Table I—Arithmetic Mean of Determination of an Accurately Weighed Capsule Formulation

Compound	Labeled Amount, mg/ Capsule	Recovered Amount, mg/Capsule		Mean Percent
Acetaminophen	325	323.5		99.5
		322.8		99.3
		322.5		99.2
		Mean 322.9	Mean	99.3
Dichloralantipyrine	100	98.3		98.3
		97.6		97.6
		98.1		98.1
		Mean 98.0	Mean	98.0
Isometheptene mucate	65	63.20		97.2
		63.90		98.3
		Mean 63.5	Mean	97.7

rivatives. They are time consuming and are readily hydrolyzed by moisture even in the presence of excess reagents.

A comparison showed that the described method is more rapid than previously described GLC methods that required preparation of a derivative (7, 8, 11). It is not more rapid than other reported methods (5, 6), but the use of the 1% OV-17 on high-performance Chromosorb WHP eliminates the tailing and, therefore, increases the efficiency and accuracy.

REFERENCES

(1) J. B. Vaughn, *J. Pharm. Sci.*, **58**, 469 (1969).

(2) L. Chafetz, R. E. Daly, H. Schriftman, and J. J. Lomnev, *ibid.*, **60**, 463 (1971).

(3) F. M. Plakogiannis and A. M. Saad, *ibid.*, **64**, 1547 (1975).

(4) A. A. D'Souza and K. C. Slenoy, *Can. J. Pharm. Sci.*, **3**, 90 (1968).

(5) J. Grove, *J. Chromatogr.*, **59**, 289 (1971).

(6) M. J. Stewart and R. G. Willis, *Ann. Clin. Biochem.*, **12**, 4 (1975).

(7) H. V. Street, *J. Chromatogr.*, **109**, 29 (1975).

(8) L. F. Prescott, *J. Pharm. Pharmacol.*, **23**, 111 (1971).

(9) R. M. Riggin, A. L. Schmidt, and R. T. Kissinger, *J. Pharm. Sci.*, **64**, 680 (1975).

(10) A. W. Archer and E. A. Hougas, *J. Pharm. Pharmacol.*, **12**, 751 (1960).

(11) C. McMartin and H. V. Street, *J. Chromatogr.*, **22**, 274 (1966).

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[x] To whom inquiries should be directed.

New Compounds: Synthesis of 2-Amino-5*H*-1,3,4-benzotriazepin-5-ones

ROBERT W. LEIBY and NED D. HEINDEL [x]

Abstract □ *N*-Methyl-2-aminobenzohydrazides, when treated with cyanogen bromide, were found to yield 2-amino-5*H*-1,3,4-benzotriazepin-5-ones.

Keyphrases □ 2-Amino-5*H*-1,3,4-benzotriazepin-5-ones—various derivatives synthesized □ Benzotriazepinones, substituted—various derivatives synthesized

Benzotriazepines as bioisosteric homologs of the well-established benzodiazepine psychotherapeutics have received considerable attention recently. Several synthetic methods and claims of sedative activity have been published (1–8) for the 1,3,4-benzotriazepine subclass, but a few earlier structural assignments (as benzotriazepines) were revised recently (9).

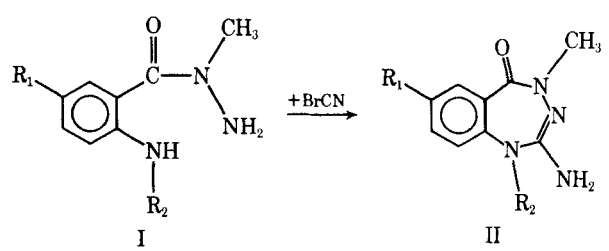
DISCUSSION

As a continuation of investigations on 1,4-benzodiazepin-3,5-diones derived from anthranilamides (10–12), this study reports the preparation of 2-amino-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (II), a new type of 1,3,4-benzotriazepine obtained from the cyclization of anthranilohydrazides (I). By use of cyanogen bromide and a suitably methylated anthranilohydrazide, cyclization can be directed in an unambiguous fashion to the hydrobromide salts of the benzotriazepines, thus avoiding the classic pitfalls and uncertainties of structure that occur when alternative closure pathways are possible (9).

Anthranilohydrazides bearing a methyl on the amide-like nitrogen (*i.e.*, *N*-methyl-2-aminobenzohydrazides, I) were obtained by the opening of isatoic anhydride with methylhydrazine (13, 14). These hydrazides condensed instantaneously in chilled ethanol with cyanogen bromide (Scheme I) to give IIa–IIg in 36–85% yield. When the *ortho*-amino group was deactivated by conjugation to a nitro moiety, *i.e.*, If and Ig, condensation in refluxing dioxane was necessary to obtain a satisfactory yield.

The monomethylated benzotriazepines displayed four NH absorptions in the IR spectra between 3440 and 3080 cm^{-1}, while the dimethylated benzotriazepines (II, $R_2 = CH_3$) displayed only three absorptions between 3360 and 3080 cm^{-1}. Since tautomerism is possible in monomethylated compounds but not in IId, IIe, or IIg, these results may indicate a tautomeric equilibrium in the monomethyl isomers. No present structural evidence can eliminate their alternative formulation as 2-amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones.

In the PMR spectra, the N_4 methyl resonances appeared between 3.75 and 3.85 ppm; the N_1 methyl singlets were observed at 2.75–2.90 ppm. The NH resonances were variable in position, with the C_2 amino protons



Scheme I

Table I—2-Amino-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones[a]

Compound	R_1	R_2	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
II*a*	H	H	80	226.0–226.5°	$C_9H_{11}BrN_4O$	C 39.87	39.75
						H 4.09	4.31
II*b*	Cl	H	72	218–219°	$C_9H_{10}BrClN_4O$	C 35.37	35.54
						H 3.30	3.51
II*c*	Br	H	36	177–179°[b]	$C_9H_{10}Br_2N_4O \cdot 1/2H_2O$	C 30.10	30.19
						H 3.08	3.05
II*d*	H	CH_3	76	212.0–212.5°	$C_{10}H_{13}BrN_4O$	C 42.12	42.07
						H 4.60	4.79
II*e*	Cl	CH_3	85	240.0–240.5°	$C_{10}H_{12}BrClN_4O$	C 37.58	37.57
						H 3.77	3.96
II*f*	NO_2	H	69	212.0–212.5°	$C_9H_{10}BrN_5O_3$	C 34.19	33.96
						H 3.19	3.43
II*g*	NO_2	CH_3	79	246–247°	$C_{10}H_{12}BrN_5O_3$	C 36.38	36.33
						H 3.65	3.73

[a] The title compounds were isolated as hydrobromide salts. [b] Compound forms hemihydrate; presence of water can also be demonstrated by PMR spectroscopy.

evident between 5.40 and 7.70 ppm and the N_1 (or N_3) protons detected at 8.55–8.80 ppm.

EXPERIMENTAL[1]

Preparation of Anthranilohydrazides—The synthesis of hydrazides I*a*–I*g* was described previously (13, 14).

General Procedure for 2-Amino-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one Hydrobromide Salts (II*a*–II*e*)—A solution of 0.10 mole of the requisite anthranilohydrazide (I*a*–I*e*) in 100 ml of absolute ethanol was chilled in an ice bath, and 0.10 mole of cyanogen bromide in 20 ml of ethanol was added rapidly. The solution was stirred vigorously, and almost immediately the yellow crystalline hydrobromide salt began to precipitate. The solid was collected on a filter, washed with 100 ml of cold ether, and recrystallized from ethanol (Table I).

2-Amino-4-methyl-7-nitro-1,4-dihydro-5*H* -1,3,4- benzotriazepin-5-one Hydrobromide (II*f*)—To a solution of 5.25 g (25.0 mmoles) of *N*-methyl-2-amino-5-nitrobenzohydrazide (I*f*) dissolved in refluxing dioxane was added a solution of 2.65 g (25.0 mmoles) of cyanogen bromide in dioxane. Immediately upon addition, the solution became cloudy and precipitated a yellow semisolid mass. This semisolid crystallized on cooling in an ice bath. The solid was recrystallized from acetic acid and washed with absolute ethanol and ether. The analytical product (II*f*) was obtained in 68.5% (5.40 g) yield as fine yellow needles, mp 212.0–212.5°.

2-Amino- 1,4- dimethyl-7-nitro-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one Hydrobromide (II*g*)—A dioxane–cyanogen bromide solution was prepared from 15 ml of dioxane and 2.65 g (25.0 mmoles) of cyanogen bromide. This solution was then added to 5.61 g (25.0 mmoles) of *N*-methyl-2-methylamino-5-nitrobenzohydrazide (I*g*) dissolved in refluxing dioxane. Upon addition, the solution became blood red with concomitant precipitation of a tan solid. The crude II*g* was recrystallized from absolute ethanol (sparingly soluble), giving 6.48 g (79%), mp 246–247°.

[1] IR spectra were obtained in potassium bromide disks on a Beckman IR-33 spectrometer. A Hitachi Perkin-Elmer R20A magnetic resonance spectrometer was employed to obtain the PMR spectra. Melting points were obtained in capillaries on a Thomas Hoover apparatus and are uncorrected. Combustion analyses were obtained from Robertson Microanalytical Laboratory, Florham Park, N.J.

REFERENCES

(1) M. Nair, *Indian J. Chem.*, **11**, 109 (1973).

(2) Ferlux-Chimie S.A., Fr. Demande 2,191,893 (1974); through *Chem. Abstr.*, **81**, 25703s (1974).

(3) D. Bailey, U.S. pat. 3,607,866 (1971); through *Chem. Abstr.*, **75**, 140910v (1971).

(4) A. Langis and M. Charest, *Chim. Ther.*, **2**, 349 (1967).

(5) A. Langis, U.S. pat. 3,542,767 (1970); through *Chem. Abstr.*, **74**, 88089 (1971).

(6) O. Hromatka, F. Krenmueller, and Knollmueller, *Monatsh. Chem.*, **100**, 934 (1969).

(7) T. Sulkowski and S. Childress, *J. Med. Chem.*, **7**, 386 (1964).

(8) T. Sulkowski and S. Childress, U.S. pat. 3,176,008 (1965); through *Chem. Abstr.*, **62**, 16284 (1965).

(9) N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).

(10) N. D. Heindel, *Psychopharm. Bull.*, **5** (2), 23 (1969).

(11) N. D. Heindel, W. P. Fives, T. F. Lemke, J. E. Rowe, H. W. Snady, and R. A. Carrano, *J. Med. Chem.*, **14**, 1233 (1971).

(12) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **32**, 3997 (1968).

(13) R. W. Leiby and N. D. Heindel, *Syn. Comm.*, **6**, 295 (1976).

(14) R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **41**, 2736 (1976).

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[x] To whom inquiries should be directed.