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Spirocyclic tetrahydropyrimidines derived from pentaerythritol

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Received October 2, 1967

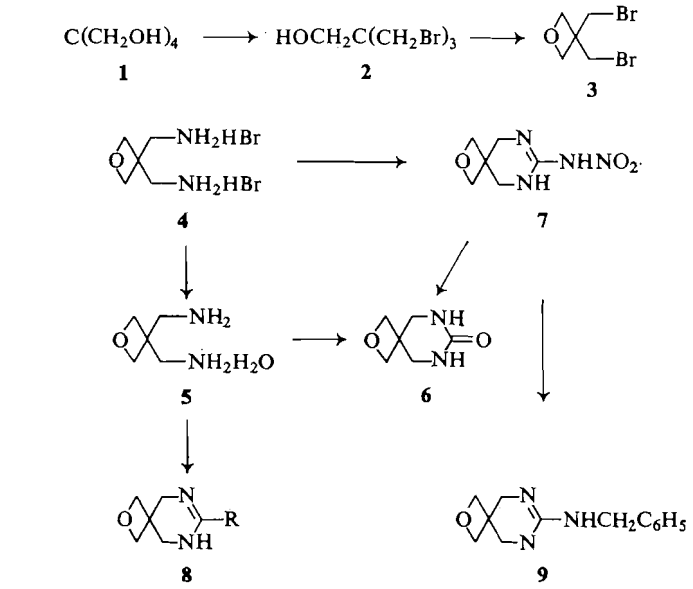
A series of seven spirocyclic compounds bearing the newly synthesized 6,8-diaza-2-oxaspiro[3·5]nonane ring system are reported. Their preparation consists in the condensation of 3,3-bis(aminomethyl)oxetane monohydrate, obtained via pentaerythritol tribromide and, 3,3-bis(bromomethyl)oxetane, with certain amidines and guanidines.

Canadian Journal of Chemistry, 46, 751 (1968)

The focus of attention in the field of hypotensive drugs has been placed for some years on certain guanidines (1–3) and amidines (4) which produce their effect by preventing the release of the adrenergic transmitter substance at sympathetic nerve endings. The series of amidines and guanidines presented in this paper were prepared as potential sympathetic blocking agents. These constitute a departure from the recognized chemical pattern of such drugs in that the amidine or guanidine moieties are part of a new spirocyclic structure, i.e., 6,8-diaza-2-oxaspiro[3·5]nonane. The spirocyclic compounds were obtained in five or six steps from pentaerythritol (**1**) according to Scheme 1.

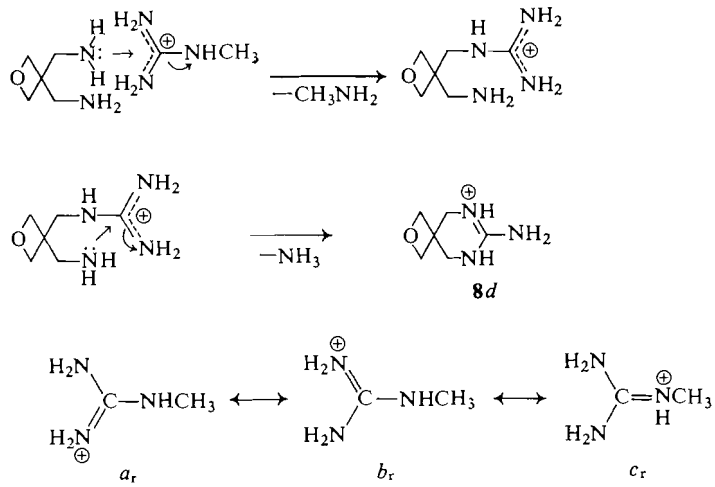
Pentaerythritol (**1**) was first converted into 2,2-bis(bromomethyl)-3-bromo-propanol (**2**) in high yields (90%) with anhydrous hydrobromic acid in acetic acid (5). The tribromo derivative **2** was then converted to 3,3-bis(aminomethyl)-oxetane dihydrobromide as described previously (6) and as illustrated in Scheme 1. Attempts to isolate base **5** by the steam distillation method of Beyaert and Govaert (6) and by the salting out process described by Campbell (7) were unsuccessful in our hands. However, good recovery (ca. 70%) of 3,3-bis(aminomethyl)oxetane monohydrate (**5**) was obtained when the dihydrobromide salt (**4**) was treated with a theoretical amount of solid potassium hydroxide and the free base was extracted with absolute alcohol.

The syntheses of structures **8** *a*, *b*, *c*, and *d*,



8*a* R = CH_3
8*b* R = C_6H_5
8*c* R = $CH_2C_6H_5$
8*d* R = NH_2

Scheme 1



Scheme 2

were performed by a general method for the preparation of 2-substituted-1,4,5,6-tetrahydropyrimidines devised by Brown and Evans (8). Accordingly, acetamidine hydrochloride, benzamidine hydrochloride, phenylacetamidine hydrochloride, and guanidine hydrochloride were condensed with 3,3-bis(aminomethyl)oxetane monohydrate (**5**) yielding the hydrochloride salts of the new spiro structures **8** *a*, *b*, *c*, *d*. These reactions proceeded smoothly at low temperatures with the evolution of two moles of ammonia.

The synthesis of compound **9** was attempted by direct condensation of benzylguanidine hydrochloride with diamine **5**, but this reaction failed to give the expected product and gave instead product **8** *d* in 16% yield. A similar condensation was attempted between phenylguanidine hydrochloride and diamine **5** producing once again compound **8** *d* in 25% yield. Ammonia was collected in both cases and estimated. In order to ascertain the importance of recurring compound **8** *d* in these reactions it was decided to react methylguanidine hydrochloride with diamine **5** and collect the volatile bases thus produced. The expected *N*-methylcyclic guanidine could not be isolated from the reaction but instead compound **8** *d* was again produced in 31% yield. The gases evolved during this reaction were collected in an alcoholic solution of anhydrous hydrogen chloride and methylamine was isolated as its hydrochloride and characterized as its phenylthiourea derivative along with ammonium chloride. As the yield of compound **8** *d* produced by the condensation of guanidine hydrochloride and diamine **5** was found to be 44% (see Table I), this reaction was taken as a basis for comparison with the aforementioned condensations. It was then reasonable to assume that the elimination of methylamine as well as the likely elimination of benzylamine and aniline from the corresponding guanidines constitutes a preferred reaction course. These observations suggested the following reaction mechanism as a possible explanation for the production of compound **8** *d* (Scheme 2).

The methylguanidinium ion is a resonating hybrid of structures a_r, b_r, and c_r. Structures a_r and b_r are equivalent and contribute strongly to the stability of the resonating molecule whereas structure c_r offers little contribution to the stability of the hybrid inasmuch as the inductive effect of the methyl group does not favor this structure and for reasons of non equivalence. As a consequence, it is reasonable to assume that the $=N^+HCH_3$ entity is more labile than its well stabilized NH_2 counterparts resulting in the elimination of methylamine from the methylguanidine molecule under attack by a nucleophile. The reaction of 3,3-bis(aminomethyl) oxetane with methylguanidine hydrochloride would imply firstly a nucleophilic attack on the central carbon atom of methylguanidine by one of the NH_2 groups of the 1,3-diamine **5** with the elimination of methylamine, followed by a second nucleophilic attack on the same carbon atom by the second NH_2 group of the diamine

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TABLE I

Data for *N*-substituted 6,8-diaza-2-oxaspiro[3·5]non-6-ene hydrochlorides

HCl Salt of compound	Reaction time	Temperature °C	Melting point °C	% yield	Formula	Analyses	%C	%H	%N	%Cl
8*a*	10 min	room temperature	241–251 d*	77	$C_7H_{13}ClN_2O$	Calcd.	47.59	7.41	15.85	20.07
						Found	47.64	7.69	15.82	20.29
8*b*	2 h	75	230–231†	76	$C_{12}H_{15}ClN_2O$	Calcd.	60.37	6.33	11.73	14.85
						Found	60.23	6.33	11.63	14.68
8*c*	1 h	50	231–231.5‡	77	$C_{13}H_{17}ClN_2O$	Calcd.	61.77	6.77	11.08	14.02
						Found	61.51	6.73	11.28	13.95
8*d*	3 h	140	225–226§	44	$C_6H_{12}ClN_3O$	Calcd.	40.56	6.80	23.65	19.95
						Found	40.55	6.80	23.40	19.50

*Recrystallized from absolute ethyl alcohol. Infrared cm^{-1}, C—O—C (split band) 970, 940; $HN{=}\overset{+}{C}{-}NH$ 1660 (Nujol mull).

†Recrystallized from dry isopropyl alcohol. Infrared cm^{-1}, C—O—C (split band) 975, 940; $HN{=}\overset{+}{C}{-}NH$ 1640 (Nujol mull).

‡Recrystallized from absolute ethyl alcohol. Infrared cm^{-1}, C—O—C (split band) 970, 940; $NH{=}\overset{+}{C}{-}NH$ 1650 (Nujol mull).

§Recrystallized from absolute ethyl alcohol. Infrared cm^{-1}, C—O—C (split band) 980, 950; $NH{=}\overset{+}{C}{-}NH$ 1670 (Nujol mull).

5 with subsequent evolution of ammonia and cyclization to produce compound **8** *d*.

Since a direct method of cyclization to compound **9** did not seem available, another synthetic pathway based on reactions described by McKay *et al.* (9, 10) was chosen. Compound **7** was thus prepared by reacting the dihydrobromide salt **4** with potassium hydroxide and nitroguanidine in aqueous solution according to these authors. This compound was then refluxed with an excess of anhydrous benzylamine to afford the cyclic guanidine **9**. The pyrimidone **6** was obtained incidentally by the hydrolysis of compound **7** with an aqueous solution of benzylamine. This reaction has been described by McKay *et al.* (10). The same pyrimidone was also prepared by the condensation of urea with the 1,3-diamine **5** according to a procedure described by Bradbury *et al.* (11).

Pharmacological testing of the above compounds is in its preliminary stage.

Experimental

The melting points reported in this work are uncorrected. The elemental analyses were performed by Dr. Daesslé, 5757 Decelles, Montreal. The infrared spectra were made on a Beckman IR 8 spectrophotometer. The hydrochloride salts were titrated potentiometrically with silver nitrate. Acetamidine hydrochloride, practical grade, was purchased from Eastman and used without further purification.

Non-cyclic Amidines and Guanidines

Benzamidine hydrochloride, phenylacetamidine hydrochloride, and nitroguanidine were prepared by methods described in the literature (12–14).

Guanidine hydrochloride was obtained by passing dry hydrochloric acid into an alcoholic suspension of guanidine carbonate (Matheson, Coleman, and Bell).

3,3-Bis(aminomethyl)oxetane Monohydrate (5)

3,3-Bis(aminomethyl)oxetane dihydrobromide (**4**) (20 g, 0.07 mole) was treated with potassium hydroxide pellets (9.4 g, 0.14 mole) while stirring rapidly. After a period of 5 min an exothermic reaction occurred. The stirring was continued until all the potassium hydroxide pellets were consumed. The liberated 1,3-diamine was taken up in 50 ml of absolute ethyl alcohol and the potassium bromide formed in the reaction eliminated by filtration. After evaporation of the alcohol, the residue was distilled under reduced pressure to afford 6.5 g (67%) of 3,3-bis(aminomethyl)oxetane monohydrate, b.p. 121° at 15 mm; lit. 121° at 15 mn (6).

7-Nitramino-6,8-diaza-2-oxaspiro[3·5]non-6-ene (7)

Nitroguanidine, 7.48 g (.07 mole) was dissolved in a solution of potassium hydroxide prepared from 9.4 g (0.14 mole) of KOH in 15 ml of water. 3,3-Bis(aminomethyl)oxetane dihydrobromide (**4**) (20 g, 0.07 mole) was then added to this solution which formed a thick paste. The mixture was heated and stirred for 20 min at 65°. At the end of the reaction, most of the solid material had dissolved. On cooling in an ice-salt bath, 4 g (31%) of a white solid precipitated out. This product was purified by several recrystallizations in a mixture of ethyl alcohol and water and identified as 7-nitramino-6,8-diaza-2-oxaspiro[3·5]non-6-ene, m.p. 254–255° (decomp.). Infrared cm^{-1}: C—O—C (split band) 968, 940; $HN{-}\overset{+}{C}{=}N$ 1620 (Nujol mull).

Anal. Calcd. for $C_6H_{10}N_4O_3$: C, 38.70; H, 5.41; N, 30.09. Found: C, 38.52; H, 5.47; N, 30.10.

7-Benzylamino-6,8-diaza-2-oxaspiro[3·5]non-6-ene (9)

7-Nitramino-6,8-diaza-2-oxaspiro[3·5]non-6-ene (**7**),

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(2 g, 0.01 mole) and freshly distilled benzylamine (10 ml) were heated at 150° until the evolution of nitrous oxide had ceased which took approximately 20 min. The benzylamine in excess was then eliminated *in vacuo*. The residual yellow oil which amounted to 1.5 g (62%) was distilled, b.p. 210–213° at 0.08 mm. This product formed a salt with picric acid which was the picrate of 7-benzylamino-6,8-diaza-2-oxaspiro[3·5]non-6-ene, m.p. 165–165.5°. Infrared cm^{-1}: C—O—C (split band) 970, 950; HN=$\overset{+}{C}$— NH 1650 (Nujol mull).

Anal. Calcd. for $C_{19}H_{20}N_6O_8$: C, 49.56; H, 4.37; N, 18.25. Found: C, 49.77; H, 4.42; N, 18.25.

6,8-Diaza-2-oxaspiro[3·5]nonan-7-one (6)

A mixture of urea (2.6 g, 0.042 mole) and 3,3-bis-(aminomethyl)oxetane monohydrate (**5**) (5.7 g, 0.642 mole) was heated over a period of 1 h at 150°. At the end of the reaction, the contents of the flask turned into a solid mass. The solid material, after recrystallization from absolute ethyl alcohol, gave 3 g (50%) of a white crystalline product m.p. 277.5–278° C. This compound was identical with a sample obtained by the hydrolysis of 7-nitramino-6,8-diaza-2-oxaspiro[3·5]non-6-ene (**7**) with aqueous benzylamine as determined by mixture melting points and infrared spectra. The pyrimidone is very soluble in water and insoluble in most other organic solvents. Infrared cm^{-1}: C—O—C (split band) 970, 945; HN—CO—NH 1670 (Nujol mull).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.08; N, 19.70; Found: C, 50.07; H, 7.17; N, 19.54.

N-Substituted 6,8-Diaza-2-oxaspiro[3·5]non-6-enes (8)

These compounds were prepared by successively condensing **5** with the hydrochloride salts of acetamidine, benzamidine, phenylacetamidine, and guanidine as follows: the amidine or guanidine (0.025 mole) was added to 3,3-bis(aminomethyl)oxetane monohydrate (**5**) (0.025 mole) in a 25 ml flask with magnetic stirring. The reaction occurred at room temperature (**8** *a*) or was heated in an oil bath (**8** *b*, *c*, *d*) for a period of 10 min to 3 h after which the mixture solidified. The product of the reaction was then crystallized in absolute ethyl alcohol or dry isopropyl alcohol yielding the hydrochloride salt of the desired spiro compound. Data pertaining to these compounds are given in Table I.

Condensation of N-Substituted Guanidine Hydrochlorides with 3,3-Bis(aminomethyl)oxetane Monohydrate (5)

Condensation with Benzylguanidine Hydrochloride

A mixture of benzylguanidine hydrochloride (2.04 g, 0.011 mole), and 3,3-bis(aminomethyl)oxetane monohydrate **5** (1.5 g, 0.011 mole) was heated over a period of 3 h at 125°. The ammonia evolved was passed into a standardized aqueous solution of hydrochloric acid. After 2 h of heating almost all evolution of ammonia had ceased. The hydrochloric acid solution was then back-titrated with aqueous standardized sodium hydroxide and was found to correspond to 0.0078 mole of ammonia. To the viscous liquid remaining in the flask was added a minimum of hot isopropyl alcohol until solution was effected. Acetone was then added to incipient cloudiness and the solution permitted to crystallize in the cold for 2 days. The yield of compound **8** *d*, m.p. 225–226°, was 0.273 g (16%) verified by mixture melting point and infrared spectroscopy.

Condensation with Phenylguanidine Hydrochloride

A similar reaction was effected with phenylguanidine hydrochloride (1.88 g, 0.011 mole) and diamine **5** (1.5 g, 0.011 mole). The ammonia evolved was passed into hydrochloric acid solution as above and back-titrated with standard sodium hydroxide corresponding to 0.012 mole of NH_3. Compound **8** *d* isolated from the reaction weighed 0.505 g (25%).

Condensation with Methylguanidine Hydrochloride

Methylguanidine hydrochloride (2.46 g, 0.019 mole) and diamine **5** (2.64 g, 0.019 mole) were reacted in a similar way. The evolved gases were collected in an anhydrous alcoholic solution of hydrogen chloride and the solution was then evaporated to dryness *in vacuo*. The crystalline solid, which weighed 1.25 g, was evaluated at 0.010 mole each for methylamine and ammonia assuming equimolar evolution of these gases. A weighed sample of the crystalline solid in aqueous solution was analyzed by gas–liquid chromatography (Perkin–Elmer model 881 equipped with flame ionization detector). The sample was determined by comparing with a standard graph prepared from pure samples of methylamine hydrochloride. The value for this determination corresponded to 0.008 mole of methylamine which is in good accord with the above estimate. The remaining portion of the solid was placed in absolute alcohol, the ammonium chloride was removed by filtration, the methylamine hydrochloride was recrystallized several times from the same solvent, and was characterized as its phenylthiourea derivative, m.p. 114.5–115°, lit. 113° (15).

Acknowledgment

The authors wish to thank the National Research Council of Canada for financial assistance in carrying out this research project. Thanks must also be expressed to Mr. Claude Sauriol of our Analytical Section who performed the analyses by gas–liquid chromatography.

1. R. A. Maxwell, R. P. Mull, and A. J. Plummer. Experientia, **15**, 267 (1959).
2. W. B. Abrams, R. Pocelinko, M. Klausner, L. Hanauer, and E. N. Whitman. J. New Drugs, **4**, 268 (1964).
3. A. L. A. Boura, F. C. Copp, A. F. Green, H. F. Hodson, G. K. Ruffell, M. F. Sim, E. Walton, and E. M. Grivsky. Nature, **191**, 1312 (1961).
4. A. L. A. Boura, F. C. Copp, and A. F. Green. Nature, **195**, 1213 (1962).
5. M. Saucier, C. Sauriol, and R. L. Salvador. Can. J. Chem. **44**, 1599 (1966).
6. M. Beyaert and F. Govaert. Proc. Acad. Sci. Amsterdam, **42**, 776 (1939).
7. T. W. Campbell. J. Org. Chem. **22**, 1029 (1957).
8. D. J. Brown and R. F. Evans. J. Chem. Soc. 4039 (1962).
9. A. F. McKay and G. F. Wright. J. Am. Chem. Soc. **70**, 430 (1948).
10. A. F. McKay, M. N. Buchanan, and A. G. Gordon. J. Am. Chem. Soc. **71**, 766 (1949).

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11. R. B. BRADBURY, N. C. HANCOX, and H. H. HATT. J. Chem. Soc. 1394 (1947).
12. A. W. DOX. *In* Organic syntheses. Coll. Vol. 1. *Edited by* H. Gilman and A. H. Blatt. John Wiley and Sons, Inc., New York. 1941. p. 5.
13. G. LUCKENBACH. Ber. deut. chem. Ges. **17**, 1421 (1884).
14. T. L. DAVIS. *In* Organic syntheses. Coll. Vol. 1. *Edited by* H. Gilman and A. H. Blatt. John Wiley and Sons, Inc., New York. 1941. p. 399.
15. R. L. SHRINER, R. C. FUSON, and D. Y. CURTIN. The systematic identification of organic compounds. 5th ed. John Wiley and Sons, New York. 1965. p. 326.

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