was set such that, to be observed, $F_{obsd} < 3.0\sigma_F$, where σ_F is the standard deviation on F_{obsd} computed from scan and background counts corrected for instrumental instability (estimated as 0.5%).

The structure was resolved through an initial three-dimensional Patterson synthesis, which gave the position of the bromine atom. Successive three-dimensional Fourier and difference-Fourier syntheses quickly lead to the placement of all other nonhydrogen atoms.

All nonhydrogen atoms were then treated with converging cycles of full-matrix least-squares refinement. In the final cycles, hydrogen positions were calculated,[12] nonunit weights were introduced, and anisotropic temperature factors were introduced for all nonhydrogen atoms. Hydrogen positional and thermal parameters were not refined but positional parameters were recalculated at the close of each least squares cycle to reposition them according to shifts in the nonhydrogen ring and methyl carbon atoms. Hydrogens were placed at 1.08 Å from the nearest phenyl-ring atoms and in the plane of the rings, at 0.99 Å from the nitrogen, N1, at approximately 109° from the two next nearest ring atoms (C2 and N8), and at 1.10 Å from the three terminal methyl carbons, C52, C62, and C31, at the proper tetrahedral angles (bonding distances are from ref 4). The phenyl-ring and nitrogen hydrogen positions checked satisfactorily against their respective positions on difference Fourier maps. It was not possible to locate hydrogens about the three methyl carbons on difference maps, possibly owing to relatively free rotation of these methyl groups.

The weighting function used in the final least-squares cycles was $w = 1/|\Delta\bar{F}|^2$, where $|\Delta\bar{F}| = A + B|\bar{F}_{obsd}|$, and A and B are obtained from a plot of $\Delta\bar{F}$ *vs.* $|\bar{F}_{obsd}|$ for 20 groups of reflections, each group containing about the same number of reflections. The plot was linear and gave values of 2.80 and 0.0492 for A and B, respectively.

The last cycle yielded a conventional R value of 0.052 and a weighted residual, $wR = 0.068$. Because the primary interest of this study was in the overall architecture of the molecule rather than in the structural details of bond lengths, angles, and thermal parameters, costly additional refinement computations were not made. A final difference Fourier synthesis having a maximum electron density of 1 e/Å^3 was judged to be free of significant features.

(12) Hydrogen positional parameters were calculated with ATMCAL, adapted from a general hydrogen position calculating program supplied by Dr. Lloyd Guggenberger, The Du Pont Co., Wilmington, Del.

Registry No.—**1a**, 36434-07-8; **1b**, 36004-93-0; **1c**, 36004-92-9; **2a**, 36411-13-9; **2b**, 36411-14-0; **2c**, 36411-15-1; **6**, 36411-16-2.

The Synthesis of 2-Aza-6-oxaadamantane

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A new synthesis of 2-aza-6-oxaadamantane from suitably substituted 9-azabicyclo[3.3.1]nonane (prepared by a double Michael addition of a primary amine to 2,7-cyclooctadienone), has been achieved. The nmr of the various azabicyclic compounds were investigated; J values of the ketones and T_c values of the N-acetyl compounds are discussed.

The 2-aza-6-oxaadamantanic skeleton has already been synthesized by another method.[1] In this paper we report a new approach which should enable the introduction of other functional groups. This method is analogous to that used in the preparation of 2-oxa-[2] and 2-phospha-6-oxaadamantanes.[3]

2-Acetyl-2-aza-6-oxaadamantane was prepared by the steps shown in Scheme I. The parent material in the synthesis, 9-benzyl-9-azabicyclo[3.3.1]nonan-3-one (**1**),[4] was prepared by the exothermic addition of benzylamine to cyclooctadienone, as was also found by Bottini;[5] consecutive reduction of **1** by $LiAlH_4$ yielded the expected endo alcohol **2**,[6] from which the benzyl group could be cleaved by hydrogenolysis under acidic conditions to yield *endo*-9-azabicyclo[3.3.1]nonan-3-ol (**3**) (milder hydrogenation conditions; *e.g.*, hydrogenation in ethanol, at room temperature and 60 psi did not affect the benzyl group). Compound **3** which is a hygroscopic material was identical in all respects with the one described in the literature.[7] Attempts to produce the 9-azabicyclo[3.3.1]nonan-3-one directly by addition of ammonia to cyclooctadienone failed; the only product which was isolated, in ~50% from the reaction mixture, seems to be 3,7-bis[9-(9-azabicyclo[3.3.1]-nonan-3-one)]cyclooctanone (**4**).

Treatment of compound **3** with acetic anhydride–pyridine acetylated the amine as well as the hydroxy group to yield *endo*-9-azabicyclo[3.3.1]nonan-3-ol (**5**) which, on mild basic hydrolysis gave the corresponding alcohol (**6**).[7] (Schotten–Baumann acetylation of **2** which should result in **6** in one step, gave much lower yields due to side reactions.)

Treatment of the endo alcohol **6** with lead tetraacetate in boiling benzene,[2,3] or better in the presence of $Pb(OAc)_4$ and iodine,[8] gave two compounds. Chromatographic separation gave the desired 2-acetyl-2-aza-6-oxaadamantane (**7**) and the parent ketone, 9-acetyl-9-azabicyclo[3.3.1]nonan-3-one (**8**). The formation of **7** from **6** confirms the endo configuration of the latter, since epimerization is not expected to occur in these radical oxidation procedures.[2] Of interest was the nmr spectrum of **7** recorded at 100° (in hexachlorobutadiene), above its coalescence temperature (*vide infra*), which indicated the higher symmetry of the compound in comparison to the spectrum at room temperature. A double irradiation experiment, carried out under these conditions, enabled the measurement of various J values of the system.

Although oxidation of tertiary amines by $Pb(OAc)_4$

(1) H. Stetter, *Justus Liebigs Ann. Chem.*, **709**, 170 (1967).

(2) M. Fisch, S. Smallcombe, J. C. Gramain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970).

(3) Y. Kashman and E. Benary, *Tetrahedron*, in press.

(4) G. F. Boehringer, Belgian Patent 623889 (1963). *Chem. Abstr.*, **60**, 13285*h* (1964).

(5) A. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971).

(6) (a) K. Stach and O. Dold, *Arzneimittel Frosch.*, **13**, 1015 (1963); (b) H. O. House, H. C. Müller, C. G. Piff, and P. P. Wickhaum, *J. Org. Chem.*, **28**, 2407 (1963).

(7) K. Alder and H. A. Dortman, *Chem. Ber.*, **86**, 1544 (1953).

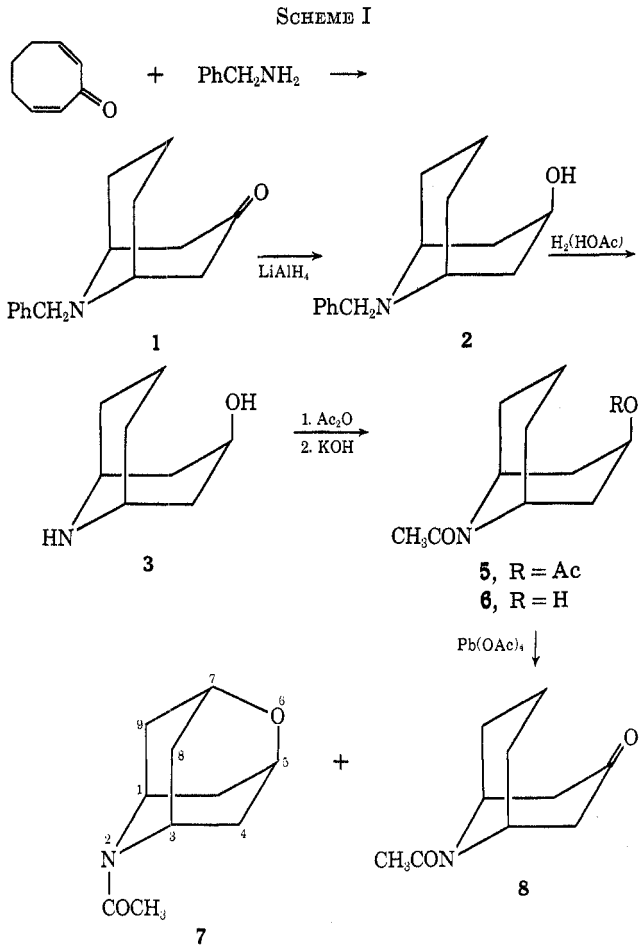
(8) (a) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964); (b) M. L. Mihailovic, Z. Cekovic, V. Andrevic, R. Matic, and D. Jeremic, *Tetrahedron*, **24**, 4947 (1968); (c) W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1964); (d) T. Mori, K. Matsui, and H. Nozaki, *Bull. Chem. Soc. Jap.*, **43**, 231 (1970).

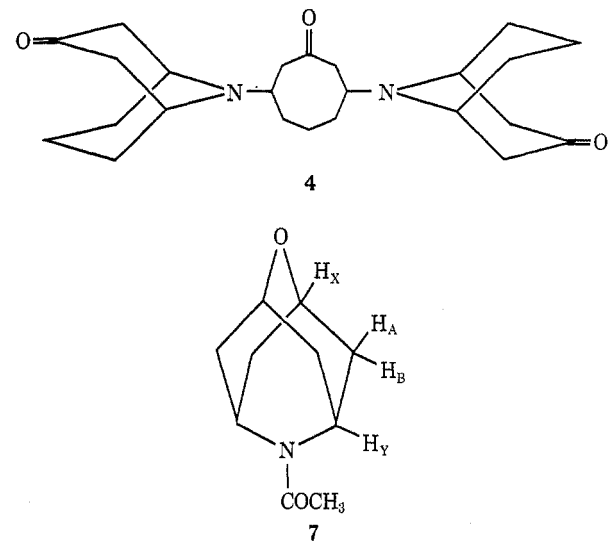
TABLE I

Compd	δ					
	H_1, H_5	H_2, H_4, H_2', H_4'	2 H_6, 2 H_7, 2 H_8	Aromatic protons	Other protons	Solvent
1	3.25–3.40	2.71 (dd)[a] 2.22 (dd)	1.34–2.67	7.18–7.48	3.88 (s, $PhCH_2$)	*b*
2	2.90–3.14	1.00–2.56	1.00–2.56	7.00–7.50	3.86 (s, $PhCH_2$) 4.23 (m, C-3 H)	*b*
3	2.88–3.12	1.64–2.82	1.64–2.82		3.26 (m, C-3 H)	*c*
5	3.98–4.24 (1 H) 4.80–5.10 (1 H)	1.40–2.50	1.40–2.50		4.86 (m, C-3 H) 2.03 (s, $NCOCH_3$) 2.06 (s, $OCOCH_3$)	*b*
6	3.94–4.26 (1 H) 4.78–5.10 (1 H)	1.40–2.50	1.40–2.50		3.62 (m, C-3 H) 2.03 (s, $NCOCH_3$)	*b*
8	4.30–4.50 (1 H) 5.10–5.30 (1 H)	2.63 (dd)[a] 2.36 (dd)	1.30–1.90		2.16 (s, $NCOCH_3$)	*b*
9	4.30–4.52	2.66 (dd)[a] 2.36 (dd)	1.44–2.14	6.70–7.40		*b*
10	4.05–4.30	1.24–2.67	1.24–2.67	6.50–7.40	3.78 (m, C-3 H)	*b*
11	4.20–4.90	1.30–2.90	1.30–2.90	7.00–7.60		*d*
12	3.50–3.70	2.65 (dd)[a] 2.38 (dd)	1.44–2.00			*b*

[a] For J values see Table II. [b] In $CDCl_3$. [c] In D_2O. [d] In hexachlorobutadiene.

SCHEME I





δ_A 1.90 (dd, J_{AB} = 4, J_{AX} = 4, $J_{AY} \simeq$ 1 Hz)
δ_B 1.57 (dd, J_{AB} = 13, J_{BY} = 4, J_{BX} = 1.5 Hz)

is possible (benzyl amines are known to yield the corresponding benzamides),[9] attempts were made to prepare the oxaazaadamantane system by ring closure of compound **2**; however, no unequivocally characterized compound could be isolated from these experiments. Furthermore, even when the weakly basic arylamine **10** (*endo*-9-phenyl-9-azabicyclo[3.3.1]nonan-3-ol) was used, no identifiable compound could be isolated from the various reaction mixtures. Amine **10** was prepared by a route analogous to that used for **2**, although it has been previously synthesized by the Robinson and Scöpff reaction.[10]

The nmr spectra of **1**–**6** and **8**–**12** appear in Table I.

Examination of the nmr spectra of the various 9-aza ketones (Table II) reveals that, in all the cases, the C-2 (C-4) geminal protons are coupled to different extents with the C-1 (C-5) protons.[11] The distorted chair which has already been suggested by Le Fevre[12] for ψ-pelletierine is in accord with the measured J values found in our measurements, although the possibility of a chair–chair ↔ chair–boat equilibria[13] (of the piperidinic and piperidonic rings) cannot be cancelled out.

It was of interest to compare the above data with that of 9-phosphabicyclo[3.3.1]nonan-3-ones (**13**, **14**, and **15**).[3]

(9) J. B. Aylward, *Quart. Rev. Chem. Soc.*, **25**, 409 (1971), and references therein.

(10) G. F. Boehringer, German Patent 1174792 (1964), *Chem. Abstr.*, **61**, 10660 (1964).

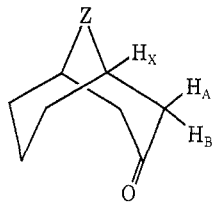
(11) (a) N. S. Bhacca, and D. H. Williams, "Application of NMR Spectroscopy in Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 50; (b) E. Eliel and M. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(12) C. Y. Chen and R. J. W. LeFevre, *J. Chem. Soc. B* 539 (1966).

(13) M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 2847 (1971).

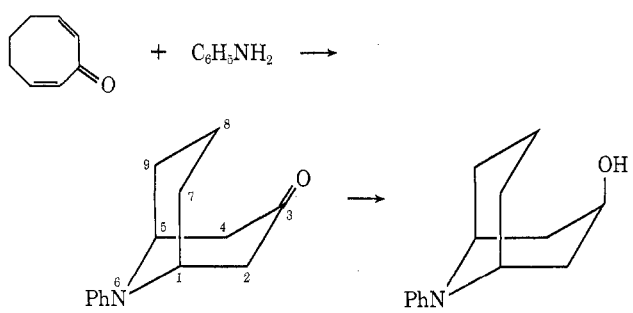
TABLE II

Z = N or P

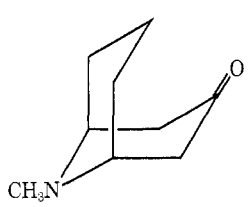


Compd	H_A (H_2,H_4)	H_B (H_2,H_4)	H_X (H_1,H_5)	J_{H_A,H_B}	J_{H_A,H_X}	J_{H_B,H_X}
ψ-Pelletierine[a]	2.82	2.00	3.30	16.2	6.6	1
9	2.66	2.36	4.47	16	6	1
1	2.71	2.22	3.32	16	7	1
8	2.63	2.36	4.42 5.20	16	6	1.5
11	2.49	2.10	4.55	16	6	1.5
13[b]	3.40	2.5–3.0	2.5–3.0	18	4	
14[b]	3.52	2.85	2.7	18	4	1
15[b]	3.26	2.60	2.2–2.5	18	4	1

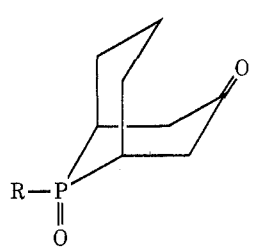
[a] Reference 12. [b] The nmr spectrum was recorded on a JEOL 60-Mc instrument with simultaneous irradiation of the P atom.



9 **10**



ψ-Pelletierine



13, R = Ph
14, R = C_6H_{11}
15, R = $PhCH_2$

The almost equal J values (Table II) found in both series seems to indicate a similar distortion of the phosphorinanonic ring compared with the piperidonic one, with the exception that in the former the preference of the distorted chair over the distorted boat seems to us more likely, because of additional interactions in the latter conformer between the axial ligand on the phosphorus and the carbonyl group.

In conclusion, it is seen that the phosphorus atom, compared with the nitrogen, does not change to any large extent the conformations of the phospha bicyclic compounds.

The activation energy of the well-known restricted rotation around the C–N bond in amides[14] depends, in the case of compound **7**, on the difference between the planar ground state in which C-1, N, C-3, and $COCH_3$ are all in the same plane, and the transition state, in which the $COCH_3$ group is perpendicular to the C-1, N, and C-3 plane. The ΔG^* value (17.5 kcal/mol)[15] calculated using the expression $\Delta G^* = RT(\ln kT/h - \ln \pi\Delta\nu/\sqrt{2})$[18] ($\Delta\nu = 0.85$, $T_c = 80°$) is similar to the value found for dimethylacetamide,[19] indicating thereby that a similar barrier of rotation exist in **7** as well as in the open-chain amide.

Activation energies for **5**, **6**, and **8** cannot be easily calculated from the T_c values (106, 110, and 86°, respectively) because of their conformational mobility; nevertheless it was interesting to find a similar T_c value for compounds **8** and **7**,[20] while for compounds **5** and **6** the value is higher by 20–30° (for similar $\Delta\nu$ values). This last enhancement may originate from a larger contribution of the chair–boat conformation,[21] upon which the C-3 proton comes into a "flag pole interaction" with the acetyl group in the transition state (in which the $COCH_3$ is perpendicular to the C-1, N, and C-3 plane). Other derivatives of these azabicyclo[3.3.1]-nonanes are now under investigation for nmr study.

Experimental Section

Melting-points were taken on a Unimelt Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord Model 337 spectrophotometer. Nmr spectra were taken either on a Varian HA-100 spectrometer or a JEOL JNM-C-60HL spectrometer, 5–10% solution in $CDCl_3$ (unless otherwise indicated), containing TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU 6 instrument.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (1).—To a solution of 2,7-cyclooctadien-1-one (10 g) in methanol (50 ml) was added slowly while swirling at 0° benzylamine (10 g), and the mixture was allowed to stand at room temperature until no more dienone could be detected by gc, tlc, or ir. The product which crystallized out from the reaction mixture (16.5 g) was recrystallized from methanol–hexane, mp 72° (lit.[4] 70–73°).

endo-**9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol** (2).—To a suspension of $LiAlH_4$ (1 g) in dry ether (80 ml) a solution of 1 (5 g) in ether (100 ml) was added dropwise, and the mixture was then heated at reflux with stirring for 2 hr. After this cooled the excess reagent was decomposed by EtOAc and a saturated solution of Na_2SO_4 was added. The solution was filtered, dried (Na_2SO_4), and evaporated. Recrystallization from benzene–hexane gave 4.7 g, mp 69° (in the literature[6] it is not given).

(14) (a) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 517 (1970); (b) P. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).

(15) As the ΔG^* expression is only strictly applicable to the coalescence of two sharp singlets, a value of ~0.2 kcal/mol[16] should probably be added as was done in the case of 7-acetyl-7-azabicyclo[2.2.1]heptane.[17]

(16) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **89**, 760 (1967).

(17) R. F. Fraser and R. B. Swingle, *Can. J. Chem.*, **48**, 2065 (1970).

(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution NMR," McGraw-Hill, New York, N. Y., 1959, p 223.

(19) R. C. Newman and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968).

(20) Another compound which belongs to this group is the 9-benzoyl-9-azabicyclo[3.3.1]nonan-3-one (**11**) which was prepared in low yields by benzoylation of nor-ψ-pelletierine (**12**). In this compound the ΔG^* value is expected to be much lower than that in **8** mainly because (a) interaction between the phenyl and C=O reduces the energy of the transition state, (b) the ground state in **11** is of higher energy due to $A_{1,3}$ interactions between the *o*-phenyl protons and those at C-1 (C-5). Indeed the ΔG^* value calculated from the T_c is only 14.8 kcal/mol.

(21) (a) W. A. C. Brown, C. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (b) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

endo-**9-Azabicyclo[3.3.1]nonan-3-ol** (**3**).—Compound **2** (2 g) dissolved in acetic acid (20 ml) was hydrogenated over 10% PtO_2 on charcoal at atmospheric pressure and room temperature for 12 hr. The product obtained following the usual work-up (1.1 gr) was crystallized from chloroform, mp 104° (lit.[7] 102–104°).

3,7-Bis[9-(9-azabicyclo[3.3.1]nonan-3-one)]cyclooctanone (**4**).—To a solution of 2,7-cyclooctadien-1-one (6 g) in methanol (20 ml) was added slowly while stirring a 10% NH_3 in MeOH solution (20 ml), and the mixture was allowed to stand at room temperature until no more dienone could be detected by ir. The methanol was concentrated and the residue filtered to give 3 g of **4**: mp 190° (acetone); ir ν_{max}^{KBr} 2920, 1700, 1280, 1225, 1200, 1150, 1115, 1055, 1010, 950, 845 cm^{-1}; nmr δ 3.60 (m, 4 H), 3.33 (m, 2 H), 2.10–3.00 (m, 12 H), 1.40–2.10 (m, 18 H); mass spectrum *m/e* (rel intensity) 400 (10), 382 (15), 262 (30), 242 (25), 218 (40), 178 (100). *Anal.* Calcd for $C_{24}H_{36}O_3N_2$: C, 71.96; H, 9.06; N, 6.99. Found: C, 72.20; H, 9.06; N, 6.57.

endo-**9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl Acetate** (**5**).—To a solution of compound **3** (1 g) in pyridine (10 ml) was added acetic anhydride (1 ml), and the solution was left at room temperature overnight. Following the usual work-up compound **5** (1.5 g) was obtained: mp 99–100° (hexane); ir $\nu_{max}^{CHCl_3}$ 1730, 1640, 1030, 800 cm^{-1}; mass spectrum *m/e* (rel intensity) 222 (35, $M\cdot^+$), 210 (10), 182 (20), 166 (28), 165 (30), 124 (100). *Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 64.06; H, 8.50; N, 6.21. Found: C, 64.15; H, 8.48; N, 6.06.

endo-**9-Acetyl-9-azabicyclo[3.3.1]nonan-3-ol** (**6**).—Compound **5** (1 g) was left overnight in a 1% KOH–MeOH solution (20 ml). After neutralization by the addition of 10% HCl in MeOH solution (2 ml), the solvent was evaporated, the residue dissolved in chloroform, and the chloroform washed with water dried (Na_2SO_4) and evaporated. The white solid thus obtained was crystallized from hexane yielding **6** (700 mg): mp 128° (lit.[7] 128–129°); ir ν_{max}^{neat} 3320, 1600, 1020, 1050 cm^{-1}.

2-Acetyl-2-aza-6-oxaadamantane (**7**) **and 9-Acetyl-9-azabicyclo[3.3.1]nonan-3-one** (**8**).—A mixture of dry benzene (120 ml), lead tetraacetate (12 g, dried over P_2O_5 at 0.1 mm), and $CaCO_3$ (6 g, dried over P_2O_5) was heated for 15 min at reflux. Compound **6** (2 g) dissolved in benzene (100 ml) and iodine (5.2 g) was then added and refluxing was continued for 3 hr. The cooled solution was filtered and the filtrate washed with 10% aqueous $Na_2S_2O_3$ (30 ml) and water (15 ml). After the solution was dried and evaporated, the residue was chromatographed on a silica gel column. The first compound which was eluted with 3% MeOH–CH_2Cl_2 was compound **8** (500 mg): mp 115° (hexane); ir ν_{max}^{neat} 1630, 1185, 1100, 1050, 1020, 1000, 980, 950, 860, 780 cm^{-1}; mass spectrum *m/e* (rel intensity) 181 (16, $M\cdot^+$), 153 (8), 138 (16), 124 (8), 96 (100). *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.39; N, 7.72. Found: C, 66.13; H, 8.29; N, 7.68. The second compound which was eluted with 5% MeOH–CH_2Cl_2 was **7** (700 mg): mp 86–87° (hexane); nmr δ 4.10–4.30 (1 H), 4.90–5.10 (1 H), 4.10–4.30 (2 H), 1.6–2.3 (8 H), 2.08 (s, $NCOCH_3$); ir ν_{max}^{neat} 1640, 1060, 1020, 1000, 970, 950, 860, 780 cm^{-1}; mass spectrum *m/e* (rel intensity) 181 (100, $M\cdot^+$), 166 (5), 138 (30), 124 (35), 111 (50). *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.39; N, 7.72. Found: C, 66.20; H, 8.26; N, 8.85.

9-Phenyl-9-azabicyclo[3.3.1]nonan-3-one (**9**).—Following the same procedure as described for **1**, the addition of aniline (0.9 g) to 2,7-cyclooctadien-1-one (1.1 g) at 50° yielded compound **9** (1.2 g): bp 160–162° (0.1 mm); mp 70° (MeOH, lit.[10] 62–64°); ir ν_{max}^{KBr} 3605, 1700, 1600, 1115, 910, 740 cm^{-1}.

endo-**9-Phenyl-9-azabicyclo[3.3.1]nonan-3-ol** (**10**).—Reduction of compound **9** (1 g) under the same conditions as described for the reduction of **1** to give **2** yielded compound **10** (900 mg): mp 98° (benzene–hexane); ir ν_{max}^{KBr} 3220, 1600, 1060, 1025, 910, 730 cm^{-1}. *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.45; H, 8.90; N, 6.55.

9-Azabicyclo[3.3.1]nonan-3-one (**12**).—Compound **1** (1 g) dissolved in methanol (25 ml) was hydrogenated over 5% palladium on charcoal at room temperature and atmospheric pressure for 48 hr in the presence of calalylic amounts of $HClO_4$. After the usual work-up compound **12** (500 mg) was obtained, identical in all respects with the one described in the literature.[7]

9-Benzoyl-9-azabicyclo[3.3.1]nonan-3-one (**11**).—To a solution of **12** (150 mg) in pyridine (2 ml) freshly distilled benzoyl chloride (0.3 ml) was added at 0°. After 4 hr the reaction mixture was poured on ice water and worked up in the usual way. The crude product was chromatographed on an Al_2O_3 column to give compound **11** (80 mg): mp 84–85° (benzene-hexane); ir ν_{max}^{neat} 3030, 1710, 1630, 1600 cm^{-1}; mass spectrum *m/e* (rel intensity) 243 (22, $M\cdot^+$), 138 (45, $C_8H_{12}NO\cdot^+$), 105 (100, $C_6H_5CO\cdot^+$).

Registry No.—**1**, 2291-58-9; **2**, 36079-66-0; **3**, 36079-67-1; **4**, 36146-86-8; **5**, 36079-68-2; **6**, 36079-69-3; **7**, 36146-87-9; **8**, 36146-88-0; **9**, 27092-81-5; **10**, 36079-70-6; **11**, 36146-90-4; **12**, 4390-39-0; 2-aza-6-oxaadamantane, 19557-29-0.

Epimerization of *cis*-4-Amino-5-phenyl-3-isothiazolidinone 1,1-Dioxide and Its 4-*N*-Acetyl Derivative

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The synthesis of *cis*- and *trans*-4-amino-5-phenyl-3-isothiazolidinone 1,1-dioxide (**3** and **5**) *via* methanolysis of the corresponding 4-acetamido derivatives **1** and **6** and base-catalyzed ring closure is described. Both **1** and **3** undergo rapid and irreversible base-catalyzed epimerizations to **6** and **5**, respectively. These results require reversal of tentative configurational assignments for **1** and **6**.

Recently we reported the synthesis of *cis*- and *trans*-4-acetamido-5-phenyl-3-isothiazolidinone 1,1-dioxide (**1** and **6**) and their rearrangement to 4-benzylidine-2-methyl-2-oxazolin-5-one (**4**) in acetic anhydride–pyridine.[1] We now described the transformation of **1** and **6** to the corresponding 4-amino derivatives **3** and **5**; these are cyclic analogs of phenylalanine, and the first 4-amino-3-isothiazolidinone 1,1-dioxides to be isolated and characterized.[2] During this work it was found that **1** and **3** can be readily epimerized to **6** and **5**, respectively; this result requires reversal of our tentative configurational assignments for **1** and **6**.[3]

Methanolysis of **1** and **6** gave the corresponding 3-sulfamyl phenylalanine methyl esters **2** and **7**; the yield of **7** was consistently low, partly because the crude material was always contaminated with some of the *N*-acetyl derivative **9**, the initial methanolysis product.

(1) J. C. Howard, *J. Org. Chem.*, **36**, 1073 (1971).

(2) The synthesis of 4-amino-3-isothiazolidinone 1,1-dioxide has been reported, but it was characterized only as the silver salt and benzoyl derivative: H. Baganz and G. Dransch, *Chem. Ber.*, **93**, 784 (1960).

(3) These were assigned (ref 1) on the basis of their nmr coupling constants, $J_{4,5}$ = 10.6 (cis) and 7.7 Hz (trans) in pyridine-d_5, but with the caveat that such assignments were valid only in the absence of substituent electronegativity effects, which in the case of **1** and **6** are unknown. The new assignments are based on relative stabilities and are less subject to uncertainty.