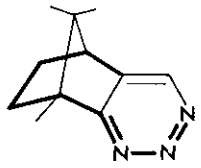
BRIDGEHEAD NITROGEN HETEROCYCLES. SYNTHESIS OF METHANOAZEPINES FUSED WITH TETRAZOLE, 1,2,4-TRIAZOLE AND 1,2,4-TRIAZINE

Shin-ichi Nagai, Naoki Kato, Taisei Ueda, Noriichi Oda, and Jinsaku Sakakibara*

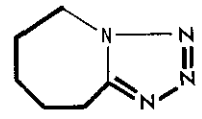
Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Abstract——Cyclohexa- (5a) and cycloheptatriazine (5b) were synthesized from the corresponding pyrazoles (3a-b). Hydrazinolysis of 2-ethoxy-3-azabicyclo[3.2.1]octan-2-ene (7c) gave 2-hydrazino-3-azabicyclo[3.2.1]-octan-2-ene (7d) which readily underwent ring closure with nitrous acid, triethyl orthoformate and ethyl pyruvate to afford tetrazolo[1,5-a]-azepine (8), 1,2,4-triazolo[4,3-a]azepine (9) and 1,2,4-triazino[4,3-a]-azepine (10).

Previously, we have designed the preparation of (5R,8R)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,3-benzotriazine (1) having a common structure unit to pentylenetetrazole (PTZ) (2), and elucidated that product 1 exhibited 5-10 times stronger central nervous system stimulant activities than PTZ.[1]
These findings prompted us to synthesize a series of the related heterocyclic compounds in order to clarify the structure-activity relationships.



1

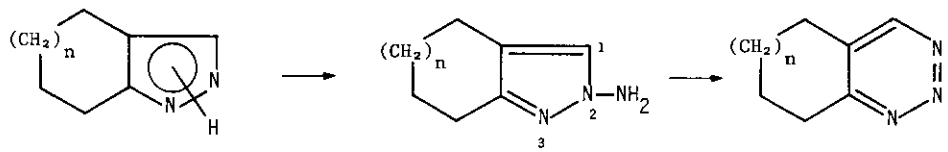


2

In this paper, we describe the synthesis of cycloalkanotriazines (5a-b) and bridgehead nitrogen heterocycles (8-10) fused with tetrazole, 1,2,4-triazole and 1,2,4-triazine rings.
Cycloalkanotriazines were prepared as outlined in Chart 1 starting from cycloalkano-pyrazoles by the method[1] described in the preparation of 1. 4,5,6,7-Tetrahydro-

2H-indazole (3a) and hydroxylamine-O-sulfonic acid was allowed to react in DMF at 30° in the presence of potassium hydroxide to give 2-amino-4,5,6,7-tetrahydro-2H-indazole (4a)[2] in 69 % yield. Similar reaction of cycloheptapyrazole (3b) with hydroxylamine-O-sulfonic acid gave the corresponding 2-aminocycloheptapyrazole (4b)[3] in 66 % yield. The position of the amino substituents was determined as at N-2 on the basis of ^{1}H-NMR spectral data. The chemical shift values of C-1 protons appeared at upfield by 0.22-0.23 ppm relative to those of 3a-b. This fact indicates that the pyrazole ring protons are in the shielding area of an amino nitrogen, and consequently, the amino group should locate at N-2 adjacent to C-1.[1]

The oxidation of compound 4a-b with lead tetraacetate in dichloromethane provided the objective cyclohexa- (5a)[4] and cyclohepta-1,2,3-triazine (5b)[5] in 75 % and 71 % yield respectively. The structures of 5a-b were confirmed by ^{1}H-NMR and mass spectra.



3a: n=1
b: n=2

4a: n=1
b: n=2

5a: n=1
b: n=2

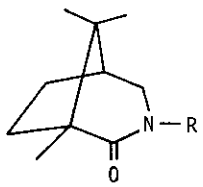
Chart 1

Since the broad utility of heterocyclic hydrazines has received increasing attention for the preparation of the condensed heterocycles[6], it appeared that (1R,5R)-2-hydrazino-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-ene (7d) could be an appropriate starting material for the construction of the bridgehead nitrogen heterocycles containing tetrazole, triazole and triazine nuclei. Therefore, the synthesis of compound 7d by hydrazinolysis of the corresponding iminoether or thioether was investigated as shown in Chart 2.

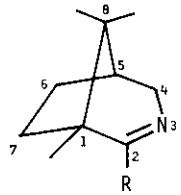
The readily available (1R,5R)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (6a)[7] was treated with dimethyl sulfate in boiling toluene for 20 h. After the separation by column chromatography on silica gel, (1R,5R)-1,3,8,8-tetramethyl-3-azabicyclo[3.2.1]octan-2-one (6b)[8] and (1R,5R)-2-methoxy-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-ene (7a)[9] were isolated as oils in 33 % and 18 % yield respectively. Two isomers were easily distinguishable on the basis of ^{1}H-NMR spectra. Attempts to improve the yield of methyl iminoether (7a) under a variety

of reaction conditions were unsuccessful.

Triflation of 6a with trifluoromethanesulfonic anhydride in dichloromethane gave (1R,5R)-3-trifluoromethanesulfonyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (6c)[10] in 89 % yield. The structure of 6c was confirmed by ^{13}C-NMR spectrum which showed the carbonyl carbon at δ 176.2 ppm.



6a: R=H
b: R=CH_3
c: R=SO_2CF_3



7a: R=OCH_3
b: R=SCH_3
c: R=OC_2H_5
d: R=$NHNH_2$

Chart 2

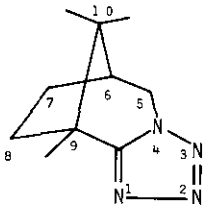
Similarly, (1R,5R)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octane-2-thione[11] prepared by the reaction of 6a with phosphorus pentasulfide, was allowed to react with dimethyl sulfate for 3 h in boiling toluene to provide predominantly (1R,5R)-1,8,8-trimethyl-2-methylthio-3-azabicyclo[3.2.1]octan-2-ene (7b)[12] in 98 % yield. Analogous reaction was performed with 6a and triethyloxonium tetrafluoroborate in dichloromethane to provide (1R,5R)-2-ethoxy-1,8,8-trimethyl-3-azabicyclo[3.2.1]-octan-2-ene (7c)[13] in 85 % yield.

Three imino or thioethers (7a-c) were then subjected to hydrazinolysis, however, only 2-ethoxy compound 7c has been found to undergo hydrazinolysis successfully to provide the objective 7d[14] in 91 % yield when 7c was heated with excess of hydrazine hydrate without solvent. Spectral data were completely consistent with the structure 7d.

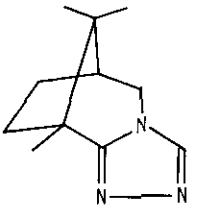
Treatment of 7d with nitrous acid for 0.5 h under cooling gave (6R,9R)-9,10,10-trimethyl-6,7,8,9-tetrahydro-6,9-methano-5H-tetrazolo[1,5-a]azepine (8)[15] in 98 % yield. This product was confirmed to be the tetrazole form as indicated in Chart 3 because IR spectrum showed no characteristic azido ($-\bar{N}=\overset{+}{N}=N$) stretching around 2120-2160 cm^{-1} and mass spectrum exhibited a base ion peak at m/z 164 (M^+-N_2).

(6R,9R)-9,10,10-Trimethyl-6,7,8,9-tetrahydro-6,9-methano-5H-[1.2.4]triazolo[4,3-a]-azepine (9) hydrochloride was prepared by stirring of 7d with triethyl orthoformate at room temperature in the presence of a limited amount of hydrochloric acid. Subsequent treatment with sodium bicarbonate solution gave free [1.2.4]triazolo-

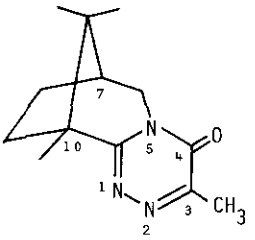
[4,3-a]azepine (9)[16] quantitatively. The structure of 9 was supported by ^{1}H-NMR spectrum which showed appearence of a new signal at δ 8.04 ppm attributable to the triazole proton.



8



9



10

Chart 3

Another triaza compound, (7R,10R)-3,10,11,11-tetramethyl-4-oxo-7,8,9,10-tetrahydro-7,10-methano-4H,6H-[1.2.4]triazino[4,3-a]azepine (10)[17] was obtained without difficulty, namely, by heating a solution of 7d and ethyl pyruvate under reflux in ethanol for 9 h. After chromatography on silica gel, compound 10 was isolated as colorless plates in 85 % yield.

The common characteristic spectral features of 8-10 were observed in their ^{1}H-NMR spectra which revealed significant downfield shifts of bridgehead methyl protons due to the strong deshielding effects by the ring current of the tetrazole, triazole, and triazine.

The investigations on the relationship between the structures and activities of the products are in progress.

ACKNOWLEDGEMENTS

We thank Miss T. Naito and Miss S. Kato of this Faculty for elemental analyses and NMR measurements.

REFERENCES AND NOTES

1. S. Nagai, N. Oda, and I. Ito, Yakugaku Zasshi, 1979, 99, 699.
2. 4a: $C_7H_{11}N_3$, colorless liquid, bp 108°(4 mmHg), IR($CHCl_3$)cm^{-1}: 3280 and 3170 (NH_2), ^{1}H-NMR($CDCl_3$)δ: 5.48(2H, br s, NH_2), 7.04(1H, s, pyrazole proton).
3. 4b: $C_8H_{13}N_3$, colorless liquid, bp 127°(4 mmHg), IR($CHCl_3$)cm^{-1}: 3280 and 3170 (NH_2), ^{1}H-NMR($CDCl_3$)δ: 5.38(2H, br s, NH_2), 7.0(1H, s, pyrazole proton).
4. 5a: $C_7H_9N_3$, light yellow oil, bp 175°C(5 mmHg), ^{1}H-NMR($CDCl_3$)δ: 1.98, 2.84 and

3.12(8H, m, cyclohexane), 8.74(1H, s, triazine). MS m/z: 135(M^+), 107(M^+-N_2).

5. 5b: $C_8H_{11}N_3$, light yellow oil, bp 182°C(1 mmHg), ^{1}H-NMR($CDCl_3$)δ: 1.99, 2.88 and 3.26(10H, m, cycloheptane), 8.75(1H, s, triazine). MS m/z: 149(M^+), 121 (M^+-N_2).

6. M. S. K. Youssef, Kh. M. Hassan, F. M. Atta, and M. S. Abbady, J. Heterocycl. Chem., 1984, 21, 1565 and references cited therein.

7. 6a: G. R. Krow and S. Szczepanski, Tetrahedron Lett., 1980, 4593, ^{13}C-NMR ($CDCl_3$)δ: 13.4(q, $\underline{C}H_3$-C(8)), 19.3(q, $\underline{C}H_3$-C(8)), 23.0(q, $\underline{C}H_3$-C(1)), 27.7(t, C-(6)), 37.9(t, C(7)), 42.3(s, C(8)), 43.6(d, C(5)), 47.1(t, C(4)), 52.1(s, C(1)), 179.0(s, C=O).

8. 6b: $C_{11}H_{19}NO$, colorless oil, IR(KBr)cm^{-1}: 1630(C=O), ^{1}H-NMR($CDCl_3$)δ: 2.80(3H, s, N-CH_3), MS m/z: 181(M^+), 166(M^+-CH_3).

9. 7a: $C_{11}H_{19}NO$: colorless oil, IR($CHCl_3$)cm^{-1}: 1658(C=N), ^{1}H-NMR($CDCl_3$)δ: 3.60 (3H, s, OCH_3), MS m/z: 181(M^+), 166(M^+-CH_3).

10. 6c: $C_{11}H_{16}F_3NO_3S$, colorless needles, mp 106-107°C(n-hexane), IR($CHCl_3$)cm^{-1}: 1130 and 1406(SO_2), ^{13}C-NMR($CDCl_3$)δ: 113.3(s, CF_3), 176.2(s, C=O), MS m/z: 299(M^+), 166($M^+-CF_3SO_2$).

11. $C_{10}H_{17}NS$, colorless plates, mp 204-205°C(n-hexane), IR(KBr)cm^{-1}: 3140(NH), ^{1}H-NMR($CDCl_3$)δ: 8.41(1H, br s, NH), ^{13}C-NMR($CDCl_3$)δ: 213.4(s, C=S), MS m/z: 183(M^+).

12. 7b: $C_{11}H_{19}NS$, colorless prisms, mp 36-37°C(petr. ether), IR(KBr)cm^{-1}: 1600 (C=N), ^{1}H-NMR($CDCl_3$)δ: 2.18(3H, s, SCH_3), ^{13}C-NMR($CDCl_3$)δ: 12.7(s, SCH_3), 174.8(s, C(2)), MS m/z: 197(M^+), 182(M^+-CH_3).

13. 7c: $C_{12}H_{21}NO$, colorless liquid, bp 156-159°C(110 mmHg), IR(film)cm^{-1}: 1650 (C=N), ^{1}H-NMR($CDCl_3$)δ: 1.24(3H, t, J=6 Hz, $OCH_2\underline{C}H_3$), 4.0(2H, q, J=6 Hz, $O\underline{C}H_2CH_3$).

14. 7d: $C_{10}H_{19}N_3$, light yellow plates, mp 30-31°C(n-hexane-Et_2O), IR(KBr)cm^{-1}: 3260 ($NHNH_2$), 1630(C=N), ^{1}H-NMR($CDCl_3$)δ: 1.12(3H, s, bridgehead CH_3), 3.14(1H, dd, J=10 and 1 Hz, C(4)-H_{endo}), 3.57(1H, dd, J=10 and 2 Hz, C(4)-H_{exo}), 4.15(3H, br s, $NHNH_2$), MS m/z: 181(M^+), 166(M^+-CH_3).

15. 8: $C_{10}H_{16}N_4$, colorless prisms, mp 192-195°C(n-hexane), ^{1}H-NMR($CDCl_3$)δ: 1.68(3H, s, bridgehead CH_3), 4.36(2H, m, CH_2N), MS m/z: 192(M^+), 164(M^+-N_2), 149($M^+-N_2-CH_3$).

16. 9: $C_{11}H_{17}N_3$, colorless prisms, mp 132-134°C(petr. ether-Et_2O), ^{1}H-NMR($CDCl_3$)δ:

1.49(3H, s, bridgehead CH_3), 8.04(1H, s, triazole proton), MS m/z: 191(M^+), 176(M^+-CH_3), 148($M^+-CH_3-N_2$).

17. 10: $C_{13}H_{19}N_3O$, colorless plates, mp 158-160°C(n-hexane), ^{1}H-NMR($CDCl_3$)δ: 1.44 (3H, s, bridgehead CH_3), 2.48(3H, s, CH_3-C=), MS m/z: 233(M^+), 218(M^+-CH_3), 190(M^+-CH_3-CO).

Received, 13th December, 1985