oil which was shown by gc analysis (column B, 176°) to be a mixture of 97% of **5** and 3% of **1**. The identity of the major peak was confirmed by isolation and comparison of its spectral properties with an authentic sample of **5**.

Acknowledgments. The authors acknowledge the financial assistance of the National Research Council of Canada and the capable technical assistance of Mr. Richard Shum. We thank Dr. M. J. Nye for several helpful discussions and for providing a sample of 2,5-dimethyl-3,4-diphenylcyclopentadienone.

Registry No.—**1,** 52920-58-8; **2,** 695-90-9; **5,** 22118-01-0; **5** *l*-menthydrazone, 52920-61-3; **5** 2,4-DNPH, 52920-62-4; **6,** 39746-31-1; **10,** 52920-63-5; **11,** 52920-64-6; **12,** 26307-17-5; **13,** 52920-59-9; **13** 2,4-DNPH, 52920-65-7; **17,** 52920-60-2.

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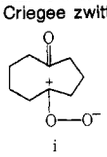

i

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(20) Note that in **13** the carbonyl group is part of a nine-membered ring.
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(23) **1** itself has a plane of symmetry and is achiral, but replacement of >C=O by >C=N– introduces the possibility of chirality into the structure *if* the rotation is sufficiently restricted.
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(25) The *l*-menthydrazone of ketone **5** was also prepared for comparison to establish that during the preparation of the derivative of **1** acid-catalyzed cyclization did not occur to ultimately give the derivative of **5** instead.
(26) A referee has suggested that the ready bending of the sp–sp^3 linkage would make **1** considerably less strained than Dreiding models indicate, *e.g.*, E. Kloster-Jensen and J. Wirz, *Angew. Chem., Int. Ed. Engl.* **12,** 671 (1973).
(27) The C, H, and N analysis for this derivative was within the usually acceptable limits of ±0.3%.
(28) If the crude product was purified by silica gel column chromatography, in addition to the isolation of **1** (eluted with 50% ether–petroleum ether), a 20% yield of the tosylhydrazone of **1**,[27] mp 144–145°, was also obtained (eluted with 2% ethyl acetate–ether). Apparently **1** was being formed before the reaction of tosylhydrazine with **6** was complete, but even when the reaction was maintained at 0° overnight before warming to room temperature the yield of **1** was not improved.
(29) Obtained from Aldrich Chemical Co.
(30) The reaction was followed by tlc with adducts **13** and **12** having R_f 0.55 and 0.65, respectively. The crude product could also be purified by plc.

Synthesis and Reactions of 4-Substituted 2-Azaadamantanes

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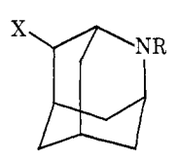
The synthesis of a series of 4-substituted 2-azaadamantyl compounds is reported. The ring system of these compounds was obtained *via* a closure reaction brought about by spontaneous intramolecular opening of an epoxide, at the former double-bond site of N-substituted bicyclo[3.3.1]non-6-en-3-ylamine (**6**), by the amide nitrogen. This unexpectedly facile closure, resulting from the unusual proximity of the amide nitrogen to the back side of the epoxide-bearing ring carbon, is one of several herein described examples of enhanced reactivity at the former double-bond site of this endo-substituted bicyclo[3.3.1]nonane ring system. Acetolysis of the *p*-toluenesulfonate ester of *N*-benzoyl-2-azaadamantan-*anti*-4-ol (**8**) was effected in buffered solution. The only product was anti acetate **14**. Rate measurements demonstrated a slight rate retardation when compared to 2-adamantyl *p*-toluenesulfonate, the analogous carbocyclic system. Attempts to obtain the epimeric syn alcohol **18** by reduction, equilibration, and displacement are described.

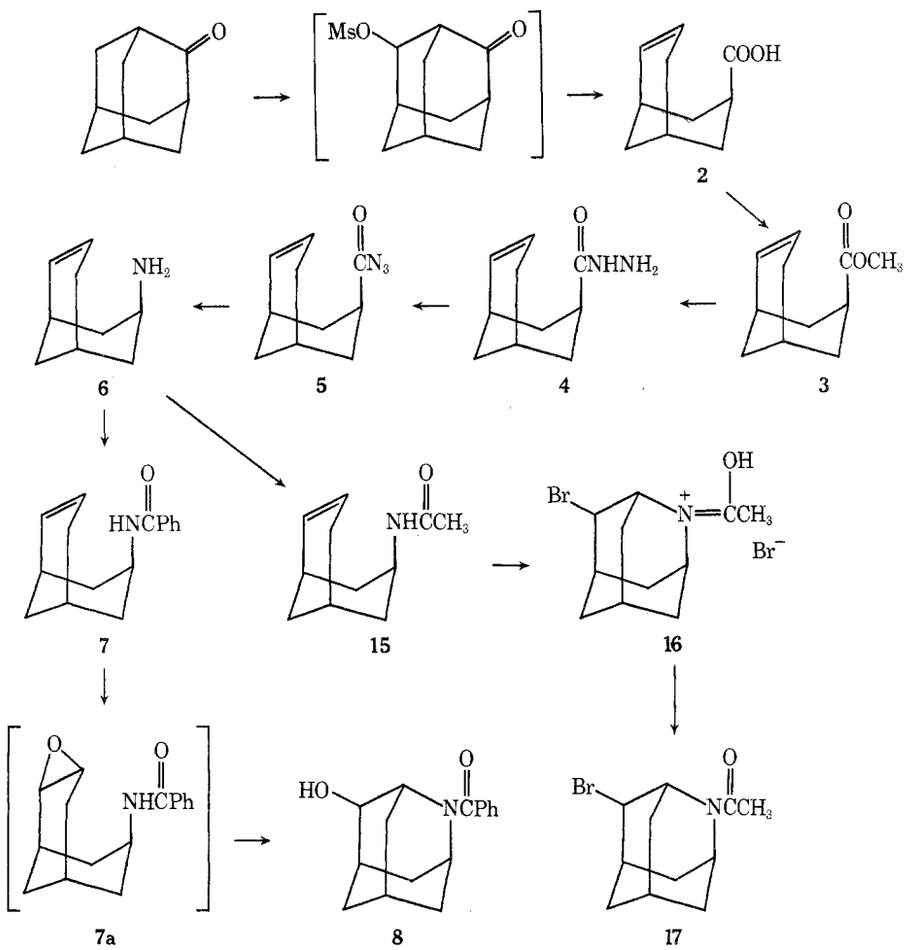
As part of a continuing effort in our laboratories to synthesize hetero analogs of rigid carbocyclic systems[3–5] and in conjunction with our interest in adamantane chemistry,[6–7] we initiated a program of research directed toward the synthesis of adamantyl analogs in which the molecular framework has been altered through replacement of a bridge carbon by a nitrogen. It was our intent, then, to synthesize compounds illustrated by structures **1**. The β-amino and β-amido sulfonate esters could then be subjected to solvolytic conditions to assess the effects of the β nitrogen upon ionization.



1, R = PhCO, $PhCH_2$, H, CH_3; X = OH, OTs

We wish to report here the synthesis of this new class of compounds and our preliminary results on the solvolysis of one of them, *N*-benzoyl-2-azaadamantan-*anti*-4-ol.

Scheme I



Results

N-Benzoyl-2-azaadamantan-*anti*-4-ol (**8**) was prepared from 2-adamantanone *via* the synthetic route shown in Scheme I. Epoxide **7a** was not obtained upon treatment of olefin **7** with 85% *m*-chloroperbenzoic acid[8] but rather afforded a product which on the basis of its infrared and nmr spectra was assigned ring-closed structure **8**.[9]

Further characterization (Scheme II) of the benzoyl azaadamantanol was accomplished by converting it to its corresponding ketone **9** by the chromium trioxide–pyridine method, and by Jones oxidation. Reduction of the ketone with sodium borohydride returned the starting anti alcohol. Other derivatives, **10–12**, were prepared by conventional synthetic procedures.

It was learned that the 4-substituted 2-azaadamantyl system was also obtainable by reaction of acetamide **15** with bromine in carbon tetrachloride. The reaction procedure yielded a product which was soluble in water and in ethanol, but insoluble in ether and other organic solvents. From its infrared spectrum, it was concluded that the hydrobromide salt of *N*-acetyl-2-azaadamantyl-*anti*-4-bromide (**16**) had been formed. It was not possible to prepare an analytically pure sample, but an elemental analysis did indicate that two bromines were present in the molecule. Neutralization of the salt gave the free bromoacetamide **17**, whose structure was confirmed by infrared, nmr, and elemental analyses.

In contrast to the behavior of the acetamide, addition of bromine to the unprotected amine **6** resulted in precipitation of a bromide salt before reaction could occur at the double bond.

Scheme II

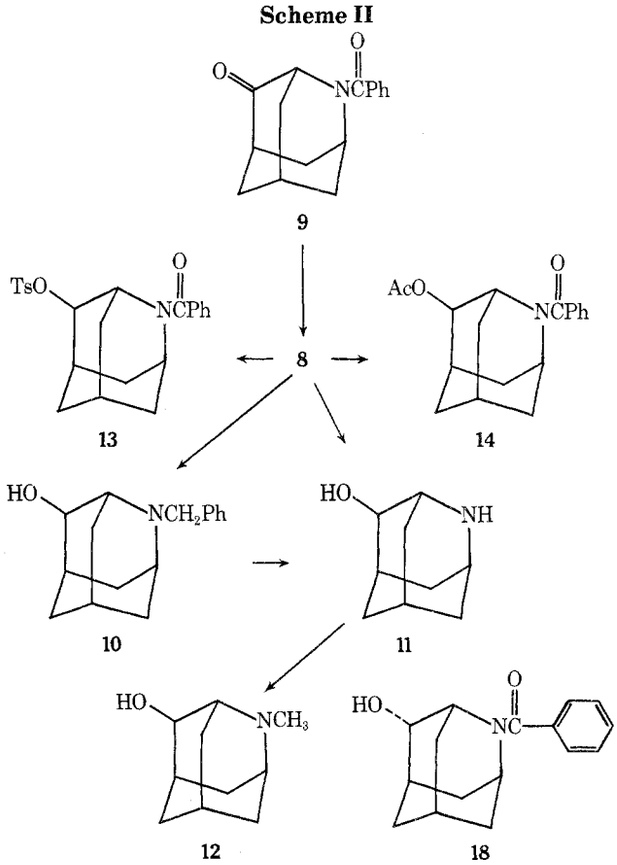


Table I
Acetolyses of *N*-Benzoyl-2-azaadamantan-4-yl *p*-Toluenesulfonate (13) and 2-Adamantyl *p*-Toluenesulfonate

Buffer	*T*, deg	10^5k, sec^{-1}	*H**, kcal	*S**, eu
N-Benzoyl-2-azaadamant-4-yl *p*-Toluenesulfonate (**13**)				
NaOAc (0.01 *M*)	120.0	18.0		
NaOAc (0.01 *M*)	100.0	2.42	29	−2
2-Adamantyl *p*-Toluenesulfonate (**11**)				
KOAc (0.1 *M*)	100.0	10.0		
KOAc (0.1 *M*)	75.15	0.55		
KOAc (0.1 *M*)	25.0	3.25×10^{-4} (calcd)	30	+3

Our synthesis of 4-hydroxy-2-azaadamantane proved to be an uncomplicated procedure due to the ring closure caused by spontaneous intramolecular opening of the epoxide by an amide nitrogen. The anti configuration was assigned assuming conventional back-side attack of the epox- the corresponding ketone with sodium borohydride in methanol and sodium borohydride in pyridine returned the anti alcohol. Attempts to equilibrate the alcohols with aluminum *tert*-butoxide, aluminum isopropoxide, and sodium methoxide failed. In another attempt to obtain syn alcohol **18**, a displacement of the *p*-toluenesulfonate group of **13** with sodium acetate was attempted. Hydrolysis of the reaction product gave a material which by infrared, thin layer chromatography, and gc analyses was shown to be the anti alcohol, exclusively.

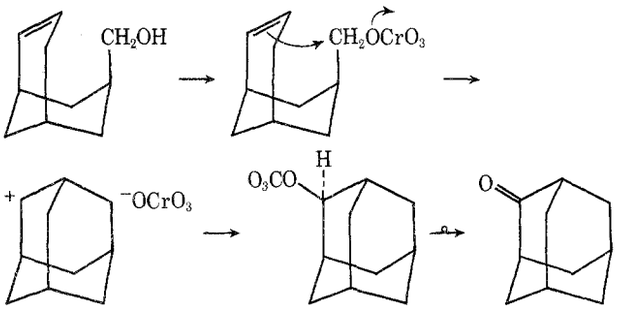
Acetolysis studies of *p*-toluenesulfonate **13** alone were therefore undertaken. Product studies at 100 and 120° in sodium acetate buffered media for a minimum of 8 half-lives revealed anti acetate **14** to be the sole product. The reaction demonstrated linear first-order kinetics at each temperature when kinetic measurements were made. Rates of reaction, which were obtained from the slopes of concentration *vs.* time plots, and are the averages of at least two runs, are given in Table I. Data from similar acetolyses of 2-adamantyl *p*-toluenesulfonate are included for comparison.[10]

Discussion

Our synthesis of 4-hydroxy-2-azaadamantane proved to be an uncomplicated procedure due to the ring closure caused by spontaneous intramolecular opening of the epoxide by an amide nitrogen. The anti configuration was assigned assuming conventional back-side attack of the epoxide. The ease of this closure to the adamantane skeleton, even though initiated by a relatively nonnucleophilic functional group, can be attributed primarily to proximity effects. Indeed, Dreiding models reveal that an atom attached to C_3 of the bicyclo[3.3.1]nonenylmethyl ring system is situated nearly within a C–C bond length of C_7. This certainly explains the similar facile π-route closures to 2-adamantyl derivatives observed by Udding, *et al.*,[11] in treatment of *endo*-bicyclo[3.3.1]non-6-en-3-ylcarbinol with dilute sulfuric acid, and by Schleyer, *et al.*,[12] in the solvolysis of *endo*-bicyclo[3.3.1]non-6-en-3-ylmethyl *p*-toluenesulfonate in aqueous acetone. A related unusual π-route closure was realized in our laboratories[13] from an attempt to oxidize *endo*-bicyclo[3.3.1]non-6-en-3-ylcarbinol to the corresponding carboxaldehyde. The only product obtained was 2-adamantanone, which presumably arose from the route shown in Scheme III.

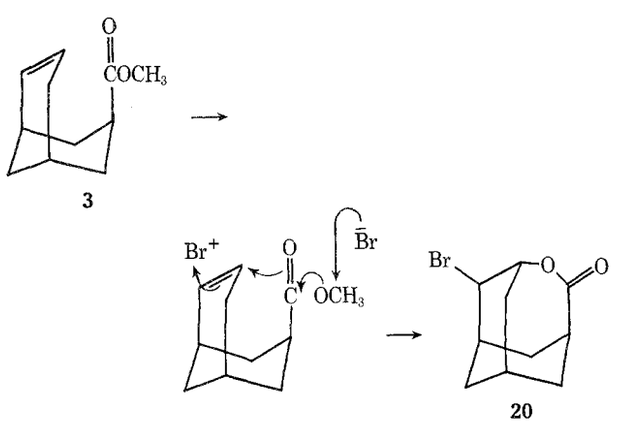
Clearly, the amide-initiated ring closure which we observed was caused by a charge distribution which is nearly

Scheme III



the reverse of these cases. For *endo*-3-*N*-benzamidobicyclo[3.3.1]non-6-ene (**7**), it is likely that any perturbation of the double bond by electrophilic reagents resulting in formation of partial positive charges at C_6 and C_7 can be satisfied at C_7 by orbital overlap with the amido group. Epoxidation of the double bond, or addition of bromine, thus results in the spontaneous ring closures observed.

For similar reasons, addition of bromine to *endo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**2**) results in formation of bromo lactone **20**. While this does not appear to be



3 20

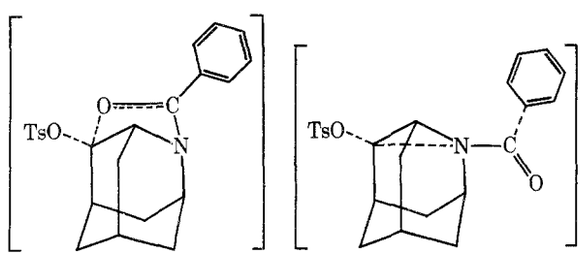
an unusual reaction, isolation of the same lactone from the addition of bromine to methyl ester **3** indicates that the carbonyl oxygen may be capable of effecting the ring closure in these cases.

Our failure, to date, to obtain the syn epimer of **8** precludes a definitive discussion of the solvolytic behavior of the 2-azaadant-4-yl cation. Yet, several points should be made. The production of only anti alcohol **8** from sodium borohydride reduction of ketone **9** seems to indicate a comparatively large steric hindrance at the anti face of the carbonyl. Still, it is possible that this stereospecificity and the failure of aluminum *tert*-butoxide and aluminum isopropoxide to effect what would seem, on this basis, to be a favorable equilibration to syn alcohol are due to complexation of the metallic reagents with the amide group, thus only allowing hydride delivery from the syn face, or to extreme steric factors, since the transition state for the reduction phase of equilibration requires that the hydride donor approach the most hindered face of the carbonyl if it is to produce syn alcohol. The failure of attempted SN2 displacement of the anti *p*-toluenesulfonate with acetate ion must be attributed either to strong steric hindrance to departure of the leaving group, repulsion of the nucleophile by the amide group, or to participation by the amide group in ionization of the ester.

The latter possibility seems the likely explanation for the stereochemical retention during acetolysis despite the fact that the rate at 100° was only one-fourth that of 2-adamantyl *p*-toluenesulfonate at the same temperature. A cal-

culation[14] of the C_3–C_4–C_5 bond angle (111.4°) in the carbonium ion from **13**, based on the position of the principal carbonyl infrared stretching frequency of ketone **9** at 1729.6 cm^{-1}, indicated only a slight difference from the corresponding angle (112.5°) of 2-adamantanone. The small increase in ring strain brought about by the amide nitrogen should thus alter the reactivity of the *p*-toluenesulfonate group of **13** only slightly in the adverse direction.[15]

It seems likely that participation by the amide in stabilizing the carbonium ion may govern the stereochemistry of the product. The precise manner of charge delocalization is not clear as two modes of amide participation appear possible. If the amide is oriented as shown in **21**, 1,3 participation *via* an oxazolinium type intermediate may occur. Otherwise, the amido nitrogen may participate in the manner represented by **22**. Molecular models do not indicate that



21 22

either arrangement is preferred, and either type of assistance would seem to involve introduction of strain in the rigid ring system.

Two rate-influencing effects may be concomitantly operative in solvolytic reactions of **13**: assistance to ionization by the amide, and retardation due to inductive and added ring strain effects of the amide. Unfortunately, our inability to obtain and solvolyze the epimeric syn alcohol complicates our assessment of the effects of the β-amido group. From data reported for the acetolyses of 2-cyclohexyl tosylates, one can estimate a 14-fold rate-retarding inductive effect for the β-benzamido group.[24] Since this leads to a predicted rate considerably smaller than the fourfold retarded rate which we observed, assistance to ionization may in fact be implicated.

Support for this assumption should become possible when other β-amido *p*-toluenesulfonates of this series and others, which have been recently prepared in our laboratories, are studied.

Experimental Section[16]

endo-**Bicyclo[3.3.1]non-6-ene-3-carboxylic acid (2)** was prepared by a modification of the method of Sasaki, *et al.*[17] To a stirred solution of 48.0 g (0.32 mol) of 2-adamantanone in 300 g of 99% methanesulfonic acid was added portionwise over 2 hr 21.6 g (0.336 mol) of sodium azide. The temperature was maintained at 20–25° during the addition. Nitrogen evolution ceased 2 hr after the addition was completed. After stirring an additional hour at room temperature, the reaction solution was diluted with 100 ml of water. An excess of 50% potassium hydroxide solution was carefully[18] added portionwise without external cooling. The exothermic reaction yielded a solution which was extracted once with ether. The aqueous layer was acidified with concentrated hydrochloric acid. The precipitated organic acid was collected by filtration, washed with five 50-ml portions of distilled water, and then dried in a vacuum desiccator over phosphorus pentoxide to give 39.4 g (74%) of **2**, mp 196–198° (lit. mp 195–198°).

Methyl *endo*-**Bicyclo[3.3.1]non-6-ene-3-carboxylate (3).** To a solution of 16.6 g (0.1 mol) of acid **2** in 200 ml of ether was added portionwise a cold ethereal solution of diazomethane, prepared from 36.3 g of Diazald.[19] Addition of diazomethane was stopped when nitrogen evolution ceased and the yellow color of diazomethane persisted in the reaction solution. The solution was then washed with saturated sodium bicarbonate solution, dried, and concentrated. The methyl ester was obtained as a colorless oil in quantitative yield and was not further purified. Infrared spectrum (film) 3025, 2930, 1730, 1460, 1440, 1360, 1220, 1200, 1100, 1020, and 780 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.30–2.70 (11 H, m), 3.56 (3 H, s), 5.55 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 180 (10), 149 (11), 148 (60), 121 (10), 120 (10), 93, (11), 92 (10), 91 (17), 87 (11), 80 (12), 79 (100), 78 (70), 67 (12), 44 (42), 31 (23), 39 (12).

endo-**Bicyclo[3.3.1]non-6-ene-3-carboxyhydrazide (4).** A solution of 18 g (0.1 mol) of methyl ester **3** in 40 ml of ethanol was heated to reflux with 15 g (0.3 mol) of 99% hydrazine hydrate. After 96 hr, 60 ml of water was added to the reaction solution. A distillation head was attached to the reaction flask and the solution was distilled at atmospheric pressure until the distillation temperature reached 100°. The residue was cooled and stored at 5° overnight. On standing, the oil which had separated from the aqueous solution crystallized. The colorless solid was collected on a filter, washed with water, and dried in a vacuum desiccator over phosphorous pentoxide to afford 15.1 g (84%) of **4**. An analytical sample was prepared by recrystallization from methylene chloride–hexane, mp 113.5–115.5°. Infrared spectrum (mull): 3300, 3200, 3000, 2850, 1630, 1500, 1465, and 725 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.50–2.68 (11 H, m), 3.82 (2 H, m), 7.36 (1 H, br, s).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.76; H, 8.95; N, 15.66.

endo-**Bicyclo[3.3.1]non-6-en-3-ylamine (6).** An aqueous solution of the hydrochloride salt of hydrazide **4** was prepared by warming 14.4 g (0.08 mol) of the hydrazide in 150 ml of water to which 7 ml (0.08 mol) of concentrated hydrochloric acid had been added. Insoluble material was removed by filtration and the aqueous solution was chilled to 0° in an ice–salt bath and 60 ml of carbon tetrachloride was added. A solution of 5.52 g (0.08 mol) of sodium nitrite in 20 ml of water was then added dropwise to the chilled hydrazide hydrochloride solution while rigorously swirling the resultant mixture. When the addition was complete, the mixture was poured into a chilled separatory funnel and the yellow-green organic layer, containing acyl azide **5**, was drawn off into a round-bottom flask containing 100 ml of water and 7 ml of concentrated hydrochloric acid. The mixture was stirred magnetically and allowed to warm until nitrogen evolution commenced. The mixture was then heated to reflux. After 56 hr, the mixture was cooled and the organic layer was separated and dried and concentrated to recover 3 g of a mixture of starting material and acid **2**. The aqueous layer was made strongly basic with solid potassium hydroxide, saturated with sodium chloride, and extracted with methylene chloride. The organic layer was washed once with water, dried, and concentrated to give 7.1 g of crude **6** as a pale brown solid. The crude product was sublimed at 70° (0.2 mm Hg) to give 5.7 g (55%) of air-sensitive pure amine as a colorless wax. Infrared spectrum (mull): 3350, 3150, 2925, 1580, 1435, 1270, 1070, 920, 900, and 860 cm^{-1}.

The amine was converted to its hydrochloride salt by dissolving 0.8 g (5.8 mmol) of **6** in 30 ml of solution of methylene chloride–ether (1:2) and bubbling dry hydrogen chloride gas through the resultant solution until no further precipitation of salt was observed. The precipitate was collected on a filter, washed with ether, and recrystallized from 2-propanol–ether, mp > 300°.

Anal. Calcd for $C_9H_{15}N \cdot HCl$: C, 62.23; H, 9.29; N, 8.07. Found: C, 61.98; H, 8.99; N, 7.89.

endo-**Bicyclo[3.3.1]non-6-en-3-ylbenzamide (7).** To a solution of 7.2 g (0.053 mol) of amine **6** in 35 ml of benzene containing 4.2 g (0.053 mol) of pyridine was added dropwise 7.45 g (0.053 mol) of benzoyl chloride. The temperature was maintained at 20–25° during the addition. The solution became yellow and a precipitate formed. When the addition was complete, the reaction mixture was stored overnight at 5°, then washed with six 25-ml portions of water, dried, and concentrated to 12.5 g of a slightly yellow oil. Trituration with *n*-hexane gave 11.5 g (85%) of **7** as a white crystalline solid. An analytical sample was obtained by recrystallization from ether–pentane, mp 83–85°. Infrared spectrum (mull); 3350, 3055, 2850, 2025, 1630, 1600, 1580, 1530, 1485, 1350, 1300, 715, and 700 cm^{-1}; nmr ($NCDCl_3$) (TMS) δ 1.34–2.70 (10 H, m), 4.50 (1 H, m), 5.70–6.40 (2 H, m), 7.20–7.80 (6 H, m).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.62; H, 7.94 N, 5.80. Found: C, 79.81; H, 8.11 N, 5.76.

N-**Benzoyl-2-azaadamantan-***anti*-**4-ol (8).** To 4.04 g (0.02 mol) of 85% *m*-chloroperbenzoic acid dissolved in 40 ml of methylene chloride was added dropwise a solution of 4.8 g (0.02 mol) of **7** dissolved in 40 ml of methylene chloride. The temperature was maintained below 25° during the addition. Afterward, the solution was allowed to stir at room temperature for 18 hr. The excess oxidizing agent was destroyed by washing with 10% sodium bisulfite

solution and the resulting solution was washed successively with saturated sodium bicarbonate solution and water until neutral. The solution was dried and concentrated to give 5.1 g of a colorless oil which crystallized upon treatment with a single drop of ethanol. The resultant oily solid was slurried with hexane and filtered to give 4.2 g (82.5%) of **8** as a white crystalline solid. An analytical sample was prepared by recrystallization from benzene–hexane, mp 143–145°. Infrared spectrum ($CHCl_3$): 3320, 2930, 2850, 1590, 1570, 1445, 1375, 1080, 1025, 970, 920, 790, 735, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.18–2.54 (10 H, m), 3.45 (1 H, s), 3.80 (2 H, m), 4.75 (1 H, m), 7.34 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.29; N, 5.46.

***N*-Benzyl-2-azaadamantan-*anti*-4-ol (10).** Reduction of amide **8** was effected using the method of Brown and Heim.[20] A 2.57-g (0.01 mol) sample of **8** in 25 ml of tetrahydrofuran was reacted with 20 ml of an approximately 1 *M* solution of diborane in tetrahydrofuran. After heating at reflux for 3 hr, the reaction was cooled in an ice bath and 10 ml of 6 *N* hydrochloric acid was added. When hydrogen evolution had ceased, the tetrahydrofuran was distilled off and the precipitated boric acid was removed by filtration. The resultant aqueous solution was saturated with sodium hydroxide and extracted with ether. The ether extract was washed with water, dried, and concentrated to give 2.3 g (90%) of **10** as a white crystalline solid. An analytical sample was prepared by recrystallization from cyclohexane–pentane, mp 94.5–96°. Infrared spectrum (mull): 3340, 2930, 2850, 1500, 1455, 1360, 1150, 1080, 1035, 1000, 740, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.18–2.33 (11 H, m), 2.67 (2 H, m), 3.81 (2 H, s), 4.00 (1 H, m), 7.24 (5 H, br, s).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.69; H, 8.58; N, 5.61.

2-Azaadamantan-*anti*-4-ol (11) was prepared by hydrogenolysis of an ethanolic solution of 0.73 g (0.003 mol) of benzylamine **10** employing 100 mg of 5% palladium on carbon as catalyst. When the theoretical amount of hydrogen had been absorbed, the reaction mixture was filtered and concentrated to obtain 0.42 g (78%) of **11** as a white solid. The hydrogen oxalate salt was prepared by dissolving the free amine in ethanol, adding an equivalent of oxalic acid dissolved in ethanol and effecting precipitation of the resultant salt with ether. Recrystallization from 2-propanol–ether gave analytically pure material, mp 172–175° dec. Infrared spectrum (mull): 3500–3100, 2900, 2850, 1640, 1580, 1460, 1060, and 1025 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO \cdot C_2H_2O_4$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.49; H, 6.55; N, 5.94.

***N*-Methyl-2-azaadamantan-*anti*-4-ol (12).** To a solution of 1.1 g of **11** (7.2 mmol) in 10.8 g (36 mmol) of 90% formic acid was added 0.8 g (8 mmol) of 30% formaldehyde. The resultant solution was heated to reflux. After 12 hr, the solution was cooled, 10 ml of water was added, and the excess formic acid was destroyed using solid sodium carbonate. The mixture was then extracted with ether and the ether solution was washed with water, dried, and ccentrated to give 1.1 g (90%) of **12** as a white solid, mp 164–165°. Infrared spectrum (mull): 3120, 2920, 2850, 1470, 1380, 1305, 1120, 1025, 1010, and 785 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.20–2.38 (10 H, m), 2.57 (3 H, s), 2.62 (2 H, m), 3.08 (1 H, s), 4.10 (1 H, m).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.65; H, 10.53; N, 8.29.

***N*-Benzoyl-4-oxo-2-azaadamantanone (9).** Alcohol **8** was oxidized to the corresponding ketone **9** by a Sarett (A)[21] and a Jones (B)[22] oxidation procedure.

Method A. To a solution of 1.9 g (0.024 mol) of dry pyridine in 30 ml of methylene chloride was added 1.2 g (0.012 mol) of chromium trioxide. The purple solution was stirred for 15 min. A solution of 0.514 g (0.002 mol) of **8** in 10 ml of methylene chloride was added in one portion to the stirring chromium trioxide–dipyridine solution. A black, tarry precipitate separated immediately. The mixture was stirred for 30 min, then the supernatant liquid was decanted and the residue rinsed with ether. The organic solutions were combined, washed with 5% aqueous sodium hydroxide solution, 5% hydrochloric acid, and finally with water. The solution was dried and concentrated to give 0.465 g (90%) of **9** as a pale yellow oil.

Method B. The Jones reagent was prepared by dissolving 6.7 g of chromium trioxide in 12.5 ml of water and adding 5.8 ml of concentrated sulfuric acid. Precipitated salts were dissolved by adding a minimal amount of water. To a solution of 0.514 g (0.002 mol) of **8** in 10 ml of acetone the oxidizing solution was added dropwise until its characteristic orange color persisted in the reaction flask. The temperature during the addition was maintained below 35°. The solution was decanted from the precipitated green chromium salts, and the residue was then washed with acetone. The combined organic solutions were treated with a few additional drops of oxidizing agent. Excess oxidizing agent was destroyed with isopropanol and then the acidic solution was neutralized with solid bicarbonate, filtered, and concentrated to remove acetone. The aqueous solution was saturated with sodium chloride and extracted with ether. The extracts were dried and concentrated to afford 0.492 g (95%) of **9** as a colorless oil.

The products of methods A and B were identical. Infrared spectrum (film): 3050, 2925, 2860, 1730, 1620, 1575, 1450, 1410, 1345, 1310, 1245, 1095, 1075, 1055, 1030, 975, 790, 720, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.77–2.50 (10 H, m), 2.75 (1 H, m), 4.50 (1 H, v br s), 7.40 (5 H, s).

***N*-Benzoyl-2-azaadamant-*anti*-4-yl *p*-Toluenesulfonate (13).** To a solution of 2.57 g (0.01 mol) of alcohol **8** in 20 ml of dry pyridine was added 1.91 g (0.01 mol) of freshly purified *p*-toluenesulfonyl chloride.[23] The reaction temperature was maintained at 5° for 14 days. The solution, which had deposited crystals of pyridine hydrochloride, was poured into ice–water and extracted with methylene chloride. The methylene chloride extracts were successively washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water. The extracts were dried and concentrated to give 3.2 g (80%) of **13** as a colorless oil which crystallized on standing at 0°. Recrystallization from ether–pentane gave an analytical sample, mp 100.5–102.5°. Infrared spectrum (mull): 3010, 2940, 2880, 1640, 1595, 1460, 1420, 1375, 1360, 1290, 1185, 1170, 980, 960, 860, 810, 720, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.40 (10 H, m), 2.47 (3 H, s), 3.90 (1 H, m), 4.68 (2 H, m), 710–800 (9 H, m).

Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.29; H, 5.89; N, 3.41; S, 7.81. Found: C, 67.01; H, 6.12; N, 3.59; S, 7.55.

***N*-Benzoyl-2-azaadamant-4-yl Acetate (14).** To a solution of 0.79 g (1 mmol) of pyridine in 10 ml of acetic anhydride was added 0.257 g (1 mmol) of alcohol **8**. The temperature was maintained at 10° during the addition. The reaction solution was stored at 5° overnight, treated with 25 ml of saturated sodium acetate solution, washed with saturated sodium bicarbonate solution and water, dried, and concentrated. Acetate **14** was obtained as a colorless oil in 85% yield. Infrared spectrum (film): 3050, 2940, 2860, 1735, 1640, 1440, 1420, 1370, 1300, 1240, 1200, 1090, 1040, 1035, 1000, 975, 780, 740, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.40 (10 H, m), 2.00 (3 H, s), 3.90 (1 H, br m), 4.40 (1 H, m), 4.98 (1 H, br m), 7.46 (5 H, br s).

***N*-Acetyl-*endo*-bicyclo[3.3.1]non-6-en-3-ylamine (15).** To a solution of 2.37 g (0.03 mol) of dry pyridine in 25 ml of acetic anhydride was added 4.1 g (0.03 mol) of freshly sublimed amine (**6**). The temperature was maintained at 5° for 12 hr. The solution was then treated as in the preparation of acetate **14** to obtain 4.6 g (85%) of **15** as a white crystalline solid, mp 94–96°. An analytical sample was recrystallized from ether–pentane. Infrared spectrum (mull): 3340, 3015, 2910, 2850, 1640, 1510, 1460, 1380, 1290, 760, 730, and 690 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.55 (13 H, m), 4.26 (1 H, m), 5.75–6.33 (2 H, m), and 6.40–7.05 (1 H, br m).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.82. Found: C, 73.65; H, 9.37; N, 7.61.

***N*-Acetyl-2-azaadamant-4-yl Bromide (17).** To a solution of 1 g (5.57 mmol) of **15** in 15 ml of carbon tetrachloride was added dropwise a 5% solution of bromine in carbon tetrachloride until the color of bromine persisted in the reaction mixture. Decolorization was slow and a gummy orange precipitate formed. When the addition was complete, the solvent was evaporated under a stream of nitrogen. The residue was triturated with ether to give an off-white solid. This hydrobromide salt **16** was recrystallized from ethanol–ether, mp 173–177° dec. Infrared spectrum (mull): 2925, 2850, 2425, 1650 (weak, broad), 1460, 1410, 1080, and 755 cm^{-1}.

The salt was dissolved in water, neutralized with sodium bicarbonate solution, extracted with ether, dried, and concentrated to give 1.0 g (70%) of **17** as a white solid. Sublimation at 70° (0.5 mm) afforded an analytical sample, mp 83–85°. Infrared spectrum (mull): 2930, 2850, 1650, 1470, 1450, 1440, 1420, 1360, 1310, 1220, 1105, 1095, 970, and 750 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.46–2.75 (10 H, m), 2.10 (3 H, s), 4.05 (1 H, m), 4.45 (1 H, m) 4.93 (1 H, m).

Anal. Calcd for $C_{11}H_{16}BrNO$: C, 51.17; H, 6.25; Br, 30.96. Found: C, 51.17; H, 6.26; Br, 31.23.

2-Bromo-4-oxa-5-oxohomoadamantane (20). Method A. To 1 g (6 mmol) of carboxylic acid **2** in 20 ml of carbon tetrachloride was added dropwise a 5% solution of bromine in carbon tetrachloride until the characteristic orange-yellow color of bromine persisted.

During the addition, decolorization was rapid and a precipitate formed. The precipitate was collected by filtration to obtain 1.1 g (80%) of **20** as a white solid, mp 132–134°.

Method B. To 0.5 g (2.8 mmol) of ester **3** in 10 ml of carbon tetrachloride was added a solution of 5% bromine in carbon tetrachloride as above. Work-up as above gave 0.45 g (70%) of **20** as a white crystalline solid. An analytical sample was obtained by recrystallization from cyclohexane, mp 132–134°. Infrared spectrum (mull): 2025, 2855, 1725, 1460, 1395, 1385, 1165, 1100, 1030, 995, 980, 920, and 725 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.38–2.92 (10 H, m), 3.12 (1 H, m), 4.33–4.70 (2 H, m).

Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.34; Br, 32.60. Found: C, 49.27; H, 5.29; Br, 32.83.

Reductions of *N*-Benzoyl-4-oxo-2-azaadamantane (9). (A) Sodium Borohydride in Methanol. A solution of 0.255 g (1 mmol) of ketone **9** in 10 ml of methanol was stirred at room temperature while 0.036 g (1.1 mmol) of sodium borohydride in a mixture of 1 ml of water and 5 ml of methanol was added. The solution was stirred for 4 hr. Hydrolysis was effected by the addition of water and 15% potassium hydroxide solution. The solution was diluted with 50 ml of water and extracted with three 15-ml portions of methylene chloride. The combined organic extractions were washed with water, dried, and concentrated to obtain 0.24 g (98%) of a viscous oil which solidified on standing. Infrared and gc analyses revealed the product to be 100% anti alcohol **8**.

(B) Sodium Borohydride in Pyridine. To a solution of 0.255 g (1 mmol) of ketone **9** in 10 ml of dry pyridine, stirring at room temperature, was added 0.108 g (3.4 mmol) of sodium borohydride in 10 ml of pyridine. After 24 hr, the reaction was worked up in the usual manner to obtain 0.216 g (85%) of 100% anti alcohol **8**.

Attempted Equilibrations of *N*-Benzoyl-2-azaadamantan-*anti*-4-ol (8). Method A. A mixture of 0.256 g (1.0 mmol) of anti alcohol **8**, 0.246 g (1.0 mmol) of aluminum *tert*-butoxide, and 0.002 g (0.01 mmol) of fluorenone in 10 ml of benzene was sealed in a tube and heated at 125° for 240 hr. After cooling, the contents of the tube were diluted with 40 ml of methylene chloride and washed with 10% hydrochloric acid until neutral and then with saturated aqueous sodium bicarbonate solution. The organic solution was dried and concentrated to give 0.248 g (98%) of alcohol plus a trace of fluorenone. The mixture was dissolved in the minimum amount of ether and percolated through a silica gel column packed in hexane. Fluorenone eluted rapidly with hexane. The alcohol was eluted with chloroform. Analysis (infrared spectra and gc) revealed that 100% starting anti alcohol was recovered.

Method B. To a solution of 0.256 g (1.0 mmol) anti alcohol **8** in 20 ml of dry 2-propanol[24] was added 0.400 g of freshly distilled aluminum isopropoxide. A 0.1-ml portion of acetone was added and the solution was heated at reflux for 96 hr. The reaction solution was poured into 100 ml of water containing 3 ml of concentrated hydrochloric acid, and the mixture was extracted with ether. The ether solution was washed with water and with saturated sodium bicarbonate solution, dried, and concentrated. Only starting alcohol was recovered.

Method C. To a solution of 0.512 g (2 mmol) of anti alcohol **8** in 25 ml of methanol was added 0.460 g (20 mg-atoms) of sodium in small pieces. A small amount of *N*-benzoyl-4-oxo-2-azaadamantane (**9**) was added and the mixture was heated at reflux for 96 hr under an argon atmosphere. After cooling, the solution was poured into 200 ml of water and extracted with five 50-ml portions of methylene chloride. The combined extracts were washed once with water, dried, and concentrated to give 0.210 g (40%) of an alcohol which upon analysis was shown to be 100% starting material.

Trimethylsilylation of Alcohols 8 and 10. To approximately 10 mg of alcohol in a 1-dram vial equipped with a micro stirring bar was added 1 ml of a silylating mixture composed of one part trimethylsilyl chloride, one part hexamethyldisilizane, and ten parts pyridine. The vial was capped and the mixture was stirred at room temperature overnight. The crude product was poured into 20 ml of water and extracted with three 15-ml portions of ether. The combined extracts were washed once with 10% hydrochloric acid, twice with water, and once with saturated sodium bicarbonate solution. Drying over magnesium sulfate and evaporation of the solvent afforded samples for gc analysis.

Acetolysis Product Studies. Eight Pyrex tubes, each containing 0.0125 g (3.02×10^{-5} mol) of **13** in 5 ml of 0.01 *M* sodium acetate buffered acetic acid containing 1% acetic anhydride, were flushed with nitrogen and sealed. The tubes were heated at constant temperature (100 and 120°) for a minimum of 8 half-lives. Duplicate runs were made for each temperature. After cooling, the contents of the tubes were combined and poured into 160 ml of water and extracted with five 20-ml portions of ether. The combined extracts were washed with water and 5% sodium bicarbonate solution and concentrated. The resulting acetate was compared by infrared spectroscopy and thin layer chromatography to an authentic sample of acetate **14** and was found to be identical. The acetate was then hydrolyzed to its corresponding alcohol by stirring overnight in ethanolic potassium hydroxide. The solution was neutralized with 6 *N* hydrochloric acid, and the ethanol was evaporated. Treatment of the residue with methylene chloride gave a solution which was dried and concentrated to afford a compound which possessed an infrared spectrum and a thin layer chromatogram identical with alcohol **8**. Approximately 5 mg of this alcohol was converted to the corresponding trimethylsilyl ether by the procedure previously described. The remaining alcohol was reduced to the corresponding benzylamino alcohol by the biborane reduction procedure previously described. This amino alcohol was also converted to its trimethylsilyl ether in the usual manner. The silyl ethers were analyzed by gc, using a 50 ft AP-L support coated open tubular (SCOT) capillary column. The following retention times were observed: trimethylsilyl ether of **8**, 235°, pressure 20 psi, retention time 7.2 min; trimethylsilyl ether of **10**, 210°, pressure 10 psi, retention time 7.0 min. In each case there was only one product peak.

Kinetic Studies. J. T. Baker reagent grade glacial acetic acid, to which was added 1% acetic anhydride, was employed in the acetolysis rate determinations. Standard 0.01 *N* perchloric acid in glacial acetic acid was prepared and standardized against potassium hydrogen phthalate. A 0.01 *N* solution of sodium acetate in glacial acetic acid was prepared and standardized against the perchloric acid solution. All titrimetric determinations were made with a 5-ml microburet precise to 0.01 ml using a 0.2% solution of crystal violet in glacial acetic acid as indicator. The end point of each titration was taken as the point at which no violet color was detectable. Constant temperature was maintained with a Neslab TEX 9-H isothermal bath filled with Dow-Corning 200 silicone fluid. Temperatures were determined with a calibrated National Bureau of Standards thermometer.

The general procedure for each kinetic run was as follows. The *p*-toluenesulfonate was weighed into a 50-ml volumetric flask and diluted to volume with standard sodium acetate in glacial acetic acid. Aliquots of this solution were sealed in ampules (Kimble Neutraglas, No. 12012-L) and immersed in the isothermal bath. At appropriate intervals, tubes were withdrawn, cooled in ice–water, and opened, and the contents were titrated with standard perchloric acid. The reaction was followed through approximately 3 half-lives, with zero time taken as the time the tubes were immersed in the bath.

The first-order rate constants were determined by the use of PLSTSQR, a specially written computer program (APL language) which plots at a terminal the graph of ln [ROTS] *vs.* time, then calculates the best rate fit to the valid points by the method of least squares.

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Registry No.—**1**, 700-58-3; **2**, 21932-98-9; **3**, 38773-17-0; **4**, 53092-70-9; **4** HCl, 53092-71-0; **6**, 53092-72-1; **6** HCl, 53092-73-2; **7**, 40923-03-3; **8**, 40810-53-5; **9**, 53092-74-3; **10**, 40810-54-6; **11**, 53092-75-4; **11** oxalate salt, 53154-31-7; **12**, 53092-76-5; **13**, 53092-77-6; **14**, 53092-78-7; **15**, 53092-79-8; **16**, 53092-80-1; **17**, 53092-81-2; **20**, 53152-40-2.

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Studies on 4-Quinazolinones. VII.[1] Some Novel Transformations

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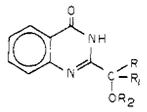
2-(1′-Hydroxydiphenylmethyl)-4-quinazolinone (**1**) or the *O*-acetate (**2**) on refluxing with acetic anhydride and sodium acetate yielded 1,1-diphenyl-3-methylene-9-oxo-9*H*-oxazolo[3,4-*a*]quinazoline (**3**), which gave 1-acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**6**) with ethanolic acetic acid. Both **3** and **6** regenerated the *O*-acetate (**2**) upon treatment with hydrochloric acid. Treatment of **3** or **6** with sodium borohydride in ethanol under reflux furnished 2-methyl-3-(*o*-hydroxymethylphenyl)-4-imino-5,5-diphenyloxazolidine (**13**) by an unusual amide reduction to a primary alcohol with concomitant hydrogenolytic cleavage of the 3,4-bond of the 4-quinazolinone system. Further hydrogenolysis of **13** in the presence of 10% Pd/C and perchloric acid gave **14**.

In continuation of our investigations of the reactions of 4-quinazolinones[1,3-5] we attempted the acetylation of 2-(1′-hydroxydiphenylmethyl)-4-quinazolinone (**1**)[4] with refluxing acetic anhydride in the presence of fused sodium acetate. The major product obtained was a new compound A, mp 163–164°, in approximately 60% yield in addition to 22% of the desired *O*-acetate **2.** The acetate **2** which also afforded compound A under the same condition was, however, the only isolable product in *ca.* 60% yield when **1** was refluxed with acetic anhydride alone.



1, R = R$_1$ = Ph, R$_2$ = H **7**, R = H, R$_1$ = Ph, R$_2$ = H
2, R = R$_1$ = Ph, R$_2$ = Ac **8**, R = R$_1$ = Me, R$_2$ = H
5, R = R$_1$ = Ph, R$_2$ = Et **9**, R = H, R$_1$ = Ph, R$_2$ = Ac
10, R = R$_1$ = Me, R$_2$ = Ac

Compound A was analyzed for $C_{23}H_{16}N_2O_2$. Although the mass spectrum did not exhibit the molecular ion, the peak at *m/e* 310 (base peak) in the highest mass region corresponding to $C_{21}H_{14}N_2O$ conceivably could arise by facile expulsion of ketene in the primary fragmentation. The intense bands at 1686, 1694 (sh), 1624, and 1594 cm^{-1} in the ir spectrum (Nujol) indicated the intact 4-quinazolinone moiety in the compound. The nmr spectrum showed a one-proton multiplet at δ 8.46 assignable to an aromatic proton peri to the carbonyl,[6] signals for 13 other aromatic protons, and a pair of sharp doublets at δ 4.67 and 5.6 (J = 3 Hz) attributed to an *exo*-methylene function. This latter assignment was confirmed by the isolation of formaldehyde on ozonolysis.

Treatment of compound A with 1% ethanolic acetic acid at room temperature resulted in recovery of starting material. However, upon refluxing it afforded a product, $C_{25}H_{22}N_2O_3$, mp 158–159°, characterized as 1-acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**6**). The nmr spectrum deserves special mention. Apart from the signals for 14 aromatic protons and a singlet at δ 2.11 for a $-COCH_3$ group, it exhibited a typical ABC_3 pattern composed of a three-proton triplet at δ 1.18 and a centrosymmetric two-proton multiplet around δ 3.38 for the $-O-CH_2-CH_3$ group clearly indicating the $-CH_2-$ protons to be diastereotopic. The first-order analysis of the AB part of the spectrum gave δ_A and δ_B values of 3.51 and 3.26, respectively, and the coupling constants J_{AB} = 9.5 Hz and J_{AC} = J_{BC} = 7 Hz were in excellent agreement with those recorded for the nonequivalent methylene protons of acetaldehyde diethyl acetal.[7] Since the nonequivalence was found to be temperature independent in the range of 30–86° and the corresponding deacetyl derivative (**5**) showed a simple A_2X_3 spectrum, the nonequivalence of the methylene protons presumably results from restricted rotation due to the presence of the acetyl function at N_1 rather than to different populations of the rotamers.[8]

Alkaline hydrolysis of either compound A or **6** with 5% alcoholic KOH furnished *N*-acetylanthranilic acid.

All the above observations (Chart I) appear best explained by the assignment of structure **3** (1,1-diphenyl-3-methylene-9-oxo-9*H*-oxazolo[3,4-*a*]quinazoline) to compound A and not the other possible alternative structure **4.**

Chart I