Studies on 4(1*H*)-Quinazolinones. 2.[1a] Synthesis of 6a,7-Dihydro-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-diones

Ken-ichi Ozaki, Yoshihisa Yamada, and Toyonari Oine*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

Received September 3, 1980

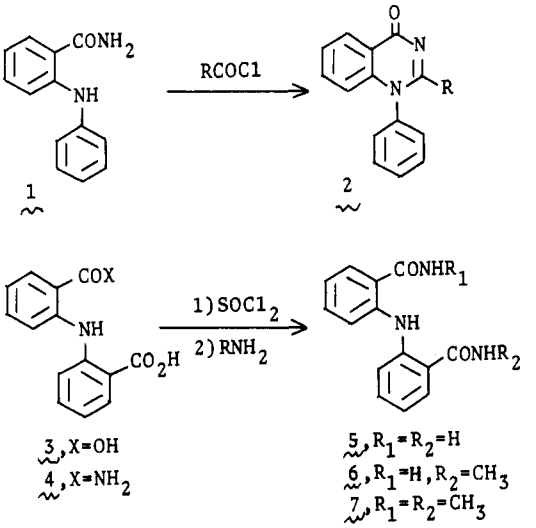
Reaction of 2,2′-dicarbamoyldiphenylamines **5–7** with acid chlorides was investigated. Condensation of **5** with acetyl chloride, isobutyryl chloride, and phenylacetyl chloride gave 4(1*H*)-quinazolinones **8, 14,** and **15**, respectively. On the other hand, reaction of **5** with chloroacetyl chloride, dichloroacetyl chloride, and methoxyacetyl chloride gave 6a,7-dihydro-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-diones **11, 16,** and **17** in good yields. The reaction of **6** with chloroacetyl chloride gave **19**, which was easily converted to the ring tautomer **20**. Compounds **23** and **24** were synthesized by the reaction of **7** with acetyl chloride and chloroacetyl chloride via 4-oxoquinazolinium salts **21** and **22**. The pentacyclic compound **28** was obtained by the condensation of **5** with 4-chlorobutyryl chloride followed by intramolecular double cyclization.

In the previous paper in this series,[1a] we reported the convenient synthesis of 1-phenyl-2-substituted-4(1*H*)-quinazolinones (**2**) by the reaction of 2-(phenylamino)-benzamide (**1**) with acid chlorides (Scheme I). Some of the 4(1*H*)-quinazolinones **2** showed potent antiinflammatory activity in our preliminary screening.[1b] Therefore, our efforts to develop nonsteroidal antiinflammatory agents were extended to synthesis of numerous 1-phenyl-4-(1*H*)-quinazolinones having various substituents on the 1-phenyl group and on C-2. In the course of this study, we found that a novel ring system, 5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione, was easily synthesized by the reaction of 2,2′-dicarbamoyldiphenylamine (**5**) with certain acid chlorides. In this paper we report a simple method for the synthesis of 5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-diones and their ring–chain tautomerism.

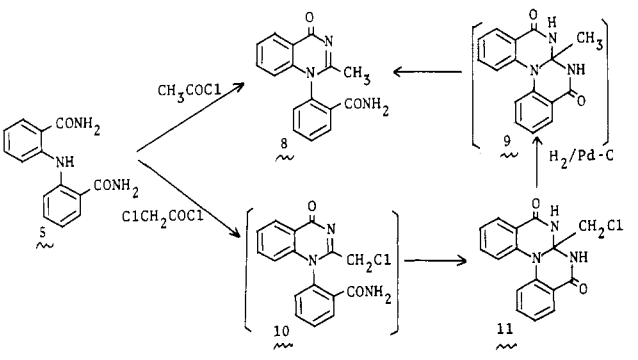
The *N*-arylanthranilic acids **3** and **4** were prepared by Ullmann reaction[2] of potassium 2-chlorobenzoate with anthranilic acid or anthranilamide. The obtained *N*-arylanthranilic acids (**3** and **4**) were converted into the amides **5–7** through the acid chlorides. Reaction of 2,2′-dicarbamoyldiphenylamine (**5**) with acetyl chloride in $CHCl_3$ at the reflux temperature gave 1-(2-carbamoylphenyl)-2-methyl-4(1*H*)-quinazolinone (**8**) in 75.2% yield (Scheme II).

On the other hand, reaction of **5** with chloroacetyl chloride under the same reaction condition gave a crystalline product in 76.5% yield. The product was not the desired 4(1*H*)-quinazolinone **10**. The structure of this compound was determined as 6a-(chloromethyl)-6a,7-dihydro-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (**11**) from analysis and spectral data. Analysis indicated the formula $C_{16}H_{12}ClN_3O_2$, and the mass spectrum showed the parent peak at *m/e* 313. The IR spectrum showed the presence of the CONH group. Further evidence in support of the structure **11** was provided by its ^1H and ^{13}C NMR spectra. The ^1H NMR spectra of **11** and the 4(1*H*)-quinolinone **8** are shown in Figure 1. The ^1H NMR spectrum of **8** exhibits typical absorption for 1-aryl-4-(1*H*)-quinazolinones.[1,3] The spectrum of **11** showed eight aromatic protons with a pattern different from that of **8**

Scheme I



Scheme II



and supportive of the symmetrical structure **11**. The symmetrical structure **11** was confirmed by the ^{13}C NMR spectrum which showed only nine signals despite the presence of 16 carbon atoms in the molecule.

Structure **11** contains a carbon atom linked by single bonds to three different nitrogen atoms. There are many reports of 2-substituted-amino-4-quinazolinone derivatives but few papers on the dihydro derivatives such as **11**. Hardtmann and co-workers prepared the tetracyclic quinazolinone **12**.[4] Cass and Katritzky[5] synthesized the novel

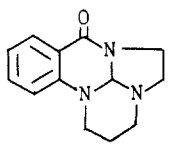
(1) (a) K. Ozaki, Y. Yamada, and T. Oine, *Chem. Pharm. Bull.*, **28**, 702 (1980); (b) T. Oine, Y. Yamada, K. Ozaki, and S. Wakamoto, Japanese Patent Kokai, 77-153983 (1977); *Chem. Abstr.*, **88**, 190882 (1978). Details of the structure–activity relationships of these compounds will be reported in a separate paper.

(2) F. Ullmann, *Justus Liebigs Ann. Chem.*, **355**, 352 (1907).

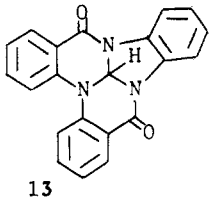
(3) H. M. Blatter, H. Lukaszewski, and G. deStevens, *J. Org. Chem.*, **30**, 1020 (1965).

(4) G. M. Coppola, G. e. Hardtmann, and O. R. Pfister, *J. Org. Chem.*, **41**, 825 (1976).

0022-3263/81/1946-1571$01.25/0



12



13

hexacyclic quinazolino[1,2-*a*]quinazoline **13** by the reaction of 2,2′-bis(chloroformyl)diphenylamine with benzimidazole. Furthermore, **11** can be considered to be a ring form of the 2-(chloromethyl)quinazolinone **10** (chain form). A number of reports concerning the ring–chain tautomerism have been reported.[6] It is rare case[7] that both an amide nitrogen atom and an imino group participate in the ring-chain tautomerism.

Our attempts to isolate **10** were unsuccessful. However, the ^{1}H NMR spectrum of **11** in CF_3CO_2D showed aromatic protons with a pattern similar to that of 1-phenyl-2-methyl-4(1*H*)-quinazolinone hydrochloride. This fact strongly suggests that **11** in CF_3CO_2D is present as the trifluoroacetate of **10**. We also attempted to isolate **9** that was considered as a possible ring tautomer of the 4-(1*H*)-quinazolinone **8**. Starting material was recovered on heating of **8** in protic or aprotic solvents. Catalytic hydrogenation of **11** gave **8** as the only isolable product in 68% yield.

In order to investigate the limitations of the formation of 5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione ring system, we examined the reaction of **5** with various acid chlorides. The results are shown in Table I. Reaction of **5** with isobutyryl chloride or phenylacetyl chloride gave 4(1*H*)-quinazolinone **14** or **15** in good yield. In contrast, treatment of **5** with methoxyacetyl chloride or dichloroacetyl chloride afforded only the ring-form product **16** or **17**, respectively. The structures of **16** and **17** were determined as being of ring form by the ^{1}H NMR spectra in which the absorption pattern of the aromatic protons closely resembled that of **11**. When the acid chlorides having an electron-withdrawing group at the α-carbon of the acid chloride were used, the ring-form products were obtained. These results show that electron deficiency at C-2 of the 4(1*H*)-quinazolinone (chain form) accelerates the intramolecular cyclization to the quinazolino[1,2-*a*]-quinazoline (ring form). This is consistent with the results reported by Alper[6c] on the ring–chain tautomerism of 3-hydroxy-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles.

To investigate the effects of the amide group, we examined the reaction of the *N*-methyl amide **6** with acetyl chloride or chloroacetyl chloride. Both reactions gave the chain tautomer (**18** or **19**) in good yield (Scheme III). The ^{1}H NMR spectrum of **18** or **19** contained a 3-H doublet [at δ 2.51 (J = 5 Hz) or 2.50 (J = 5 Hz)] due to NCH_3 and aromatic proton signals similar to those of **8**. It was found with ^{1}H NMR spectroscopy that allowing a solution of **19** in Me_2SO-d_6 to stand at room temperature gave a mixture of **19** and **20**. The ring tautomer **20** was isolated in good yield when a DMF solution of **19** was heated at 100 °C for 12 h. The structure of **20** was confirmed by the ^{1}H NMR

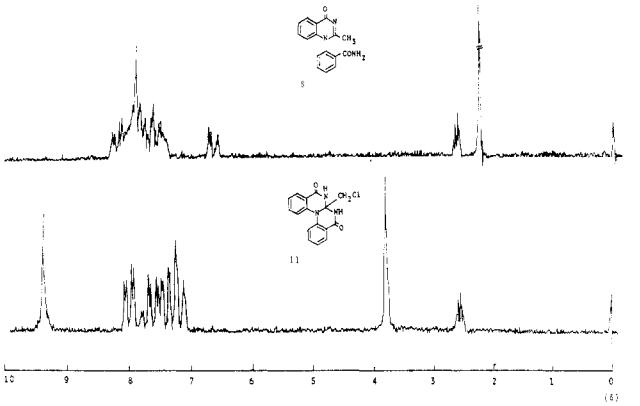
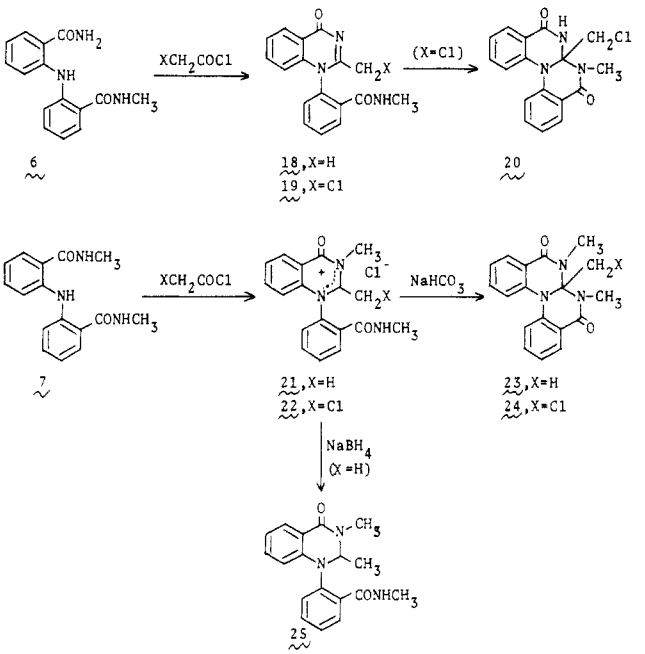


Figure 1. NMR spectra of **8** and **11** in Me_2SO-d_6.

Scheme III



spectrum in which the aromatic proton signals closely resembled those of **11** and the NCH_3 signal appeared at δ 2.99 as a singlet. Contrary to this, compounds **18** and **20** were stable in DMF or Me_2SO even on heating. Compound **19** was reproduced by treatment of **20** with trifluoroacetic acid at room temperature followed by neutralization with aqueous $NaHCO_3$. Thus, both of the ring and chain tautomers (**20** and **19**) could be isolated, in contrast with the unsuccessful isolation of **10**. It is considered that the steric effect of the methyl group enabled us to isolate the chain tautomer **19**.

Reaction of **7** with acetyl chloride or chloroacetyl chloride provided the 4-oxoquinazolinium salts **21** or **22** in quantitative yields. The structures of **21** and **22** were assigned from the spectroscopic and chemical evidence described below. The IR spectra of **21** and **22** showed typical absorption bands[8] of 4-oxoquinazolinium salts at 1725, 1620, and 1550 cm^{-1}. Reduction of **21** with $NaBH_4$ gave the 2,3-dihydro-4(1*H*)-quinazolinone **25**. Treatment of **21** and **22** with aqueous $NaHCO_3$ afforded the quinazolino[1,2-*a*]quinazolines **23** and **24** in yields of 67.5% and 73.8%, respectively. In the ^{1}H NMR spectrum of **23** in Me_2SO-d_6 at room temperature, two sharp singlets due to

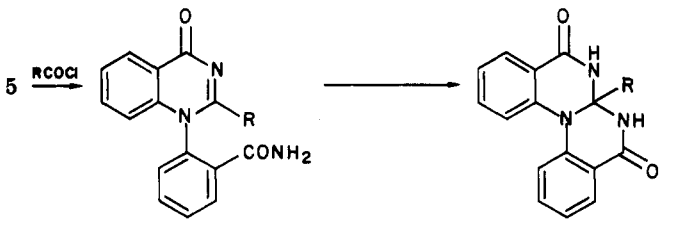
(5) (a) J. C. Cass and A. R. Katritzky, *J. Chem. Soc., Chem. Commun.*, 48 (1976); (b) A. Banerji, J. C. Cass, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans 1*, 1162 (1977).

(6) For example: (a) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963), and references cited therein; A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1 (1968); (c) H. Alper, *Chem. Commun.*, 383 (1970); (d) R. E. Harmon, J. L. Parsons, and S. K. Gupta, *J. Org. Chem.*, **34**, 2760 (1969); (e) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).

(7) T. Hino and M. Taniguchi, *J. Am. Chem. Soc.*, **100**, 5564 (1978).

(8) K. Okumura, T. Oine, Y. Yamada, G. Hayashi, M. Nakama, and T. Nose, *J. Med. Chem.* 11, 788 (1968).

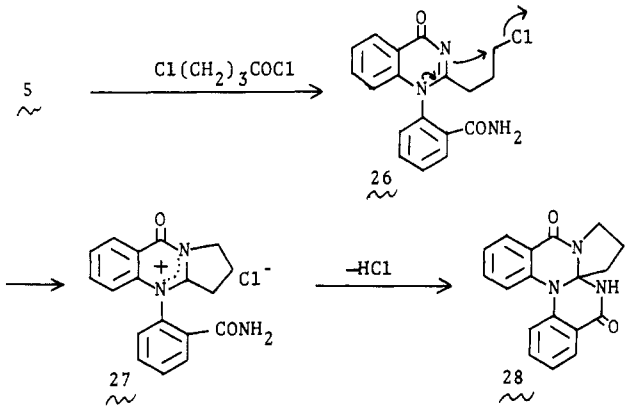
Table I. Reaction of 5 with Acid Chlorides



R	pK_a[a]	chain form compd	chain form yield,[b] %	chain form mp, °C	ring form compd	ring form yield,[b] %	ring form mp, °C
$CH(CH_3)_2$	4.88	**14**	78.1	>280		[c]	
CH_3	4.76	**8**	75.2	>280	**9**	[c]	
CH_2Ph	4.31	**15**	80.0	231-233		[c]	
CH_2OCH_3	3.53		[c]		**16**	80.9	261-265
CH_2Cl	2.86	**10**	[c]		**11**	76.5	217-219[d]
$CHCl_2$	1.29		[c]		**17**	61.8	233-234[d]

[a] The pK_a values of RCOOH are shown: H. C. Brown, D. H. McDaniel, and O. Häfliger, "Determination of Organic Structures by Physical Methods", E. A. Braude and F. C. Nachod, Eds., Academic Press, New York, 1955, p 567. [b] Isolated yield. [c] Could not isolate. [d] Decomposition.

Scheme IV



the two NCH_3 groups were observed at δ 2.83 and 3.34. However, when the ^1H NMR spectrum was recorded at 100 °C, six protons of the two NCH_3 groups appeared as a sharp singlet at δ 3.09, and the spectrum supported the structure **23**. The same behavior was observed for **24**. It can be considered that the positive charge on the quinazolinone ring of **21** and **22** promotes the intramolecular cyclization of those compounds to the quinazolino[1,2-*a*]quinazolines (**23** and **24**) in basic conditions.

One application of the above reaction is a simple synthesis of the unique pentacyclic compound **28**. Condensation of **5** with 4-chlorobutyryl chloride followed by treatment with aqueous $NaHCO_3$ for intramolecular double cyclization afforded **28** in 50% yield. A possible mechanism of the formation of **28** is outlined in Scheme IV.

Experimental Section

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were determined by using a Shimadzu IR-27G spectrometer. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A instrument, while ^{13}C NMR spectra were recorded on a JEOL FX-100 spectrometer in the pulsed Fourier transform mode. All NMR spectra were measured with Me_4Si as an internal standard. Mass spectra were measured with a Hitachi M-60 mass spectrometer.

***N*-(2-Carbamoylphenyl)anthranilic Acid (4).** A mixture of anthranilamide (10 g, 73 mmol), potassium *o*-chlorobenzoate (14.2 g, 73 mmol), and copper powder (0.1 g) in *i*-AmOH (70 mL) was stirred under reflux for 3 h. The solvent was removed by steam distillation. The dark brown residue was acidified to pH 4 with 10% HCl to give a crystalline product. The product was collected on a filter, dissolved in 10% NaOH, treated with charcoal, and filtered. The filtrate was acidified to pH 4 with 10% HCl to give a crude product: 7.4 g (39.6%); mp 198–203 °C dec. Recrystallization from EtOH gave a pure sample of **4** (6.7 g, 35.6%) as colorless prisms: mp 203–205 °C dec; IR (Nujol) 3450–3270, 1658, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.60–8.20 (m, 11 H), 10.62 (s, 1 H).

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.22; H, 4.87; N, 10.76.

2,2′-Dicarbamoyldiphenylamine (5). A suspension of 2,2′-dicarboxydiphenylamine (**3**; 5.4 g, 21 mmol), $SOCl_2$ (9.6 g, 80.6 mmol), and DMF (1 mL) in CH_2Cl_2 (50 mL) was stirred under reflux for 6 h. The cooled reaction mixture was poured into ice-cold 25% NH_4OH (100 mL) with vigorous stirring. The mixture was stirred at room temperature for 3 h to give a crystalline product: 4.6 g (86.4%); mp 218–220 °C. Recrystallization from DMF–MeOH gave **5** as pale yellow needles: mp 219–220 °C; ^1H NMR (Me_2SO-d_6) δ 6.72–8.35 (m, 12 H), 10.50 (s, 1 H).

Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65,47; H, 5.26; N, 16.27.

2-Carbamoyl-2′-(methylcarbamoyl)diphenylamine (6). A mixture of **4** (12 g, 47 mmol), $SOCl_2$ (12 g, 0.1 mol), and DMF (1 mL) in CH_2Cl_2 (150 mL) was reacted as described above, and the reaction mixture was added to ice-cold 40% $MeNH_2$ (100 mL) to give a crude product. Recrystallization from DMF–H_2O gave **6** (6.2 g, 49.2%) as colorless prisms: mp 218–220 °C; IR (Nujol) 3470, 3350, 3250, 1650, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.75 (d, 3 H, J = 5 Hz), 6.70–7.93 (m, 10 H), 8.05–8.50 (m, 1 H), 10.38 (s, 1 H).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.79; H, 5.75; N, 15.67.

2,2′-Bis(methylcarbamoyl)diphenylamine (7). The amine **7** was prepared from **3** by a procedure similar to that used for the synthesis of **6**. The crude product was recrystallized from DMF to give pure **7** (76%) as colorless prisms: mp 252–256 °C; IR (Nujol) 3340, 3250, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.76 (d, 6 H, J = 5 Hz), 6.71–7.69 (m, 8 H), 8.10–8.54 (m, 2 H), 10.33 (s, 1 H).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.65; H, 6.15; N, 14.83.

Typical Procedure for Preparation of 1-(2-Carbamoylphenyl)-4(1*H*)-quinazolinones 8, 14, 15, 18, and 19. 1-(2-Carbamoylphenyl)-2-methyl-4(1*H*)-quinazolinone (8). Acetyl chloride (2.37 g, 30 mmol) was added to a stirred suspension of **5** (2.55 g, 10 mmol) in $CHCl_3$ (30 mL) at room temperature. Stirring was continued under reflux for 8 h. The precipitate that had formed was collected by filtration and suspended in water (50 mL). The suspension was neutralized by addition of 5%

aqueous $NaHCO_3$ (ca. 20 mL) at room temperature. The resulting precipitate was collected by filtration and washed with water to yield 2.6 g (93.2%) of crude **8**, mp >280 °C. Recrystallization from DMF gave **8** (2.1 g, 75.2%) as colorless prisms: mp >280 °C; IR (Nujol) 3340, 3170, 1678, 1648 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.17 (s, 3 H), 6.43–6.68 (m, 1 H), 7.26–8.31 (m, 9 H).

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.51; H, 4.87; N, 15.30.

1-(2-Carbamoylphenyl)-2-isopropyl-4(1*H*)-quinazolinone (14). A stirred suspension of **5** (5.1 g, 20 mmol) in $CHCl_3$ (50 mL) was treated with isobutyryl chloride (6.42 g, 60 mmol) and the reaction mixture worked up as described above to give crude **14**. Recrystallization from DMF gave 4.8 g (78.1%) of **14** as colorless prisms: mp >280 °C; IR (Nujol) 3400, 3150, 1670, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.15 (d, 3 H, J = 7 H), 1.26 (d, 3 H, J = 7 Hz), 2.28–3.02 (m, 1 H), 6.40–6.63 (m, 1 H), 6.98–8.00 (m, 8 H), 8.04–8.27 (m, 1 H).

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.17; H, 5.71; N, 13.59.

1-(2-Carbamoylphenyl)-2-benzyl-4(1*H*)-quinazolinone (15). By a procedure similar to that described above, reaction of **5** (1.0 g, 3.9 mmol) and phenylacetyl chloride (1.6 g, 11.7 mmol) provided **15** (1.13 g, 80.0%), which was recrystallized from MeOH-diisopropyl ether: mp 231–233 °C; IR (Nujol) 3375, 3190, 1673, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.73, 3.87 (AB q, 2 H, J = 15.5 Hz), 6.40–6.63 (m, 1 H), 6.95–8.20 (m, 14 H).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.84. Found: C, 74.12; H, 4.93; N, 11.71.

1-[2-(Methylcarbamoyl)phenyl]-2-methyl-4(1*H*)-quinazolinone (18). Acetyl chloride (1.8 g, 22 mmol) was added to a stirred suspension of **6** (2.0 g, 7.4 mmol) in $CHCl_3$ (30 mL) at room temperature. The mixture was stirred under reflux for 3.5 h and worked up as described above. The crude product was recrystallized from DMF to give **18** (1.6 g, 73.4%) as colorless prisms: mp >280 °C; IR (Nujol) 3230, 1660, 1625 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.16 (s, 3 H), 2.51 (d, 3 H, J = 5 Hz), 6.36–6.60 (m, 1 H), 7.16–7.86 (m, 6 H), 7.94–8.16 (m, 1 H), 8.32 (br, 1 H).

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.32; H, 5.16; N, 14.24.

1-[2-(Methylcarbamoyl)phenyl]-2-chloromethyl-4(1*H*)-quinazolinone (19). This compound was obtained in 97.7% yield by reaction of **6** and chloroacetyl chloride: mp 239–241 °C; IR (Nujol) 3280, 1655, 1647 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.50 (d, 3 H, J = 5 Hz), 4.27, 4.39 (AB q, 2 H, J = 11 Hz), 6.34–6.61 (m, 1 H), 7.10–7.94 (m, 6 H), 7.98–8.21 (m, 1 H), 8.25–8.60 (br, 1 H). The compound was not analyzed because the recrystallization from DMF gave a mixture of **19** and **20**.

Typical Procedure of Preparation of 5*H*-Quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-diones 11, 16, and 17. 6a-(Chloromethyl)-6a,7-dihydro-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (11). Chloroacetyl chloride (1.7 g, 15 mmol) was added to a suspension of **5** (1.28 g, 5 mmol) in $CHCl_3$ (20 mL) at room temperature. The mixture was refluxed for 8 h. The precipitate that had formed was collected by filtration and suspended in H_2O (25 mL). The aqueous suspension was neutralized by addition of 5% $NaHCO_3$. The resulting precipitate was collected by filtration to give a crystalline product: 1.3 g (82.9%); mp 210–216 °C dec. Recrystallization from EtOH gave **11** (1.2 g, 76.5%) as colorless needles: mp 217–219 °C dec; IR (Nujol) 3175, 1690, 1661 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.78 (s, 2 H), 7.15 (dd, 2 H, J = 8 Hz, J = 2 Hz), 7.31 (dt, 2 H, J = 8 Hz, J = 2 Hz), 7.68 (dt, 2 H, J = 8 Hz, J = 2 Hz), 7.98 (dd, 2 H, J = 8 Hz, J = 2 Hz), 9.38 (s, 2 H); ^1H NMR (CF_3CO_2D) δ 4.69, 4.87 (AB q, 2 H, J = 16 Hz), 6.91–7.18 (m, 1 H), 7.74–8.44 (m, 6 H), 8.67–8.80 (m, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 47.71 (t), 82.01 (s), 120.58 (s), 120.73 (d), 123.99 (d), 127.65 (d), 133.27 (d), 141.07 (s), 160.86 (s); mass spectrum, m/e 315, 313, 277, 264, 235, 227, 195.

Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 61.24; H, 3.86; Cl, 11.30; N, 13.40. Found: C, 60.98; H, 4.21; Cl, 11.47; N, 13.22.

6a,7-Dihydro-6a-(methoxymethyl)-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (16). By a procedure similar to that described for the preparation of **11**, reaction of **5** (2.04 g, 8 mmol) and methoxyacetyl chloride (2.62 g, 24 mmol) afforded crude **16**. Recrystallization from DMF–H_2O gave **16** (2.0 g, 80.9%) as colorless needles: mp 265 °C; IR (Nujol) 3240, 1680, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.19 (s, 3 H), 3.42 (s, 2 H), 7.07 (dd, 2 H, J = 8 Hz, J = 2 Hz), 7.23 (dt, 2 H, J = 8 Hz, J = 2 Hz), 7.54 (dt, 2 H, J = 8 Hz, J = 2 Hz), 7.94 (dd, 2 H, J = 8 Hz, J = 2 Hz), 9.03 (s, 2 H).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.73; H, 4.89; N, 13.47.

6a-Dichloromethyl-6a,7-dihydro-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (17). By a procedure similar to that described for the preparation of **11**, reaction of **5** (0.51 g, 2 mmol) with dichloroacetyl chloride (0.89 g, 6 mmol) in $CHCl_3$ (15 mL) gave **17** (0.43 g, 61.8%), which was recrystallized from EtOH to give a pure sample of **17** as colorless prisms: mp 233–234 °C dec; IR (Nujol) 3210, 1698, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.86 (s, 1 H), 7.26 (dd, 2 H, J = 8 Hz, J = 2 Hz), 7.32–7.82 (m, 4 H), 7.99 (dd, 2 H, J = 8 Hz, J = 2 Hz), 8.92 (s, 2 H).

Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.19; H, 3.18; Cl, 20.37; N, 12.07. Found: C, 55.09; H, 3.38; Cl, 20.36; N, 12.08.

Catalytic Reduction of 11. A mixture of **11** (156 mg), NaOAc (49 mg), and EtOH (90 mL) was hydrogenated with 5% Pd/C (20 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with H_2O to give a crystalline product: 95 mg (68.3%); mp >280 °C. The IR and ^1H NMR spectra of this product were identical with those of a sample of **8** obtained by the reaction of **5** with acetyl chloride.

6a-(Chloromethyl)-6a,7-dihydro-6-methyl-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (20). A solution of **19** (0.5 g) in DMF (10 mL) was stirred at 100 °C for 12 h. The solvent was evaporated in vacuo, and the residue was tritutated with H_2O to give crude **20**: 0.45 g (90.0%); mp 230–240 °C dec. Recrystallization from EtOH gave a pure sample of **20** as colorless prisms: mp 239–241 °C dec; IR (Nujol) 3250, 1691, 1632 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.99 (s, 3 H), 3.59, 3.89 (AB q, 2 H, J = 12.5 Hz), 6.49–8.10 (m, 8 H), 9.59 (s, 1 H).

Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.31; Cl, 10.82; N, 12.82. Found: C, 62.09; H, 4.67; Cl, 10.73; N, 12.70.

Conversion of 20 to 19. A solution of **20** (100 mg) in CF_3CO_2H (5 mL) was allowed to stand at room temperature for 30 min, and the solvent was evaporated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ to give a crystalline product: 70 mg; mp 234–238 °C. The IR and NMR spectra of this product were identical with those of **19**.

Preparation of 4-Oxoquinazolinium Salts 21 and 22. 2,3-Dimethyl-1-[2-(methylcarbamoyl)phenyl]-4-oxoquinazolinium Chloride (21). Acetyl chloride (2.94 g, 37 mmol) was added to a stirred suspension of **7** (3.5 g, 12.4 mmol) in $CHCl_3$ (50 mL). The mixture was refluxed for 2 h. Removal of the solvent under reduced pressure gave a crystalline product: 4.2 g; mp 240–243 °C dec. Recrystallization from EtOH–diisopropyl ether gave **21** (4.1 g, 96.2%) as colorless prisms: mp 241–243 °C dec; IR (Nujol) 3176, 1725, 1655, 1620, 1550 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 2.87 (s, 3 H), 2.91 (s, 3 H), 4.08 (s, 3 H), 6.76–6.98 (m, 1 H), 7.60–8.36 (m, 6 H), 8.48–8.72 (m, 1 H).

Anal. Calcd for $C_{18}H_{18}ClN_3O_2$: C, 62.87; H, 5.28; Cl, 10.31; N, 12.22. Found: C, 62.67; H, 5.40; Cl, 10.66; N, 12.24.

2-(Chloromethyl)-3-methyl-1-[2-(methylcarbamoyl)phenyl]-4-oxoquinazolinium Chloride (22). Chloroacetyl chloride (1.8 g, 16 mmol) was added to a mixture of **7** (1.5 g, 5.3 mmol) and $CHCl_3$ (25 mL). The mixture was refluxed for 2 h and then evaporated to dryness to give a crystalline product. Recrystallization from EtOH gave **22** (1.8 g, 89.8%) as colorless prisms: mp 207–208 °C dec; IR (Nujol) 3175, 1725, 1657, 1620, 1550 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 2.90 (s, 3 H), 4.24 (s, 3 H), 4.65, 5.06 (AB q, 2 H, J = 14 Hz), 6.80–7.05 (m, 1 H), 7.75–8.30 (m, 6 H), 8.48–8.76 (m, 1 H).

Anal. Calcd for $C_{18}H_{17}Cl_2N_3O_2$: C, 57.15; H, 4.53; Cl, 18.15; N, 11.11. Found: C, 57.20; H, 4.72; Cl, 18.50; N, 10.84.

6a,7-Dihydro-6,6a,7-trimethyl-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (23). To an aqueous solution (30 mL) of **21** (1.75 g) was added 5% aqueous $NaHCO_3$ (15 mL) at room temperature. A crystalline precipitate formed with the addition of $NaHCO_3$. The mixture was stirred for 30 min. The precipitate was collected and washed with water to give crude **23**: 1.45 g (92.7%); mp 257–261 °C. Recrystallization from $CHCl_3$–diisopropyl ether afforded **23** (1.05 g, 67.5%) as colorless prisms: mp 258–261 °C; IR (Nujol) 1668, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6, room temperature) δ 1.80 (s, 3 H), 2.83 (s, 3 H), 3.34

(s, 3 H), 6.21–6.68 (m, 1 H), 6.75–8.17 (m, 7 H); ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 1.80 (s, 3 H), 3.09 (s, 6 H), 6.58–7.80 (m, 6 H), 7.97 (dd, 2 H, J = 7 Hz, J = 2 Hz).

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.28; H, 5.80; N, 13.47.

6a-(Chloromethyl)-6a,7-dihydro-6,7-dimethyl-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (24). To an aqueous solution of **22** (1.5 g) was added aqueous $NaHCO_3$ to give a crystalline precipitate. Recrystallization from $CHCl_3$–diisopropyl ether gave **24** (1.0 g, 73.8%) as colorless prisms: mp 196–197 °C dec; IR (Nujol) 1675, 1660 cm^{-1}; ^{1}H NMR (Me_2SO-d_6, room temperature) δ 2.96 (s, 3 H), 3.46 (s, 3 H), 3.77, 4.59 (AB q, 2 H, J = 14.5 Hz), 6.36–6.70 (m, 1 H), 6.90–8.20 (m, 7 H); ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 3.21 (s, 6 H), 4.11 (s, 2 H), 6.64–7.75 (m, 6 H), 7.98 (dd, 2 H, J = 8 Hz, J = 2 Hz).

Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; Cl, 10.37; N, 12.29. Found: C, 63.21; H, 5.05; Cl, 10.40; N, 11.99.

Reduction of 21 with $NaBH_4$. $NaBH_4$ (0.277 g, 7.3 mmol) was added to a stirred solution of **21** (2.5 g, 7.3 mmol) in MeOH (20 mL) under ice cooling. The mixture was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness. The residual crystals were recrystallized from 2-PrOH–diisopropyl ether to give 2,3-dihydro-2,3-dimethyl-1-[2-(methylcarbamoyl)-phenyl]-4(1*H*)-quinazolinone (**25**; 1.55 g, 68.9%) as colorless prisms: mp 144–146 °C; IR 3300, 1650, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3 H, J = 7 Hz), 2.85 (d, 3 H, J = 6 Hz), 3.03 (s, 3 H), 4.94 (q, 1 H, J = 7 Hz), 6.60–6.83 (m, 1 H), 6.85–7.70 (m, 6 H), 7.83–8.22 (m, 2 H).

Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.67; H, 6.11; N, 13.55.

Pentacyclic Compound 28. A mixture of **5** (2.0 g, 7.8 mmol), 4-chlorobutyryl chloride (3.36 g, 23.4 mmol), and $CHCl_3$ (30 mL) was stirred under reflux for 9.5 h. The precipitate that had formed was collected by filtration, neutralized with aqueous $NaHCO_3$, and dissolved in $CHCl_3$. The $CHCl_3$ solution was allowed to stand for 5 h at room temperature. The solvent was removed in vacuo, and the residue was triturated with aqueous $NaHCO_3$ to give a crystalline product (1.4 g, 58.5%) which was recrystallized from DMF to give a pure sample of **28** (1.2 g, 50.5%) as colorless needles: mp >280 °C; IR (Nujol) 3240, 1678, 1642 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.70–2.35 (m, 4 H), 3.47–4.01 (m, 2 H), 6.39–6.62 (m, 1 H), 6.82–8.13 (m, 7 H), 9.37 (s, 1 H).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.55; H, 5.30, N, 13.54.

Acknowledgment. We thank Dr. I. Chibata (Director of this laboratory) and Dr. M. Miyoshi for their encouragement throughout the present study.

Registry No. **3**, 579-92-0; **4**, 76403-55-9; **5**, 32615-84-2; **6**, 76403-56-0; **7**, 76403-57-1; **8**, 66492-18-0; **11**, 76403-58-2; **14**, 70344-50-2; **15**, 76403-59-3; **16**, 76403-60-6; **17**, 76403-61-7; **18**, 76403-62-8; **19**, 76403-63-9; **20**, 76403-64-0; **21**, 76403-65-1; **22**, 76403-66-2; **23**, 76403-67-3; **24**, 76403-68-4; **25**, 76403-69-5; **28**, 76403-70-8; anthranilamide, 88-68-6; potassium *o*-chlorobenzoate, 16463-38-0; acetyl chloride, 75-36-7; isobutyryl chloride, 79-30-1; phenylacetyl chloride, 103-80-0; chloroacetyl chloride, 79-04-9; methoxyacetyl chloride, 38870-89-2; dichloroacetyl chloride, 79-36-7; 4-chlorobutyryl chloride, 141-75-3.

Synthesis of Aminoalkyl-Substituted Imidazo[1,2-*a*]- and Imidazo[1,5-*a*]benzodiazepines

Martin Gall* and Bharat V. Kamdar

CNS Diseases Research, The Upjohn Company, Kalamazoo, Michigan 49001

Received November 4, 1980

Aminoalkyl-substituted imidazo[1,2-*a*]benzodiazepines were prepared in good yields from benzodiazepine thione **1** and the novel amino ketals **2**. The 1-(hydroxymethyl)- and 1-unsubstituted-imidazo[1,2-*a*][1,4]benzodiazepines (i.e., **4a** and **9**) were easily transformed into 1-[(dimethylamino)methyl]imidazo[1,5-*a*][1,4]benzodiazepines (i.e., **7** and **16**) via a three-step procedure. This involved consecutive ring-opening, reductive methylation, and subsequent hydroxymethylation of the 1-unsubstituted starting material under Eschweiler–Clarke reaction conditions, followed by transformation of the hydroxyl group to a phthalimide and hydrazinolysis–cyclization to the imidazo[1,5-*a*] products. The preparations of the useful amino ketals **2** are also described.

Since Hester[1] and Meguro[2] reported that the fusion of a triazole ring to the a face of 1,4-benzodiazepines enhanced the potency and imparted novel biological activity to the parent molcule, there has been renewed[3] worldwide interest in the preparations and pharmaceutical properties of other, particularly five atom,[4] heterocyclic fused diazepine ring systems. Much of this interest has focused on the preparation of various imidazo[1,2-*a*][1,4]-,[5] -[1,2-*a*][1,5]-,[6] and -[1,5-*a*][1,4]benzodiazepines[7] and -diazepin-1-ones.[8] With the exception of one very novel approach,[7d] these methods were used to prepare only alkyl or unsubstituted imidazoles. Recently, Hester and co-workers[9] showed that 1-(aminoalkyl)triazole[1,4]benzodiazepines have activity in animal test models designed to find potential antidepressant activity. We now report the preparation of aminomethyl-substituted imidazo[1,2-*a*]- and

(1) (a) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971); (b) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971).

(2) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).

(3) The preparation of 8-chloro-6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepine was reported by scientists at Hoffmann-LaRoche in 1968: E. E. Garcia, J. B. Riley, and R. I. Fryer, *J. Org. Chem.*, **33**, 1359 (1968).

(4) For syntheses of pyrrolo- and pyrazolobenzodiazepines see: (a) T. Hara et al., *J. Med. Chem.*, **21**, 263 (1978); (b) N. W. Gilman and R. I. Fryer, *J. Heterocycl. Chem.*, **14**, 1171 (1977); (c) N. Gilman, R. I. Fryer, U.S. Patent 4 130 716 (1978).

(5) (a) J. B. Hester, Jr., and M. Gall, U.S. Patent 3 852 461 (1974); (b) A. R. Hanze and J. B. Hester, Jr., U.S. Patent 3 917 627 (1975); (c) J.-P. Maffrand, G. Ferrand, and F. Eloy, *Tetrahedron Lett.*, 3449 (1973); (d) J.-P. Maffrand, G. Ferrand, and F. Eloy, *Eur. J. Med. Chem.*, **9**, 539, (1974); (e) T. Hara, K, Itoh and N. Itoh, *J. Heterocycl. Chem.*, **13**, 1233 (1976).

(6) (a) T. Hara, H. Fujimori, Y. Kayama, T. Mori, K. Itoh, and Y. Hashimoto, *Chem. Pharm. Bull. Jpn.*, **25**, 2584 (1977); (b) A. W. Chow, R. J. Gyurik, and R. C. Parish, *J. Heterocycl. Chem.*, **13**, 163 (1976).

(7) (a) N. W. Gilman, B. C. Holland, and R. I. Fryer, *J. Heterocycl. Chem.*, **14**, 1163 (1977); (b) A. Walser, L. E. Benjamin, Sr., T. Flynn, C. Mason, R. Schwartz, and R. I. Fryer, *J. Org. Chem.*, **43**, 936 (1978); (c) A. Walser, R. F. Lauer and R. I. Fryer, *J. Heterocycl. Chem.*, **15**, 855 (1978); (d) A. Walser, T. F. Flynn and R. I. Fryer *ibid.*, **15**, 577 (1978); (e) A. Walser, U.S. Patents 4 118 386 (1978), 4 125 726 (1978), 4 146 722 (1979), 4 147 875 (1979).

(8) I. R. Ager, G. W. Danswan, D. R. Harrison, D. P. Kay, P. D. Kennewell, and J. B. Taylor, *J. Med. Chem.*, **20**, 1035 (1977).

(9) (a) J. B. Hester, Jr., A. D. Rudzik and P. F. VonVoigtlander, *J. Med. Chem.*, **23**, 392 (1980). (b) See also Swiss Patents 567-023, 567-024, and 568-319 to Ciba-Geigy (1975). (c) K. Meguro and Y. Kuwada, South African Patent Application 718,044 (1971).

(10) G. A. Archer and L. H. Sternback, *J. Org. Chem.*, **29**, 231 (1964).

0022-3263/81/1946-1575$01.25/0