# Synthesis and CNS Activity of 3-Substituted 7-Chloro-5-phenyl-1,3,4-benzotriazepin-2-ones

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**Abstract** □ Several new 3-substituted 7-chloro-5-phenyl-1,3,4-benzotriazepin-2-ones were synthesized from appropriate 5-chloro-2-aminobenzophenone hydrazones by condensation with phosgene or treatment with chloroformic acid esters and subsequent cyclization. In an evaluation of their CNS depressant properties, all of the compounds exhibited mild depressant and anticonvulsant activity which was only marginally influenced by the 3-substituent.

**Keyphrases** □ 7-Chloro-5-phenyl-1,3,4-benzotriazepin-2-ones, 3-substituted—synthesis and evaluation of CNS activity □ Benzotriazepinones—synthesis of 3-substituted 7-chloro-5-phenyl-1,3,4-benzotriazepin-2-ones, evaluation of CNS activity □ CNS activity—synthesis and evaluation of 3-substituted 7-chloro-5-phenyl-1,3,4-benzotriazepin-2-ones

Interest (1, 2) in 5-chloro-2-aminobenzophenone-derived heterocyclic compounds related to chlordiazepoxide and diazepam prompted the synthesis of some 3-substituted 7-chloro-5-phenyl-1,3,4-benzotriazepin-2-ones (I) for evaluation as central nervous system (CNS) depressants. Anticonvulsant, antispasmodic, analgesic, and muscle relaxant properties have been attributed to some previously reported 7-chloro-5-phenyl-1,3,4-benzotriazepin-2-ones (3–6). Only one reported compound, however, has a substituent, a phenyl group, in the 3-position (4), and no report is available concerning the influence of the substituent on the biological properties of the compound.

## DISCUSSION

The desired 3-substituted benzotriazepinones (I*a*–I*f*) were readily synthesized in yields of 75–82% by treatment of appropriate 5-chloro-2-aminobenzophenone hydrazones (II) with phosgene (Scheme I), using minor modifications of previously reported procedures (4, 7).

Physical data on newly prepared hydrazones (II*b*, II*c*, II*e*, II*f*) and on the benzotriazepinones (I*a*–I*f*) are provided in Tables I and II, respectively. Spectral data (mass spectroscopy, UV, IR, and NMR) for I*a*–I*f* were consistent with the assigned structures (4).

An alternative route, previously adopted for the synthesis of benzotriazepinones (7), was investigated for the synthesis of the compounds. The hydrazones, II*a*–II*f*, were treated with chloroformic acid esters, and the products were cyclized in refluxing collidine or diphenyl ether–diphenyl (3:1) (Scheme II). In the reaction with chloroformic acid esters, the hydrazones produced the known carbalkoxyhydrazone (IV*a*) (7) when $R_1$ = H, urethanes (V*d*–V*f*) when $R_1$ = aryl, and a mixture of both types of compounds (IV*b*, IV*c* and V*b*, V*c*) when $R_1$ = alkyl (Table III). The carbalkoxyhydrazones were distinguished from the urethanes through their NMR

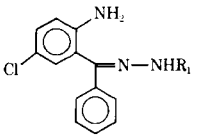



**Table I**—5-Chloro-2-aminobenzophenone *N*-Substituted Hydrazones (II)

| Compound | $R_1$ | Melting Point | Yield, % | Formula[a] | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|
| II*a*[b] | H | 133° | 85 | $C_{13}H_{12}ClN_3$ | C | 63.53 | 63.40 |
| | | | | | H | 4.92 | 5.0 |
| | | | | | Cl | 14.43 | 14.41 |
| | | | | | N | 17.10 | 17.22 |
| II*b* | $CH_3$ | 112° | 82 | $C_{14}H_{14}ClN_3$ | C | 64.74 | 64.39 |
| | | | | | H | 5.43 | 5.64 |
| | | | | | Cl | 13.65 | 14.01 |
| | | | | | N | 16.17 | 16.41 |
| II*c* | iso-$C_3H_7$ | 123° | 64 | $C_{16}H_{18}ClN_3$ | C | 66.79 | 66.80 |
| | | | | | H | 6.30 | 6.24 |
| | | | | | Cl | 12.32 | 12.07 |
| | | | | | N | 14.60 | 14.46 |
| II*d*[c] | $C_6H_5$ | 107° | 80 | $C_{19}H_{16}ClN_3$ | C | 70.91 | 70.97 |
| | | | | | H | 5.01 | 5.15 |
| | | | | | Cl | 11.03 | 11.23 |
| | | | | | N | 13.05 | 12.78 |
| II*e* | *p*-$ClC_6H_4$ | 140° | 50 | $C_{19}H_{15}Cl_2N_3$ | C | 64.07 | 64.26 |
| | | | | | H | 4.24 | 4.29 |
| | | | | | Cl | 19.91 | 19.77 |
| | | | | | N | 11.80 | 11.91 |
| II*f* | *p*-$OCH_3C_6H_4$ | 106° | 73 | $C_{20}H_{18}ClN_3O$ | C | 68.28 | 68.16 |
| | | | | | H | 5.15 | 5.14 |
| | | | | | Cl | 10.08 | 9.88 |
| | | | | | N | 11.95 | 12.00 |

[a] IR, NMR, and mass spectra are in agreement with assigned structures. [b] Lit. (8, 9) mp 134–135°. [c] Lit. (4) melting point not reported.

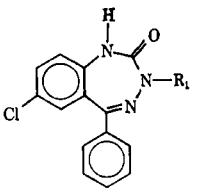


**Table II**—3-Substituted 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones (I)

| Compound | $R_1$ | $R_2$ | Melting Point | Yield, % | Formula[a] | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| I*a*[b] | H | H | 242–243° | 75 | $C_{14}H_{10}ClN_3O$ | C | 61.89 | 62.00 |
| | | | | | | H | 3.71 | 3.77 |
| | | | | | | N | 15.46 | 15.72 |
| I*b* | $CH_3$ | H | 215–218° | 80 | $C_{15}H_{12}ClN_3O$ | C | 63.05 | 62.92 |
| | | | | | | H | 4.23 | 4.20 |
| | | | | | | N | 14.71 | 14.93 |
| I*c* | iso-$C_3H_7$ | H | 226° | 78 | $C_{17}H_{16}ClN_3O$ | C | 65.58 | 65.74 |
| | | | | | | H | 5.18 | 5.11 |
| | | | | | | N | 13.50 | 13.80 |
| I*d*[c] | $C_6H_5$ | H | 237–238° dec. | 82 | $C_{20}H_{14}ClN_3O$ | C | 69.07 | 69.31 |
| | | | | | | H | 4.05 | 4.23 |
| | | | | | | N | 12.08 | 11.93 |
| I*e* | *p*-$ClC_6H_4$ | H | 235–236° | 76 | $C_{20}H_{13}Cl_2N_3O$ | C | 62.85 | 63.00 |
| | | | | | | H | 3.42 | 3.57 |
| | | | | | | N | 10.99 | 11.04 |
| I*f* | *p*-$OCH_3C_6H_4$ | H | 246° | 78 | $C_{21}H_{16}ClN_3O_2$ | C | 66.76 | 66.41 |
| | | | | | | H | 4.27 | 4.42 |
| | | | | | | N | 11.13 | 11.30 |
| I*g* | $CH_3$ | $CH_3$ | 226–228° | 85 | $C_{16}H_{14}ClN_3O$ | C | 64.12 | 63.92 |
| | | | | | | H | 4.70 | 4.40 |
| | | | | | | N | 14.02 | 14.26 |
| I*h* | $CH_3$ | $CH_2PO(CH_3)_2$ | 196–198° | 90 | $C_{18}H_{19}ClN_3O_2P$[d] | C | 57.53 | 57.36 |
| | | | | | | H | 5.09 | 5.12 |
| | | | | | | N | 11.18 | 11.00 |
| I*i* | $C_6H_5$ | $CH_2PO(CH_3)_2$ | 245° | 87 | $C_{23}H_{21}ClN_3O_2P$[e] | C | 63.10 | 62.83 |
| | | | | | | H | 4.83 | 4.97 |
| | | | | | | N | 9.59 | 9.81 |

[a] UV, IR, NMR, and mass spectra are in agreement with the assigned structures. For typical spectral data, refer to the *Experimental* section. [b] Lit. (4, 7) mp 235–237° and 246–248°, respectively. [c] Lit. (4) mp 243–244°. [d] *Anal.*—Calc.: P, 8.24. Found: P, 8.13. [e] *Anal.*—Calc.: Cl, 8.09: P, 7.07. Found: Cl, 8.01; P, 7.35.

spectra, in which predictable differences were observed for the —CONH—, $-NH_2$, and =NNH— protons (spectral data under *Experimental*). On cyclization, the carbalkoxyhydrazones formed only the benzotriazepinones (I*a*–I*c*), the urethanes in which $R_1$ = alkyl formed mixtures of the corresponding benzotriazepinones (I*b*, I*c*) and the known quinazolinone (VI) (4, 10), and the urethanes in which $R_1$ = aryl produced only the quinazolinone VI. The nature of the results provide new contributions to the chemistry of a previously little studied reaction sequence (4, 7).

Representative benzotriazepinones (I*b*, I*d*) were easily alkylated at the *N*-1 position by treatment with an alkyl halide and sodium hydride to give I*g*–I*i* (Table II).

## EXPERIMENTAL[1]

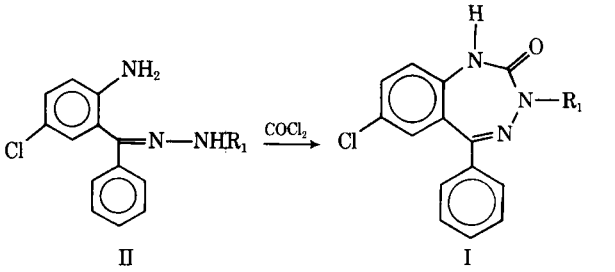
**5-Chloro-2-aminobenzophenone *N*-Substituted Hydrazones (II*a*–II*f*)**—The benzophenone (0.21 mole) and the appropriate hydrazine (0.42 mole) were added to a solution of potassium (9.0 g) in *tert*-butanol (200 ml). The mixture was refluxed for 6 hr and the solvent was distilled *in vacuo*. The residue was treated with water–ice, acidified with acetic acid, and extracted with methylene chloride. The extract was washed with water and 10% aqueous $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated to give the desired compounds which were recrystallized from ligroin–cyclohexane (Table I).

**3-Substituted 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones (I*a*–I*f*) (4, 7)**—A 15% solution of phosgene (0.1 mole) in toluene was added dropwise to a solution of the hydrazone (0.05 mole) in benzene (150 ml) at 20°. The reaction mixture was stirred for 3 hr at room temperature and then at reflux for 3 hr more. The solvents were removed *in vacuo* and the residue was triturated with methanol. Recrystallization from monomethylethylene glycol gave the desired products (Table II). Spectral data for a typical product are as follows.

*I*a—Mass spectroscopy (70 ev, 170°): *m/e* 271 ($M^+$); UV: $\lambda_{max}$ (ethanol) ($\epsilon \times 10^{-4}$) 224 (4.61), 250 sh (2.50), and 302 (0.92) nm; IR: 1710 (CO), 1660, 1600, 1550, 1510, and 1490 $cm^{-1}$; NMR (dimethyl sulfoxide): 7.5 (m, 8H), 9.4 (s, NH), and 9.7 (s, NH) ppm.

*I*b—Mass spectroscopy (70 ev, 170°): *m/e* 285 ($M^+$); UV: $\lambda_{max}$ (ethanol) ($\epsilon \times 10^{-4}$) 224 (4.24), 249 sh (2.21), and 305 (0.78) nm; IR: 1710 (CO), 1660, 1600, 1550, 1510, and 1490 $cm^{-1}$; NMR (dimethyl sulfoxide): 3.4 (s, 3H, $-NCH_3$) and 7.4 (m, 8H, aromatic protons) ppm.

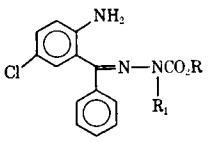
**5-Chloro-2-aminobenzophenone Carbalkoxyhydrazones (IV*a*–IV*c*) and 5-Chloro-2-alkoxycarbonylaminobenzophenone *N*-Substituted Hydrazones (V*b*–V*f*)**—The appropriate alkyl chloroformate (0.07 mole) was added dropwise to a well-stirred



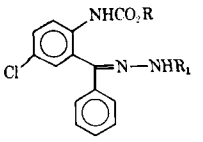
II I

*Scheme I*

[1] Melting points were taken on a Kofler heating bench, type 7841, and are uncorrected. UV spectra were obtained on a Pye-Unicam spectrophotometer, model SP500. The IR spectra were recorded on a Perkin-Elmer spectrophotometer, model 521, using KBr pellets. NMR spectra were obtained on Varian A-60 and T-60 spectrometers, using tetramethylsilane as the internal standard. The mass spectra were recorded on an MS9 (AEI).



IV



V

**Table III**—5-Chloro-2-aminobenzophenone Carbalkoxyhydrazones (IV) and 5-Chloro-2-alkoxycarbonylaminobenzophenone *N*-Substituted Hydrazones (V)

| Compound | $R_1$ | R | Yield, % | Melting Point | Formula[a] | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| IV*a* | H | $C_2H_5$ | 85 | 208°[b] dec. | $C_{16}H_{16}ClN_3O_2$ | C | 60.47 | 60.41 |
| | | | | | | H | 5.07 | 5.10 |
| | | | | | | Cl | 11.15 | 10.97 |
| | | | | | | N | 13.22 | 13.52 |
| IV*b* | $CH_3$ | $C_2H_5$ | 50 | 122° | $C_{17}H_{18}ClN_3O_2$ | C | 61.55 | 61.60 |
| | | | | | | H | 5.46 | 5.63 |
| + | | | + | | | Cl | 10.70 | 10.65 |
| | | | | | | N | 12.67 | 12.82 |
| V*b* | $CH_3$ | $C_2H_5$ | 30 | 117° | $C_{17}H_{18}ClN_3O_2$ | C | 61.55 | 61.50 |
| | | | | | | H | 5.46 | 5.57 |
| | | | | | | Cl | 10.70 | 10.61 |
| | | | | | | N | 12.67 | 12.61 |
| IV*c* | iso-$C_3H_7$ | $CH_3$ | 30[c] | — | $C_{18}H_{20}ClN_3O_2$ | C | 62.53 | 62.37 |
| | | | | | | H | 5.83 | 5.92 |
| + | | | + | | | Cl | 10.25 | 10.29 |
| | | | | | | N | 12.15 | 12.08 |
| V*c* | iso-$C_3H_7$ | $CH_3$ | 26[c] | — | $C_{18}H_{20}ClN_3O_2$ | C | 62.53 | 62.35 |
| | | | | | | H | 5.83 | 5.71 |
| | | | | | | Cl | 10.25 | 10.06 |
| | | | | | | N | 12.15 | 12.10 |
| V*d* | $C_6H_5$ | $CH_3$ | 60 | 205° | $C_{21}H_{18}ClN_3O_2$ | C | 66.40 | 66.26 |
| | | | | | | H | 4.77 | 4.79 |
| | | | | | | Cl | 9.33 | 9.24 |
| | | | | | | N | 11.06 | 11.40 |
| V*e* | *p*-$ClC_6H_4$ | $C_2H_5$ | 65 | 175–178° | $C_{22}H_{19}Cl_2N_3O_2$ | C | 61.70 | 61.94 |
| | | | | | | H | 4.47 | 4.65 |
| | | | | | | Cl | 16.55 | 16.41 |
| | | | | | | N | 9.81 | 10.01 |
| V*f* | *p*-$OCH_3C_6H_4$ | $CH_3$ | 42 | 134° | $C_{22}H_{20}ClN_3O_3$ | C | 64.48 | 64.62 |
| | | | | | | H | 4.91 | 4.79 |
| | | | | | | Cl | 8.65 | 8.93 |
| | | | | | | N | 10.25 | 10.68 |

[a] IR, NMR, and mass spectra are in agreement with the assigned structures. For relevant NMR spectral data, refer to the *Experimental* section. [b] Lit (7) mp 209°. [c] The products were oils which resisted all attempts at crystallization.

solution of the hydrazone II (0.06 mole) in chloroform (200 ml)–pyridine (15 ml) at 10°. After allowing the reaction mixture to stand overnight, a further amount of alkyl chloroformate (0.04 mole) was added and stirring was continued at room temperature for 2 hr. In the experiments in which the *N*-aryl-substituted hydrazones (II*d*–II*f*) were used, the reaction mixture was refluxed for 3–6 hr more. The mixture was poured on ice-chilled water and the organic layer was separated, washed with water and 10% aqueous $NaHCO_3$, and dried over anhydrous sodium sulfate. The extract was evaporated *in vacuo* and the residue was separated into IV and V by column chromatography on silica gel (eluants: benzene, ethyl acetate, methanol); crystallization from ligroin–cyclohexane yielded the pure products (Table III). NMR spectral data (dimethyl sulfoxide/ppm) that help distinguish between IV and V are as follows.

*IV*a—3.4 (s, 2H, $-NH_2$) and 9.02 (s, 1H, —NNHCO); IR and NMR spectra were identical with those of the compound prepared as described previously (7).

*IV*b—3.5 (s, 2H, $NH_2$) and 2.94 [s, 3H, $NN(CH_3)CO$].

*V*b—2.68 (s, 3H, $NNHCH_3$) and 9.55 (s, 1H, NHCO).

*IV*c—3.5 (s, 2H, $NH_2$).

*V*c—9.57 (s, 1H, NHCO).

*V*d—11.7 (s, 1H, $NNHC_6H_5$) and 9.58 (s, 1H, NHCO).

*V*e—11.7 (s, 1H, NNHAr) and 9.60 (s, 1H, NHCO).

*V*f—11.7 (s, 1H, NNHAr) and 9.59 (s, 1H, NHCO).

**Cyclization of IV and V**—Compound IV or V (0.1 mole) was added to collidine (150 ml) or to diphenyl ether–diphenyl (3:1) and refluxed for 1–2 hr. When collidine was used, the reaction mixture was distilled *in vacuo* and the residue was triturated with ligroin–acetone (1:1, 100 ml). When diphenyl ether–diphenyl was used, ligroin–acetone (1:1, 500 ml) was added. A solid precipitated and was filtered. Crystallization from monomethylethylene glycol (using charcoal) gave different proportions of I*a*–I*c* and VI, mp 313–315° [lit. mp 310–312° (10) and 256–258° (4)], depending on the $R_1$ substituent (*cf.*, text). Compound VI was identified by the following spectral data: mass spectroscopy (70 ev/210°): *m/e* 256 ($M^+$); IR: 1640 (C=O) and 1620 (C=N) $cm^{-1}$; NMR (dimethyl sulfoxide): 7.7 (m, 8H, aromatic protons) ppm.

***N*-1 Alkylation of I*b* and I*d* (I*g*–I*i*)**—Compound I*b* or I*d* (0.06 mole) in xylene (150 ml) was treated with sodium hydride (55% in paraffin oil) under reflux conditions for 5 hr. A solution of methyl bromide (0.063 mole, 6.0 g) or of dimethylchloromethylphosphine oxide (0.063 mole, 8.0 g) in xylene (40 ml) was added with stirring. The mixture was refluxed for 3 hr, then cooled to 20°, and filtered. The filtrate was evaporated *in vacuo*, and the residue was crystallized from toluene. When dimethylchloromethylphosphine oxide was used, the residue was extracted with hot water. The water extract was filtered through charcoal-diatomaceous earth[2]. The filtrate was evaporated *in vacuo*, and the residue was recrystallized from toluene (Table II). The spectral data for I*h* follows: mass spectroscopy (70 ev, 240°): *m/e* 375 ($M^+$) and 298 [$M^+$, $-PO(CH_3)_2$]; IR: 1675 (C=O) and 1170 (broad, P=O) $cm^{-1}$; NMR ($CDCl_3$): 1.4 and 1.62 [2d, 3H, 3H, $J$ = 14 Hz, $PO(CH_3)_2$], 3.82 (s, 3H, $N-CH_3$), 4.3 (pseudo t, 2H, $J$ = 7 Hz, $N-CH_2-P$), and 7.6 (m, 8H, aromatic protons) ppm.

## PHARMACOLOGICAL EVALUATION

Compounds I*a*–I*i* were tested in mice (11–19) to evaluate their potential as CNS depressants, using chlordiazepoxide and diazepam as reference compounds. Details of biological procedures

[2] Celite.

**Table IV**—CNS Depressant Activity of Some 7-Chloro-5-phenyl-1,3,4-benzotriazepin-2-ones

| Compound | $LD_{50}$[a], mg/kg ip | Behavioral Screening[bc]: CNS Depressant Activity, mg/kg ip | Anticonvulsant Activity[d]: Pentylenetetrazol Infusion, $ED_{50}$, mg/kg ip | Potentiation of Hexobarbital Narcosis[e]: $ED_{+300\%}$, mg/kg ip | Methamphetamine: $ED_{50}$ (Mouse), mg/kg po |
|---|---|---|---|---|---|
| I*a* | ≫1000 | ++ 400 | >400 | 50 | 220 |
| I*b* | ≫1000 | + 400 | 280 | ≫400 | ≫300 |
| I*d* | ≫1000 | ++ 400 | >400 | >400 | ≫300 |
| Chlordiazepoxide | 390 | ++++ 6 | 15 | 22 | 20 |
| Diazepam | 560 | ++++ 3 | 7 | 3.6 | 15 |

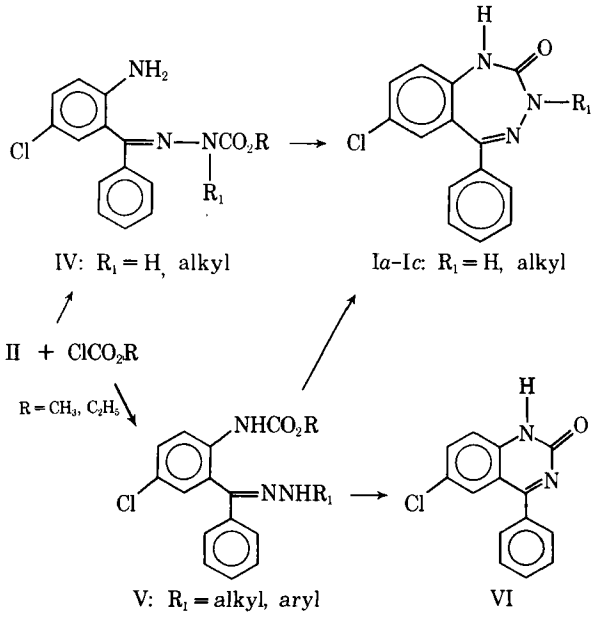
[a] References 1 and 11. [b] References 1 and 12. [c] Rating of CNS depressant activity: −, nil; +, very mild; ++, mild; +++, good; and ++++, very good. [d] Reference 13, six animals per dose. [e] References 1, 15, and 16. [f] Reference 17. Dose of methamphetamine = 0.5 mg/kg sc; 2 × 6 mice per dose.

used were described previously (1). Table IV summarizes only the most interesting results.

All compounds had $LD_{50}$ values ≫ 1000 mg/kg (1, 11). In a primary Irwin neuropharmacological mouse profile (1, 12), all compounds caused CNS depression, as measured by a series of parameters including mild sedation, reduction in activity, relaxation of the muscle tonus, and diminution of the holding reflex. Mild anticonvulsant activity was exhibited against pentylenetetrazol-induced convulsions in mice (13) by all of the compounds, of which I*b* was the most active with an $ED_{50}$ value of 280 mg/kg. None of the compounds, however, offered any protection at 400 mg/kg against maximal electroshock seizures (14). Only I*a* significantly potentiated hexobarbital-induced narcosis (1, 15, 16) and reduced the exploration and motility of a mouse given methamphetamine (17) (Table IV). None of the compounds at doses of 400 mg/kg exhibited a significant taming effect of Syrian hamsters (18) and stimulation of apomorphine-induced gnawing (19).

## CONCLUSIONS

All benzotriazepinones described exhibited some mild CNS depressant and anticonvulsant activity. In comparison with the standard drugs, chlordiazepoxide and diazepam, the compounds were active only at relatively high doses. Introduction of alkyl or aryl substituents at the 3-position, as well as at the 1-position, did not significantly alter the CNS depressant activity of the parent 1,3-unsubstituted benzotriazepinone, and no structure–activity correlations were discernible.




*Scheme II*

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