Ring Closure Reactions of Methyl *N*-(Haloacetyl)anthranilates with Ammonia

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In the presence of ammonia, methyl *N*-(bromoacetyl)anthranilate (**4**) is cyclized into 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**). However, when **4** is replaced with methyl *N*-(chloroacetyl)anthranilate (**6**), the only heterocyclic product formed in the reaction is 2-(chloromethyl)quinazoline-4(3*H*)-one (**7**). Under analogous conditions, 3-haloacetamidocrotonates (**9**, **10**) do not yield any heterocyclic products and no 1,4-diazepines can be obtained.

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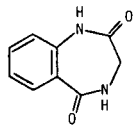
As a continuation of our systematic search for new potential anticancer, antiviral, and anti-AIDS agents [1-7], we have decided to investigate the ring closure reactions of methyl *N*-(haloacetyl)anthranilates with ammonia expected to lead to the formation of 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) [8-10].

Our interest in diazepines is based on the fact that 3*H*-1,3-diazepine-2,4-dione (**2**) is a seven-membered ring analog of uracil (**3**) which is one of the pyrimidine bases present in nucleic acids. And, of course, several isomers of **1** can be envisioned as well. A number of 1,4-benzodiazepines exhibit outstanding psychopharmacological properties and this ring system is present in such widely used pharmaceuticals as the hypnotic flurazepam (Dalmane®) and the tranquilizers diazepam (Valium®) and chlordiazepoxide (Librium®).

One of the synthetic approaches to 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) involves condensation of methyl *N*-(bromoacetyl)anthranilate (**4**) with ammonia [8-10], however, because of the various interesting properties of the derivatives of **1** (*e.g.*, they are useful as anticonvulsants) [9-17], a number of other synthetic methods have been developed during the past twenty years [11-28].

In our study, the reaction of methyl *N*-(bromoacetyl)-anthranilate (**4**) with ammonia in a methanolic solution afforded the expected 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) whose structure has been confirmed by elemental microanalysis, its melting point, and the ^{1}H and ^{13}C nmr, ir, and mass spectra (for the spectra and their interpretation, see Experimental). A by-product in this reaction, methyl *N*-glycylanthranilate hydrobromide (**5**), is formed in a 60% yield. The yield of **1** is only 8% but it can be increased by adding triethylamine to the reaction mixture. Triethylamine acts as an additional excellent hydrogen bromide acceptor and decreases the formation of methyl *N*-glycylanthranilate hydrobromide (**5**). Table I shows the various reaction conditions studied, with the best yield of



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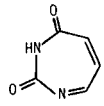

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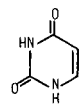

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Table I

Yields of 3*H*-1,4-Benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) in the Presence of Triethylamine

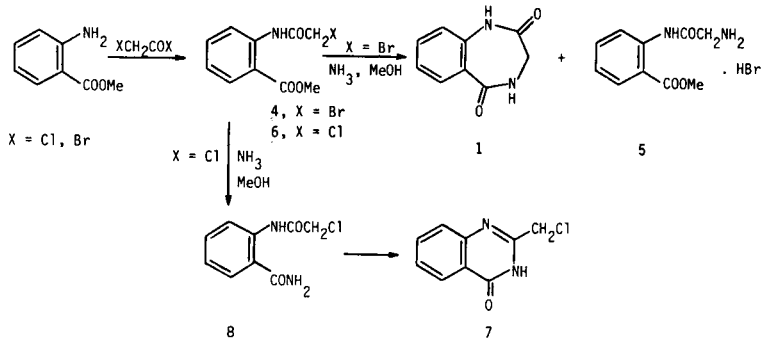
Starting Material (mmoles) [a]	Et_3N (mmoles)	Yield of **1**, % [b]	Yield of **5**, % [c]
14.8	0 [d]	0	62
14.8	0 [e]	8	60
3.9	3.9 [f]	32	47
3.9	11.7 [f]	47	51

[a] Methyl *N*-(bromoacetyl)anthranilate (**4**). [b] 3*H*-1,4-Benzodiazepine-2,5(1*H*,4*H*)-dione (**1**). [c] Based on the starting material. [d] Reaction time: 4 hours. [e] Reaction time: 8 hours. [f] Reaction time: 4 days.

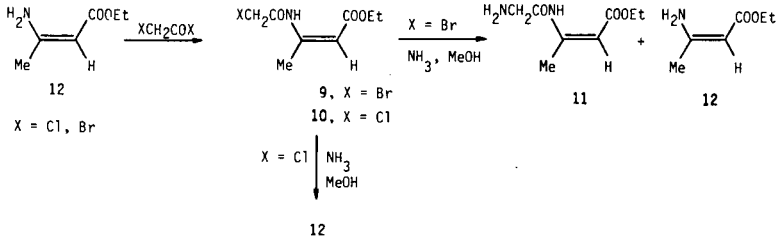
1 reaching 47%. For the sake of comparison, we have carried out a reaction between methyl *N*-(chloroacetyl)anthranilate (**6**) with ammonia under conditions similar to those described above for **4**. To our surprise, the cyclization reaction proceeded in a different fashion and the only heterocyclic product we were able to isolate was 2-(chloromethyl)quinazoline-4(3*H*)-one (**7**) obtained in a 48% yield and identified on the basis of its elemental analysis, melting point, and spectral data (Experimental).

The differences between the two reactions can be explained as follows. In the synthesis of 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) from methyl *N*-(bromoacetyl)anthranilate (**4**) with ammonia, one can assume an intermediate formation of methyl *N*-glycylanthranilate (**5**) which then undergoes cyclization to **1**. On the other hand, the most likely process in the second case is the intermediate

Scheme 1



Scheme 2



generation of *N*-(chloroacetyl)anthranilamide (**8**) from methyl *N*-(chloroacetyl)anthranilate (**6**) and ammonia which subsequently gives 2-(chloromethyl)quinazoline-4(3*H*)-one (**7**) (Scheme 1). A similar reaction has been reported in the literature [29] in which methyl *N*-acetylanthranilate underwent ring closure in the presence of ammonia and sodium hydroxide to afford 2-methylquinazoline-4(3*H*)-one *via* the intermediate *N*-acetylanthranilamide. In our particular case, ammonia served both as a reactant and as a catalyst. The two different pathways can be explained as due to the fact that the bromide ion is a much better leaving group than the chloride ion, hence in the first case the bromoacetyl group is easily transformed into the aminoacetyl group. In the second case, ammonolysis of methyl *N*-(chloroacetyl)anthranilate (**6**) gives the corresponding *N*-(chloroacetyl)anthranilamide (**8**) as an intermediate which then affords **7**.

We have also tried to obtain 1,4-benzodiazepines without a fused benzene ring by attempted cyclization of ethyl 3-(bromoacetamido)crotonate (**9**) and ethyl 3-(chloroacetamido)crotonate (**10**) under conditions similar to those described above. Unfortunately, no cyclization takes place. In the case of **9**, ethyl 3-(aminoacetamido)crotonate (**11**) and ethyl 3-aminocrotonate (**12**) were obtained, while ethyl 3-(chloroacetamido)crotonate (**10**) afforded ethyl 3-aminocrotonate (**12**) as the sole reaction product (Scheme 2).

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer apparatus, model 240, at Korea Research Institute of Chemical Technology, Dae Jeon, Korea. The ^{1}H nmr spectra were recorded on a 60 MHz Varian EM-360 spectrometer and the ^{13}C nmr spectra were obtained on a 200 MHz Bruker AM-200 spectrometer, with tetramethylsilane (TMS) as the internal standard. Infrared (ir) spectra were determined on a Jasco A-1 spectrophotometer. Mass spectra were measured on a Shimadzu QP-1000 instrument at 70 eV.

Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company, Milwaukee, WI.

Methyl *N*-(Bromoacetyl)anthranilate (**4**) [8,9].

Bromoacetyl bromide (2.0 ml, 4.63 g, 0.023 mole) was added dropwise to a solution of methyl anthranilate (2.6 ml, 3.04 g, 0.020 mole) in benzene (150 ml) and the solution was refluxed for 4 hours. After cooling, the reaction mixture was washed with 3*N* sodium hydroxide and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and vacuum distillation of the residue afforded methyl *N*-(bromoacetyl)anthranilate (**4**), 4.35 g (yield 80%), mp 84-87° (lit [8,9] mp 86-87°); ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, OMe), 4.0 (s, 2H, CH_2Br), 7.0-8.9 (m, 4H, C_6H_4), 11.8 ppm (b, 1H, NH).

The following compounds were obtained in the above manner from the appropriate starting materials.

Methyl *N*-(Chloroacetyl)anthranilate (**6**) [30,31].

From methyl anthranilate and chloroacetyl chloride, yield 95%, mp 97-100°; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, OMe), 4.2 (s, 2H, CH_2Cl), 7.0-8.9 (m, 4H, C_6H_4), 12.0 ppm (b, 1H, NH).

Ethyl 3-(Bromoacetamido)crotonate (**9**).

From 3-aminocrotonate and bromoacetyl bromide, yield 33%, mp 47-49°; ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, OCH_2Me), 2.35 (s, 3H, =CMe), 3.9 (s, 2H, CH_2Br), 4.2 (q, 2H, OCH_2Me), 5.0 (s, 1H, CH=), 11.7 ppm (b, 1H, NH).

Ethyl 3-(Chloroacetamido)crotonate (**10**) [32].

From 3-aminocrotonate and chloroacetyl chloride, yield 65%, mp 59-61° (lit [32] mp 56°); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, OCH_2Me), 2.4 (s, 3H, =CMe), 4.1 (s, 2H, CH_2Cl), 4.2 (q, 2H, OCH_2Me), 5.05 (s, 1H, CH=), 12.0 ppm (b, 1H, NH) (*cf* [32]).

Reaction of Methyl *N*-(Bromoacetyl)anthranilate (**4**) with Ammonia [8-10].

Methyl *N*-(bromoacetyl)anthranilate (**4**, 4.0 g, 0.015 mole) was dissolved in methanol (300 ml) saturated with ammonia gas (39 g) and the reaction mixture was stirred at room temperature for 8 hours. Then the excess ammonia and the solvent were evaporated under reduced pressure and 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**1**) was precipitated by addition of chloroform, filtered off, and recrystallized from acetone-dimethyl formamide (4:1 vol), giving 0.2 g of the purified product (yield 8%), mp 320-325° (lit [8,9] mp 327-328.5°); ^{1}H nmr (DMSO-d_6): δ 3.6 (d, 2H, CH_2), 7.0-8.0 (m, 4H, C_6H_4), 8.6 (t, 1H, NH), 10.4 ppm (b, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 44.5, 120.5, 123.8, 125, 130.5, 132, 136.8, 168.1, 171 ppm; ir (potassium bromide pellet): ν max 1670 (C=O), 1690 (C=O), 3270 (NH), 3400 cm^{-1} (NH) (*cf* [8]); ms: M$^+$ 176 (mol wt calcd. 176.2).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.22; H, 4.55; N, 15.49.

The chloroform filtrate was concentrated under reduced pressure and the residue was recyrstallized from methanol-petroleum ether (9:1 vol) giving methyl *N*-glycylanthranilate hydrobromide (**5**, 2.6 g, yield 60% based on the starting **4**), mp 222-224° (lit [33] mp 210-212°); ^{1}H nmr (DMSO-d_6): δ 3.9 (s, 3H, Me), 3.95 (s, 2H, CH_2), 7.2-8.7 (m, 7H, C_6H_4 + NH_3), 10.8 ppm (b, 1H, NH) (*cf* [33]); ir (potassium bromide pellet): ν max 1700 (C=O), 1720 (C=O), 3400 cm^{-1} (NH) (*cf* [33]); ms: M$^+$ 209 (mol wt calcd. 209.1 for the free base), 80:82 = 1:1 (HBr) (natural abundance, $_{35}Br^{79}$:$_{35}Br^{81}$ = 1:1) (*cf* [33]).

In the presence of triethylamine, the yield of **1** can be increased (see Table I).

Reaction of Methyl *N*-(Chloroacetyl)anthranilate (**6**) with Ammonia.

Methyl *N*-(chloroacetyl)anthranilate (**6**, 1.0 g, 0.0046 mole) was dissolved in methanol (80 ml) saturated with ammonia gas (20 g) and the reaction mixture was stirred at room temperature for 3 days. Then the excess ammonia and the solvent were evaporated under reduced pressure.The residue was washed with chloroform to remove the unreacted **6** (54%) and purified by recrystallization from methylene chloride-diethyl ether (1:1 vol) to give 0.34 g of 2-(chloromethyl)quinazoline-4(3*H*)-one (**7**) (yield 38%), mp 246-250° (lit [34] mp 247-248°); ^{1}H nmr (DMSO-d_6): δ 4.6 (s, 2H, CH_2), 7.5-8.1 (m, 4H, C_6H_4), 12.5 ppm (b, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 43, 121, 125.5, 127, 134.5, 148.5, 152.3, 161.8 ppm; ir (potassium bromide pellet): ν max 1470 (pyrimidine ring), 1610 (ring), 1690 (C=O), 3400 cm^{-1} (NH); ms: M$^+$ 194 (mol wt calcd. 194.6), 194:196 = 3:1 (natural abundance, $_{17}Cl^{35}$:$_{17}Cl^{37}$ = 3:1).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39. Found: C, 54.81; H, 3.64; N, 13.52.

The yield of **7** increases with longer reaction time; reaction time (yield, %): 20 hours (20), 24 hours (22), 3 days (38).

Reaction of Ethyl 3-(Bromoacetamido)crotonate (**9**) with Ammonia.

Ethyl 3-(bromoacetamido)crotonate (**9**, 2.5 g, 0.010 mole) was dissolved in methanol (90 ml) saturated with ammonia gas (12 g) and the reaction mixture was stirred at room temperature overnight. Then the excess ammonia and the solvent were distilled off under reduced pressure and the residue was chromatographed on a silica gel column. One isolated product was ethyl 3-aminocrotonate (**12**), identical in all respects with an authentic sample (mp, bp, nmr and ir spectra) [35-37]. The second reaction product was ethyl 3-(aminoacetamido)crotonate (**11**), eluted with chloroform-methanol (50:1 vol), 0.093 g (yield 5%), mp 71-75°; ^{1}H nmr (deuteriochloroform): δ 1.35 (t, 3H, OCH_2Me), 1.8 (b, 2H, NH_2), 2.5 (s, 3H, =CMe), 3.5 (s, 2H, CH_2NH_2), 4.2 (q, 2H, OCH_2Me), 5.0 (s, 1H, CH=), 12.1 ppm (b, 1H, NH); ir (potassium bromide pellet), ν max 1670 (C=O amide), 1690 (C=O), 3180 (NH amide), 3300 (NH_2 sym), 3380 cm^{-1} (NH_2 asym).

Anal. Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.45; H, 7.51; N, 14.96.

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