The Synthesis of 7-(Substituted-amino)-3-azabicyclo[3.2.0]heptanes

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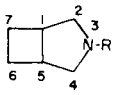
Received May 10, 1974

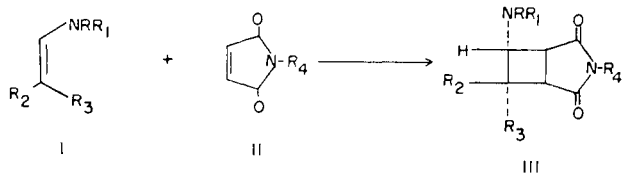
1,2-Cycloaddition reactions of several enamines with *N*-substituted maleimides and 4-phenyl-1,2,4-triazoline-3,5-dione have been carried out. The adducts were transformed into 7-(substituted-amino)-3-azabicyclo[3.2.0]heptanes and a 1,2,4-triazolidine-1-acetaldehyde, respectively. These are the first reported examples of 3-azabicyclo[3.2.0]heptanes substituted in any position other than the 3-position. The reaction of an ynamine with *N*-benzylmaleimide afforded a bicyclic intermediate which upon hydrolysis gave a 2,5-dioxo-3-pyrrolidineacetic acid.

There are no reported examples of 3-azabicyclo[3.2.0]-heptanes substituted in any position other than the 3-position. As part of a program aimed at the preparation of



unique heterocyclic compounds, it was desirous to prepare a series of 7-(substituted-amino)-3-azabicyclo[3.2.0]heptanes. It was decided that the most facile entry into this class of compounds would be the 1,2-cycloaddition reaction of an enamine with a maleimide to afford the substituted cyclobutanedicarboximide. Lithium aluminum hydride reduction would then be expected to afford the substituted 3-azabicyclo[3.2.0]heptane. The synthesis of the desired 7-(substituted-amino)-3-azabicyclo[3.3.0]heptanes by this synthetic sequence has been realized. In addition, the reaction of an enamine with 4-phenyl-1,2,4-triazoline-3,5-dione and the reaction of an ynamine with a maleimide have been studied.

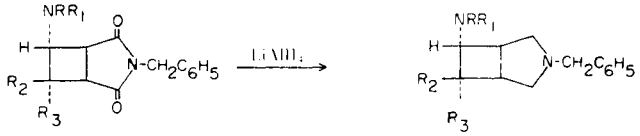
1,2-Cycloaddition reactions of enamines with activated olefins have been reported by Brannock and co-workers (1-3). When solutions of equal molar quantities of an enamine I and a maleimide II in benzene were heated at reflux for 10-48 hours, good yields of 1,2-cyclobutanedicarboximides



I II III

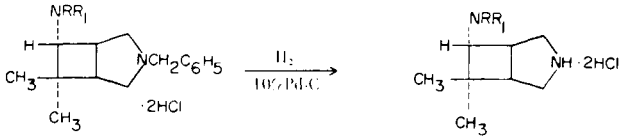
III were obtained (see Table I). The gross structures of IIIa-g were assigned on the basis of ir, nmr, mass spectra, and elemental analyses. The assignment of a *trans* relationship between the amino and imido functions is based upon the commonly accepted mechanism of 1,2-cycloaddition reactions of enamines, *i.e.*, a zwitterionic intermediate with free rotation (1).

An attempt to reduce IIa with lithium aluminum hydride to 3-phenyl-6,6-dimethyl-7-dimethylamino-3-azabicyclo-[3.2.0]heptane resulted in extensive cleavage of the imide ring. This probably resulted from the fact that the phenyl group can stabilize a negative charge on the nitrogen atom in a ring-opened intermediate. Lithium aluminum hydride reduction of the cyclobutanedicarboximides IIId-f afforded good yields of the corresponding 7-(substituted-amino)-3-benzyl-3-azabicyclo[3.2.0]heptanes IVa-c (see Table II). Hydrogenolysis (palladium-on-carbon) of IVa and IVb afforded the secondary amines 6,6-dimethyl-*trans*-7-mor-



IIId-f IVa-c

pholino-*cis*-3-azabicyclo[3.2.0]heptane dihydrochloride (Va) and 6,6-dimethyl-*trans*-7-(*N*-methylanilino)-*cis*-3-azabicyclo[3.2.0]heptane dihydrochloride (Vb) respectively.



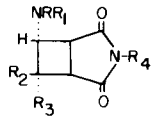
IVa,b Va,b

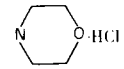
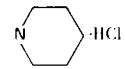
a, NRR_1 = 

b, NRR_1 = $N(CH_3)C_6H_5$

TABLE I

Addition Products from Enamines and Maleimides

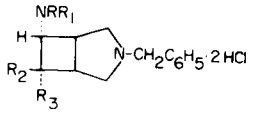


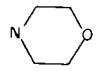
Comp'd. III	NRR_1	R_2,R_3	R_4	Yield (%)	M.P., (C°)	Formula	Analyses (%) (a) C	H	N	Cl
a	$N(CH_3)_2$	CH_3,CH_3	C_6H_5	72 (b)	121-123	$C_{16}H_{20}N_2O_2$	70.54 (70.78)	7.42 (7.41)	10.29 (9.99)	
b		CH_3,CH_3	C_6H_5	89 (b)	149-151	$C_{18}H_{22}N_2O_3$	68.79 (68.37)	7.01 (7.18)	8.92 (9.11)	
c		-$(CH_2)_5$-	C_6H_5	75 (b)	105-108	$C_{22}H_{28}N_2O_2$	74.96 (74.65)	8.01 (8.02)	7.95 (7.83)	
d		CH_3,CH_3	$CH_2C_6H_5$	90 (b)	170-171	$C_{19}H_{25}ClN_2O_3$	62.55 (62.91)	6.86 (6.85)	7.68 (7.56)	9.74 (9.61)
e (c)	$N(CH_3)C_6H_5$·HCl	CH_3,CH_3	$CH_2C_6H_5$	60 (b)	149-150	$C_{22}H_{25}ClN_2O_2$	68.64 (69.07)	6.53 (6.43)	7.28 (7.42)	9.28 (8.94)
f		-$(CH_2)_5$-	$CH_2C_6H_5$	60 (d)	182-183	$C_{23}H_{31}ClN_2O_2$	68.57 (68.58)	7.70 (7.78)	6.96 (6.97)	8.82 (8.58)
g (e)	$N(CH_3)_2$·HCl	CH_3,CH_3	H	40 (b)	195-196	$C_{10}H_{17}ClN_2O_2$	51.61 (51.21)	7.31 (7.31)	12.04 (12.04)	15.27 (15.21)

(a) Found values in parentheses. (b) Recrystallized from ethanol. (c) Reaction run in acetonitrile. (d) Recrystallized from ethanol-ether. (e) Reaction run in dichloromethane at 25°.

TABLE II

7-(Substituted-amino)-3-benzyl-3-azabicyclo[3.2.0]heptanes

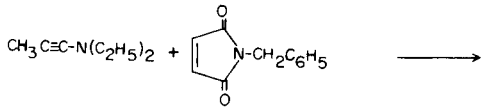


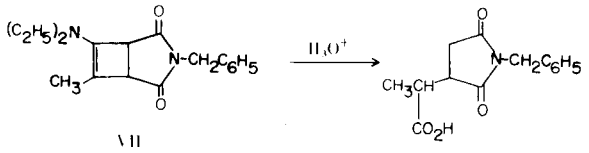
Comp'd. IV	NRR_1	R_2,R_3	Yield (%)	M.P., (C°)	Formula	Analyses (%) (a) C	H	N	Cl
a		CH_3,CH_3	90 (b)	269-270	$C_{19}H_{30}Cl_2N_2O$	61.12 (60.87)	8.04 (8.26)	7.51 (7.48)	19.03 (18.97)
b	$N(CH_3)C_6H_5$	CH_3,CH_3	87 (b)	196-197	$C_{22}H_{30}Cl_2N_2$ ·2/3 C_2H_5OH	66.08 (65.87)	8.02 (7.93)	6.61 (6.53)	17.66 (17.23)
c		$-(CH_2)_5-$	84 (c)	270-271	$C_{23}H_{36}Cl_2N_2$	67.15 (67.12)	8.76 (9.12)	6.81 (6.80)	17.27 (17.16)

(a) Found values in parentheses. (b) Recrystallized from ethanol. (c) Recrystallized from Et_2O-EtOH.

Compounds IVa-c and Va,b are the first reported examples of 3-azabicyclo[3.2.0]heptanes substituted in any position other than the 3-position.

Treatment of *N*-benzylmaleimide with *N,N*-diethylamine-1-propyne (VI) in benzene at 25° afforded a good yield of the bicyclic adduct VII. Repeated attempts to obtain this material in a crystalline state were unsuccessful. The ir, nmr, and mass spectrum were in accord with the assigned structure (see Experimental). Simply shaking an ethereal solution of VII with 10% hydrochloric acid

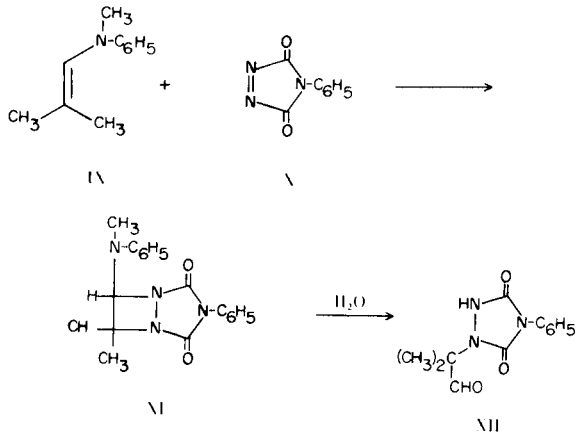




VII VIII

afforded a good yield of 1-benzyl-α-methyl-2,5-dioxo-3-pyrrolidineacetic acid (VIII). The sharp melting point and the nmr spectrum of VIII (see Experimental) demonstrate that it is one diastereomer. The selective formation of one diastereomer is in accord with the work of Ficini and Krief who observed only one diastereomer in the hydrolysis of 7-(*N,N*-diethylamino)-6-methyl[3.2.0]-6-heptene-2-one (4). The explanation of Ficini and Touzin for this stereoselectivity can be extended to the stereoselectivity observed in the hydrolysis of VIII (5).

The reaction of *N*-methyl-*N*-(2-methylpropenyl) aniline (IX) with 4-phenyl-1,2,4-triazoline-3,5-dione (X) occurred



IX X XI XII

very rapidly at -60°. The bicyclic intermediate XI could not be isolated in a pure state. Atmospheric water caused rapid hydrolysis to α,α-dimethyl-3,5-dioxo-4-phenyl-1,2,4-triazolidine-1-acetaldehyde (XII).

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, the nmr spectra were recorded on a Varian A-60D spectrometer, and the mass spectra were determined on a Varian A-60D spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer.

Preparation of 1,2-cyclobutanedicarboximides (General Procedure) (IIIa-g).

A solution of the enamine I (0.10 mole) and maleimide II (0.10 mole) in benzene (600 ml.) was heated at reflux for 10-48 hours. The solution was cooled and the solvent was removed on a rotary evaporator. The residue was then either recrystallized as such or converted into the hydrochloride and recrystallized. The yields,

recrystallization solvents, and physical data for these compounds are shown in Table I.

7-(Substituted-amino)-3-benzyl-3-azabicyclo[3.2.0]heptanes (General Procedure (IVa-c).

A solution of IIId-f (0.050 mole) was converted into the free base and dissolved in THF (150 ml.). This solution was added dropwise to a stirred slurry of lithium aluminum hydride (8 g., 0.21 mole) in THF (300 ml.). After the addition was completed, the mixture was heated at reflux for 48 hours and cooled. The following were added dropwise to the cooled solution: 1) water (8 ml.); 2) 20% sodium hydroxide (8 ml.); and 3) water (24 ml.). The mixture was stirred at room temperature for one hour and filtered. The solvent of the filtrate was removed on a rotary evaporator to afford an oil. The free amine was converted into the dihydrochloride and recrystallized. The yields, recrystallization solvents, and physical data for these compounds are shown in Table II.

6,6-Dimethyl-*trans*-7-morpholino-*cis*-3-azabicyclo[3.2.0]heptane Dihydrochloride (Va).

A solution of IVa (0.0844 mole) was converted into the free base and dissolved in ethanol (200 ml.). Ten percent Pd-C (2g) was added and the mixture was hydrogenolyzed for five days at an initial pressure of 3.5 kg./cm^2. The catalyst was removed by filtration and the solvent was removed on a rotary evaporator to afford 16 g. (90% yield) of crude product. A 4 g. sample was converted into the dihydrochloride and recrystallized from ethanol to afford 4.1 g. of Va, m.p. 284-285°.

Anal. Calcd. for $C_{12}H_{24}ClN_2O$: C, 50.88; H, 8.48; N, 9.89. Cl, 25.09. Found: C, 50.93; H, 8.50; N, 9.97; Cl. 24.79.

6,6-Dimethyl-*trans*-7-(*N*-methylanilino)-*cis*-3-azabicyclo[3.2.0]heptane Dihydrochloride (Vb).

A solution of IVb (0.050 mole) was converted into the free base and hydrogenolyzed in a manner analogous to that used in the preparation of Va. The reaction required six weeks for completion. The dihydrochloride was recrystallized from ether-ethanol to afford 10 g. (67% yield) of Vb, m.p. 232-233°.

Anal. Calcd. for $C_{15}H_{24}Cl_2N_2$: C, 59.14; H, 8.11; N, 8.90; Cl, 22.58. Found: C, 58.86; H, 8.28; N, 8.85; Cl, 22.73.

N-Benzyl-3-methyl-4-diethylamino-*cis*-1,2-cyclobut-3-enedicarboximide (VII).

A solution of *N*-benzylmaleimide (18.7 g., 0.10 mole) in benzene (150 ml.) was added dropwise to a stirred solution (25°) of *N,N*-diethylamino-1-propyne (11.1 g., 0.10 mole) in benzene (150 ml.). The solvent was removed on a rotary evaporator to afford VII: ir 1765 and 1700 (C=O), 1670 (C=C); nmr (deuteriochloroform): δ 7.16 (s, 5H, aromatic), δ 4.51 (s, 2H, -CH_2Ph), δ 3.65-2.70 (m, 6H, 2N-CH_2, C_1H, C_2H), δ 2.71 (m, 3H, =C-CH_3), 0.99 (t, 6H, 2CH_3); M+ m/e = 283. Repeated attempts to obtain VII in a crystalline state failed.

1-Benzyl-α-methyl-2,5-dioxo-3-pyrrolidineacetic Acid (VIII).

Compound VII (*ca.* 0.10 mole) was dissolved in ether (1 l.) and extracted with cold 10% hydrochloric acid (2 x 200 ml.). The combined ether extracts were dried (sodium sulfate) and the solvent was removed on a rotary evaporator. The residue was recrystallized from benzene to afford 18.9 g. (73% yield) of VIII, m.p. 121-122°; nmr (deuteriochloroform): δ 7.28 (s, 5H, aromatic), δ 4.62 (s, 2H >NCH_2), δ 3.40-2.25 (broad m, 4H), δ 1.13 (d, 3H, CH_3); M+ m/e = 261.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.56; H, 5.86; N, 5.48.

4-Phenyl-α,α-dimethyl-3,5-dioxo-1,2,4-triazolidine-1-acetaldehyde (XII).

A solution of X (2.0 g., 0.0114 mole) in ether (100 ml.) was added dropwide to a stirred solution of IX (1.85 g., 0.0114 mole) in ether (200 ml.) which was maintained at -60°. After stirring an additional 0.5 hour at this temperature, the mixture was allowed to warm to room temperature. The solvent was removed on a rotary evaporator and the residue was recrystallized from benzene to afford 1.2 g. (41% yield) of XII, m.p. 186-188°: nmr (deuteriochloroform): δ 9.45 (s, 1H, -CHO), δ 7.6-7.3 (m, 5H, aromatic), δ 1.48 (s, 6H, 2CH_3); M+ m/e = 247.

Anal. Calcd. for $C_{12}H_{13}N_3O_3 \cdot 1/6\ C_6H_6$: C, 59.98; H, 5.42; N, 16.16. Found: C, 60.11; H, 5.32; N, 16.28.

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