posited 1.11 g (38%) of **19** as scarlet prisms, mp 178–182°; recrystallization from acetone gave long scarlet needles, mp 181–183°; ν (Nujol) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; mol wt 201.3. Found: C, 77.86; H, 7.53; N, 6.96; mol wt 170 (vapor osmometry in dimethylformamide).

Registry No.—**2e,** 33777-57-0; **2f,** 33777-56-9; **2g,** 33872-68-3; **2h,** 33777-52-5; **5a,** 27109-24-6; **5a** mono-2,4-DNP, 31451-10-2; **5b,** 33777-54-7; **5c,** 33872-66-1; **5d,** 33777-55-8; **5e,** 33886-25-8; **5f,** 33777-30-9; **5g,** 33872-67-2; **19,** 33777-31-0.

The Synthesis of 2-Keto-4a-phenyloctahydro-Δ^8-naphthyridine and 2-Keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane[1]

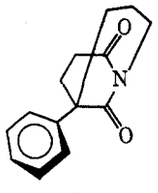
EDWARD E. SMISSMAN* AND JAMES W. AYRES

The Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

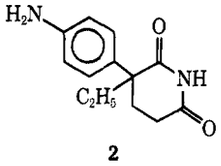
Received November 23, 1970

The synthesis of 2-keto-4a-phenyloctahydro-Δ^8-naphthyridine (**10**) and 2-keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (**16**) is presented. A number of new 2,2-dialkylphenylacetonitrile and *N*-alkylglutarimide derivatives were synthesized as intermediates in the formation of **10** and **16**.

The synthesis of 5-phenyl-2,9-diketo-1-azabicyclo-[3.3.1]nonane (**1**) was proposed as part of a continuing study of the steric aspects of the antiepileptic action of drugs having the ureide or imide function. The major anticonvulsant drugs all contain this function and it was desired to prepare a bridged analog of the toxic but efficacious drug aminoglutethimide (**2**).



1



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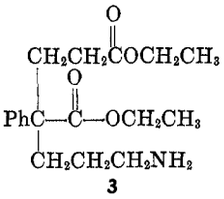
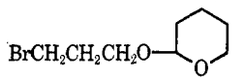
The initial approach to the desired bicyclic glutarimide ring system involved the attempted synthesis of compound **3**. It was predicted that a base-catalyzed



3

intramolecular attack by the amino group on the ester functions would produce **1**.

Phenylacetonitrile was allowed to react with 2-(3-bromopropoxy)tetrahydropyran (**4**) to yield 2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**). The latter compound (**5**) was converted to 2-cyanoethyl-2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**6**) *via* cyanoethylation. The protecting group (pyranyl ether) was removed under acidic conditions to give 2-cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile (**7**). The alcohol **7** was converted to the *p*-toluenesulfonate **8** and the tosylate function was displaced by ammonia to yield 2-(3-aminopropyl)-2-cyanoethylphenylacetonitrile (**9**). Treatment of **9** with ethanolic hydrogen chloride did not convert the



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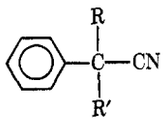
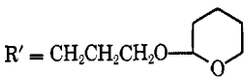
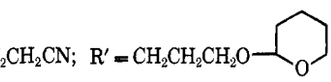




5, R = H; R′ = $CH_2CH_2CH_2O$–

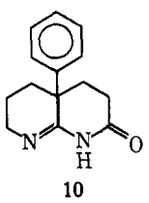


6, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2O$–

7, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2OH$

8, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2OTs$

9, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2NH_2$



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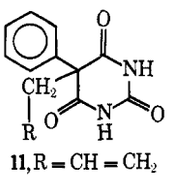
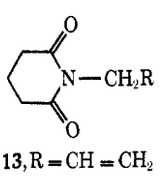


11, R = CH = CH_2

12, R = CH_2CH_2Br



13, R = CH = CH_2

14, R = CH_2CH_2Br

15, R = $CHBrCH_3$

dinitrile to the diester **3** as expected but to a product which was assigned the structure **10** on the basis of spectral and elemental analysis. The treatment of **9** with base afforded the same product. When the reaction was performed in the presence of aqueous hydrogen chloride no identifiable products were obtained.

The failure of **9** to yield **3** can be rationalized by the apparent facility of the intramolecular attack by the primary amine function to yield **10** as compared to the less facile intermolecular attack by ethanol.

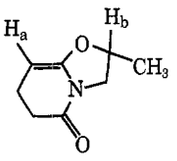
A previous publication[2] reported the light-catalyzed addition of hydrogen bromide to 5-phenyl-5-allylbarbituric acid (**11**) to produce the primary bromo compound **12**. In a similar manner, the treatment of *N*-allylglutarimide (**13**) was found to yield *N*-(3-bromo-

(1) Taken in part from the dissertation presented by J. W. Ayres, Aug 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

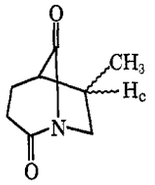
(2) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *J. Org. Chem.*, **35**, 3823 (1970).

propyl)glutarimide (**14**). If a small amount of acetic acid was included in this reaction, the product was found to be *N*-(2-bromopropyl)glutarimide (**15**).

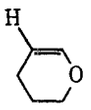
In an effort to secure a general synthetic route to the carbon-bridged bicyclic glutarimides at attempt was made to cyclize **15** to the desired compound. However, compound **15** was converted to 2-keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (**16**) by treatment with



16



17



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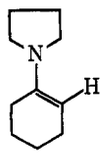


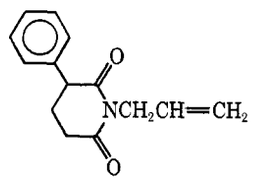
19

sodium hydride in dioxane. The ir spectrum (neat) showed a broad absorption from 1630 to 1750 cm^{-1} and in carbon tetrachloride a sharper peak at 1685 cm^{-1} with slight shoulders at 1665 and 1700 cm^{-1}. The nmr spectrum showed a three-proton doublet at δ 1.35 (methyl), a four-proton multiplet at δ 2.35, and one proton each at δ 3.3, 3.9, 4.15, and 4.5. Decoupling studies indicated that the proton at δ 4.5 was coupled with the methyl protons. Structure **17** was eliminated as a possibility on the basis of these spectral data and the chemical reactivity of the compound. The proton H_c (**17**) would not be predicted to appear as far downfield as δ 4.5 but this is a reasonable absorption for H_b (**16**). H_a (**16**) appears as a triplet at δ 4.15 and a similar proton in dihydropyran (**18**) at δ 4.65,[3] while the analogous proton in compound **19** absorbs at δ 4.21.[4]

Compound **16** was unstable in air and it is likely that it was undergoing hydrolysis to produce a secondary alcohol.

Compound **14** was recovered unchanged after treatment with sodium hydride in dioxane. When dimethylformamide was utilized as the solvent, a crude oil was obtained but it could not be purified.

α-Phenylglutaric anhydride was converted to *N*-allyl-α-phenylglutarimide (**20**). Irradiation of **20** in



20

the presence of hydrogen bromide afforded an oil whose nmr spectrum was consistent with the desired compound, but it could not be purified.

(3) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Analytical Instrument Division of Varian, 1962, National Press, Spectrum No. 111.

(4) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

Experimental Section[5]

2-(3-Bromopropoxy)tetrahydropyran (**4**).—The method utilized was essentially that of Robinson.[6] 2-Bromo-1-propanol (100.0 g, 0.720 mol) and 2,3-dihydropyran (67.5 g, 0.804 mol) yielded 124.6 g (80%) of a clear liquid, bp 86° (0.5 mm).

2[3-(2-Tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**).—Sodium hydride (12.0 g, 0.268 mol), 53.5% in mineral oil, was stirred for 20 min in 100 ml of dry C_6H_6 in a N_2 atmosphere to wash away the mineral oil, and to this suspension was added 100 ml of dry DMF. A solution of phenylacetonitrile (30.0 g, 0.256 mol) in 30 ml of DMF was added dropwise. After H_2 evolution ceased the mixture was transferred to a dropping funnel and added dropwise to a stirring, heated (80°) solution of 2-(3-bromopropoxy)tetrahydropyran (**4**) (54.0 g, 0.242 mol) in 50 ml of DMF. The mixture was stirred and maintained at 80° for 2 hr, poured into 400 g of crushed ice, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and distilled to yield **5** (16.6 g, 25.6%), bp 142–148° (0.3 mm). The spectral data are consistent with the assigned structure.

2-Cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile (**7**).—A solution of 2[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**) (3.9 g, 0.02 mol) in 6 ml of *tert*-BuOH was added dropwise to a stirred solution of acrylonitrile (1.6 g, 0.03 mol) in 4 ml of *tert*-BuOH. After the first 10 drops were added, 5 drops of 30% KOH–MeOH were added. After addition was complete the reaction mixture was heated at 60° for 1 hr, poured into 25 ml of H_2O, and extracted with Et_2O. The organic layer was dried (K_2CO_3) and the Et_2O was removed *in vacuo* to yield 2-cyanoethyl-2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**6**). Compound **6** was refluxed in 20 ml of Me_2CO and 10 ml of 10% HCl overnight and the solution was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and distilled to yield **7** (1.0 g, 29.4%), bp 190° (0.25 mm).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.75; H, 7.33; N, 12.16.

2-Cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile *p*-Toluenesulfonate (**8**).—*p*-Toluenesulfonyl chloride (9.5 g, 0.05 mol) was added to a stirred solution of 2-cyanoethyl-2-(3-hydroxypropyl)-phenylacetonitrile (**7**) (5.0 g, 0.02 mol) and 1,4-diazabicyclo-[3.3.3]octane (11 g, 0.10 mol) in 130 ml of C_6H_6 which was cooled in an ice bath. The mixture was placed in the refrigerator overnight, allowed to melt, and washed with 10% HCl. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to yield **8** as a crude oil (6.6 g, 78%). The spectral data are consistent with the assigned structure.

2-(3-Aminopropyl)-2-cyanoethylphenylacetonitrile (**9**).—Liquid NH_3 (90 g, 5.3 mol) was added to 2-cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile *p*-toluenesulfonate (**8**) (14 g, 0.04 mol) in a stainless steel reaction vessel with a glass liner and allowed to react at 25° overnight. The vessel was cooled to −50° and opened, and the NH_3 allowed to evaporate. The residue was washed with $CHCl_3$, the solid was filtered, and the filtrate was evaporated *in vacuo* to yield **9** as a crude oil (6.3 g, 72.5%).

2-Keto-4a-phenyloctahydro-Δ^8-naphthyridine (**10**).—Hydrogen chloride was bubbled through a stirred solution of 2-(3-aminopropyl)-2-cyanoethylphenylacetonitrile (**9**) (5.0 g, 0.02 mol) in 90 ml of absolute EtOH for 1 hr. The solution was stirred overnight, added to 90 ml of H_2O, made basic (10% NaOH), and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and removed *in vacuo* to yield an oil. Addition of a small volume of acetone yielded a solid **10**, which was collected on a filter and purified by sublimation at 130° (0.2 mm) (400 mg, 8.8%): mp 236° dec; ir ($CHCl_3$) 3380 (NH), 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.9 (m, 8 H, CH_2), 3.8 (m, 2 H, CH_2N), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.19; H, 7.08; N, 12.13.

N-**Allylglutarimide** (**13**).—Allylamine (7.53 g, 0.132 mol) was added dropwise to a stirred solution of glutaric anhydride (15.0 g, 0.132 mol) in 25 ml of C_5H_5N. After the reaction cooled, 125 ml of Ac_2O was added and the reaction was maintained at reflux for 2 hr. The excess solvent was removed by distillation and the

(5) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F and M 185 C, H, N Analyzer, University of Kansas.

(6) R. A. Robinson, Ph.D. Thesis, University of Kansas, 1969.

residue was distilled *in vacuo* to yield **13** (14.1 g, 71%), bp 76° (0.2 mm).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.23; N, 9.14. Found: C, 62.98; H, 7.54; N, 8.97.

N-(**3-Bromopropyl**)**glutarimide** (**14**).—A solution of *N*-allylglutarimide (**13**) (50.0 g, 0.326 mol) stirred in 1600 ml of toluene was irradiated (G. E. Sunlamp-275W-100-125V) overnight. During the irradiation HBr was bubbled through the solution. The reaction was cooled, the toluene was removed *in vacuo*, and the residue was distilled to yield **14** (33.8 g, 44.5%), bp 132° (0.2 mm).

N-(**2-Bromopropyl**)**glutarimide** (**15**).—A stirred solution of *N*-allylglutarimide (**13**) (230 g, 1.50 mol) which still contained some HOAc in 4000 ml of toluene was irradiated (G. E. Sunlamp-275W-110-125V) overnight. During the irradiation HBr was bubbled through the solution. The toluene was removed *in vacuo* and the solid residue was dissolved in boiling EtOH and immediately cooled in an ice bath. Compound **15** (28.4 g, 8.5%), mp 58–60° (petroleum ether, bp 60–70°), was collected by filtration.

Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.09; H, 5.16. Found: C, 40.73; H, 5.36.

The EtOH was removed from the filtrate to yield an oil (70.0 g) which was identified as the ethyl ester of the ring-opened imide from its nmr spectrum.

2-Keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (**16**).—A solution of *N*-(2-bromopropyl)glutarimide (**15**) (15.0 g, 0.06 mol) in 15 ml of ethylene glycol dimethyl ether was added to a stirred suspension of NaH (2.64 g of 57% in mineral oil, 0.063 mol) and refluxed for 3 days. The solid was removed by filtration and the filtrate was concentrated *in vacuo* to leave an oil which was distilled to yield **16** (7.10 g, 73.5%): bp 57° (0.2 mm); ir ($CHCl_3$) 1660 (C=O), 1710 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.40 (d, 3 H, CH_3), 2.35 (m, 4 H, CH_2CH_2), 3.3 (d, 1 H, HCH–), 3.9 (d, 1 H, HCH), 4.15 (m, 1 H, C=CH), 4.5 (m, 1 H, OCH).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.23; N, 9.14. Found: C, 62.42; H, 7.28; N, 8.75.

N-**Allyl-α-phenylglutarimide** (**20**).—Allylamine (6.0 g, 0.10 mol) was added dropwise to a stirred solution of α-phenylglutaric anhydride (20 g, 0.10 mol) in 40 ml of C_5H_5N. The exothermic reaction was allowed to cool to 25° and then 200 ml of Ac_2O was added and the solution was refluxed for 3 hr. The solution was concentrated by distillation and the residue was distilled *in vacuo* to yield **20** (19.7 g, 82%), bp 148–152° (0.2 mm).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.06; H, 6.56.

Registry No.—**4**, 33821-94-2; **5**, 33821-95-3; **7**, 33821-96-4; **10**, 33821-97-5; **13**, 3880-20-4; **14**, 33821-99-7; **15**, 33822-00-3; **16**, 33822-01-4; **20**, 33822-02-5.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants GM-09254 and GM-01341. We appreciate the assistance rendered by Mr. Darrell Abernethy in the preparation of starting materials.

Characteristics of Various Reactions of Bromine with Arylcyclopropanes[1]

Robert T. LaLonde,* Paul B. Ferrara, and Anthony D. Debboli, Jr.

Department of Chemistry, State University College of Forestry, Syracuse, New York 13210

Received August 12, 1971

The reaction of bromine with *cis*- and *trans*-diphenylcyclopropane gives 1,3-addition products only while phenylcyclopropane gives 1,3-addition products and/or aromatic substitution. The rate of reaction and product composition for all arylcyclopropanes is highly sensitive to light, temperature, and change in solvent but insensitive to the presence of nitrobenzene and trinitrobenzene.

There is ample evidence for the ionic addition of halogen to an array of cyclopropanes taking place under diverse conditions. Cyclopropanes undergo C–C fission with halogen in the presence of Lewis acids to give mixtures of rearranged and unrearranged dihalides.[2] More highly strained cyclopropanes, such as those incorporated into polycyclic systems,[3] and cyclopropanols[4] undergo ionic C–C fission without catalysts.

Contrasting with the generality of ionic additions, free-radical addition to cyclopropanes is less frequent and when it does occur is often competing with free-radical substitution. The free-radical addition of chlorine to bicyclo[2.1.0]pentane has been reported[5] as has the peroxide-catalyzed addition of bromine to 1-alkyl-2-phenylcyclopropanes.[6] Spiropentane gives a mixture of nearly equal amounts of ring-opened and ring-substituted products on photochemical chlorination.[7] Thermal, photochemical, or peroxide-catalyzed chlorination of cyclopropane gives minor amounts of addition product,[8] and arylcyclopropanes are inert to *N*-bromosuccinimide addition of bromine in the presence of free-radical initiators.[9] Consistent with the last mentioned lack of reactivity are the reports that some cyclopropanes also are inert, or are nearly so, to free-radical chain polymerization[10] and halomethane and mercaptan additions.[11]

Our interest in the various modes by which halogens add to cyclopropanes and the conditions which promote one mode of addition as opposed to the other arose during an initial stage of study of bromine addition to *cis*- and *trans*-1,2-diphenylcyclopropane. We observed that the reaction of bromine with these two cyclopropanes in carbon tetrachloride solution was strongly influenced by light and consequently we suspected at first the involvement of a free-radical

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for their support of this work.

(2) (a) N. C. Deno and D. N. Lincoln, *J. Amer. Chem. Soc.*, **88**, 5357 (1966); (b) N. C. Deno and W. E. Billups, *Chem. Commun.*, 1387 (1970).

(3) (a) S. Masamune, *Tetrahedron Lett.*, 945 (1965); (b) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, **92**, 4013 (1970); R. T. LaLonde, *ibid.*, **87**, 4217 (1965).

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(8) (a) J. D. Roberts and P. H. Dirstine, *ibid.*, **67**, 1281 (1945); (b) P. G. Stevens, *ibid.*, **68**, 620 (1946).

(9) (a) R. Ya. Levina, P. A. Gembitskii, and E. G. Treschchova, *Zh. Obshch. Khim.*, **29**, 3233 (1959); (b) Yu. S. Shabarov, S. N. Burenko, and R. Ya. Levina, *Zh. Org. Khim.*, **4**, 66 (1968); (c) E. C. Friedrich and R. L. Holmstead, *J. Org. Chem.*, **36**, 971 (1971).

(10) G. S. Hammond and R. W. Todd, *J. Amer. Chem. Soc.*, **76**, 4081 (1954).

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