, CH_3), 4.06 (d, 2, J = 5 Hz, CH_2, and 8.45 ppm (t, 1, J = 5 Hz, NH).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29. Found: C, 62.25; H, 6.11.

(6) Melting points were determined in capillaries and are corrected. The nmr spectra were determined on a Varian A-60 instrument. Alumina refers to Woelm grade I and petroleum ether to a fraction of bp 40–60°. The ultraviolet spectra were taken in 2-propanol.

SCHEME V



B. From 4.—A mixture of 2-aminobenzamide (4) (27.4 g, 0.2 mol), calcium carbonate (13.7 g, 0.137 mol), 2-chloropropanone (18.4 g, 0.2 mol), and water (200 ml) was stirred under reflux for 1 hr. The reaction mixture was cooled to room temperature and the precipitate collected to give **8** as tan needles, mp 162–165° (21.5 g, 54.7%), identified by mixture melting point and ir spectrum.

C. From 6.—A solution of 1,2,3,4-tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (6) (2.1 g, 10 mmol) in 75 ml of concentrated hydrochloric acid was allowed to stand overnight at room temperature. The solution was then diluted with water, neutralized with solid sodium bicarbonate, and extracted with methylene chloride in four portions. The extracts were dried over sodium sulfate and concentrated *in vacuo* to leave 1.2 g of solid, which on recrystallization from ethanol gave 1.0 g of 2-acetonylaminobenzamide (**8**), mp 161–163°. The infrared spectrum was identical with that of authentic material.

2-Acetylindoxyl (10).—A solution of 2-acetonylaminobenzamide (38.4 g, 0.2 mol) in 1 *N* aqueous sodium hydroxide (200 ml, 0.2 mol) was stirred under an atmosphere of nitrogen for several min. The internal temperature was gradually increased to 100° over a 45-min period and then maintained at this temperature for an additional 15 min. The solution was cooled to room temperature, filtered by gravity, and neutralized with 1 *N* aqueous hydrochloric acid. The precipitated solids were filtered and recrystallized from dilute methanol to give green needles, mp 157–162° (10.6 g, 30%). An analytical sample was obtained as greenish needles after three recrystallizations from dilute methanol: mp 158–159.5° (lit.[5] mp 161–161.5°); uv max 239 mμ (ε 15,000), 255 (sh) (9000), 316 (21,000), and 353 (7000).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.55; H, 5.17. Found: C, 68.38; H, 5.43.

1,2,3,4-Tetrahydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (9).—1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (**7**) (21.5 g, 0.128 mol) was hydrogenated in ethyl acetate (240 ml) at room temperature and atmospheric pressure in the presence of platinum oxide (2.6 g, 0.0115 mol). After 2.5 hr, 3.4 l. (0.152 mol) of hydrogen had been absorbed and the uptake had stopped. The mixture was concentrated to a small volume *in vacuo* and filtered through a bed of Celite. The bed of Celite was slurried with hot ethanol and filtered through a second bed of Celite into the original filtrate. The combined filtrates were concentrated to dryness *in vacuo*, and the residue was crystallized from ethanol to give yellowish plates, mp 213–216° (14.0 g, 62.2%). An analytical sample was obtained as off-white plates after two recrystallizations from ethanol: mp 214–216°; ir (KBr) 1630 cm^{-1} (CO); uv max 222 mμ (ε 26,000), 258 (8000), and 338 (9500).

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 67.95; H, 7.09.

2-Amino-5-chloro-*N*-methylbenzamide (11).—To a solution of methylamine hydrochloride (6.7 g, 0.1 mol) in 100 ml of 1 *N* sodium hydroxide was added 6-chloroisatoic anhydride (7.9 g, 40 mol), and the mixture was stirred and heated under reflux for 0.5 hr. On cooling **11** (5.2 g, 70%), mp 131–133°, separated. Recrystallization from water gave colorless needles, mp 133–134°.

Anal. Calcd for $C_8H_9ClN_2O$: C, 52.04; H, 4.91. Found: C, 51.85; H, 5.00.

6-Chloro-2-chloromethyl-1,2-dihydro-2,3-dimethyl-4(3*H*)-quinazolone (12).—A mixture of 5-chloro-2-amino-*N*-methylbenzamide **11** (67.0 g, 0.363 mol), 2-chloropropanone (70.6 g, 0.76 mol), and benzene (1.2 l.) was stirred under reflux under a Dean-Stark trap for 4 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue triturated with ethyl acetate–hexane to give **12** as tan prisms, mp 186–192° (84.4 g, 89.8%). An analytical sample was obtained as colorless prisms after three recrystallizations from ethyl acetate: mp 198–200°; ir (KBr) 1635 cm^{-1} (CO); uv max 225 mμ (ε 32,000), 243 (sh) (12,000), 257 (7500), and 353 (3000).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.98; H, 4.67. Found: C, 51.13; H, 5.05.

7-Chloro-1,2-dihydro-3-methylene-4-methyl-5*H*-1,4-benzodiazepin-5-one (14).—Potassium *tert*-butoxide (11.2 g, 0.1 mol) was added to a cooled (10–15°) solution of 6-chloro-2-chloromethyl-1,2-dihydro-2,3-methyl-4(3*H*)-quinazolone (**12**) (25.9 g, 0.1 mol) in tetrahydrofuran (600 ml) with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite, the clear filtrate concentrated to dryness *in vacuo*, and the residue crystallized from ethyl acetate–benzene to give **14** as off-white needles, mp 145–155° (15.5 g, 69.7%). An analytical sample was obtained as off-white needles after four recrystallizations from 2-propanol: mp 162.5–165°; ir ($CHCl_3$) 1620, 1600, and 1500 cm^{-1}; uv max 228 mμ (ε 21,000), 250 (18,000) and 357 (3500); nmr (DMSO) δ 3.23 (s, 3, NCH_3), 3.81 (d, 2, NCH_2), 4.67 (s, 1, C=CH_2), and 4.74 ppm (s, 1, C=CH_2).

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.34; H, 4.98. Found: C, 59.67; H, 4.78.

7-Chloro-1,2,3,4-tetrahydro-3,4-methyl-5*H*-1,4-benzodiazepin-5-one (15).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold solution (10–15°) of 6-chloro-2-chloromethyl-1,2-dihydro-2,3-dimethyl-4(3*H*)-quinazoline (**12**) (77.7 g, 0.3 mol) in tetrahydrofuran (1.6 l.) with stirring. After stirring overnight at room temperature, the reaction mixture was filtered through a bed of Celite.

The clear filtrate was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (4.0 g, 0.0176 mol). After 6 hr, 6.372 l. (0.2844 mol) of hydrogen had been absorbed and the uptake had stopped. The catalyst was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was crystallized from ethanol to yield off-white needles, mp 165–178° (41.0 g, 60.9%). An analytical sample was obtained as colorless needles after four recrystallizations from ethanol: mp 190–192°; ir ($CHCl_3$) 1625 cm^{-1} (CO); nmr (DMSO) δ 1.1 ppm (d, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83. Found: C, 59.26; H, 6.01.

5-Chloro-2-acetonylamino-*N*-methylbenzamide (13). A. From 14.—7-Chloro-1,2-dihydro-3-methylene-4-methyl-5*H*-1,4-benzodiazepin-5-one (**14**) (5.0 g, 0.0225 mol) was dissolved in concentrated hydrochloric acid (75 ml). The solution was stirred at room temperature overnight, neutralized with 50%

aqueous sodium hydroxide, and diluted with water (3 vol) to give off-white needles, mp 164–167° (5 g, 92.6%) of **13**. An analytical sample was obtained as colorless needles after two recrystallizations from ethanol: mp 167–168°; ir ($CHCl_3$) 1730, 1625, 1520 cm^{-1}; uv max 260 mμ (ε 15,500) and 349 (4500).

Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44. Found: C, 54.89; H, 5.54.

B. From 11.—A mixture of 5-chloro-2-amino-*N*-methylbenzamide **11** (22 g, 0.119 mol), 2-chloropropanone (12.2 g, 0.132 mol), calcium carbonate (8.3 g, 0.083 mol), and water (200 ml) was stirred under reflux for 4 hr. After cooling to room temperature, the precipitated solids were filtered and recrystallized from ethanol to give off-white plates of **13**, mp 164–168° (17.2 g, 59.5%). The infrared spectrum was superimposable with that of the sample from method A.

2-Chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (17).—A mixture of 2-methylaminobenzamide (**16**) (38 g, 0.253 mol), 2-chloropropanone (46.7 g, 0.506 mol), *p*-toluenesulfonic acid (1 g), and benzene (1.5 l.) was stirred under reflux overnight; the water produced was collected with a Dean-Stark trap. The reation mixture was chilled to 10° and the crystals filtered to give off-white needles of **17**, mp 165–170° (55 g, 96.8%). An analytical sample was obtained as colorless needles after three recrystallizations from ethyl acetate: mp 168–169.5°; ir ($CHCl_3$) 1675, and 1615 cm^{-1}; uv max 223 mμ (ε 36,000), 255 (5000), and 345 (3000).

Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83. Found: C, 59.09; H, 5.83.

2-Methylamino-*N*-acetonylbenzamide (18).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold (10–15°) solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (67.3 g, 0.3 mol) in tetrahydrofuran (1.2 l.) with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite; the clear filtrate was concentrated to dryness *in vacuo*. The residue was stirred with water (1 l.) on the steam bath for 1 hr. The mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from benzene–hexane to give **18**, mp 69–73° (43.4 g, 70.2%). An analytical sample was obtained as colorless prisms after four recrystallizations from benzene–hexane: mp 72–73°; ir ($CHCl_3$) 1730 and 1645 cm^{-1}; uv max 256 mμ (ε 11,000) and 345 (5000).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.21; H, 6.50.

1,2-Dihydro-2-methylene-1-methyl-5*H*-1,4-benzodiazepin-5-one (19).—Potassium *tert*-butoxide (2.24 g, 0.02 mol) was added to a solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (4.49 g, 0.02 mol) in tetrahydrofuran (150 ml) at room temperature with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite; the clear filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from benzene–hexane to give **19** as colorless plates, mp 120–129° (1.8 g, 47.9%). An analytical sample was obtained as colorless plates after three recrystallizations from benzene–hexane: mp 127–129°; ir ($CHCl_3$) 1665 cm^{-1}; uv max 240 mμ (sh) (ε 12,000), 260 (sh) (8000), 278 (4400), and 340 (5400); nmr (DMSO) δ 3.03 s, 3, NCH_3), 3.69 (d → s, 2, J = 6 Hz, $NHCH_2$), 3.76 (s, 1, $C{=}CH_2$), and 3.91 ppm (s, 1, $C{=}CH_2$).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.03; H, 6.69.

1,2,3,4-Tetrahydro-1,2-dimethyl-5*H*-1,4-benzodiazepin-5-one (20).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold (10–15°) solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (67.3 g, 0.3 mol) in tetrahydrofuran (1.2 l.) with stirring. The reaction mixture was stirred at room temperature overnight and filtered through a bed of Celite.

The clear filtrate was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (4 g, 0.0176 mol). After 1.25 hr, 5.4 l. (0.241 mol) of hydrogen had been absorbed and the uptake had stopped. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to yield **20**, mp 165–170° (26 g, 45.6%). An analytical sample was obtained as colorless prisms after three recrystallizations from ethyl acetate: mp 170–172.5°; ir ($CHCl_3$) 1660 cm^{-1}; uv max 262 mμ (ε 6000) and 322 (2000); nmr (DMSO) δ 0.97 (d, 3, J = 6 Hz, $CHCH_3$) and 2.79 ppm (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42. Found: C, 69.36; H, 7.29.

2-Dichloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolinone (21).—A mixture of anthranilamide (13.6 g, 0.1 mol), 1,1-dichloro-2-propanone, (20 g, 0.158 mol), *p*-toluene sulfonic acid (1 g), and benzene (500 ml) was stirred and heated under reflux with azeotropic removal of water for 17.5 hr. At this time 2 ml of water had been collected. The reaction mixture was cooled and concentrated to dryness *in vacuo* to give 25 g of residue. This residue was dissolved in ethyl acetate and filtered through alumina (600 g). The filtrate was concentrated to dryness *in vacuo* and the residue recrystallized from ethyl acetate–hexane to give **21** (18.5 g, 75%), mp 178–184°. Recrystallization from ethyl acetate gave colorless prisms: mp 184–187° dec; ir ($CHCl_3$) 1680 cm^{-1}; uv max 222 mμ (ε 35,000), 250 (5000), and 340 (3000).

Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11. Found: C, 49.02; H, 3.99.

1,2,3,4-Tetrahydro-2,3-dimethoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (22).[7]—A mixture of 2-dichloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolinone (**21**) (4.9 g, 20 mmol), methanol (100 ml), and sodium methoxide (4.32 g, 80 mmol) was heated under reflux for 2.5 hr. The reaction mixture was then cooled and concentrated to dryness. The residue was extracted with boiling ethyl acetate (200 ml); 1.5 g of product was deposited, mp 179–183° dec, on cooling. A further 2.3 g of product, mp 165–170° dec, was obtained on concentration of the ethyl acetate. Recrystallization from methanol gave colorless needles: mp 153–156° dec; ir ($CHCl_3$) 1640 cm^{-1}; uv max 220 mμ (ε 30,000), 250 (10,000), and 339 (5000); nmr (DMSO) δ 1.47 (s, 3, CCH_3), 3.04 (s, 3, OCH_3), 3.25 (s, 3, OCH_3), and 4.23 (d, 1, J = 7 Hz, CH).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 60.99; H, 6.82. Found: C, 61.08; H, 6.97.

Reduction of 22 to 9.—A solution of **22** (2.36 g, 10 mmol) in dry tetrahydrofuran (100 ml) was added to a suspension of lithium aluminum hydride (1 g, 26.4 mmol) in dry tetrahydrofuran (200 ml). The mixture was stirred and heated under reflux for 2.6 hr. Excess lithium aluminum hydride was destroyed by addition of ethyl acetate and ethanol. The mixture was then diluted with water, filtered through Celite, and extracted with methylene chloride in three portions. The extracts were combined, dried over sodium sulfate, and concentrated *in vacuo* to give 1.2 g of crude product, mp 205–215°. Recrystallization from ethanol gave pure **9**, mp 213–216°, identified by mixture melting point and infrared spectra.

2-Acetoxy-1,2,3,4-tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (23).[7]—A mixture of **22** (47.6 g, 0.2 mol), sodium acetate (32.8 g, 0.4 mol), and acetic acid (800 ml) was heated on the steam bath for 10 min, cooled, and concentrated *in vacuo*. The residue was partitioned between methylene chloride and water. The aqueous phase was washed with more methylene chloride in three portions. The methylene chloride extracts were combined, washed with 10% sodium bicarbonate solution and with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to give **23** (22 g), mp 171–175°. The mother liquor was concentrated to dryness, dissolved in tetrahydrofuran, and filtered through a plug of alumina. The eluate was concentrated *in vacuo*, and the residue was crystallized from ethyl acetate to give a second crop of 6.5 g of **23**. The two crops were combined and recrystallized from ethyl acetate to give **23** (21 g, 40%), mp 179–182°. Further recrystallization from ethyl acetate gave off-white prisms: mp 180–183°; ir ($CHCl_3$) 1745 and 1670 cm^{-1}; uv max 223 mμ (ε 34,000), 250 (5000), and 344 (3300); nmr (DMSO) δ 1.40 (s, 3, $C{=}CH_3$), 2.02 (s, 3, $COCH_3$), 3.33 (s, 3, OCH_3), and 5.58 ppm (s, 1, CH).

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.07; H, 6.11. Found: C, 59.29; H, 6.38.

2,2-Bis(chloromethyl)-1,2-dihydro-4(3*H*)-quinazolone (24).—A mixture of anthranilamide (13.6 g, 0.1 mol), 1,3-dichloro-2-propanone (19.1 g, 0.15 mol), and benzene (250 ml) was stirred and heated under reflux with azeotropic removal of water for 17 hr. The reaction mixture was then concentrated to dryness *in vacuo*, and the residue was crystallized from ether and washed with methanol to give **24** (16.4 g, 67%), mp 180–186°. Recrystal-

(7) The stereochemistry of this compound was not established.

lization from ethyl acetate gave **24** as off-white needles: mp 186–188°; ir ($CHCl_3$) 1650 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11. Found: C, 49.21; H, 4.23.

3-Chloromethylene-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (25).—A solution of **24** (15 g, 61.2 mmol) in dry tetrahydrofuran (350 ml) was cooled in a Dry Ice–acetone bath. To the cold solution was added cautiously potassium *tert*-butoxide (6.7 g, 60 mmol), and the cooling bath was removed. The reaction mixture was then stirred for 17 hr and filtered through Celite. The residue left on concentrating the solution *in vacuo* was crystallized from ether–hexane to give 11 g of tacky solid. Recrystallization from ethyl acetate gave 7.7 g (60%) of **25**, mp 101–103° dec. Careful recrystallization from ethyl acetate gave **25** as off-white prisms: mp 107–108° dec; ir (KBr) 1610 cm^{-1}; nmr (DMSO) δ 3.85 (d, 2, J = 5 Hz, CH_2), 5.67 (s, 1, =CH), 7.00 (t, 1, J = 4 Hz, NH), and 8.51 ppm (s, 1, NH).

Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.35. Found: C, 57.64; H, 4.20.

3-Chloromethyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (27).—A solution of **25** (23.5 g, 0.113 mol) in methanol (350 ml) was cooled in an ice bath and treated with tetramethylammonium borohydride (23.5 g, 0.258 mol). The mixture was removed from the ice bath and allowed to stand at room temperature for 20 hr. It was then diluted with several volumes of water, neutralized with glacial acetic acid, and cooled in an ice bath to give **26** (20.1 g, 85%), mp 177–184°. Recrystallization from ethanol gave colorless needles: mp 179–181°; ir ($CHCl_3$) 1635 cm^{-1}; uv max 223 mμ (ϵ 28,000), 250 (7600), and 337 (4200).

Anal. Calcd for $C_{10}H_{11}ClN_2O$: C, 57.02· H, 5.26. Found: C, 56.93 H, 5.15.

Reduction of 25 to 9.—To a solution of **25** (8.35 g) in diglyme (100 ml) which had been cooled to 10° was added sodium borohydride (8.35 g). The reaction mixture was allowed to stand at room temperature overnight, neutralized with acetic acid, diluted with water, and extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to give crude **9** (5.2 g), mp 195–205°. Recrystallization from ethanol gave colorless plates, mp 210–215°, which had an infrared spectrum identical with that of authentic material.

1,2,3,4-Tetrahydro-3-piperidinomethyl-5*H*-1,4-benzodiazepin-5-one (26a).—A solution of **27** (2.1 g) in piperidine (100 ml) was heated under reflux for 5 hr and cooled. The piperidine hydrochloride was filtered, and the filtrate concentrated to dryness. Crystallization from ethanol of the residue left on evaporation of the solvent *in vacuo* gave **26a** (2 g), mp 174–176°. Recrystallization from ethanol gave colorless plates: mp 175–177° ir ($CHCl_3$) 1630 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.46 H, 8.16. Found: C, 69.28; H, 8.48.

1,2,3,4-Tetrahydro-3-*n*-butylaminomethyl-5*H*-1,4-benzodiazepin-5-one (26b).—A solution of **27** (2.1 g, 10 mmol) in *n*-butylamine (100 ml) was heated under reflux for 24 hr and then allowed to stand at room temperature for 24 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was partitioned between water and methylene chloride, and the aqueous phase was washed with methylene chloride in three portions. The combined methylene chloride extracts were washed with 10% sodium bicarbonate and then with brine, dried over sodium sulfate, and concentrated *in vacuo* to leave a yellow residue which gave 1.7 g of **26b**, mp 135–147°, on crystallization from ethyl acetate–hexane. Recrystallization from ethyl acetate gave colorless lozenges: mp 145–147°; ir ($CHCl_3$) 1625 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56. Found: C, 68.36; H, 8.20.

1,2,3,4-Tetrahydro-3-morpholinomethyl-5*H*-1,4-benzodiazepin-5-one (26c).—A solution of **27** (2.1 g) in morpholine (50 ml) was heated under reflux overnight, and the reaction mixture was worked up as for the reaction with *n*-butylamine. This procedure gave crude **26c** (1.8 g), mp 145–150°. Recrystallization from ethyl acetate gave **26c** as off-white plates: mp 151–152.5°; ir ($CHCl_3$) 1630 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33. Found: C, 64.47; H, 7.15.

Registry No.—**5**, 27545-02-4; **6**, 27545-03-5; **7**, 27610-05-5; **8**, 27545-04-6; **9**, 27545-05-7; **10**, 27545-06-8; **11**, 19178-37-1; **12**, 27545-08-10; **13**, 27545-09-1; **14**, 27545-10-4; **15**, 27545-15-9; **17**, 27545-16-0; **18**, 27545-17-1; **19**, 27610-13-5; **20**, 27545-18-2; **21**, 27545-19-3; **22**, 27545-20-6; **23**, 27545-21-7; **24**, 27545-22-8; **25**, 27545-23-9; **26a**, 27537-82-2; **26b**, 27537-83-3; **26c**, 27537-84-4; **27**, 27537-85-5.

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3-Amino-3,4-dihydroquinazolines[1]

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The reaction of hydrazine with the 2′-benzoyl-4′-chloroanilides **2** and **3** has been shown to yield the 3-amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazolines **5** and **6**. Chemical transformations of these compounds to give both cyclic and ring-opened products are discussed.

Our interest in the reaction of amines with amides to give amidines[3] led us to investigate the reaction of hydrazine with amides. The *o*-benzoylanilides chosen for this study contained both amide and ketone functions and were expected to yield heterocyclic products on treatment with hydrazine.

Thus, 2′-benzoyl-4′-chloroformanilide (**2**) [prepared by formylation of the corresponding aminochlorobenzophenone **1** (Scheme I)] gave, on treatment with a 50% excess of hydrazine, a condensation product which was shown by elemental and mass spectral analyses to have lost only one molecule of water. Furthermore, the product did not retain the amide carbonyl group as evidenced by the ir spectrum. Of the possible structures **5**, **7**, **8**, and **9**, the quinazoline **5** seemed most reasonable on chemical and spectral grounds. Structure **7** was rejected since such a carbinolamine would be expected to undergo ready, if not spontaneous, dehydration. Attempts to dehydrate the product led only to a dimer of unknown structure (M^+ at m/e 510), and in no instance were we able to detect a dehydrated monomer. The mass spectral fragmentation pattern[1] of the product was

(1) A part of this work has been reported in preliminary form: M. E. Derieg, J. Blount, R. I. Fryer, and S. S. Hillery, *Tetrahedron Lett.*, 3869 (1970).

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