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Synthesis and Some Chemical Transformations of 2-Azidomethylindoles

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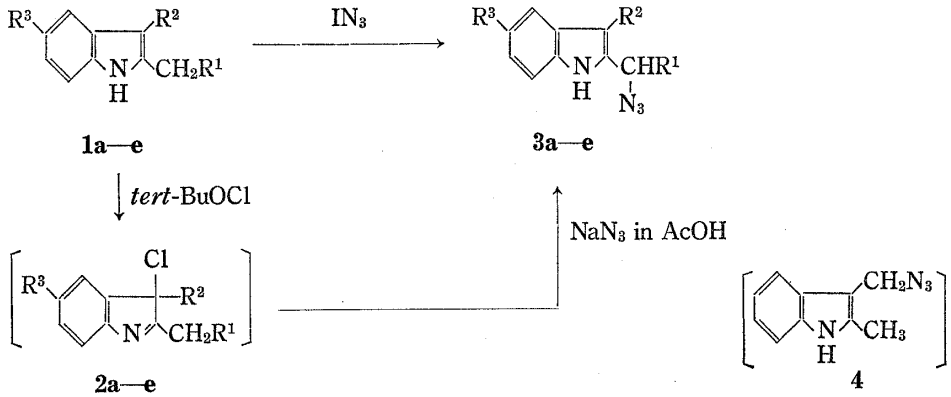
Several 3-substituted 2-azidomethylindoles have been synthesized in high yields either by the reaction of 3-substituted 2-alkylindoles with iodine azide in dry acetonitrile or by treatment of 3-substituted 2-alkyl-3-chloroindolenines with sodium azide in acetic acid. 1,3-Dipolar cycloaddition of the 2-azidomethylindoles with dimethyl acetylenedicarboxylate gives 2-triazolylmethylindole derivatives. Ozonolysis of 3-phenyl-2-azidomethylindoles in acetic acid gives 2-azidoacetamidobenzophenones, which cyclize to 1,4-benzodiazepines by treating with triphenylphosphine in toluene at room temperature and then refluxing.

Keywords——3-chloroindolenines; [3,3]sigmatropic rearrangement; 1,3-dipolar cycloaddition; ozonolysis; 1,4-benzodiazepines; a new phase-transfer catalyst; intramolecular Wittig-type reaction of iminophosphorane

In contrast to the reaction of 3-methyl-2-phenylindole with iodine azide which produces 3-azido-3-methyl-2-phenylindolenine,[2] it was found that similar treatment of 2,3-dimethylindole affords 2-azidomethyl-3-methylindole in high yield. In this paper we describe the details of the synthetic methods of 2-azidomethylindoles and their transformations to 2-triazolylmethylindoles and 1,4-benzodiazepines.

The synthesis of the 2-azidomethylindoles **3a—e** was initially accomplished in high yields by treating the 2-alkylindoles **1** with 2 molar equiv. of iodine azide[3] prepared *in situ* in dry acetonitrile (Method A). Alternatively, treatment of the 2-alkylindoles **1** with *tert*-butyl



1a—e **3a—e** **2a—e** **4**

a : $R^1=R^3=H$, $R^2=Me$; **b** : $R^1=R^2=Me$, $R^3=H$;
c : $R^1=R^3=H$, $R^2=Ph$; **d** : $R^1=H$, $R^2=Ph$, $R^3=Cl$;
e : $R^1=R^2=-(CH_2)_3-$, $R^3=H$

Chart 1

1) Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*
2) *a*) M. Ikeda, F. Tabusa, Y. Nishimura, S. Kwon, and Y. Tamura, *Tetrahedron Lett.*, **1976**, 2347; *b*) Y. Tamura, M.W. Chun, H. Nishida, S. Kwon, and M. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **26**, 2866 (1978).
3) A. Hassner and F.W. Fowler, *J. Org. Chem.*, 33, 2686 (1968).

hypochlorite and triethylamine in methylene chloride for 30 min[4] gave solutions of the 3-chloroindolenines **2** which were then treated with sodium azide in methylene chloride and acetic acid to give the 2-azidomethylindoles **3** in high overall yields (Method B). The results are summarized in Table I.

The structures of **3a—e** were readily confirmed by spectral data (Table II). All of the compounds showed a strong band at 2070—2100 cm^{-1} in the infrared (IR) spectra and essentially the same ultraviolet (UV) spectra as those of the starting indoles **1a—e**. Although the nuclear magnetic resonance (NMR) spectra of **3a** and **3e** did not preclude the alternative structure (*e.g.*, **4**), the NMR spectrum of **3b** exhibits a quartet (1H, J=7 Hz, 2-C$\underline{H}$CH$_3$) at δ 4.96, a doublet (3H, J=7 Hz, 2-CHC$\underline{H}_3$) at δ 1.53, and a singlet (3H, 3-CH$_3$) at δ 2.24, indicating that the azido group was introduced at the 2-methylene group. The NMR spectra of **3c** and **3d** revealed a singlet (2H) due to the 2-methylene group at δ 4.38 and 4.49, respectively.

Reasonable mechanistic schemes are outlined in Chart 2. Initially formed 3-haloindoleninium ions **5** can undergo either (a) initial isomerization of the C–N double bond followed by S_N2' or S_N1 substitution by azide anion at 2-methylene group, or (b) initial substitution at the 3-position by azide anion (probably *via* S_N1 mechanism) followed by the isomerization of the C–N double bond and then [3,3] sigmatropic rearrangement of the azido group to the observed products. Path a is consonant with the generally accepted mechanism in the related substitution reaction of 3-haloindolenines.[5] Path b is unprecedent[6] and we have examined this possibility. When **2e** was treated with sodium azide in methylene chloride, 4a-azido-1,2,3,4-tetrahydrocarbazoleindolenine (**6**) was obtained in 84% yield. The structure of **6** was assigned on the basis of the spectroscopic and chemical evidence. The IR spectrum shows the absence of an NH band and the presence of a strong azide band at 2100 cm^{-1}, and the UV spectrum exhibits typical indolenine absorption [222, 226, 260, and 284 nm]. Reduc-

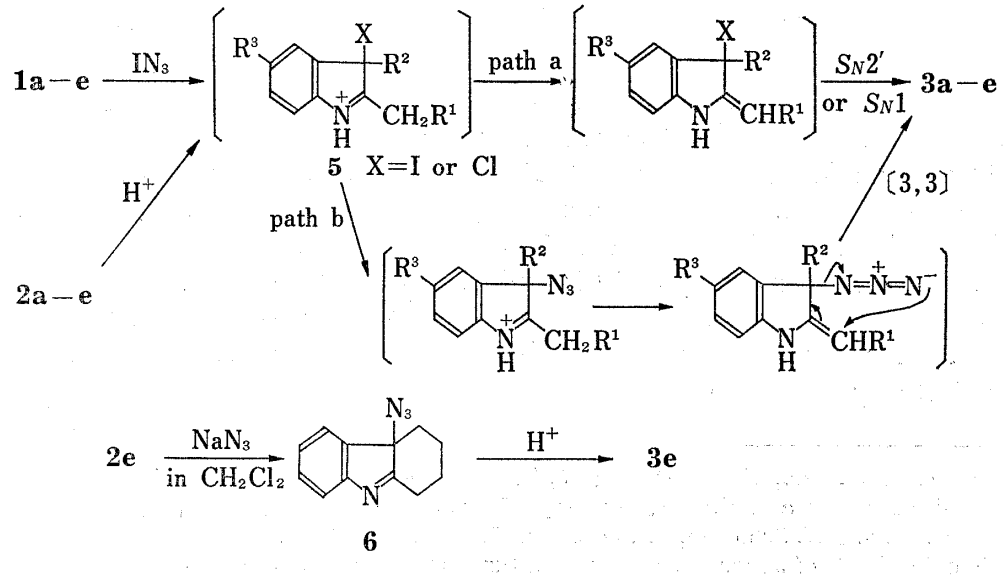


Chart 2

4) W.O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).
5) *a*) W.I. Taylor, *Proc. Chem. Soc.*, **1962**, 247; *b*) L.J. Dolby and G.W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967); *c*) J.P. Kutney, J. Beck, F. Bylsma, J. Cook, W.J. Cretney, K. Fuji, R. Imhof, and A.M. Treasurywala, *Helv. Chim. Acta*, **58**, 1690 (1975); *d*) R.J. Owellen and C.A. Hartke, *J. Org. Chem.*, **41**, 102 (1976).
6) Very recently, an analogous mechanism has been proposed in the rearrangement of some steroidal azides. [R.C. Cambie, P.S. Rutledge, T. Smith-Palmer, and P.D. Woodgate, *J.C.S. Perkin I*, **1977**, 2250.]

tion of **6** with lithium aluminum hydride in ether gave **1e** in high yield. Compound **6** was surprisingly stable in basic media and remained unchanged in refluxing methanol in the presence of sodium hydroxide or triethylamine, but converted into **3e** by stirring in acetic acid at room temperature for 1 hr. The final choice of the mechanism for the formation of **3** must await further experimental verification.

Reduction of **3a** and **3c** with lithium aluminum hydride in ether gave the parent indoles **1a** and **1c**, in high yields, respectively. Catalytic hydrogenation of **3c** or **3d** over palladium charcoal in ethanol resulted in the formation of a complex mixture and was not further examined.

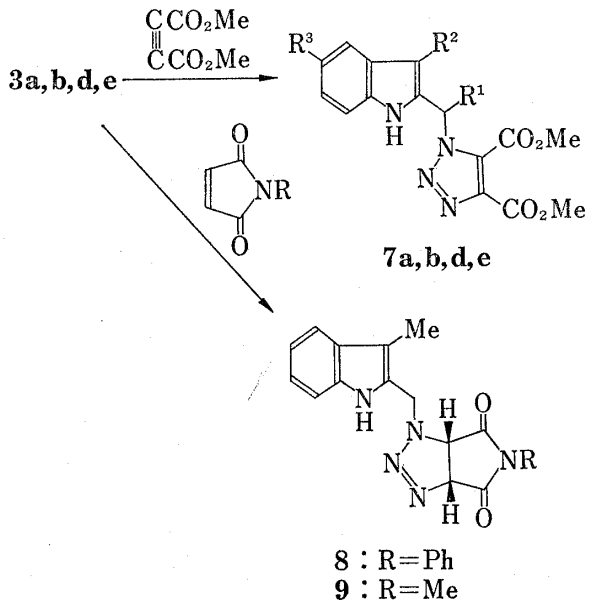


Chart 3

It is well known that organic azides undergo 1,3-dipolar cycloaddition reactions[7] with a variety of olefins and acetylenes to give triazolines and triazoles, respectively. Partly for the characterization of the oily 2-azidomethylindoles **3** and partly for preparation of new indole derivatives, we have examined the reaction of **3** with dimethyl acetylenedicarboxylate and maleimides. Thus, refluxing **3** with dimethyl acetylenedicarboxylate in toluene gave the nicely crystalline cycloadducts **7**. Similarly, **3a** reacted with N-phenylmaleimide or N-methylmaleimide to give triazoline derivatives **8** and **9**. The structures of these cycloadducts were elucidated on the basis of elemental analyses and spectral data (see Experimental).

Ozonolysis[8,9] of **3c, d** in acetic acid gave 2-azidoacetamidobenzophenones **10** and **11** in 45 and 30% yields, respectively. The structures were confirmed by an independent synthesis from 2-chloroacetamidobenzophenones[11a] **12** and **13**; treatment of **12** or **13** with sodium azide in water–benzene in the presence of a new phase-transfer catalyst, benzyl tri-*n*-butyl phosphonium chloride[12] afforded **10** and **11** in 95 and 98% yields, respectively. Conversion of **10** and **11** into 1,4-benzodiazepines[11] **15** and **16** was readily achieved in quantitative yields by treating with triphenylphosphine in toluene at room temperature for 1 hr and then refluxing for 4 hr. This reaction may proceed *via* iminophosphoranes **14**[13] which undergo intramolecular Wittig-type reaction.[14]

7) *a*) G. Lábbe, *Chem. Rev.*, **69**, 345 (1969); *b*) T. Sheradsky, "The Chemistry of the Azido Group," ed. by S. Patai, Interscience Publishers, London, 1971, p. 373.
8) B.W. Ockenden and K. Schofield, *J. Chem. Soc.*, **1953**, 612 and 3440.
9) Chromic oxidation[10] of **3d** gave a complex mixture, from which an unidentified product was obtained in 40% yield.
10) K. Schofield and R.S. Theobald, *J. Chem. Soc.*, **1950**, 1505.
11) *a*) L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962); *b*) S.C. Bell, T.S. Sulkowski, C. Gochman, and S.J. Childress, *J. Org. Chem.*, **27**, 562 (1962); *c*) S. Inaba, M. Akatsu, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 1076 (1976).
12) This compound was prepared by heating equimolar amounts of tri-*n*-butylphosphine and benzyl chloride at 100° for 4 hr, mp 153—155°. (S. Kwon and H. Nishida, unpublished work).
13) *a*) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919); *b*) E. Bergmann and H.A. Wolff, *Ber.*, **63**, 1176 (1930).
14) R. Appel and A. Hauss, *Chem. Ber.*, **93**, 405 (1960).

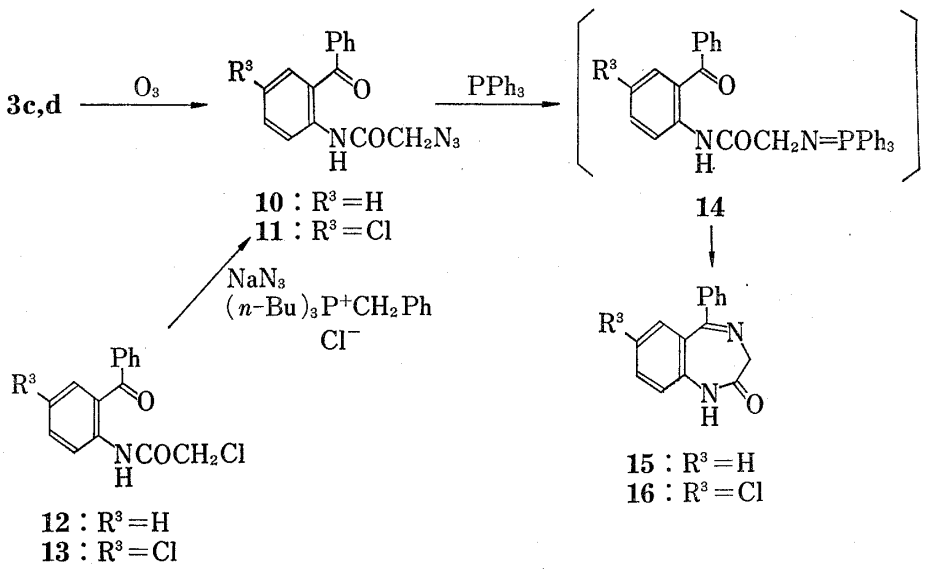


Chart 4

Experimental[15]

General Procedures for 2-Azidomethylindoles (3a—e)——Method A (by iodine azide). A solution of **1** (5 mmol) in dry acetonitrile (10 ml) was added dropwise to a stirred solution of IN_3[3] [prepared *in situ* from ICl (10 mmol) and NaN_3 (15 mmol) at 0°] in dry acetonitrile (10 ml) at −20——−30°. After the reaction mixture was stirred at the same temperature for 3 hr and then at room temperature for 2 hr, the mixture was diluted with H_2O and extracted with ether. The extract was washed with an aqueous $Na_2S_2O_3$ solution and H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to give a crude product **3**, which was purified either by recrystallization (for **3a**, **c**, **e**) or by silica gel column chromatography with *n*-hexane–ether (for **3b**, **d**). The results are summarized in Tables I and II.

Method B (*via* 3-chloroindolenines). The 3-chloroindolenines **2** were prepared *in situ* by the method of Godtfredsen and Vangedal.[4] To a solution of **1** (5 mmol) and triethylamine (5 mmol) in methylene chloride (5ml) was added dropwise *tert*-butyl hypochlorite (0.45 ml) at −20——−30° with stirring. After the reaction mixture was stirred at the same temperature for 30 min, NaN_3 (10 mmol) and acetic acid (1 ml) were added and stirring was continued at the same temperature for 2 hr and then at room temperature for 2 hr. The reaction mixture was neutralized with 5% Na_2CO_3 and the organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to give a crude product **3**, which was purified by the same procedure as that described above in method A. The results are summarized in Tables I and II.

Table I. Preparation of 2-Azidomethylindoles

3	mp (°C) (Recryst'd from)	Yield (%) Method A	Yield (%) Method B	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	83—84 (MeOH)	94	93	$C_{10}H_{10}N_4$	64.50	5.41	30.09	64.57	5.40	29.92
b	Oil	91	94	—						
c	124 (*n*-hexane)	100	72	$C_{15}H_{12}N_4$	72.56	4.89	22.57	72.27	4.92	22.26
d	Oil	93	99	—						
e	53—54.5 (MeOH)	89	92	$C_{12}H_{12}N_4$	67.90	5.70	26.40	67.78	5.61	26.36

15) All melting points are uncorrected. The NMR spectra were recorded with a Hitachi R-20A (60 MHz) spectrometer with tetramethylsilane as internal standard, IR spectra with a Hitachi EPI-G2 spectrophotometer, and UV spectra with a Hitachi 124 spectrophotometer. Preparative TLC was carried out on Merck Silica gel GF_{254} and Alumina PF_{254}.

Table II. Physical Data of 2-Azidomethylindoles

3	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR ($CDCl_3$) δ
a	3450, 2100	225(4.38), 280(3.79) 284(3.80), 292(3.73)	7.8 (b, 1H, NH), 4.37 (s, 2H, 2-CH_2), 2.28 (s, 3H, 3-CH_3)
b	3460, 2100	225(4.47), 278(3.90) 284(3.91), 293(3.83)	7.85 (b, 1H, NH), 4.96 (q, 1H, J=7 Hz, 2-C<u>H</u>CH_3), 2.24 (s, 3H, 3-CH_3), 1.53 (d, 3H, J=7 Hz, 2-CH-C<u>H</u>$_3$)
c	3450, 2080	225(4.50), 272(4.09) 276(4.10), 281(4.10) 290(4.04)	8.05 (b, 1H, NH), 4.38 (s, 2H, 2-CH_2)
d	3450, 2100	228(4.48), 236(4.44) 266(3.97), 295(3.85) 303(3.79)	8.90 (b, 1H, NH), 4.49 (s, 2H, 2-CH_2)
e	3430, 2070	224(4.30), 277(3.70) 284(3.71), 293(3.62)	7.75 (b, 1H, NH), 4.4 (bt, 1H, C<u>H</u>), 1.5—2.8 [m, 6H, -$(CH_2)_3$-]

4a-Azido-1,2,3,4-tetrahydrocarbazoleindolenine (6)——To a solution of **1e** (342 mg) and triethylamine (0.18 ml) in methylene chloride (20 ml) was added dropwise *tert*-butyl hypochlorite (0.18 ml) at −20——−30° with stirring. After the reaction mixture was stirred at the same temperature for 30 min, NaN_3 (114 mg) was added, and stirring was continued for 8 hr at room temperature. The mixture was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to give a crude product, which was purified by silica gel column chromatography with *n*-hexane–ether to give **6** (356 mg, 84%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3). UV λ_{max}^{EtOH} nm (log ε): 222 (4.19), 226 (4.09), 260 (3.43), and 284 (3.27). NMR ($CDCl_3$) δ: 7.7—7.0 (m, 4H, arom. protons) and 1.15—2.95 [m, 8H, -$(CH_2)_4$-].

Reduction of 6 with $LiAlH_4$——A mixture of **6** (100 mg) and $LiAlH_4$ (80 mg) in ether (5 ml) was stirred at room temperature for 3 hr. The reaction mixture was treated with ethyl acetate and H_2O to decompose excess $LiAlH_4$ and extracted with ether. The extract was dried ($MgSO_4$) and concentrated to give **1e** (75 mg, 93%), mp 120—121° (from ethanol).

Rearrangement of 6 to 3e——A solution of **6** (300 mg) in acetic acid (5 ml) was stirred at room temperature for 1 hr. The reaction mixture was neutralized with 5% Na_2CO_3 solution and extracted with ether. The extract was washed with H_2O, dried ($MgSO_4$), concentrated, and submitted to silica gel column chromato-

Table III. Preparation of 2-Triazolylmethylindoles

7	mp (°C) (Recryst'd from)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	160—161 (MeOH)	63	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	58.67	5.02	16.98
b	122—123 (EtOH–H_2O)	79	$C_{17}H_{18}N_4O_4$	59.64	5.30	16.37	59.63	5.32	16.38
d	176.5—177.5 (MeOH–H_2O)	73	$C_{21}H_{17}ClN_4O_4$	59.37	4.03	13.19	59.17	4.08	13.04
e	191—192 (MeOH)	89	$C_{18}H_{18}N_4O_4$	61.01	5.12	15.81	61.01	5.13	15.72

Table IV. Physical Data of 2-Triazolylmethylindoles

7	IR ν_{max}^{KCl} cm^{-1}	NMR ($CDCl_3$) δ
a	3250, 1715	8.70 (b, 1H, NH), 5.92 (s, 2H, 2-CH_2), 3.94 (s, 6H, 2×OCH_3), 2.40 (s, 3H, 3-CH_3)
b	3350, 1740, 1725	8.60 (b, 1H, NH), 6.28 (q, 1H, J=7 Hz, 2-C<u>H</u>CH_3), 3.95 (s, 6H, 2×OCH_3), 2.35 (s, 3H, 3-CH_3), 2.00 (d, 3H, J=7 Hz, 2-CHC<u>H</u>$_3$)
d	3250, 1730	9.36 (b, 1H, NH), 5.90 (s, 2H, 2-CH_2), 3.89 (s, 3H, OCH_3), 3.76 (s, 3H,OCH_3)
e	3250, 1720	8.30 (b, 1H, NH), 5.92 (b, 1H, 2-C<u>H</u>), 3.95 (s, 6H, 2×OCH_3), 1.7—3.0 [m, 6H, -$(CH_2)_3$-]

graphy. Elution with *n*-hexane–ether gave **3e** (298 mg), mp 52—53°, which was identified by mixed melting point determination and IR spectral comparison with an authentic sample.

Reduction of 3a with $LiAlH_4$——A mixture of **3a** (100 mg) and $LiAlH_4$ (90 mg) in dry ether (5 ml) was stirred at room temperature for 3 hr. Work up as usual gave **1a** (76 mg), mp 106—107°, which was identified by a direct comparison (mixed melting point determination and IR spectra) with an authentic sample.

Reduction of 3b with $LiAlH_4$——Similar treatment of **3b** (100 mg) with $LiAlH_4$ (90 mg) in dry ether (5 ml) gave **1b** (71 mg), mp 64—66°.

General Procedure for 2-(4,5-Dimethylcarbonyl-1,2,3-triazol-1-ylmethyl)indoles 7——A solution of **3** (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in toluene (2 ml) was heated under reflux for 8 hr. The solvent was removed *in vacuo* and the residual solid was purified by recrystallization. The results are summarized in Tables III and IV.

2-(5-Phenyl-3a,6a-dihydro-4,6-diketopyrrolidino[3,4-*d*]-1,2,3-triazol-1-ylmethyl)-3-methylindole (8)——A solution of **3a** (100 mg) and N-phenylmaleimide (93 mg) in toluene (5 ml) was refluxed for 8 hr. Work up as described above gave **8** (192 mg, 99%), mp 207.5—209° (from methanol–ethyl acetate). IR ν_{max}^{KCl} cm^{-1}: 3340 (NH) and 1715 (C=O). NMR (DMSO-d_6) δ: 10.9 (b, 1H, NH), 7.5—6.9 (m, 9H, arom. protons), 5.69 (d, 1H, J=11 Hz, CH), 5.31 and 4.94 (ABq, 1H each, J=15 Hz, 2-CH_2), 4.35 (d, 1H, J=11 Hz, CH), and 2.31 (s, 3H, 3-CH_3). *Anal.* Calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.84; H, 4.70; N, 19.32.

2-(5-Methyl-3a,6a-dihydro-4,6-diketopyrrolidino[3,4-*d*]-1,2,3-triazol-1-ylmethyl]-3-methylindole (9)——A solution of **3a** (100 mg) and N-methylmaleimide (60 mg) in toluene (5 ml) was refluxed for 8 hr. Work up gave **9** (129 mg, 81%), mp 182.5—184° (from methanol). IR ν_{max}^{KCl} cm^{-1}: 3350 (NH) and 1700 (C=O). NMR (DMSO-d_6) δ: 10.76 (b, 1H, NH), 7.6—6.8 (m, 4H, arom. protons), 5.48 (d, 1H, J=11 Hz, CH), 5.28 and 4.86 (ABq, 1H each, J=15 Hz, 2-CH_2), 4.17 (d, 1H, J=11 Hz, CH), 2.85 (s, 3H, N-CH_3), 2.32 (s, 3H, 3-CH_3). *Anal.* Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.54; H, 5.11; N, 23.24.

2-Azidoacetamidobenzophenone (10)——(A) From **3c**: A solution of **3c** (200 mg) in acetic acid (10 ml) was treated with 5% ozonized oxygen at room temperature for 2 hr. The reaction mixture was neutralized with 28% ammonia and extracted with ether. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography with *n*-hexane–ether to give colorless needles of **10** (102 mg, 45%), mp 79.5—80° (from *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3275 (NH), 2100 (N_3), 1680 (C=O), and 1635 (C=O). NMR ($CDCl_3$) δ: 11.30 (b, 1H, NH), 8.5—8.7 (m, 1H, arom. proton), 6.9—7.8 (m, 8H, arom. protons), and 4.08 (s, 2H, CH_2). *Anal.* Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.17; H, 4.36; N, 20.16.

(B) From 2-Chloromethylamidobenzophenone (**12**): A mixture of **12**[11a] (231 mg), NaN_3 (260 mg), tri-*n*-butyl benzyl phosphonium chloride (17 mg) in benzene (1 ml) and H_2O (1 ml) was heated under reflux for 2 hr. The organic layer was separated. The aqueous layer was extracted with benzene, and the combined extract was dried ($MgSO_4$) and concentrated to give crystals of **10** (212 mg, 90%), mp 79.5—80° (from *n*-hexane).

2-Azidomethylamido-5-chlorobenzophenone (11)——(A) From **3d**: Using procedure (A) described above for preparation of **10**, **11** (65 mg, 30%) was obtained from **3d** (200 mg) as colorless needles, mp 75—77° (from *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 2110 (N_3), 1690 (C=O), and 1640 (C=O). NMR ($CDCl_3$) δ: 11.16 (b, 1H, NH), 8.58 (d, 1H, J=10 Hz, arom. proton), 7.4—7.9 (m, 7H, arom. protons), and 4.10 (s, 2H, CH_2). *Anal.* Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.38; H, 3.64; N, 17.85.

(B) From 2-Chloromethylamido-5-chlorobenzophenone (**13**): Using procedure (B) described above for preparation of **10**, **11** (292 mg, 93%) was obtained from **13** (308 mg), mp 75—77°.

1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (15)——A solution of **10** (200 mg) and triphenylphosphine (187 mg) in toluene (10 ml) was kept to stand at room temperature for 1 hr (nitrogen gas was evolved) and then the reaction mixture was heated under reflux for 4 hr. The solvent was removed and the residue was purified by silica gel column chromatography with benzene–ethyl acetate to give **15** (160 mg, 95%), mp 177—179° (from benzene) lit.[11b] 179—180°), whose spectral data were identical with the reported ones.

1,3-Dihydro-7-chloro-5-phenyl-2H-1,4-benzodiazepin-2-one (16)——Using a similar procedure described above, **16** (128 mg, 98%) was obtained from **11** (152 mg), mp 212—214° (from ethanol) (lit.[11b] 214—216°).

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