Quinazolines and 1,4-Benzodiazepines. LXXI (1). Reactions of 2-(Triazol-4-yl)benzophenones

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Some new triazolylbenzophenones **3** were prepared by reaction of the corresponding quinazolines **2** with formic acid. Conversions of compounds **3** to known triazolobenzodiazepines are described. One of the processes proceeds *via* the double bond isomer **13**. The reaction of the aldehyde **9** with hydrazine interestingly yielded the triazoloquinolines **11** and **12**. The cyclization of the benzophenones **3** to the triazoloindoles **15** and the alkylation of the latter to derivatives with basic and acidic side chains are also reported. Quaternization of compound **16** with ethyl bromoacetate followed by treatment with hydroxide resulted in the formation of the triazinoindole **12**.

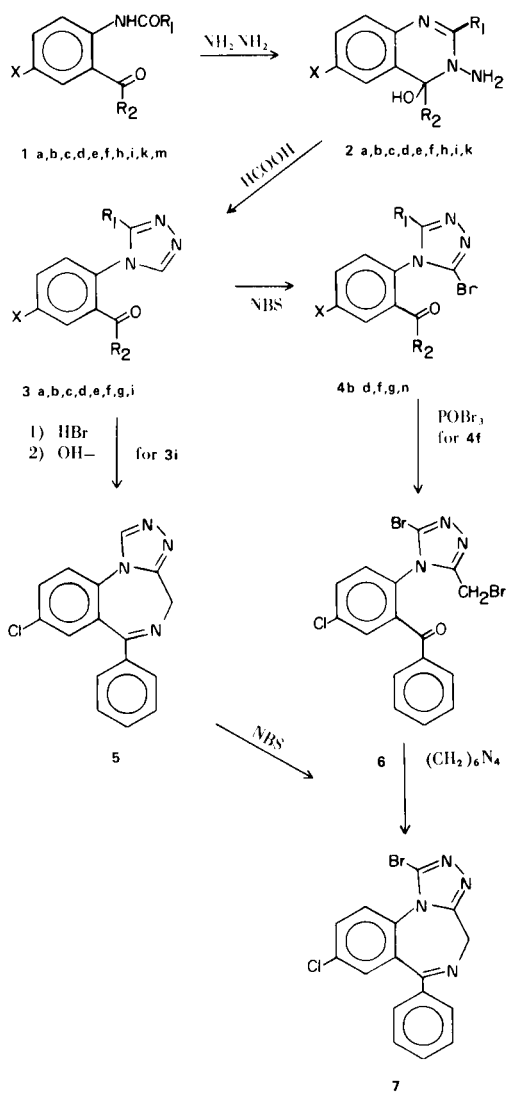
Derieg and coworkers (2) had shown that the reaction of the 2-formamidobenzophenone **1a** (Scheme I) with hydrazine led to the 3-amino-4-hydroxyquinazoline **2a** which they converted to the triazole **3a** by boiling in formic acid. The discovery of the pharmacologically interesting triazolobenzodiazepines (3) made us investigate the conversion of these triazolylbenzophenones **3** to the triazolobenzodiazepines. In the meantime such conversions have been realized by Meguro and coworkers (4) and by Hester (5). We would like to add to the published material some of the results of our related studies.

Since we experienced that the transformation of the quinazolines **2** to the triazoles **3** worked well only with formic acid, we introduced the functionalities required for formation of the diazepine ring into the acetyl group of the acetaminobenzophenone **1**. With exception of the chloroacetate **1m** which yielded the hydrazinomethylquinazoline **2k**, all acylaminobenzophenones reacted cleanly with hydrazine at room temperature to give the corresponding quinazolines. Unfortunately the 2-aminomethylquinazoline **2h** which carried the correct functions for the closure of the diazepine ring gave a complex mixture upon heating in formic acid. Some of the desired triazolobenzodiazepine **5** could be detected by thin layer chromatography. The corresponding carbobenzoxy derivative **2i** on the other hand could be converted to the triazole **3i**. This compound was not obtained crystalline, but was characterized by nmr. Cleavage of the protecting group with hydrogen bromide in acetic acid followed by ring closure afforded the triazolobenzodiazepine **5** (3a). The hydroxymethyltriazole **3f** was accessible in good yield *via* the corresponding formate **3g** from the hydroxymethylquinazoline **2f**.

Bromination of the 3-methyltriazole **3b** with *N*-bromosuccinimide occurred on the triazole nucleus rather than on the methyl group and yielded **4b**. Accordingly **3a** was brominated to **4n**, **3d** to **4d** and the formyloxytriazole **3g** to **4g**. Alkaline hydrolysis of **4g** led to the hydroxymethyltriazole **4f** which upon treatment wiht phosphorus oxybromide gave the bromomethyl derivative **6**. This compound was converted in known fashion to the bromotriazolobenzodiazepine **7** (6) by reacting with hexamethylenetetramine. Compound **7** is also accessible by direct bromination of **5** (6).

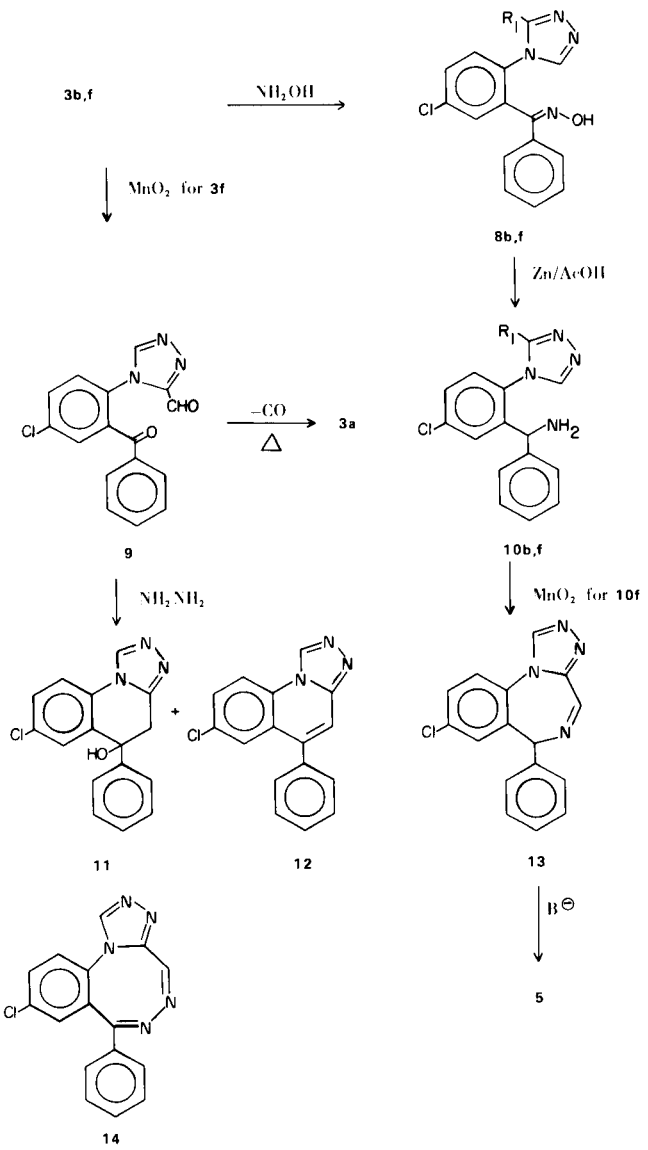
A new approach to compound **5** *via* the double bond isomer **13** is shown in Scheme II. Oximation of the triazolylbenzophenones **3b** and **3f** yielded the corresponding oximes **8b** and **8f** respectively which could be reduced with zinc and acetic acid to the benzhydrylamines **10b** and **10f**. Treatment of the hydroxymethyl derivative **10f** with activated manganese dioxide at room temperature led directly to the ring closed product **13** which was isomerized to **5** with sodium methoxide in methanol. The aldehyde **9** which was analogously prepared by oxidation of **3f** was found to decarbonylate easily to **3a** and any heating of **9** had to be avoided. Reaction of the aldehyde **9** with hydrazine at room temperature did not lead to the triazolotriazocine **14** but to a mixture of compounds **11** and **12** which were separated by chromatography. The interesting formation of these compounds under such mild Wolf-Kischner conditions may be explained by the mechanistic considerations (7) depicted in

Scheme I



a:	X = Cl,	R_1 = H,		$R_2 = C_6H_5$
b:	X = Cl,	R_1 = CH_3,		$R_2 = C_6H_5$
c:	X = Cl,	R_1 = CH_3,		R_2 = 2-F-C_6H_4
d:	X = H,	R_1 = CH_3,		R_2 = 2-pyridyl
e:	X = Br,	R_1 = CH_3,		R_2 = 2-pyridyl
f:	X = Cl,	R_1 = CH_2OH,		$R_2 = C_6H_5$
g:	X = Cl,	R_1 = CH_2OCHO		$R_2 = C_6H_5$
h:	X = Cl,	R_1 = CH_2NH_2,		$R_2 = C_6H_5$
i:	X = Cl,	R_1 = $CH_2NHCOOCH_2C_6H_5$,		$R_2 = C_6H_5$
k:	X = Cl,	R_1 = CH_2NHNH_2,		$R_2 = C_6H_5$
m:	X = Cl,	R_1 = CH_2Cl,		$R_2 = C_6H_5$
n:	X = Cl,	R_1 = Br,		$R_2 = C_6H_5$

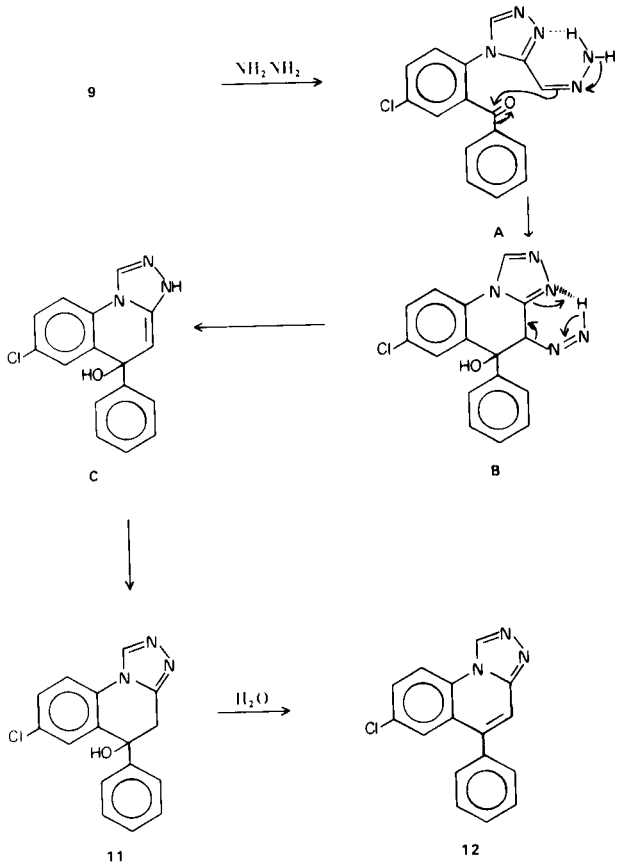
Scheme II



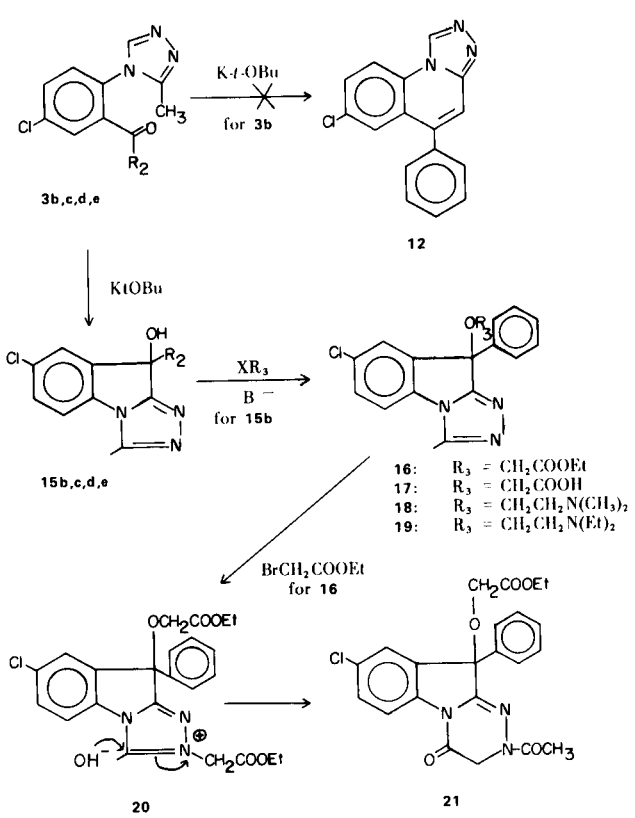
Scheme III. The initially formed hydrazone **A** is assumed to cyclize to intermediate **B** in the indicated fashion. Loss of nitrogen by a fragmentation facilitated by a six-membered cyclic arrangement would then lead to **C**. Formation of compound **11** from **C** only requires aromatization of the triazole by a 1,3-proton shift. The elimination of water from **11** is apparently rather slow under neutral or basic conditions, thus allowing its isolation as the major product by chromatography. Compound **11** was of course readily dehydrated to **12** by hot acetic acid.

We expected that compound **12** would be conveniently prepared by base catalyzed cyclization of the methyltriazole **3b**. However, treatment of **3b** with potassium *t*-butoxide in tetrahydrofuran yielded the triazoloindoline **15b** (Scheme IV). Also the fluorinated analog **3c** underwent the same cyclization to the indoline **15c**. While strong base was necessary to effect the cyclization of the triazoles **3b** and **3c**, the pyridyl analogs **15d** and **15e** were already formed along with the triazoles **3d** and **3e** by reaction of the quinazolines **2d** and **2e** with formic acid. It seems that protonation of the pyridine nitrogen enhances the electrophilic character of the carbonyl group

Scheme III



Scheme IV



to such extent as to make an acid catalyzed cyclization possible.

For pharmacological screening purposes, the tertiary alcohol of **15b** was alkylated to yield the ester **16**, the acid **17** and the amines **18** and **19**. Further reaction of the ester **16** with ethyl bromoacetate followed by alkaline workup led to a new compound to which we have assigned structure **21** on the basis of analytical and spectral data. The formation evidently implies opening of the quaternary salt **20** by hydroxide as indicated in Scheme IV and recyclization to the six-membered lactam.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or on a Reichert hot stage microscope. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer and mass spectra on a CEC-100 B instrument. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying purposes.

3-Amino-6-chloro-3,4-dihydro-4-(2-fluorophenyl)-4-hydroxy-2-methylquinazoline, **2c**.

A mixture of 50 g. of 4'-chloro-2'-(2-fluorobenzoyl)acetanilide, **1c** (m.p. 100-102°) and 100 ml. of hydrazine (97%) was stirred at room temperature for 1 1/2 hours. The product started to crystallize out after 10 minutes. The reaction mixture was diluted with ice/water and the precipitated material was collected, washed with water, methanol and ether to leave 49.8 g. (94%). The analytical sample was recrystallized from methanol/chloroform, m.p. 218-220°; uv: λ max 216 mμ (ε = 18,600), sh 256 (4,500), sh 263 (6,020), max 288 (12,820), infl 315 (4,500); ir (potassium bromide): no carbonyl.

Anal. Calcd. for $C_{15}H_{13}ClFN_3O$: C, 58.9; H, 4.3; N, 13.7. Found: C, 58.9; H, 4.2; N, 13.9.

3-Amino-3,4-dihydro-4-hydroxy-2-methyl-4-(2-pyridyl)quinazoline, **2d**.

Reaction of 20 g. of 2-(2-acetaminobenzoyl)pyridine, **1d** (m.p. 143-146°) with 40 ml. of hydrazine yielded 20.6 g. (97%) of product. It was recrystallized from methanol/tetrahydrofuran for analysis. m.p. 214-216°.

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 66.1; H, 5.5; N, 22.0. Found: C, 66.0; H, 5.5; N, 22.3.

3-Amino-6-bromo-3,4-dihydro-4-hydroxy-2-methyl-4-(2-pyridyl)-quinazoline, **2e**.

This compound was obtained in 93% yield by reaction of 10 g. of 2-[2-acetamino-5-bromobenzoyl]pyridine, **1e** (m.p. 129-131°) with 20 ml. of hydrazine. The analytical sample was recrystallized from dimethylformamide, m.p. 224-227°.

Anal. Calcd. for $C_{14}H_{13}BrN_4O$: C, 50.5; H, 3.9; N, 16.8. Found: C, 50.4; H, 3.9; N, 17.1.

3-Amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenyl-quinazolin-2-methanol, **2f**.

A mixture of 20 g. of 2'-benzoyl-4'-chloro-2-hydroxyacetanilide, **1f** (8) and 40 ml. of hydrazine was stirred at room temperature for 3 hours. It was diluted with water and layered with 200 ml. of hexane and stirred for 15 minutes. The solid product was collected and washed well with water and dried. Recrystallization from tetrahydrofuran/hexane yielded 16.3 g. (78%) of product with m.p. 196-199° dec.; uv: λ max 221 mμ (ε = 18,000), 285 (12,390) infl. 310 (5,250).

Anal. Calcd. for $C_{15}H_{14}ClN_3O_2$: C, 59.3; H, 4.7; N, 13.8. Found: C, 59.5; H, 4.7; N, 13.9.

3-Amino-2-aminomethyl-6-chloro-3,4-dihydro-4-hydroxy-4-phenyl-quinazoline, **2h**.

A solution of 2.86 g. (0.01 mole) of 2-amino-2'-benzoyl-4-chloroacetanilide, **1h** (9) in 5 ml. of hydrazine was allowed to stand at room temperature for 1 hour. After dilution with 2-propanol the separated crystals were collected, washed with 2-propanol and either to yield 2 g. (66%) with m.p. 198-201°dec.; uv: λ sh 221 mμ (ε = 17,000), max 287 (12,600) infl 310 (6,100); ir: no carbonyl.

Anal. Calcd. for $C_{15}H_{15}ClN_4O$: C, 59.5; H, 5.0; N, 18.5. Found: C, 59.7; H, 4.9; N, 18.7.

3-Amino-2-(benzyloxycarbonylamino)methyl-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline, **2i**.

Reaction of 20 g. of 2-benzyloxycarbonylamino-2'-benzoyl-4'-chloroacetanilide, **1i** (10) with 20 ml. of hydrazine at room temperature for 2 hours yielded 14 g. (67%) of product with m.p. 168-170° dec. The analytical sample was recrystallized from tetrahydrofuran/2-propanol; uv: λ sh 223 mμ (ε = 16,600), max 287 (12,900), infl 310 (6,000).

Anal. Calcd. for $C_{23}H_{21}ClN_4O_3$: C, 63.2; H, 4.8; N, 12.8. Found: C, 63.1; H, 4.6; N, 12.7.

3-Amino-6-chloro-3,4-dihydro-2-hydrazinomethyl-4-hydroxy-4-phenylquinazoline, **2k**.

2'-Benzoyl-4'-chloro-2-chloroacetanilide, **1m** (9), 30.8 g. was added to 75 ml. of hydrazine cooled in ice/water. Following addition, the mixture was stirred in ice/water for 2 hours and at room temperature overnight. The precipitated crystals were collected, washed with tetrahydrofuran, methanol and ether to yield 24.9 g. (78%) of product with m.p. 180-185° dec.; uv: λ max 224 mμ (ε = 16,000), 287 mμ (12,850), infl 310 (6,500).

Anal. Calcd. for $C_{15}H_{16}ClN_5O$: C, 56.7; H, 5.1; N, 22.0. Found: C, 56.5; H, 4.9; N, 22.3.

4-[4-Chloro-2-(2-fluorobenzoyl)phenyl]-3-methyl-1,2,4-triazole, **3c**.

A solution of 30.6 g. (0.1 mole) of **2c** in 300 ml. of formic acid was heated to reflux for 4 hours. The formic acid was evaporated, at the end azeotropically with toluene, and the residue was crystallized from ether and recrystallized from methylene chloride/ether to yield 19 g. (60%) with m.p. 118-120°. The analytical sample was recrystallized from the same solvents; uv: λ max 217 mμ (ε = 25,550), 250 (13,150) 286 (3,300); ir (chloroform): 1665 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.27 ppm (s, 3, CH_3) 6.9-7.8 (m, 7, aromatic H) 8.0 (s, 1, C_5-H).

Anal. Calcd. for $C_{16}H_{11}ClFN_3O$: C, 60.9; H, 3.5; N, 13.3. Found: C, 60.9; H, 3.6; N, 13.4.

4-[2-Benzoyl-4-chlorophenyl]-3-hydroxymethyl-1,2,4-triazole, **3f**.

A solution of 15 g. (0.048 mole) of **2f** in 100 ml. of formic acid was treated as described in previous experiments to yield 17 g. of crude formate. This material was dissolved in 125 ml. of hot ethanol. Sodium hydroxide solution, 17 ml. of 3*N*, was added and the mixture was stirred for 15 minutes, diluted with water and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 8.3 g. (55%) of product which was recrystallized from tetrahydrofuran/hexane for analysis, m.p. 186-188°; λ infl 215 mμ (ε = 25,400), max 255 (14,500), infl 285 (3,200); ir (potassium bromide): 3150 cm^{-1} OH, 1660 (CO).

Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.3; H, 3.9; N, 13.4. Found: C, 61.3; H, 3.8; N, 13.3.

4-(2-Benzoyl-4-chlorophenyl)-3-(formyloxy)methyl-1,2,4-triazole, **3g**.

A solution of 24.3 g. (0.08 mole) of **2f** in 250 ml. of formic acid was heated to reflux for 16 hours. The formic acid was evaporated under reduced pressure, at the end azeotropically with xylene. Crystallization of the residue from 2-propanol yielded 10.2 g. (37.5%) of product with m.p. 127-129°. Hydrolysis of the mother liquor yielded another 6.4 g. (26%) of the alcohol **3f**. Recrystallization of the formate from 2-propanol raised the m.p. to 128-130°; uv: λ infl 215 mμ (ε = 33,600), max 255 (14,500), infl 290 (2,500); nmr (d-DMSO): δ 5.18 ppm (s, 2, OCH_2) 7.2-8 (m, 8, aromatic H) 8.1 (s, 1, C_5-H) 8.6 (s, 1, CHO); ir (chloroform): 1740 (OCO) 1680 cm^{-1} (CO).

Anal. Calcd. for $C_{17}H_{12}ClN_3O_3$: C, 59.7; H, 3.5; N, 12.3. Found: C, 59.7; H, 3.4; N, 12.2.

4-[2-Benzoyl-4-chlorophenyl]-3-(benzyloxycarbonylamino)methyl-1,2,4-triazole, **3i**.

A solution of 5 g. of **2i** in 100 ml. of formic acid was heated to reflux for 3 hours. The formic acid was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was dried and evaporated. The residue was chromatographed over 200 g. of silica gel using 2% (v/v) of ethanol in ethyl acetate. The clean fractions were combined and evaporated to yield 3 g. (58%) of a light yellow resin which could not be crystallized; nmr (deuteriochloroform): δ 4.38 (d, 2, J = 6 Hz, -NHCH_2) 4.96 (s, 2, OCH_2) 6.06 (broad t, 1, J = 6 Hz, -NH) 7-7.8 (m, 13, aromatic H) 7.93 (s, 1, C_5-H).

4-[2-Benzoyl-4-chlorophenyl]-3-bromo-5-methyl-1,2,4-triazole, **4b**.

A mixture of 29.8 g. (0.1 mole) of **3b**, 27 g. (0.15 mole) of *N*-bromosuccinimide, 200 ml. of carbon tetrachloride and 200 ml. of glacial acetic acid was stirred and heated to reflux for 1 hour. After dilution with methylene chloride the reaction mixture was washed with water and 10% aqueous sodium carbonate solution, was dried and evaporated. The residue was crystallized from methylene chloride/ether to yield 27.2 g. (72%) of product with m.p. 178-181°. The analytical sample was recrystallized twice from methylene chloride/ether/hexane, m.p. 195-198°; uv: λ max 214 mμ (ε = 26,600), 255 (13,600), infl 285 (3,600); nmr (deuteriochloroform): 2,33 ppm (s, 3, CH_3) 7.2-7.9 (m, 8, aromatic H).

Anal. Calcd. for $C_{16}H_{11}BrClN_3O$: C, 51.0; H, 2.9; N, 11.2. Found: C, 50.9; H, 2.9; N, 11.1.

3-Bromo-5-methyl-4-[2-(2-pyridoyl)phenyl]-1,2,4-triazole, **4d**.

Analogously, the reaction of 5.3 g. (0.02 mole) of **3d** with 2.7 g. (0.03 mole) of *N*-bromosuccinimide in 50 ml. of carbon tetrachloride and 50 ml. of acetic acid yielded 5.1 g. (74%) of product which after recrystallizations from methylene chloride/-

hexane and ethanol had m.p. 175-178°.

Anal. Calcd. for $C_{15}H_{11}BrN_4O$: C, 52.5; H, 3.2; N, 16.3. Found: C, 52.4; H, 3.1; N, 16.5.

4-(2-Benzoyl-4-chlorophenyl)-3-bromo-5-hydroxymethyl-1,2,4-triazole, **4f**.

Aqueous sodium hydroxide solution, 10 ml. of 3*N*, was added to a hot solution of 8.4 g. (0.02 mole) of **4g** in 100 ml. of ethanol. After standing for 15 minutes, the mixture was diluted with water and extracted with methylene chloride. The extracts were dried and evaporated and the residue was crystallized from methylene chloride/ether to yield 5.9 g. (75%) of colorless crystals with m.p. 146-149°. The analytical sample was recrystallized from methylene chloride/ether/hexane, m.p. 147-149°; uv: λ sh 212 mμ (ε = 30,000), max 254 (13,850) infl 385 (3,300); ir (chloroform): 3300 cm^{-1} (OH), 1670 (CO).

Anal. Calcd. for $C_{16}H_{11}BrClN_3O_2$: C, 48.9; H, 2.8; N, 10.7. Found: C, 48.7; H, 2.5; N, 11.0.

4-(2-Benzoyl-4-chlorophenyl)-3-bromo-5-formyloxymethyl-1,2,4-triazole, **4g**.

A mixture of 34.1 g. (0.1 mole) of **3g**, 27 g. (0.15 mole) of *N*-bromosuccinimide, 200 ml. of carbon tetrachloride and 200 ml. of glacial acetic acid was heated to reflux for 1 1/2 hours. It was then diluted with water and the carbon tetrachloride layer was separated. The aqueous phase was extracted twice with methylene chloride. The combined organic layers were washed with water, dried and evaporated. Crystallization of the residue from ether yielded 33.9 g. (80%) with m.p. 142-145°. The analytical sample was recrystallized from ethyl acetate and had m.p. 147-149°; uv: λ sh 212 mμ (ε = 31,400), max 255 (14,200), infl 290 (3,100); nmr (deuteriochloroform): δ 5.28 ppm (s, 2, OCH_2) 7.3-8.0 (m, 9, aromatic H and CHO); ir (chloroform): 1740 cm^{-1} (HCO), 1670 (CO).

Anal. Calcd. for $C_{17}H_{11}BrClN_3O_3$: C, 48.5; H, 2.6; N, 10.0. Found: C, 48.5; H, 2.5; N, 10.0.

4-[2-Benzoyl-4-chlorophenyl]-3,5-dibromo-1,2,4-triazole, **4h**.

A mixture of 23 g. (0.08 mole) of **3a**, (2) 35.6 g. (0.2 mole) of *N*-bromosuccinimide and 300 ml. of glacial acetic acid was heated on the steam bath for 1 hour. The acetic acid was removed under reduced pressure and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 26.7 g. (74%) of product with m.p. 219-221°. For analysis it was recrystallized from the same solvents; uv: λ max 214 mμ (ε = 32,600), 254 (13,150), infl 285 (4,150); ir (chloroform): 1675 cm^{-1} (CO).

Anal. Calcd. for $C_{15}H_8Br_2ClN_3O$: C, 40.8; H, 1.8; N, 9.5. Found: C, 41.1; H, 1.6; N, 9.8.

8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, **5**(3a).

a) Hydrogenbromide in acetic acid (30%), 10 ml., was added to a solution of 1 g. of crude **3i** in 10 ml. of methylene chloride. After standing at room temperature overnight, the reaction mixture was partitioned between ether and water. The aqueous phase was washed with ether, made alkaline with ammonia and extracted with methylene chloride. The extracts were dried and evaporated and the residue was boiled up in ethanol and crystallized by cooling to yield 0.38 g. (56%) of product with m.p. 226-228°.

b) Potassium *t*-butoxide, 25 mg., was added to a solution of 0.2 g. of **13** in 10 ml. of methanol. After stirring for 1 hour under nitrogen at room temperature, the solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and water. The organic phase was dried and evaporated. Crystallization of the residue from methylene chloride/-hexane yielded 90 mg. (45%) of **5** with m.p. and mix m.p. 224-227°.

4-(2-Benzoyl-4-chlorophenyl)-3-bromo-5-bromomethyl-1,2,4-triazole Etherate **6**.

Phosphorus oxybromide, 5.72 g. (0.02 mole), was added to a solution of 7.84 g. (0.02 mole) of **5** in 175 ml. of methylene chloride. After stirring for 4 hours at room temperature the mixture was diluted with 150 ml. of methylene chloride and layered with saturated aqueous sodium bicarbonate solution. The two phase system was stirred until carbon dioxide evolution had stopped. The methylene chloride solution was separated, dried and evaporated. Crystallization of the residue from ether yielded 7.6 g. (80%) of product with m.p. 80-83°. The analytical sample was recrystallized from ether, m.p. 80-83°. Analytical data and nmr indicated the crystals to contain 0.25 equivalents of ether. Other solvents also formed solvates; uv: λ max 213 mμ (ε = 30,000), 255 (13,500), infl 290 (2,800); nmr (deuteriochloroform): δ 4.36 ppm (d, 1) and 4.73 (d, 1) (AB-system J = 12 Hz, $-CH_2$-Br) 7.3-8.0 (m, 8, aromatic H); ir (chloroform): 1670 cm^{-1} (CO).

Anal. Calcd. for $C_{16}H_{10}Br_2ClN_3O \cdot 0.25\ Et_2O$: C, 43.1; H, 2.7; N, 8.9. Found: C, 43.1; H, 2.5; N, 8.9.

1-Bromo-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, **7**.

A mixture of 4.75 g. (0.01 mole) of **6**, 1.7 g. (0.12 mole) of hexamethylene tetramine and 100 ml. of ethanol was heated to reflux for 4 hours. The solvent was evaporated under reduced pressure. The residue was partitioned between methylene chloride and sodium bicarbonate solution, dried and evaporated. The residue was run over a pad of silica gel with ethyl acetate. Crystallization of the evaporated filtrate from methylene chloride/ether yielded 1.15 g. (31%) of colorless crystals with m.p. 202-204°. The analytical sample was recrystallized from the same solvents, m.p. 205-207°; uv: λ max 223 mμ (ε = 36,000), infl 245 (16,900), infl 290 (3,000); nmr (deuteriochloroform): δ 4.08 ppm (d, 1) and 5.53 (d, 1) (AB-system, J = 13 Hz, $-C_4$-H) 7.3-8.0 (m, 8, aromatic H).

Anal. Calcd. for $C_{16}H_{10}BrClN_4$: C, 51.4; H, 2.7; N, 15.0. Found: C, 51.3; H, 2.7; N, 14.9.

4-[4-Chloro-2-(α-hydroxyiminobenzyl)phenyl]-3-methyl-1,2,4-triazole, **8b**.

A mixture of 29.75 g. (0.1 mole) of **3b**, 8.35 g. (0.12 mole) of hydroxylamine hydrochloride, 80 ml. of pyridine and 500 ml. of ethanol was stirred and heated to reflux for 16 hours. After evaporation of the bulk of the solvent, the residue was diluted with water and the precipitated solid material was collected and washed with water and ether to yield 30.8 g. (98%) of product with m.p. 241-244°. The analytical sample was recrystallized from ethylacetate/hexane, m.p. 252-254°; uv: λ infl 225 mμ (22,000) infl 260 (10,400); nmr (d-DMSO): δ 1.93 ppm (s, *ca.* 0.9) and 2.06 (s, *ca.* 2.1) (*syn* and *anti* isomers, CH_3) 7-8.1 (m, 9, aromatic H and C_5-H) 11.83 (s, *ca.* 0.3) and 11.9 (s, *ca.* 0.7) (*syn* and *anti* isomer, OH).

Anal. Calcd. for $C_{16}H_{13}ClN_4O$: C, 61.4; H, 4.2; N, 17.9. Found: C, 61,3; H, 4.1; N, 17.9.

4-[4-Chloro-2-(α-hydroxyiminobenzyl)phenyl]-3-hydroxymethyl-1,2,4-triazole, **8f**.

A mixture of 15.7 g. (0.05 mole) of **3f**, 4.15 g. of hydroxylamine hydrochloride, 17 ml. of pyridine and 200 ml. of ethanol was heated to reflux for 16 hours. The solvent was removed under reduced pressure and the residue was crystallized from methanol/water and recrystallized from methanol to yield 9.65 g. (59%) with m.p. 262-266°. The analytical sample was recrystallized from benzene/methanol; uv: λ infl 225 mμ (ε = 20,900), infl 260 (10,700); nmr (d-DMSO): δ 4.28 ppm (d, 2, J = 5 Hz, -CH_2-O) 5.46 (t, 1, J = 5 Hz, OH) 7.34 (s, 5, C_6H_5) 7.4-7.8 (m, 3, aromatic H) 8.1 (s, 1, C_5-H) 11.8 (s, 1, =NOH).

Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$: C, 58.5; H, 4.0; N, 17.0. Found: C, 58.5; H, 3.9; N, 17.0.

4-(2-Benzoyl-4-chlorophenyl)-1,2,4-triazole-3-carboxaldehyde, **9**.

A mixture of 10 g. of **3f**, 30 g. of activated manganese dioxide and 500 ml. of methylene chloride was stirred overnight at room temperature. The manganese dioxide was filtered off and the filtrate was evaporated. The residue was chromatographed over 200 g. of silica gel using 20% methylene chloride in ethyl acetate. Crystallization of the combined clean fractions from methylene chloride/ether/hexane yielded 4.4 g. (44%) of product with m.p. 120-123°. The analytical sample was recrystallized from the same solvents, m.p. 121-123°; uv: λ max 212 mμ (ε = 27,000), 253 (17,800), infl 290 (3,000); ir (chloroform): 1710 cm^{-1} (CHO) 1670 (CO); nmr (deuteriochloroform): δ 7.2-7.9 (m, 8, aromatic H) 8.35 (s, 1, C_5-H) 9.9 (s, 1, CHO).

Anal. Calcd. for $C_{16}H_{10}ClN_3O_2$: C, 61.6; H, 3.2; N, 13.5. Found: C, 61.5; H, 3.1; N, 13.4.

4-[2-(α-Aminobenzyl)-4-chlorophenyl]-3-methyl-1,2,4-triazole, **10b**.

A mixture of 3.12 g. (0.01 mole) of **8b**, 3 g. of zinc dust and 100 ml. of glacial acetic acid was stirred at room temperature for 3 hours. The zinc was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was partitioned between methylene chloride and aqueous saturated bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from ether yielded 1.95 g. (65%) of product with m.p. 148-150°. The analytical sample was recrystallized from methylene chloride/hexane; uv: λ infl 225 mμ (ε = 20,500), max 252 (440), 259 (492), 265 (460), 276 (230); nmr (deuteriochloroform): δ 1.63 and 2.2 (broad bands, 3, CH_3, rotational isomers) 1.8 (broad s, 2, NH_2) 4.93 (broad s, 1, C*H*-NH_2) 6.7-8.2 (m, 9, aromatic H and C_5-H).

Anal. Calcd. for $C_{16}H_{15}ClN_4$: C, 64.3; H, 5.1; N, 18.8. Found: C, 64.4; H, 5.0; N, 19.0.

7-Chloro-4,5-dihydro-5-hydroxy-5-phenyl-*s*-triazolo[4,3-*a*]quinoline **11**, and 7-chloro-5-phenyl-*s*-triazolo[4,3-*a*]quinoline, **12**.

The crude product obtained by oxidation of 9.4 g. (0.03 mole) of **3f** with 30 g. of manganese dioxide in 500 ml. of methylene chloride was dissolved in 50 ml. of hydrazine (97%). After stirring at room temperature overnight, the mixture was diluted with water and the precipitated material was collected by filtration. It was chromatographed over 250 g. of silica gel using 10% (v/v) of ethanol in methylene chloride. The less polar minor product was crystallized from ether to yield 0.6 g. (7%) of **12** which had m.p. 265-267° after recrystallization from methylene chloride/ethanol; uv: λ max 281 mμ (ε = 36,200), 240 (34,400), 302 (8,950), 316 (5,930) 331 (5,275); nmr (d-DMSO): δ 7.63 ppm (s, 6, C_6H_5 and C_6-H) 7.66 (s, 1, C_4-H) 7.91 (q, 1, J_{AB} = 8 Hz, J_{AX} = 2.5 Hz, C_8-H) 8.62 (d, 1, J = 8 Hz, C_9-H) 10.06 (s, 1, C_1-H).

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.7; H, 3.6; N, 15.0. Found: C, 68.8; H, 3.5; N, 15.1.

The more polar major product was crystallized from ether to yield 4.2 g. (47%) of **11**. The analytical sample was recrystallized from methylene chloride/ether, m.p. 168-171°; uv: λ max 249 mμ (ε = 13,900), sh 278 (1,000), sh 286 (690); nmr (d-DMSO): δ 3.37 ppm (d, 1) and 3.8 (d, 1) (AB-system, J = 16 Hz, $-C_4$-H) 6.5 (s, 1, OH) 7.22 (d, 1, J = 2.5 Hz, C_6-H) 7.36 (s, 5, C_6H_5) 7.6 (q, 1, J_{AB} = 8 Hz, J_{AX} = 2.5 Hz, $-C_8$-H) 7.96 (d, 1, J = 8 Hz, $-C_9$-H) 9.33 (s, 1, C_1-H).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.5; H, 4.1; N, 14.1. Found: C, 64.2; H, 4.0; N, 14.2.

When this compound was heated in acetic acid it dehydrated quantitatively to **12**.

8-Chloro-6-phenyl-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, **13**.

A mixture of 5 g. (0.015 mole) of **8f**, 10 g. of zinc dust and 200 ml. of glacial acetic acid was stirred at room temperature for 3 1/2 hours. The zinc was removed by filtration and the filtrate was evaporated. The residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was dried and evaporated to leave 2.6 g. of crude 4-[2-(α-aminobenzyl)-4-chlorophenyl]-3-hydroxymethyl-1,2,4-triazole, **10f**.

This material was dissolved in 200 ml. of methylene chloride and 15 g. of activated manganese dioxide was added. After stirring for 2 hours at room temperature, the manganese dioxide was removed by filtration over celite. The filtrate was evaporated and the residue was crystallized from ether to yield 1.3 g. (29.5%) of product with m.p. 215-217°. The analytical sample was recrystallized from methylene chloride/hexane; uv: λ infl 225 mμ (ε = 24,300), infl 250 (8,100), infl 295 (1,060); nmr (deuteriochloroform): δ 5.42 ppm (d, 1, J = 2 Hz, $-C_6$-H) 6.88 (s with fine structure 1, $-C_7$-H) 7.3-7.8 (m, 7, aromatic H) 8.85 (m, 2, C_1-H and C_4-H.

Anal. Calcd. for $C_{16}H_{11}ClN_4$: C, 65.2; H, 3.8; N, 19.0. Found: C, 64.8; H, 3.5; N, 18.7.

6-Chloro-4-hydroxy-1-methyl-4-phenyl-4*H*-*s*-triazolo[4,3-*a*]indole, **15b**.

Potassium *t*-butoxide, .23 g. (0.203 mole) was added to a solution of 20 g. (0.0674 mole) of 4-(2-benzoyl-4-chlorophenyl)-3-methyl-1,2,4-triazole **3b** (4) in 500 ml. of dry tetrahydrofuran. After stirring at room temperature for 3 hours under an atmosphere of nitrogen, the solvent was partially evaporated under reduced pressure and the residue was partitioned between water and methylene chloride. The organic phase was dried and evaporated. The crystalline residue was collected with ether to yield 13.9 g. (69%) of product with m.p. 224-226°. The analytical sample was recrystallized from dimethylformamide/ether, and had the same m.p.; uv: λ max 207 mμ (ε = 46,600), 252 (10,150), 284 (1,100), 294 (700); nmr (d-DMSO): δ 2.7 ppm (s, 3, CH_3) 7.24 (s, 1, OH) 7.3-7.8 (m, 8, aromatic H).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.5; H, 4.1; N, 14.1. Found: C, 64.2; H, 4.1; N, 14.2.

6-Chloro-4-(2-fluorophenyl)-4-hydroxy-1-methyl-4*H*-*s*-triazolo-[4,3-*a*]indole, **15c**.

Reaction of 6.3 g. (0.02 mole) of **3c** with 6.75 g. (0.06 mole) of potassium *t*-butoxide in 125 ml. of tetrahydrofuran produced in the same manner 5.2 g. (82%) of **15c**, which was recrystallized from tetrahydrofuran for analysis, m.p. 223-225°.

Anal. Calcd. for $C_{16}H_{11}ClFN_3O$: C, 60.9; H, 3.5; N, 13.3.

Found: C, 70.0; H, 3.8; N, 13.2.

4-Hydroxy-1-methyl-4-(2-pyridyl)-4*H*-*s*-triazolo[4,3-*a*]indole, **15d**, and 3-Methyl-4-[2-(2-pyridoyl)phenyl]-1,2,4-triazole, **3d**.

A mixture of 25.4 g. (0.1 mole) of **2d** and 250 ml. of formic acid was heated to reflux for 4 hours. The formic acid was removed under reduced pressure, at the end azeotropically with xylene. Crystallization of the residue from methylene chloride yielded 10.4 g. (39.5%) of **15d** with m.p. 271-273°. For analysis it was recrystallized from chloroform/methanol, m.p. 278-280°; uv: λ max 211 mμ (ε = 35,700), max 249 (8,050), infl 266 (3,800), sh 295 (625); nmr (d-DMSO): δ 2.68 ppm (s, 3, CH_3) 7.0-8.3 (m, 9, aromatic H and OH).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.4; H, 4.2; N, 21.3. Found: C, 68.2; H, 4.5; N, 20.9.

The methylene chloride soluble portion of the product was crystallized from ether to yield 12.9 g. (45%) of **3d**. For analysis it was recrystallized from methylene chloride/hexane, m.p. 150-152°; uv: λ max 239 mμ (ε = 9,220), 269 (7,790); ir (chloroform): 1680 cm^{-1} (CO); nmr (d-DMSO): δ 2.24 ppm (s, 3, CH_3) 7.4-8.1 (m, 7, aromatic H), 8.34 (s, 1, triazole-H) 8.58 (m, 1, pyridyl-H).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.4; H, 4.2; N, 21.3. Found: C, 68.2; H, 4.5; N, 21.3.

6-Bromo-4-hydroxy-1-methyl-4-(2-pyridyl)-4*H*-*s*-triazolo[4,3-*a*]-indole, **15e** and 4-[4-Bromo-2-(2-pyridoyl)phenyl]-3-methyl-1,2,4-triazole, **3e**.

Similarly, refluxing 100 g. (0.3 mole) of **2e** in 1 l. of formic acid for 4 hours yielded 47.4 g. (46%) of **15e** which was recrystallized for analysis from chloroform/methanol, m.p. 265-267°.

Anal. Calcd. for $C_{15}H_{11}BrN_4O$: C, 52.5; H, 3.2; N, 16.3. Found: C, 52.4; H, 3.3; N, 16.7.

Crystallization of the evaporated mother liquor from ether gave 45 g. (43.5%) of **3e** which was recrystallized from methylene chloride/ether, m.p. 168-170°.

Anal. Calcd. for $C_{15}H_{11}BrN_4O$: C, 52.5; H, 3.2; N, 16.3. Found: C, 52.4; H, 3.2; N, 16.3.

Ethyl [6-Chloro-1-methyl-4-phenyl-4*H*-*s*-triazolo[4,3-*a*]indolyl-4-oxy]acetate, **16** and [6-Chloro-1-methyl-4-phenyl-4*H*-*s*-triazolo-[4,3-*a*]indolyl-4-oxy]acetic Acid, **17**.

Potassium *t*-butoxide, 22.4 g. (0.2 mole) was added to a suspension of 40 g. (0.135 mole) of **15b** in 800 ml. of dry tetrahydrofuran. After stirring for 30 minutes at room temperature under nitrogen, 45.2 g. (0.27 mole) of ethyl bromoacetate was added and stirring was continued for 2 hours. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between water and methylene chloride. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ether with seeding yielded 15.1 g. (29%) of the ester **16** with m.p. 119-122°. Seeds were obtained by chromatographic purification. (silica gel, 5% (v/v) methanol in methylene chloride). The analytical sample was recrystallized from methylene chloride/-hexane, m.p. 120-122°; uv: λ infl 230 mμ (ε = 18,600), max 254 (9,750), infl 264 (7,000), infl 285 (1,100), infl 299 (700); ir (chloroform): 1750 cm^{-1} (COOEt); nmr (deuteriochloroform): δ 1.2 ppm (t, 3, J = 7 Hz, $-CH_2CH_3$) 2.77 (s, 3, CH_3) 4.15 (q, 2, J = 7 Hz, $-OCH_2-CH_3$) 4.3 (AB-system, J = 15 Hz, $-OCH_2-$) 7.3-7.7 (m, 8, aromatic H).

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.6; H, 4.7; N, 10.9. Found: C, 62.5; H, 4.6; N, 10.8.

The mother liquors were combined and evaporated and dissolved in 125 ml. of ethanol. A solution of 8 g. (0.2 mole) of sodium hydroxide in 20 ml. of water was added and the mixture was heated to reflux for 2 hours, diluted with water and extracted with ether. The aqueous phase was acidified with acetic acid and extracted with methylene chloride. The extracts were dried and evaporated. The residue was crystallized from methylene chloride/-ethanol to yield 8.9 g. (18.5%) of acid **17** which after recrystallization from the same solvents had m.p. 256-258°; uv: λ max 209 mμ (ε = 31,700), infl 230 (17,600), max 255 (9,750), infl 265 (7,400), max 286 (1,120), sh 296 (800); nmr (d-DMSO): δ 2.74 ppm (s, 3, CH_3) 4.0 (s, 2, OCH_2) 7.3-7.8 (m, 8, aromatic H).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_3$: C, 60.8; H, 4.0; N, 11.8. Found: C, 60.6; H, 3.9; N, 12.0.

6-Chloro-4-(2-dimethylaminoethoxy)-1-methyl-4-phenyl-4*H*-*s*-triazolo[4,3-*a*]indole, **18**.

A mixture of 11.9 g. (0.04 mole) of **15b**, 6.7 g. (0.06 mole) of potassium *t*-butoxide and 200 ml. of dry dimethylformamide was stirred at room temperature for 30 minutes. A solution of 2-dimethylaminoethylchloride in 50 ml. of toluene (liberated with sodiumhydroxide from 11.5 g. (0.08 mole) of its hydrochloride) was added and the reaction mixture was heated on the steam bath for 3 hours. It was then diluted with water and extracted with methylene chloride. The methylene chloride layer was washed with water and extracted with 3 *N* hydrochloric acid. The extracts were made alkaline with ammonia and the precipitated base was extracted with ether. The ether extracts were dried and evaporated. Crystallization of the residue from ether yielded 8.7 g. (58%) of product with m.p. 130-132°. The analytical sample was recrystallized from ether and had m.p. 133-135°; nmr (deuteriochloroform): δ 2.23 ppm, (s, 6, $N(CH_3)_2$) 2.55 (t, 2, J = 5.5 Hz, $-CH_2-N$) 2.78 (s, 3, CH_3) 3.63 (m, 2, OCH_2) 7.1-7.6 (m, 8, aromatic H).

Anal. Calcd. for $C_{20}H_{21}ClN_4O$: C, 65.1; H, 5.7; N, 15.2. Found: C, 65.1; H, 5.7; N, 15.3.

6-Chloro-4-(2-diethylaminoethoxy)-1-methyl-4-phenyl-4*H*-*s*-triazolo[4,3-*a*]indole, **19**.

Alkylation of 11.9 g. (0.04 mole) of **15b** with 6.72 g. (0.06 mole) of potassium *t*-butoxide and 21.8 ml. of a 3.68 *M* solution of 2-diethylaminoethylchloride in toluene in 200 ml. of dimethylformamide at room temperature for 2 hours yielded after the same workup and crystallization from ether 9.1 g. (58%) of **19** with m.p. 100-104°. The analytical sample was recrystallized from ether, m.p. 107-109°.

Anal. Calcd. for $C_{22}H_{25}ClN_4O$: C, 66.6; H, 6.4; N, 14.1. Found: C, 66.7; H, 6.4; N, 14.2.

Ethyl 2-[2-Acetyl-8-chloro-2,3,4,10-tetrahydro-4-oxo-10-phenyl-*as*-triazino[4,3-*b*]indol-10-yloxy]acetate, **21**.

A mixture of 3.84 g. (0.01 mole) of **16**, 3.34 g. (0.02 mole) of ethyl bromoacetate and 200 ml. of toluene was heated to reflux for 18 hours. The cool solution was shaken with 50 ml. of 3 *N* sodium hydroxide solution, dried and evaporated. Crystallization of the residue from ethanol yeilded 2.75 g. (62%) of colorless crystals with m.p. 154-157°. The product was recrystallized for analysis from methylene chloride/ethanol, m.p. 156-158°; uv: λ infl 220 mμ (ε = 26,600), max 261 (26,000), 306 (3,070); ir (chloroform): 1755, 1720, 1700, 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.21 ppm (t, 3, J = 7 Hz, CH_2CH_3) 2.23 (s, 3, $COCH_3$) 4.15 (s, 2, CH_2) 4.15 (q, 2, J = 7 Hz, OCH_2CH_3) 4.54

(AB-system, 2, J = 18 Hz, CH_2) 7.2-7.6 (m, 7, aromatic H) 8.15 (d, 1, J = 8 Hz, C_6-H); MS: m/e 441 (M+) 338, 296, 240, 215, 190, 43.

Anal. Calcd. for $C_{22}H_{20}ClN_3O_5$: C, 59.8; H, 4.6; N, 9.5; Cl, 8.0. Found: C, 59.8; H, 4.7; N, 9.5; Cl, 7.9.

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