Novel Synthesis of the Pharmacologically Important 1-Substituted-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines

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Several 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines have useful biological activity both in experimental animals and in man. This manuscript describes a novel synthesis of these compounds from intermediates that do not have a pre-formed benzodiazepine ring system.

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A variety of 1-substituted-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines have been found to have interesting pharmacological activity in laboratory animals (1-3). Alprazolam (**1**) and triazolam (**2**) respectively have also been shown to have useful anxiolytic (4) and hypnotic (5) activity in man. Most of these compounds were initially prepared from starting materials that had a pre-formed benzodiazepine ring system, however, it soon became apparent that a new synthesis beginning with acyclic precursors would be desirable. This manuscript describes such a synthesis.

Conceptually the triazoloquinoline **8** seemed to be a suitable precursor to the triazolobenzodiazepine **1** since it required only the insertion of a nitrogen between carbons 4 and 5 to achieve the conversion. We reasoned that the 4,5 double bond, lying between the relatively stable benzene and triazole ring systems should be susceptible to reactions that might lead to this conversion. We thus prepared **8** by the reaction of **9** with triethyl orthoacetate and studied its chemistry. Oxidation of **8** was accomplished with ozone, potassium permanganate-sodium periodate and ruthenium dioxide-sodium periodate. The triazolobenzophenone **10**, obtained in 72% yield, was the only product of the potassium permanganate reaction (6). With the ruthenium dioxide system the aldehyde (**11**) was obtained in addition to **10**. Crystalline **11** was isolated as a methanol solvate which appeared to exist as a hemiacetal; the ir (Nujol) spectrum of this material had only a weak shoulder at 1700 cm^{-1} for the aldehyde carbonyl. In chloroform solution, however, the aldehyde was present as shown by a singlet at δ 9.75 in the nmr spectrum for the proton on the aldehyde carbon. Silver oxide oxidation of **11** gave **10** in 60% yield. The apparent facile decarboxylation of the carboxylic acid expected from this reaction suggests that the aldehyde **11** is a likely intermediate in the oxidative formation of **10** from **8**. Further characterization of **11** was achieved by the preparation of the oxime **12** and *O*-acetyloxime **13** (7) both of which retained the benzophenone carbonyl band at 1660 cm^{-1} in the ir spectrum. Oxidation of **8** with ozone gave in addition to **10** and **11**, a third product which has been tentatively assigned structure **28** based on the physical and analytical data. Conversion of the key intermediate **10** to the benzodiazepine **1** was straight forward when we discovered that **10** could be hydroxymethylated with formaldehyde. Precedent for this reaction was supplied by Jones and Ainsworth (8) who obtained a hydroxymethyl derivative by heating 1-benzyl-1,2,4-triazole with formalin at 130-140°. At about 125° in xylene, paraformaldehyde depolymerizes to the gaseous monomer which at this temperature readily reacts with the unsubstituted triazole ring. Under these conditions **14** was obtained from **10** in 73% yield (7). The synthesis was completed by the conversion of **14** to **15** with phosphorus tribromide and the reaction of **15** with ammonia to give **1**. Alternatively the reaction of alcohol **14** with phthalimide, triphenylphosphine and diethyl azodicarboxylate (9) gave the phthalimide **16** which when allowed to react with hydrazine gave **1**.

The discovery by Derieg and coworkers (10) that the aminoquinazoline **29** could be converted to the triazolobenzophenone **20** with refluxing formic acid has been utilized by Meguro, *et al.*, (11) and by Walser, *et al.* (12) to prepare substituted 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepines. We have extended this chemistry to the preparation of **2** from **31** *via* the intermediates **17**,**18**, and **19**. We were, however, particularly intrigued by the possibility of preparing the phthalimide **21** from **29** since such an intermediate could potentially be used for the preparation of a wide variety of 1-substituted-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines. This was accomplished in two steps by acylating **29** with two equivalents of α-phthalimidoacetyl chloride to give **32** (13) and cyclizing **32** with trifluoroacetic acid in toluene to give **21** in 48% overall yield. Hydroxymethylation of **21** with paraformaldehyde in xylene gave **22** which was treated with hydrazine hydrate to give **3** (3,14) a major metabolite of alprazolam (**1**) in man (15). Bromination of **21** with *N*-bromosuccinimide in benzene gave **23** in 78% yield. Hydrazinolysis of **23** gave the benzodiazepine **4** (16) which is a useful intermediate for the preparation

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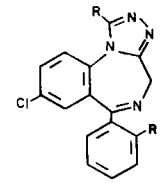
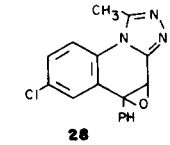
of the 1-amino-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (3) and the 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones (17). The Mannich reaction of **21** in DMF with dimethylmethyleneammonium chloride (18), prepared *in situ* by the reaction of *N,N,N',N'*-tetramethyldiaminomethane with one equivalent of acetyl chloride, gave **24** in 85% yield. Conversion of **24** to the pharmacologically important benzodiazepine **5** (2) was accomplished with either hydrazine or methylamine. Alternatively **5** was prepared from the unsubstituted triazolylbenzophenone **20** by bishydroxymethylation to give **26** which was converted *via* the diphthalimide **27** to the benzodiazepine **6**. Reductive methylation of **6** to give **5** was accomplished with formaldehyde and sodium cyanoborohydride (19) under slightly acidic conditions. The latter reaction deserves special note for two reasons. First, it documents the great selectivity of sodium cyanoborohydride as a reducing agent; reductive alkylation of the primary amine was accomplished under conditions that would not reduce the weakly basic N-5, C-6 double bond of the benzodiazepine system. Second, the rather stable boron-nitrogen complexes that can result from the interactions of cyanoborohydride or diborane with compounds such as **5** can be effectively hydrolyzed with aqueous ethylenediamine by the procedure described here.

Finally the pharmacologically important benzodiazepine **7** (2) was prepared in two steps from the phthalimide **16**. Thus the reaction of **16** with dimethylmethyleneammonium chloride in DMF at 0° in the presence of

SCHEME I



1, R = CH_3; R' = H
2, R = CH_3; R' = Cl
3, R = CH_2OH; R' = H
4, R = BR; R' = H
5, R = $CH_2N(CH_3)_2$; R' = H
6, R = CH_2NH_2; R' = H
7, R = $(CH_2)_2N(CH_3)_2$; R' = H



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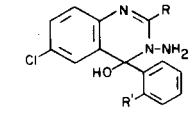
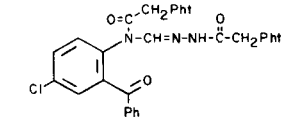


29, R = R' = H
30, R = CH_3; R' = H
31, R = CH_3; R' = Cl



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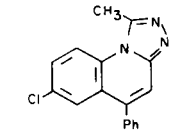
Pht = Phthalimide



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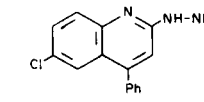

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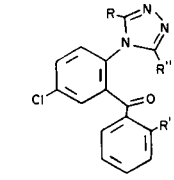

10, R = CH_3; R' = R'' = H
11, R = CH_3; R' = H; R'' = CHO
12, R = CH_3; R' = H; R'' = CHNOH
13, R = CH_3; R' = H; R'' = CHNOAc
14, R = CH_3; R' = H; R'' = CH_2OH
15, R = CH_3; R' = H; R'' = CH_2Br
16, R = CH_3; R' = H; R'' = CH_2Pht
17, R = CH_3; R' = Cl; R'' = H
18, R = CH_3; R' = Cl; R'' = CH_2OH
19, R = CH_3; R' = Cl; R'' = CH_2Pht
20, R = R' = R'' = H
21, R = R' = H; R'' = CH_2Pht
22, R = CH_2OH; R' = H; R'' = CH_2Pht
23, R = Br; R' = H; R'' = CH_2Pht
24, R = $CH_2N(CH_3)_2$; R' = H; R'' = CH_2Pht
25, R = $(CH_2)_2N(CH_3)_2$; R' = H; R'' = CH_2Pht
26, R = R'' = CH_2OH; R' = H
27, R = R'' = CH_2Pht; R' = H

Table I

Experimental Data for the 6-Phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (e)

Compound	Procedure	Starting Material	Yield %	M.p., °C	Recrystallization Solvent	Ref. (f)
1	B (b)	16	59	229-230	Ethyl acetate	1
	C	15	83.3	226-227	Dichloromethane-ether	
2	B (d)	19	94	226-228	Methanol-ethyl acetate	1
3	B (a)	22	69.8	209-211	Ethyl acetate	3
4	B (a)	23	52.8	205.5-206, dec.	Ethyl acetate	3
5	B (a)	24	63.1	171.5-174	Ethyl acetate-Skelly B	2
	A	24	70.2	171-173.5	Ethyl acetate-Skelly B	
	D	6	64.3	170.5-173	Ethyl acetate-Skelly B	
6	A (c)	27	30.5	166.5-168.5	Dichloromethane-ethyl acetate	2
7	A	25	44.4	198-199	Ethanol	2
	B	25	44.4	197-198	Ethanol	

(a) Isolated without chromatography. (b) Chromatographed on silica gel with 2% methanol-98% chloroform. (c) Chromatographed on silica gel with 5% methanol-95% chloroform. (d) Chromatographed on silica gel with 3% methanol-97% chloroform. (e) These compounds were identical by direct comparison to authentic samples prepared by other methods. (f) Literature reference.

Table II

Analytical Data

Compound No.	Formula	C	H	Cl	N	X	
8	$C_{17}H_{12}ClN_3$	69.50 69.38	4.12 4.02	12.07 12.10	14.31 14.49		
9	$C_{15}H_{12}ClN_3$	66.79 67.15	4.49 4.65	13.15 13.19	15.58 15.32		
10	$C_{16}H_{12}ClN_3O$	64.54 64.56	4.06 4.35	11.91 11.93	14.11 14.29		
16	$C_{25}H_{17}ClN_4O_3$	65.72 65.86	3.75 3.83	7.76 7.72	12.26 12.63		
19	$C_{24}H_{16}Cl_2N_4O_3$	61.11 60.77	3.28 3.26	14.43 14.49	11.40 11.45		
21	$C_{24}H_{15}ClN_4O_3$	65.09 65.01	3.41 3.67	8.00 8.01	12.65 12.84		
22	$C_{25}H_{17}ClN_4O_4$	63.50 63.30	3.62 3.90	7.50 7.43	11.85 11.92		
23	$C_{24}H_{14}BrClN_4O_3$	55.25 55.15	2.70 2.59	6.79 6.78	10.74 10.91	Br	15.32 15.40
24	$C_{27}H_{22}ClN_5O_3$	64.87 64.51	4.44 4.59	7.09 7.17	14.01 13.90		
27	$C_{33}H_{20}ClN_5O_5$	65.84 66.02	3.35 3.34	5.89 5.95	11.63 11.62		
28	$C_{17}H_{12}ClN_3O$	65.92 65.46	3.91 3.72	11.44 11.48	13.57 13.59		
31	$C_{15}H_{13}Cl_2N_3O$	55.92 55.88	4.07 4.38	22.01 22.34	13.04 12.67		
32	$C_{34}H_{22}ClN_5O_7$	63.02 63.10	3.42 3.59	5.47 5.50	10.81 10.97		

acetyl chloride as a catalyst gave **25** in 65% yield (20). Conversion of **25** to **7** was accomplished with either hydrazine or methylamine.

EXPERIMENTAL

Chemistry.

Melting points taken in a capillary tube, are corrected. The structures of all compounds were supported by ir, uv and nmr spectra. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer, uv spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model A60-A or XL 100 spectrometer; chemical shifts were recorded in ppm downfield from TMS. Mass spectra were obtained with a Varian MAT CH7 or LKB spectrometer. The analytical results obtained were within ± 0.4% of the theoretical values if not otherwise stated. The silica gel used for chromatography was obtained from E. Merck A. G., Darmstadt, Germany. Skellysolve B (Sk B) is a commercial hexane, b.p. 60-70°, made by Skelly Oil Co., Kansas City, MO.

8-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *p*-Toluenesulfonate (**7**). Procedure A.

A stirred solution of **25** (1.03 g., 0.002 mole) in absolute ethanol (10 ml.) and dichloromethane (10 ml.) was treated with 40% aqueous methylamine (1.56 ml.) and kept under nitrogen, at ambient temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue was mixed with absolute ethanol and again concentrated. The residue was chromatographed on silica gel with methanol. The oily product which resulted amounted to 0.467 g.; it was dissolved in ethanol and treated with one equivalent of *p*-toluenesulfonic acid in ethanol. The salt was crystallized to give **7**.

8-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *p*-Toluenesulfonate (**7**). Procedure B.

A stirred mixture of **25** (1.03 g., 0.002 mole) in absolute ethanol (10 ml.) was treated with hydrazine hydrate (0.117 ml., 0.0024 mole) and kept at ambient temperature, under nitrogen for 2.5 hours. The resulting solution was warmed to 63° and kept for about 3 hours. The mixture was cooled and filtered; the solid was washed with dichloromethane and ethanol, and the combined filtrates were concentrated under reduced pressure. The residue was chromatographed on silica gel (50 g.) with methanol. The product which amounted to 0.458 g. was dissolved in ethanol and acidified with one equivalent to *p*-toluenesulfonic acid in ethanol. The salt was crystallized to give **7**.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**1**) from **15**. Procedure C.

A solution of **15** (7) (782 mg., 0.002 mole) in dichloromethane (10 ml.) was cooled in a Dry Ice-methanol bath and treated with about 10 ml. of anhydrous ammonia. The mixture was allowed to reflux for 5 hours. A slow stream of nitrogen was then passed through the flask for 18 hours to evaporate the ammonia and dichloromethane. The residue was mixed with ice water and extracted with dichloromethane. The extract was washed with water, dried (calcium chloride) and concentrated *in vacuo*. The residue was dissolved in a small amount of dichloromethane and diluted with ether to give **1**. The ir (Nujol) spectrum of this material was identical to that of an authentic sample (1).

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

A stirred suspension of **6** (0.647 g., 0.002 mole) and acetonitrile (8 ml.), under nitrogen, was treated successively with 37% formalin (1 ml.) and sodium cyanoborohydride (250 mg.). This mixture was treated periodically, dropwise, during 1 hour 45 minutes with 1.6 ml. of a solution of 0.2 ml. of acetic acid in acetonitrile (2 ml.). (The addition was continued until no exotherm was noted and the *p*H of the mixture was 6.4-6.8). The mixture was kept at ambient temperature for an additional 15 minutes and concentrated *in vacuo*. The residue was mixed with methanol (20 ml.) and 25% aqueous ethylenediamine (10 ml.) and refluxed for 45 minutes. The mixture was diluted with cold water, saturated with sodium chloride and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and concentrated *in vacuo*. The residue was chromatographed on silica gel (75 g.) with 2% methanol-98% chloroform. The product thus obtained was crystallized from ethyl acetate-Skelly B to give **5**. The mixture melting point of this material with an authentic sample was undepressed.

7-Chloro-1-methyl-5-phenyl-*s*-triazolo[4,3-*a*]quinoline (**8**).

According to the method of Reynolds and Van Allan (21), a stirred mixture of **9** (1.4 g., 0.0052 mole), triethyl orthoacetate (0.925 g., 0.0057 mole) and xylene (100 ml.) was refluxed, under nitrogen for 2 hours 40 minutes. During this period ethanol formed in the reaction was removed by distillation through a short, glass-helix-packed column. The mixture was concentrated to dryness *in vacuo* and the residue was crystallized from methanol-ethyl acetate to give 1.02 g., m.p. 253.5-255° and 0.26 g., m.p. 253.5-255° (83.9% yield) of **8**. The analytical sample was crystallized from dichloromethane-methanol and had m.p. 252.5-253°; uv (ethanol): end absorption, λ max 232 mμ (ε 37,950), 303 (9250), 313 (8700), 327 (6050), inflections 225 (36,150), 238 (34,950), 250 (20,350); nmr (deuteriochloroform): δ 3.17 (s, 3, C*H*$_3$).

Oxidation of **8** with Potassium Permanganate and Sodium Periodate.

A stirred suspension of **8** (2.94 g., 0.01 mole) in acetone (120 ml.), under nitrogen, was treated with a solution of potassium carbonate (2.76 g., 0.02 mole) in water (10 ml.). To this mixture was added, portionwise, a solution prepared by mixing a solution of sodium periodate (16 g.) in water (100 ml.) with a solution of potassium permanganate (0.62 g.) in water (10 ml.); 25 ml. portions of this solution were added at the start of the reaction and after 2 hours 20 minutes and 4 hours 40 minutes. The remaining oxidant was added after 21 hours 40 minutes and the reaction was allowed to proceed for an additional 3 days. The mixture was then treated with 2-propanol (10 ml.), stirred for several hours and concentrated *in vacuo* to remove acetone. The resulting aqueous suspension was filtered through Celite. The solid and aqueous filtrate were extracted with dichloromethane. The extract was washed with a dilute sodium chloride solution, dried (potassium carbonate) and concentrated. The residue was crystallized from methanol-ethyl acetate to give 0.054 g. of recovered **8**, m.p. 255-257°. The mother liquor was concentrated and crystallized from ethyl acetate to give 0.208 g. of **10**, m.p. 170-172°.

The solid and aqueous filtrate were combined, cooled in an ice bath and acidified with dilute hydrochloric acid to about *p*H 3. The *p*H was adjusted to 4-5 with sodium bicarbonate and the mixture was filtered. The solid and aqueous filtrate were extracted thoroughly with dichloromethane. The extract was washed with a dilute sodium chloride solution, dried (sodium sulfate) and concentrated. Crystallization of the residue gave in two crops 1.939 g. (72.1% yield) of **10**, m.p. 170-172°.

Oxidation of **8** with Ruthenium Oxide and Sodium Periodate.

A stirred suspension of **8** (2.94 g., 0.01 mole) and acetone (200 ml.) was cooled in an ice bath and treated, dropwise, during 15 minutes with a solution prepared from ruthenium dioxide (200 mg.), sodium periodate (4 g.) and water (35 ml.). A slight exothermic reaction was noted and the mixture became dark. After 10 minutes, 29 ml. of a solution of sodium periodate (12 g.) in water (70 ml.) was added during 10 minutes. This mixture was stirred for 2 hours and then the remaining sodium periodate solution (41 ml.) was added during the next 3 hours. The mixture was allowed to remain at 4° for 18 hours. The excess sodium periodate was then decomposed by the successive addition of sodium iodide and sodium thiosulfate to the reaction mixture. This mixture was concentrated *in vacuo* to remove acetone. The resulting aqueous mixture was extracted with dichloromethane. The extract was washed with water, dried (magnesium sulfate) and concentrated. The residue was chromatographed on silica gel (150 g.) with 2% methanol-98% chloroform. Recovered starting material was eluted first and crystallized from dichloromethane-methanol to give 0.069 g., m.p. 251.5-253.5°. A mixture of the two products was eluted next. Crystallization of this mixture from ethyl acetate gave 618 mg. (20.8%) of 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**10**), m.p. 165.5-168°. The analytical sample had m.p. 168° [lit. m.p. 168-170° (11); 168.5-169.5° (7)].

Crystallization of the mother liquor from methanol gave 0.126 g., m.p. 108-112° dec., and 0.588 g., m.p. 101.5-105.5° dec. (18% yield) of a methanol solvate of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldehyde (**11**). The analytical sample was dried at ambient temperature and had m.p. 109-112.5° dec.; uv (ethanol): λ max 253 nm (ε 14,560), inflection 211 (29,760), 286 (3,360); ir (Nujol): 3340, 3220 cm^{-1} (OH), 1700 (w sh), 1665 (C=O), 1595, 1580, 1570, 1535 (C=C/C=N); nmr (deuteriochloroform): δ 2.40 (s, 3, C*H*$_3$), 9.75 (s, 1, C*H*O); ms: m/e (relative intensity) 325 (308), 296 (665), 268 (278), 255 (280), 220 (379).

Anal. Calcd. for $C_{17}H_{12}ClN_3O_2 \cdot 2CH_3OH$: C, 58.54; H, 5.17; Cl, 9.09; N, 10.78; CH_3OH, 16.44. Found: C, 58.30; H, 4.89; Cl, 9.27; N, 11.04; CH_3OH, 15.4; H_2O, 2.06.

Oxidation of **8** with Ozone.

A vigorous stream of ozone in oxygen was bubbled for 12 hours into a stirred, ice-cold solution of **8** (31.1 g., 0.106 mole) in methanol (750 ml.) and dichloromethane (500 ml.). The resulting mixture was filtered and the filtrate was added to an

ice cold solution of sodium iodide (47.5 g.) and acetic acid (63 ml.) in water (200 ml.). The solution was decolorized by the addition of sodium thiosulfate and concentrated *in vacuo*. The residue was mixed with water and extracted with dichloromethane. The extract was washed (water), dried (magnesium sulfate) and concentrated. The residue was chromatographed on silica gel (1.5 kg.) with mixtures of methanol in chloroform containing 1-5% methanol. The first product eluted from the column was crystallized from methanol-ethyl acetate to give 0.769 g., m.p. 229.5-231° dec., and 0.535 g., m.p. 228° dec. (4% yield) of **28**. The analytical sample had m.p. 232-233°; uv (ethanol): λ max 210 nm (ε 37,600), 251 (16,300), 293 (579), inflections 243 (15,500), 281 (1068); ir (Nujol): 3120, 3060, 3020, 1605, 1585, 1555, 1525, 1500, 1485, 1315, 1170, 935, 885, 845, 835, 825, 740, 700 cm^{-1}; nmr (deuteriochloroform): δ 2.94 (s, 3, CH_3), 4.60 (s, 1, C-4*H*); ms: m/e 309 (M^+), 308, 293, 281.

Recovered starting material (**8**) was next eluted and crystallized from dichloromethane-methanol to give 0.737 g., m.p. 251-253.5°. A mixture of the two remaining products was finally eluted. Crystallization of this mixture from ethyl acetate gave 10.8 g., m.p. 166.5-167.5°, 0.987 g., m.p. 166-167° and 2.52 g., m.p. 164-165.5° (45.3% yield) of **10**. Crystallization of the mother liquor from methanol gave 5.62 g., m.p. 140-141.5°, 1.23 g., m.p. 100.5-102.5° dec., and 1.04 g., m.p. 105-137.5° (20.8% yield) of **11**.

6-Chloro-2-hydrazino-4-phenylquinoline (**9**).

According to the method of Perkin and Robinson (22) a stirred mixture of 2,6-dichloro-4-phenylquinoline (23) (2.7 g., 0.01 mole) and hydrazine hydrate (6.8 g.) was refluxed under nitrogen for 1 hour and concentrated *in vacuo*. The residue was suspended in warm water, and the solid was collected by filtration, dried and recrystallized from ethyl acetate-Skelly B to give 1.81 g., m.p. 156.5-157.5° and 0.20 g., m.p. 152-155° (74.5% yield) of **9**. The analytical sample had m.p. 156.5-157°; uv (ethanol): λ max 219 nm (ε 34,500), 249 (37,750), 354 (5100), inflection 275 (13,250).

5-Chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**10**) from **11**.

A stirred solution of silver nitrate (0.357 g., 0.0021 mole) in water (1.8 ml.) was treated with 1*N* sodium hydroxide (4.1 ml.). To the resulting stirred suspension of silver oxide was added a warm solution of **11** (326 mg.) in methanol (15 ml.), and the resulting mixture was stirred under nitrogen, at ambient temperature for 18 hours. The solid was collected by filtration and washed with water and methanol. The filtrate was concentrated *in vacuo* to remove methanol, and the resulting aqueous solution was cooled in an ice bath, neutralized with hydrochloric acid and extracted with chloroform. The extract was washed with brine, dried (magnesium sulfate) and concentrated. The residue was crystallized from ethyl acetate to give 0.162 g. (59.7%) of **10** m.p. 169.5-171°. The mixture melting point with the authentic sample was undepressed. It was identical to the authentic sample by ir and uv comparison.

N-[[4-(2-Benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazol-3-yl]-methyl]phthalimide (**16**).

A stirred mixture of **14** (7) (0.656 g., 0.002 mole), phthalimide (0.325 g., 0.0022 mole), triphenylphosphine (0.576 g., 0.0022 mole) and dry THF (20 ml.) under nitrogen, was treated with diethyl azodicarboxylate (0.383 g., 0.0022 mole) and stirred at ambient temperature for 23 hours. It was concentrated *in vacuo* and the residue was chromatographed on silica gel (75 g.) with 1.5% methanol-98.5% chloroform. The product thus obtained was crystallized from methanol-ethyl acetate to give in four crops 0.676 g. (74%) of **16**, m.p. 217.5-220.5°. The analytical sample had m.p. 219-221°; uv (ethanol); λ max 219 nm (ε 65,150), 256 (14,750), inflections 238 (16,750), 285 (5300); ir (Nujol): 1770, 1720, 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.16 (s, 3, CH_3), 4.75 (q, 2, J = 16 Hz, CH_2).

2',5-Dichloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**17**).

A stirred solution of **31** (1.0 g., 0.0031 mole) and 97% formic acid (10 ml.) was heated to 110° for 5 hours, under nitrogen, and then kept at ambient temperature for 18 hours. The solution was mixed with water, neutralized with sodium bicarbonate and extracted with dichloromethane. The extract was washed with water, dried (sodium sulfate), and the residue chromatographed on silica gel (75 g.) with 5% methanol-chloroform. The product thus obtained was crystallized from chloroform-ethyl acetate-Skelly B to give 0.56 g., m.p. 156-159° and 0.06 g., m.p. 148-154° (59% yield) of **17** (lit. (7) m.p. 155.5-157.5°). The mixture melting point of this material with an authentic sample was not depressed.

N-[[4-[4-Chloro-2-(2-chlorobenzoyl)phenyl]-5-methyl-4*H*-1,2,4-triazol-3-yl]methyl]phthalimide (**19**).

This material was prepared from **18** (7) in 81% yield by the procedure described for compound **16**. It was crystallized from methanol-ethyl acetate, m.p. 262-265°.

N-[[4-(2-Benzoyl-4-chlorophenyl)-4*H*-1,2,4-triazol-3-yl]methyl]-phthalimide (**21**).

A stirred mixture of **32** (8.0 g., 0.0123 mole) and toluene (200 ml.) was treated with trifluoroacetic acid (0.9 ml.) and heated to 100-110° for 1.5 hours. It was concentrated *in vacuo*, and the residue was mixed with cold water and chloroform and made alkaline with sodium hydroxide. This mixture was extracted with chloroform; the extract was washed with brine, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel (400 g.) with 1.5% methanol-98.5% chloroform. The product thus obtained was crystallized from dichloromethane-methanol to give 2.54 g., m.p. 228-228.5° and 0.361 g., m.p. 229-230° (53% yield) of **21**. The analytical sample had m.p. 229.5-230.5°; uv (ethanol): λ max 218 nm (ε 67,300); 256 (14,750), inflections 238 (17,400), 285 (5,250); ir (Nujol): 1770, 1720, 1665 cm^{-1} (C=O), 1615, 1595, 1580, 1565, 1530, 1495 (C=C/C=N); nmr (deuteriochloroform): δ 4.83 (s, 2, CH_2).

N-[[4-(2-Benzoyl-4-chlorophenyl)-5-(hydroxymethyl)-4*H*-1,2,4-triazol-3-yl]methyl]phthalimide (**22**).

A stirred suspension of **21** (4.429 g., 0.01 mole) and paraformaldehyde (3.0 g.) in xylene (100 ml.) was warmed, under nitrogen in an oil bath at 120-123° for 50 minutes. Additional paraformaldehyde (1 g.) was added and heating was continued for an additional 45 minutes. The mixture was concentrated and the residue was dissolved in dichloromethane and filtered to remove residual paraformaldehyde. The filtrate was concentrated and the residue chromatographed on silica gel (200 g.) with mixtures of chloroform and methanol containing from 1.5 to 5% methanol. The product thus obtained was crystallized from dichloromethane-methanol to give 4.25 g. (90%) of **22**, m.p. 229.5-231°. The analytical sample had m.p. 229.5-230.5°; uv (ethanol): λ max 218 nm (ε 67,400), 255 (14,850), inflections

238 (16,550), 285 (5700); ir (Nujol): 3530 cm^{-1} (OH), 1770, 1710, 1665 (C=O).

N-[[4-(2-Benzoyl-4-chlorophenyl)-5-bromo-4*H*-1,2,4-triazol-3-yl]-methyl]phthalimide (**23**).

A stirred mixture of **21** (4.429 g., 0.01 mole), *N*-bromosuccinimide (2.31 g., 0.013 mole) and benzene (250 ml.) was refluxed under nitrogen for 7 hours and kept at ambient temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue was mixed with water and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and concentrated. The residue was crystallized from dichloromethane-methanol (Darco) to give 3.00 g., m.p. 201.5-203.5° and 1.05 g., m.p. 201.5-202.5° (77.6% yield) of **23**. The analytical sample had m.p. 204-205°; uv (ethanol): λ max 218 nm (ε 69,750), 257 (14,650), inflections 237 (17,350), 287 (5,350); ir (Nujol): 1770, 1720, 1670, 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.59, 5.20 (d, 1, J = 16 Hz; d, 1, J = 16 Hz, CH_2).

N-[[4-(2-Benzoyl-4-chlorophenyl)-5-(dimethylamino)methyl-4*H*-1,2,4-triazol-3-yl]methyl]phthalimide (**24**).

A stirred solution of *N,N,N',N'*-tetramethyldiaminomethane (1.531 g., 0.015 mole) in dry DMF (45 ml.) was cooled in an ice bath, under nitrogen, and treated dropwise with freshly distilled acetyl chloride (1.06 ml., 0.015 mole). The resulting suspension was allowed to warm to 25° and stand for about 2 hours. Compound **21** (4.429 g., 0.01 mole) was added and the resulting mixture was kept at 50-54° for 25 hours. It was then cooled and poured into cold water. The resulting solution was neutralized with sodium bicarbonate. The product which precipitated was collected by filtration, washed with water and dissolved in dichloromethane. The dichloromethane solution was washed with water and brine, dried (sodium sulfate) and concentrated. The residue was crystallized from dichloromethane-methanol (Darco) to give 4.02 g., m.p. 206-207.5° and 0.224 g., m.p. 206-208.5° (84.9% yield) of **24**. The analytical sample had m.p. 206.5-208.5°; uv (ethanol): end absorption, λ max 217 nm (ε 66,900), 256 (15,500), inflections 239 (18,550), 287 (5400); ir (Nujol): 1780, 1725, 1665 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.74 [s, 6, $N(CH_3)_2$], 3.32 [s, 2, $CH_2N(CH_3)_2$], 4.62, 5.26 (d, 1, J = 16 Hz; d, 1, J = 16 Hz, CH_2-phthalimide).

N-[[4-(2-Benzoyl-4-chlorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-1,2,4-triazol-3-yl]methyl]phthalimide (**25**).

A stirred solution of **16** (4.57 g., 0.01 mole) in dry DMF (50 ml.) was cooled in an ice bath, under nitrogen, and treated successively with *N,N,N',N'*-tetramethyldiaminomethane (1.229 g., 0.012 mole) and, dropwise, with acetyl chloride (0.923 ml., 0.013 mole). The mixture was kept in the ice bath for 5 hours and poured into a mixture of crushed ice and water. It was neutralized with saturated sodium bicarbonate and extracted with chloroform. The extracts were washed with dilute sodium chloride, dried (sodium sulfate) and concentrated *in vacuo*. The residue was chromatographed on silica gel (200 g.) with methanol. The product thus obtained was crystallized from 2-propanol to give 2.753 g., m.p. 145-152.5°; 0.245 g., m.p. 148.5-153°; 0.079 g., m.p. 148-154.5° and 0.251 g., m.p. 147-151.5° (64.8% yield) of **25** as an 2-propanol solvate. The analytical sample had m.p. 147-153° dec.; uv (ethanol): end absorption, λ max 218 nm (ε 61,900), 257 (14,150), inflections 238 (16,150), 288 (5,100); nmr (deuteriochloroform, 100 MHz): δ 2.18 (s, 6, $(CH_3)_2N$), 2.59 (m, 4, CH_2CH_2), 4.56, 5.07 (d, 1, J = 16 Hz; CH_2); ms: m/e (relative intensity) 513 (41.3), 512 (83.9), 160 (73.8), 58 (999.9).

Anal. Calcd. for $C_{28}H_{24}ClN_5O_3$: C, 65.48; H, 4.71; Cl, 6.90; N, 13.63. Found: C, 64.99; H, 5.20; Cl, 6.60; N, 12.61; 2-propanol, 4.14. Analytical data corrected for 2-propanol: C, 65.22; H, 4.85; Cl, 6.89; N, 13.15.

2-[3,5-Bis(hydroxymethyl)-4*H*-1,2,4-triazol-4-yl]-5-chlorobenzophenone (**26**).

A stirred mixture of **20** (10,11) (2.84 g., 0.01 mole), paraformaldehyde (3.0 g.) and xylene (100 ml.) was warmed, under nitrogen, in an oil bath at 118-124° for 1 hour 20 minutes, and concentrated *in vacuo*. The residue was dissolved in dichloromethane, filtered and crystallized from ethanol-ethyl acetate to give 0.916 g., m.p. 199-200.5°, 1.642 g., m.p. 200-200.5° and 0.452 g., m.p. 200.5-201.5° (87.6% yield) of **26** as an ethyl acetate solvate. The analytical sample had m.p. 201.5-202.5°; uv (ethanol): end absorption, λ max 255 nm (ε 12,950), inflections 212 (27,050), 285 (3,200); ir (Nujol): 3210 cm^{-1} (OH), 1735 (EtOAc), 1665, 1655 (C=O); nmr (perdeuteriodimethylformamide): δ 4.5 [AB q, 4, J = 13 Hz, $(CH_2\text{-}OH)_2$]; ms: m/e (relative intensity) 344 (91), 343 (96), 325 (418), 314 (456), 297 (270), 296 (969).

Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; Cl, 10.31; N, 12.22. Found: C, 59.49; H, 4.47; Cl, 9.76; N, 11.59; ethyl acetate, 6.07. Analytical data corrected for ethyl acetate: C, 59.83; H, 4.18; Cl, 10.39; N, 12.34.

N,N'-[[4-(2-Benzoyl-4-chlorophenyl)-4*H*-1,2,4-triazol-3,5-diyl]-dimethylene]diphthalimide (**27**).

A stirred mixture of **26** (2.06 g., 0.006 mole), phthalimide (1.94 g., 0.0132 mole), triphenylphosphine (3.455 g., 0.0132 mole), and dry THF (60 ml.), under nitrogen, was treated during 10 minutes with diethyl azodicarboxylate (2.295 g., 0.0132 mole). (A slight exotherm during the addition was moderated with an ice water bath.) The suspended solid dissolved; the solution was allowed to stand at ambient temperature for 18 hours. It was concentrated *in vacuo* and the residue was mixed with water and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel (200 g.) with 2% methanol-98% chloroform. The resulting product was crystallized from dichloromethane-methanol to give 0.935 g., m.p. 251.5-253.5°; 0.580 g., m.p. 250.5-252°; 0.872 g., m.p. 251-253° and 0.201 g., m.p. 250-251° (71.6% yield) of **27**. The analytical sample had m.p. 250.5-252.5°; ir (Nujol): 1775, 1720, 1670 cm^{-1} (C=O).

3-Amino-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxy-2-methylquinazoline (**31**).

According to the procedure of Kuwada, Meguro and Tawada (24) a stirred solution of 2-amino-2',5-dichlorobenzophenone (26.6 g., 0.1 mole) in benzene (200 ml.) was mixed with triethyl orthoacetate (27.5 ml., 0.15 mole) and acetic acid (12 ml.). The mixture was refluxed, under nitrogen, for 20 minutes and concentrated *in vacuo*. This residue was dissolved in absolute ethanol (300 ml.), treated with 15 ml. (0.3 mole) of hydrazine hydrate and 6 ml. of acetic acid and kept at ambient temperature for 17 hours. The solid which had begun to form soon after the addition of hydrazine hydrate was collected by filtration, washed with ethanol and dried *in vacuo* to give 28.7 g. of **31**, m.p. 225-229° dec. A sample of this material (1 g.) was suspended in a mixture of chloroform and dilute sodium bicarbonate and stirred for several hours. The solid was collected by filtration, washed with water and dried to give 0.946 g., m.p. 225-229° dec. which by ir was unchanged. This material was

recrystallized once from THF-chloroform for analysis, m.p. 220.5-223.5° dec.

1,3-Dioxo-2-isoindolineacetic Acid, [[*N*-(2-Benzoyl-4-chlorophenyl)-1,3-dioxo-2-isoindolineacetamido]methylene]hydrazide (**32**).

A stirred mixture of 3-amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (**29**) (25) (2.74 g., 0.01 mole) in dry THF (150 ml.) was cooled in an ice bath, under nitrogen, and treated with dry pyridine (1.77 ml., 0.022 mole). This mixture was then treated dropwise, during 1 hour, with a solution of α-phthalimidoacetyl chloride (26) (4.92 g., 0.022 mole) in THF (25 ml.). The mixture was kept in the ice bath for 1 hour and at ambient temperature (25°) for 4 hours. It was then poured into ice water and extracted with chloroform. The extract was washed with brine, dried (sodium sulfate) and concentrated. The solid residue was suspended in ethyl acetate, collected by filtration, washed with ethyl acetate and dried to give 5.36 g. of **32**, m.p. 167-172.5° dec. A small second crop, 0.517 g., m.p. 164.5-167° dec. (90.7% yield) was obtained by concentrating the ethyl acetate filtrate. The analytical sample was crystallized from dichloromethane-ethyl acetate and had m.p. 196.5-198.5°; uv (ethanol): λ max 218 nm (ε 101,450), 239 (39,750), 255 (37,800), inflection 295 (7,900); ir (Nujol): 3300 cm^{-1} (NH), 1775, 1730, 1725, 1710, 1695, 1665 (C=O).

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