Base-Catalyzed Intermolecular Condensation of α,β-Unsaturated Ketones. Dimerization of 2,4-Diarylidenecyclobutanones to 2-Spiro(2-oxocyclobutyl)bicyclo[3.2.0]heptan-6-one Derivatives[1]

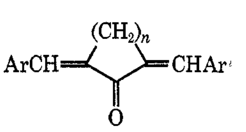
ARNOLD T. NIELSEN,* RICHARD C. WEISS, AND DONALD W. MOORE

Chemistry Division, Code 605, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

Received October 1, 1971

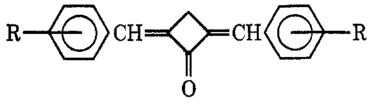
The self-condensation of 2,4-dibenzylidenecyclobutanone (**2a**) in aqueous ethanolic sodium hydroxide produces a crystalline dimer, 7-benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]-heptan-6-one (**5a**) in 20–30% yield. Its structure has been established from chemical and spectral evidence, including nmr spectra of **5a** and its d_1, d_{20}, d_{24}, and d_{25} deuterio derivatives (**5b–e**), prepared by dimerization of **2a**, **2a**-d_{10}, and **2a**-d_{12} in aqueous ethanol or deuterium oxide–ethanol-*O-d*. Other 2,4-diarylidenecyclobutanones (4-methylbenzylidene and 3,4-dimethoxybenzylidene) form crystalline dimers (**5f,g**). The base-catalyzed dimerization reactions proceed through the unique 2,4-diarylidenecyclobutanone anion intermediate and involve an intermolecular Michael addition followed by intramolecular Michael cyclization. The stereochemistry of dimer **5a** is discussed.

Many α,α′-diarylidenecycloalkanones (**1**, n = 2–7) have been prepared in good yields by base-catalyzed condensation of aromatic aldehydes (2 molar equiv) with cycloalkanones.[2-5] The α,β-unsaturated ketones obtained from cyclopentanone and larger ring cycloalkanones are stable in basic media and undergo no known self-condensation reactions under normal reaction conditions. By contrast, 2,4-diarylidenecyclobutanones (**1**, n = 1) are sensitive to base and difficult to purify.



1

Pure 2,4-diarylidenecyclobutanones (**2a–d**) were first reported only recently by Thieme.[6] A substance previously described as **2a** by Demjanov[7] is believed to be a dimer. In the present work a modified procedure has produced **2b** in improved yield and new ketones **2e**,**f**.



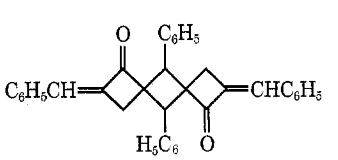
2a, R = H
b, R = 4-CH_3
c, R = 4-CH_3O
d, R = 4-Cl
e, R = 3,4-$(CH_3O)_2$
f, R = 4-$(CH_3)_2N$

The only other aldehydes reported to undergo aldol condensation with cyclobutanone are formaldehyde and acetaldehyde. These produced 2,2,4,4-tetramethylolcyclobutanone and epimeric 2-(1-hydroxyethyl)-cyclobutanones, respectively.[8,9]

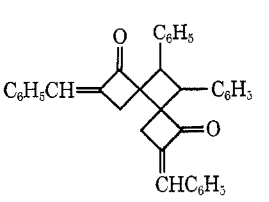
2,4-Dibenzylidenecyclobutanone (**2a**, mp 190–191°) in basic media reacts rapidly to form dimers of unknown structure, $C_{36}H_{28}O_2$. Three such dimers have been isolated in crystalline form, including a new one described in the present work. By condensing benzaldehyde (2 molar equiv) with cyclobutanone in 60% ethanolic potassium hydroxide at ambient temperature, Demjanov[7] obtained a crystalline product (large yellow leaflets from chloroform, mp 170–171°) which he described as monomer **2a**. It is now believed to be a dimer of **2a**. Conia,[8] in carrying out the same reaction under similar conditions, obtained a dimeric product, $C_{36}H_{28}O_2$, mp 168–170°. Both workers experienced great difficulty in securing a crystalline sample and satisfactory elemental analyses. Yields were not stated. Conia's sample was amorphous and contained some ketol impurity.

Thieme,[6] by treating pure 2,4-dibenzylidenecyclobutanone (**2a**) with 95% ethanolic sodium hydroxide (*ca.* 0.075 *M*) at 50°, obtained a crystalline dimer in 20% yield (yellow cubes from acetonitrile, mp 223–225°). In our hands his procedure gave amorphous products. However, employing a lower concentration of sodium hydroxide (0.01–0.035 *M*) in 85–95% aqueous ethanol at 25–45°, we obtained a new dimer in 20–30% yield (mp 191–193°, yellow spear-shaped prisms from acetonitrile). Heating a sample of our dimer in refluxing ethanolic sodium hydroxide converted it into an amorphous product from which no crystalline material could be isolated. Thieme determined the nmr and infrared spectra of his dimer but did not speculate on its structure.

Conia, principally on the basis of ultraviolet and infrared spectra, suggested structures **3** or **4** for his dimer.[8] He noted that dimers of benzylidene α,β-unsaturated ketones formed by irradiation, or in alkaline media, may have a cyclobutane structure. However, we have demonstrated that such structures are incorrect for dimers produced in alkali-catalyzed re-



3



4

---

[1] A preliminary account of this work has appeared: A. T. Nielsen, R. C. Weiss, and D. W. Moore, *Chem. Commun.*, 1281 (1969).

[2] A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 38, 238 (1968).

[3] E. A. Braude and B. F. Gofton, *J. Chem. Soc.*, 4720 (1957).

[4] (a) F. Mattu, *Rend. Semin. Fac. Sci. Univ. Cagliari*, **32**, 230 (1962); *Chem. Abstr.*, **63**, 17935 (1965); (b) F. Mattu and M. R. Manca-Mura, *Rend. Semin. Fac. Sci. Univ. Cagliari*, **34**, 286 (1964); *Chem. Abstr.*, **63**, 13126 (1965).

[5] S. V. Tsukerman, L. A. Kutulya, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **34**, 3597 (1964).

[6] P. Thieme, *Chem. Ber.*, **101**, 378 (1968).

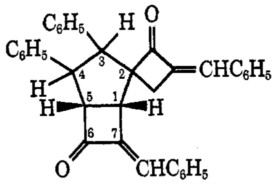
[7] N. J. Demjanov and M. Dojarenko, *ibid.*, **55**, 2737 (1922).

[8] J.-M. Conia and J.-P. Sandré, *Bull. Soc. Chim. Fr.*, 744 (1963).

[9] J.-E. Dubois and M. Dubois, *ibid.*, 3120 (1969).

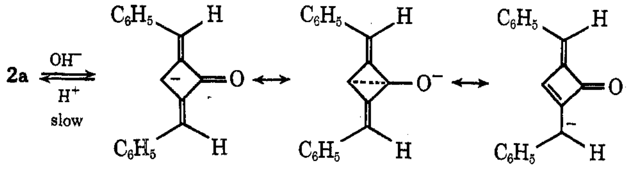
actions.[10] Styryl alkyl ketones dimerize to 3,5-diaryl-4-alkanoylcyclohexanones or 5-aryl-3-styryl-2-cyclohexen-1-ones in aqueous ethanolic sodium hydroxide.[11-13] Thieme demonstrated that **2a** dimer is not produced photochemically or thermally.[6]

We have established the structure of 2,4-dibenzylidenecyclobutanone dimer prepared in the present work as 7-benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-6-one (**5a**) on the basis of chemical evidence, spectral data, and deuterium-labeling experiments. The complete configuration of **5a** is unknown. It appears likely that dimers of **2a** described by Thieme[6] and Conia[8] are epimers of **5a**.



5a

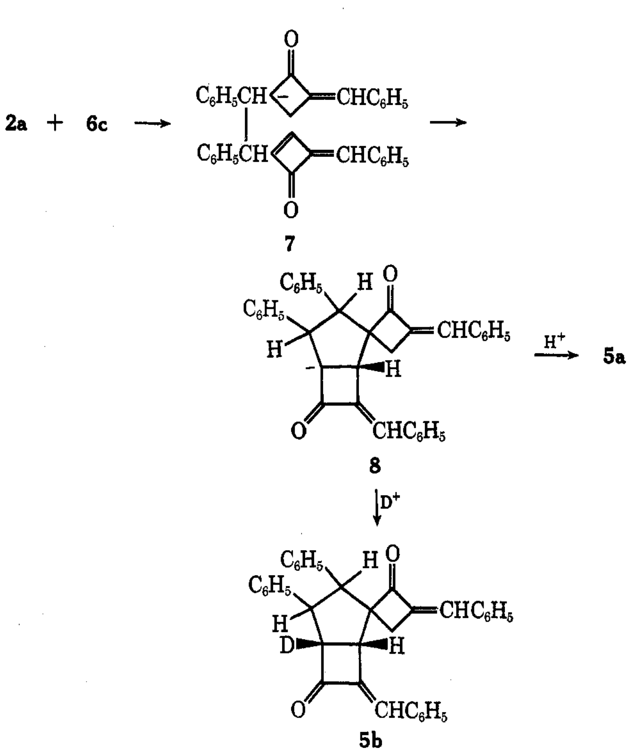
The 2,4-dibenzylidenecyclobutanone anion **6** has been postulated as an intermediate in the base-catalyzed dimerization leading to **5a**.[1] α,α'-Diarylidenecycloalkanones other than **1** ($n = 1$) cannot form such an anion. Anion **6** is unique in that, unlike other α,β-unsaturated ketone derived anions, it cannot participate in classical enolate anion resonance. Charge delocalization on oxygen (**6b**) is believed to contribute to its stabilization, however. It was observed that the anion does not undergo rapid deuterium exchange under the reaction conditions, since in ethanol-*O-d* the dimer product is found to have but one deuterium.

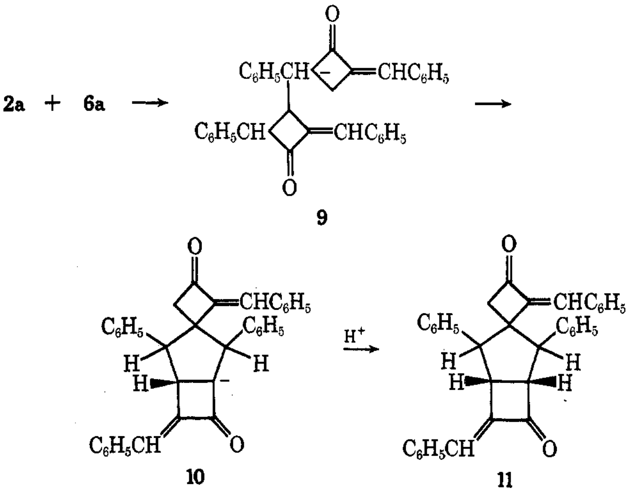


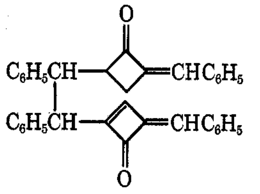
6a **6b** **6c**

The mechanism of the base-catalyzed formation of **2a** dimer is believed to follow that of other base-catalyzed α,β-unsaturated ketone dimerizations.[10-13] The initial step is a Michael addition leading to anion **7**, a step faster than reprotonation of **6a** to regenerate **2a**. A second, intramolecular Michael addition would produce anion **8**, and protonation of **8** would lead to dimer **5a**. The ring closure **7** → **8** is probably more rapid than retrogression to **2a** or protonation of **7**, since in ethanol-*O-d* only one deuterium is incorporated in product **5b**.

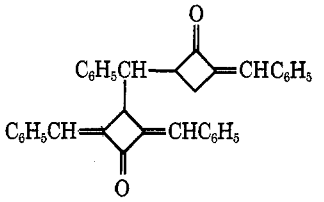
Other structures may be considered for **2a** dimer. An alternate Michael addition path involving C-3 of anion **6** would produce a different bicyclo[3.2.0]heptanone (**11**) *via* anion intermediates **9** and **10**. C-Protonation of anions **7** and **9** would produce acyclic diketones **12** and **13**, respectively. Double-bond isomers of these compounds might arise by prototropic rearrangement, *e.g.*, **14** and **15**; in ethanol-*O-d* such products would be expected to incorporate at least two deuterium atoms, however.



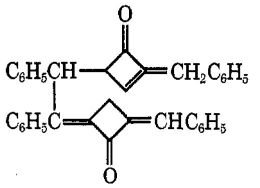




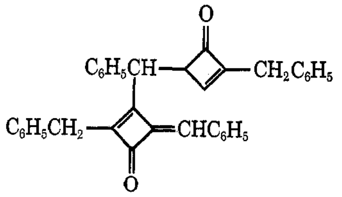
12



13



14



15

Spectral data support **5a** over alternate structures. The infrared and ultraviolet spectra of 2-benzylidenecyclobutanone (**16**) were determined by Conia,[8] who first prepared this compound. When these data are

---

[10] A. T. Nielsen and H. J. Dubin, *J. Org. Chem.*, **28**, 2120 (1963).

[11] A. T. Nielsen and S. Haseltine, *ibid.*, **33**, 3264 (1968).

[12] A. T. Nielsen and D. W. Moore, *ibid.*, **34**, 444 (1969).

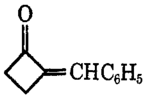
[13] A. T. Nielsen, H. Dubin, and K. Hise, *ibid.*, **32**, 3407 (1967).

TABLE I

INFRARED AND ULTRAVIOLET SPECTRA OF 2,4-DIBENZYLIDENECYCLOBUTANONE AND DERIVED COMPOUNDS

Compd	ν, cm^{-1} (KBr) C═O	ν, cm^{-1} (KBr) C═C	λ_{max} (EtOH), nm (ϵ_{max})
16	1735[a]	1645	223 (10,000)[a]
			229.5 (11,500)
			299 (27,500)
2a	1720[b,c]	1670	236 (18,300)[b]
		1635	349 (36,500)
5a (mp 191–193°)	1746[b,d,e]	1638	227 (20,500)[b]
	1734		233 (21,400)
			318 (50,500)
Conia's dimer (mp 168–170°)	1740[a,f]	1645	310 (24,000)[a,f]
Thieme's dimer (mp 223–225°)	1746[g]	1643	
5a 2,4-DNP[h]	1735[b,e]	1640	

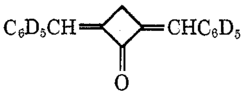
[a] Data of Conia, ref 8. [b] This work. [c] Thieme (ref 6) reports 1721 (C═O), 1669, 1636 cm^{-1} (C═C) for **2a**. [d] In chloroform solution a single carbonyl band is observed at 1739 cm^{-1}; C═C at 1638 cm^{-1}. [e] Measurement with Perkin-Elmer 620 grating instrument. [f] A moderately intense band at 1770 cm^{-1} and a weak band at 3400 cm^{-1} (OH) are also present suggesting the presence of ketol (ref 8). [g] Data of Thieme, ref 6. [h] Mono-2,4-dinitrophenylhydrazone of **5a**, mp 279–280°.



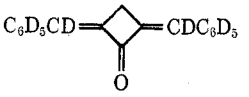
16

compared with the spectra of dibenzylidene derivative **2a** and dimer **5a** (Table I) it is clear, as Conia concluded,[8] that the dimer contains two 2-benzylidenecyclobutanone ring units and that the 2,4-dibenzylidenecyclobutanone structure is absent (**13**, **14**, and **15** are excluded). Benzaldehyde is produced by osmium tetroxide–sodium periodate oxidation of **5a**. That both oxygens in **5a** are carbonyl groups was established by preparing the mono-2,4-dinitrophenylhydrazone derivative (reaction with excess 2,4-dinitrophenylhydrazine). It retained one carbonyl group absorbing at 1735 cm^{-1}, suggesting that reaction had occurred at the bicycloheptanone carbonyl while the spirocyclobutanone carbonyl group did not react. The dimer is stable in acidic medium under the conditions of hydrazone formation.

Deuterium-labeled dimers were prepared and their nmr spectra were determined to distinguish structure **5a** from others. Monomers **2g** and **2h** were prepared from cyclobutanone and benzaldehyde-*2,3,4,5,6*-d_5 and benzaldehyde-d_6, respectively. Dimerizations of **2a,g,h**



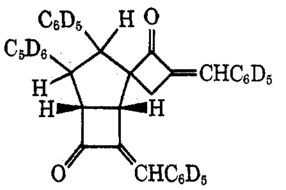
2g



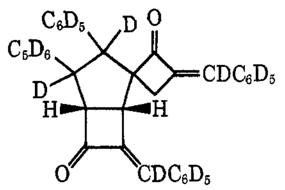
2h

were conducted in aqueous ethanolic sodium hydroxide or ethanol-*O-d*-deuterium oxide–NaOD to prepare deuterio dimers **5b–e**. The nmr spectra of monomers **2a,g,h** and dimers **5a–e** are summarized in Table II.

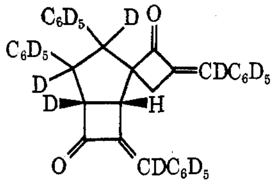
Dimer **5b** was prepared from **2a** in ethanol-*O-d*-D_2O. The four ring protons which appear in **5a** as a complex multiplet at δ 4.0–4.4 are reduced to three: the two benzylic protons at C-3 and C-4 now appear as an AB quartet at δ 4.20 and 4.08 (J = 7 Hz) and the C-1 proton as a doublet at δ 4.14 (J = 1 Hz) due to weak coupling to the C-7 benzylidene vinyl proton. The phenyl protons appear as three sharp peaks at δ 7.25, 7.18, and 7.12. The methylene group protons of the spirocyclobutanone ring are structurally nonequivalent and appear as a poorly resolved ABX multiplet at δ 2.80 owing to a strong geminal spin coupling as well as the 2.5-Hz coupling to the adjacent benzylidene vinyl proton. In the monomer **2a** the methylene protons are equivalent and appear as a simple 2.5-Hz triplet, since each methylene proton is spin-coupled to two equivalent benzylidene protons.



5c

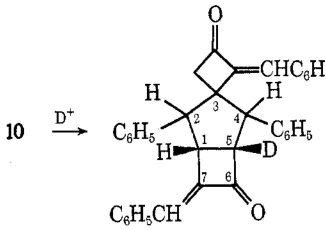


5d



5e

Structure **11a** produced by deuteration of anion **10** is not possible, since in it the C-2 and C-4 benzylic proton



11a

signals would not be coupled to each other. Also, in **11a** the C-1 proton signal would be complex since it is coupled to two protons; furthermore, the C-4 benzyl proton signal should appear in **11a** as a singlet.

Dimer **5c** (d_{20}) was prepared from monomer **2g** (d_{10}) in aqueous ethanol. Its nmr spectrum revealed two vinyl proton signals. The one on the C-7 benzylidene group appears as a doublet at δ 7.21 (J = 1 Hz) due to coupling with the C-1 proton. This signal is hidden under the phenyl proton signal in **5a** and **5b**. The benzylidene vinyl proton signal in the spirocyclobutanone ring appears as a triplet at δ 6.64 (J = 2.5 Hz). The bicycloheptane ring protons appear as a multiplet as in **5a**. The appearance of only two vinyl proton signals in **5c** rules out dimeric structures such as **12** and **13**. Also, since only one of the vinyl proton signals is a 2.5-Hz split triplet, there is only one benzylidene group having an adjacent methylene group; thus structures **3**, **4**, and **15** are eliminated.

Dimer **5d** (d_{24}) was prepared from monomer **2h** (d_{12}) in aqueous ethanol. In deuteriochloroform its nmr spectrum revealed the AB quartet of the C_1–C_5 protons as two strong inner lines (δ 4.27, 4.22); the spirocyclo-

TABLE II

NMR SPECTRA OF 2,4-DIBENZYLIDENECYCLOBUTANONE AND ITS DIMERS, δ VALUES IN $CDCl_3$ (TETRAMETHYLSILANE INTERNAL STANDARD)

Compd	Phenyl protons CH	Cyclobutanone and spirocyclobutanone protons: =CH (exocyclic)	Cyclobutanone and spirocyclobutanone protons: CH_2	Bicyclo[3.2.0]heptane ring protons: C_7=CH (exocyclic)	Bicyclo[3.2.0]heptane ring protons: C-1 CH	C-5 CH	C-3 CH	C-4 CH
2a[a]	7.28 m	7.05 t (J = 2.5 Hz)	3.75 t (J = 2.5 Hz)					
2g (d_{10})		7.11 t (J = 2.5 Hz)	3.77 t (J = 2.5 Hz)					
2h (d_{12})			3.78 s					
5a	7.25, 7.18, 7.12[b]	6.63 t (J = 2.5 Hz)	2.88 m[c]	Not visible	[4.0–4.4 m]			
5b (d_1)	7.25, 7.18, 7.12[b]	6.52 t (J = 2.5 Hz)	2.80 m[c]	Not visible	4.14 d (J = 1 Hz)		[4.20, 4.08 q] (J = 7 Hz)	
5c (d_{20})		6.64 t (J = 2.5 Hz)	2.83 m[c]	7.21 d (J = 1 Hz)	[4.0–4.4 m]			
5d (d_{24})			2.79, 2.77 q,[d] 2.68 s[e,f]		[4.27, 4.22 q[d]] [4.07, 3.88 q[e]] (J = 9 Hz)			
5e (d_{25})			2.85, 2.83 q,[d]		4.27 s			

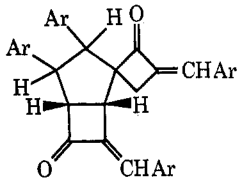
[a] Thieme (ref 6) reports δ 7.4 m, 7.2 t (J = 2.5 Hz), 3.8 t (J = 2.5 Hz) in $CDCl_3$. [b] Signal appears as three principal peaks of nearly equal intensity. [c] Unresolved ABX multiplet. [d] The outer lines of the AB quartet are not visible. [e] Solvent is 1:1 toluene-d_8–$CDCl_3$. [f] Apparent singlet.

butanone methylene protons produced a similar signal (δ 2.79, 2.77). However, in 1:1 toluene–deuteriochloroform the C_1–C_5 protons appear as an AB quartet with weak outer lines (δ 4.07, 3.88, J = 9 Hz).

Dimer **5e** (d_{25}), prepared from monomer **2h** (d_{12}) in ethanol-O-d-D_2O, has but one proton in the bicycloheptane ring (at C-1) which appears as a singlet at δ 4.27. The spirocyclobutanone ring methylene signal remains as an unresolved multiplet at δ 2.84.

The stereochemistry of dimer **5a** cannot be completely deduced from its nmr spectrum alone, even though coupling constants have been obtained for the C_1–C_5 and C_3–C_4 protons in deuterio derivatives **5b** and **5d**, respectively. The ring juncture in the bicycloheptane ring is necessarily cis and the coupling constant observed for the protons at this ring juncture in **5d** (C_1–C_5 J = 9 Hz) agrees with reported values for cyclobutane systems; J_{cis} = 8–12 Hz and J_{trans} = 8–10 Hz.[14] The coupling constant for the C_3–C_4 proton coupling observed in **5b** (J = 7 Hz) is within the range of either a cis or trans configuration (2–8 Hz).[15] In studies of Michael addition stereochemistry the initially formed carbon–carbon bond is observed to have trans stereochemistry when produced under conditions of kinetic or thermodynamic control.[12,16,17] In product **5a** there is no possibility of subsequent base-catalyzed epimerization at C_3 or C_4, exclusive of retro-Michael reaction. Assuming trans stereochemistry at C_3–C_4, eight diastereoisomers of **5a** are possible. The dimers of **2a** reported by Conia[8] and Thieme[6] are probably epimers of **5a**; the method of their synthesis and the observed similarity in their spectra (Table I) favors this assumption. (The three known styryl isobutyl ketone dimers formed in ethanolic sodium hydroxide are epimers.[12]) Although not shown in **5a**, the exocyclic benzylidene groups are presumed to have the favored trans stereochemistry; structure **6a** illustrates the preferred configuration.[18,19]

The base-catalyzed dimerization reaction has been extended to other 2,4-diarylidenecyclobutanones. 2,4-(4-Methylbenzylidene)cyclobutanone (**2b**) forms a crystalline dimer (assigned structure **5f**) in 32% yield in aqueous ethanolic sodium hydroxide at 50–68°, mp 215–218°. Its nmr and infrared spectra are very similar to those of **5a**. 2,4-Bis(3,4-dimethoxybenzylidene)cyclobutanone (**2e**) by reaction under the same conditions as employed with **2b** gave crystalline dimer **5g** by fractional crystallization from acetonitrile, mp 232–235° (1% yield). 2,4-Bis(4-methoxybenzylidene)cyclobutanone (**2c**) under similar conditions gave a trace of product (mp 240–260°), believed to be principally dimer **5h**. 2,4-Bis(4-chlorobenzylidene)cyclobutanone (**2d**) gave an amorphous product from which no crystalline product could be isolated; its infrared spectrum resembles that of dimers **5a–h**, except for the presence of bands at 3500 and 1770 cm^{-1} which suggest ketol impurity. The effect of aryl substituents on the dimerization of 2,4-diarylidenecyclobutanones parallels results for dimerization of styryl alkyl ketones to 3,5-diaryl-4-alkanoylcyclohexanones (13–22% yield);[10] electron-releasing groups such as alkyl and alkoxy



5f, Ar = $4\text{-}CH_3C_6H_4$
g, Ar = $3,4\text{-}(CH_3O)_2C_6H_3$
h, Ar = $4\text{-}CH_3OC_6H_4$

---

(14) W. A. Thomas in "Annual Review of NMR Spectroscopy," Vol. 1, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1968, pp 74–77.

(15) A. A. Bothner-By in "Advances in Magnetic Resonance," Vol. 1, J. S. Waugh, Ed., Academic Press, New York, N. Y., 1965, pp 239–243.

(16) L. Gorrichon-Guigon, Y. Maroni-Barnaud, and P. Maroni, *Bull. Soc. Chim. Fr.*, 128 (1970).

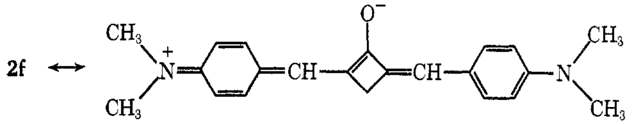
(17) A.-M. Baradel, J. Dreux, and R. Longeray, *ibid.*, 3543 (1966).

(18) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964).

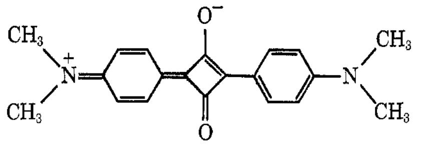
(19) M. Brink, *Tetrahedron*, **25**, 995 (1969).

favor these reactions, which involve a Michael cyclization in an acyclic dimer intermediate.

The preparation of 2,4-bis(4-dimethylaminobenzylidene)cyclobutanone (**2f**) deserves comment. Under conditions used for preparing **2a–e** (43–69% yield) this compound is formed much more slowly and in lower yield (14%). It is isolated as deep-red prisms having a relatively high melting point (274–275°) and, unlike **2a–e**, is very insoluble in most organic solvents. α,α'-Bis(4-dimethylaminobenzylidene)cycloalkanones prepared from cyclopentanone, cyclohexanone, and cycloheptanone are orange, high-melting substances, but are more soluble in organic solvents than is **2f**.[2] The carbonyl stretching frequency of **2f** (1680 cm^{-1}) is relatively low compared to that of **2a** (1720 cm^{-1}), characteristic of charge delocalization in β-amino ketones. The delocalized structure of **2f** (**17**) and its physical properties resemble somewhat the highly colored, high-melting cyclobutendiylium dyes (*e.g.*, **18**, deep blue, mp 276°).[20]

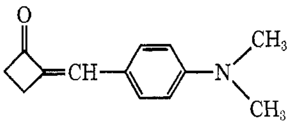


17



18

The principal product of condensation of 4-dimethylaminobenzaldehyde (2 molar equiv) with cyclobutanone at 25° is the 2-benzylidene derivative **19** (scarlet prisms from acetone, mp 181–183°, 38% yield). Only



19

one monoarylidenecyclobutanone other than **19** is known, *i.e.*, 2-benzylidenecyclobutanone (**16**). The latter was prepared in a pure state with some difficulty by condensing benzaldehyde with excess cyclobutanone.[8]

Experimental Section[21]

Materials.—Cyclobutanone (99.7%) from Columbia Chemicals Co., $n^{25}\text{D}$ 1.4198, was assayed by vpc. Aldehydes were commercial samples, distilled immediately before use if liquid; melting points of solid samples were checked before use.

Benzaldehyde-d_6 was prepared from toluene-d_8 by chlorination to benzal dichloride-d_6 followed by alkaline hydrolysis;[22] assay by mass spectrum 96% d_6 (112), 4% d_5 (111).

Benzaldehyde-*2,3,4,5,6*-d_5.—Benzyl alcohol-*2,3,4,5,6*-d_5 (2.49 g), prepared by lithium aluminum hydride reduction of benzoic acid-*2,3,4,5,6*-d_5,[23] was dissolved in 200 ml of ether and shaken with 15 g of activated manganese dioxide (catalyst B)[24] at ambient temperature for 118 hr. The solution was filtered and the filtrate was distilled to yield 1.81 g (75%) of benzaldehyde-*2,3,4,5,6*-d_5, bp 179–180°, assay by mass spectrum 96% d_5 (111), 4% d_4 (110).

2,4-Dibenzylidenecyclobutanone (2a) was prepared by the procedure of Thieme[6] as flat yellow prisms from acetone, 47% yield, mp 191–193° (lit.[6] mp 191–192°, 47% yield).

2,4-Di(benzylidene-*2,3,4,5,6*-d_5)cyclobutanone (2g).—A solution of cyclobutanone (0.57 g, 0.00815 mol) and benzaldehyde-*2,3,4,5,6*-d_5 (1.81 g, 0.0163 mol, 96% assay d_5) in 10 ml of 95% ethanol was added dropwise during 2 hr to 40 ml of aqueous ethanol (75% ethanol) containing 4 ml of 1% aqueous sodium hydroxide solution (temperature 20°). After standing for 4 hr at 20° the mixture was chilled in an ice bath for 20 min and filtered to yield 0.30 g of crystals, mp 185–192°; standing at 25° for an additional 17 hr deposited 0.54 g of additional crystalline product, mp 170–185° (46% total yield); recrystallization from acetone gave **2g** as prisms, mp 193–195°, 99% pure by nmr assay.

2,4-Di(benzylidene-α,*2,3,4,5,6*-d_6)cyclobutanone (2h).—A solution of cyclobutanone (0.78 g, 0.011 mol) and benzaldehyde-d_6 (2.77 g, 0.022 mol, 96% assay) in 15 ml of 95% ethanol gave, by the procedure used for preparation of **2g**, 1.15 g (42%) of crude **2h**, mp 175–185°; recrystallization from acetone gave prisms, mp 191–194°; 98% pure by nmr assay.

7-Benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-6-one (5a).—2,4-Dibenzylidenecyclobutanone (1.0 g, 0.0046 mol) was pulverized in a mortar and dissolved in 25 ml of absolute ethanol at 45°; 4.0 ml of 1% aqueous sodium hydroxide solution was added and the solution was heated at 45° for 10 min. The solution after cooling to 25° was shaken in a mechanical shaker for 50 min. The mixture was filtered to yield 0.27 g of dimer **5a**, mp 190–191°. The filtrate was acidified with 20 ml of 2 *N* sulfuric acid, diluted with 50 ml of water, and allowed to stand overnight to deposit 0.70 g of a solid which was crystallized from acetonitrile to yield 0.13 g of additional product, mp 170–185° (0.40 g total); recrystallization from acetonitrile gave 0.30 g (30%) of small, yellow, spear-shaped crystals, mp 191–193°; when mixed with 2,4-dibenzylidenecyclobutanone (mp 191–192°) the melting point was depressed to 155–160°. In a parallel run (2.0 g of monomer, sodium hydroxide 0.011 *M* in 95% ethanol) **5a** was obtained in 23% yield, mp 188–192°.

Anal. Calcd for $C_{36}H_{28}O_2$: C, 87.77; H, 5.73; mol wt 492.6. Found: C, 87.55; H, 5.65; mol wt 492 (mass spectrum).

Reaction of **2a** by the procedure of Thieme[6] gave an amorphous product, mp 108–118°, from which no crystalline product could be isolated by crystallization from various solvents, including acetonitrile. The infrared spectrum [ν KBr 1745 s (C=O), 1770 m (C=O), 1640 s (C=C), 3500 w cm^{-1} (OH)] suggested the presence of ketol in the crude product.

A 10-mg sample of dimer **5a** in 5 ml of 95% ethanol containing 2 drops of concentrated hydrochloric acid was heated under reflux for 1 hr. Removal of the solvent gave recovered dimer, 10 mg, mp 192–194°.

A 10-mg sample of dimer **5a** in a solution of 10 ml of absolute ethanolic sodium methoxide (prepared from 10 mg of sodium) was warmed on the steam bath for 10 min; 1 ml of water was added and the solution was heated for an additional 15 min. Cooling, followed by addition of 10 ml of water and 10 ml of 2 *N* sulfuric acid, gave 10 mg of amorphous solid, mp 75–80°, from which no crystalline material could be isolated by crystallization from acetonitrile.

A 30-mg sample of dimer **5a** in a solution of 1 ml of acetonitrile and 1 ml of 1% sodium hydroxide in 70% ethanol was heated on the steam bath for 15 min. After standing at 25° for 15 min there precipitated 20 mg of recovered **5a**, mp 184–189°.

Mono-2,4-dinitrophenylhydrazone of Dimer 5a.—A 100-mg (0.0204 mmol) sample of dimer **5a** and 150 mg (0.076 mmol) of 2,4-dinitrophenylhydrazine were dissolved in 50 ml of hot 95%

---

[20] H.-E. Sprenger and W. Ziegenbein, *Angew. Chem., Int. Ed. Engl.*, **7**, 530 (1968).

[21] Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer (95% ethanol solvent); infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer unless otherwise stated; nmr spectra were determined on a Varian A-60 spectrometer (10–20% solutions) in $CDCl_3$ unless otherwise stated. Mass spectra were determined on a Hitachi Model RMU-6E. Magnesium sulfate was employed as drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

[22] J. Ronayne, D. H. Williams, and J. H. Bowie, *J. Amer. Chem. Soc.*, **88**, 4980 (1966).

[23] J. C. Evans, *Spectrochim. Acta*, **17**, 129 (1961).

[24] M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

ethanol. Concentrated hydrochloric acid (10 drops) was added and the mixture was heated on the steam bath for 1 hr. After standing at 25° for 14 hr there was obtained 130 mg (95%) of **5a** mono-2,4-dinitrophenylhydrazone, mp 271–273°; recrystallization from ethylene dichloride gave small orange prisms, mp 279–280°.

Anal. Calcd for $C_{42}H_{32}N_4O_5$: C, 74.98; H, 4.79; N, 8.33. Found: C, 74.72; H, 4.91; N, 8.25.

Sodium Periodate–Osmium Tetroxide Oxidation of Dimer 5a.[25]—To dimer **5a** (0.40 g, 0.08 mmol) in 15 ml of acetonitrile was added 7 ml of water and, with stirring, 25 mg (1.0 mmol) of osmic acid (nitrogen atmosphere maintained). The brown solution was treated with sodium periodate (0.67 g, 3.3 mmol), added in small portions at frequent intervals with stirring during 30 min, causing the color to change to yellow. After stirring for an additional 90 min, the solution was diluted with 100 ml of water and steam-distilled; 150 ml of distillate was collected, diluted with water, and extracted several times with ether. The dried ether extracts were distilled, leaving 0.10 g of crude benzaldehyde which was isolated as its 2,4-dinitrophenylhydrazone, 0.185 (40%), mp 225–236°; recrystallization from ethyl acetate gave orange prisms, mp 240–242°; when mixed with an authentic sample (mp 242–243°) the melting point was not depressed (lit.[25] mp 241–242.5°). In the flask remaining after steam distillation was 0.17 g of amorphous material, from which no crystalline product could be isolated, mp 185–195°, having an infrared spectrum characterized by broad bands, ν (KBr) 1720 cm^{-1} (C=O).

7-Benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-*5*-d-6-one (5b).—2,4-Dibenzylidenecyclobutanone (0.50 g, 2.03 mmol) was dissolved in an alkaline solution, prepared by dissolving 20 mg of sodium in 30 ml of absolute ethanol-*O*-*d* and 2 ml of D_2O, and the solution was kept at 45° for 10 min. The clear solution was then shaken mechanically for 50 min while allowing it to cool to 25°. Deuterium oxide (10 ml) and *N*-deuteriosulfuric acid in D_2O (10 ml) were added and the mixture, now containing a yellow precipitate, was allowed to stand at 25° for 16 hr. Filtration gave 0.47 g of product, mp 130–180°; crystallization from acetonitrile gave 0.10 g (20%) of crystalline dimer **5b**, mp 180–190°; recrystallization gave 0.05 g, mp 188–190°.

7-(Benzylidene-*2,3,4,5,6*-d_5)-3,4-di(phenyl-*2,3,4,5,6*-d_5)-2-spiro[2-oxo-3-(benzylidene-*2,3,4,5,6*-d_5)cyclobutyl]bicyclo[3.2.0]-heptan-6-one (5c).—A solution of 2,4-di(benzylidene-*2,2,4,5,6*-d_5)cyclobutanone (**2g**, 0.40 g, 1.56 mmol) in 25 ml of absolute ethanol and 2.5 ml of 1% aqueous sodium hydroxide was kept at 45° for 10 min. After shaking at 45–25° (self-cooling) for 50 min the mixture was diluted with 10 ml of 2 *N* aqueous sulfuric acid and 100 ml of water. Standing at 25° for 16 hr deposited 0.3 g of product, mp 92–100°, which was crystallized from acetonitrile to give 0.09 g (23%) of dimer **5c** as small prisms, mp 190–193°.

7-(Benzylidene-α,*2,3,4,5,6*-d_6)-3,4-di(phenyl-*2,3,4,5,6*-d_5)-2-spiro[2-oxo-3-(benzylidene-α,*2,3,4,5,6*-d_6)cyclobutyl]bicyclo-[3.2.0]heptan-*3,4*-d_2-6-one (5d).—2,4-Di(benzylidene-α,*2,3,4,5,6*-d_6)cyclobutanone (**2h**, 220 mg) was dissolved in 12 ml of absolute ethanol and 1.2 ml of 1% aqueous sodium hydroxide at 45°; after keeping at 45° for 15 min and shaking for 45 min while cooling to 25°, water (25 ml) and 2 *N* sulfuric acid (5 ml) were added and the mixture was stored at 25° overnight. Filtration gave 0.20 g of product, mp 98–103°, which was recrystallized from acetonitrile to yield 31 mg (14%) of crude dimer **5d** as spear-shaped crystals, mp 168–188°. This sample was not purified further; assay 90% dimer **5d** and 10% monomer **2h** by nmr.

7-(Benzylidene-α,*2,3,4,5,6*-d_6)-3,4-di(phenyl-*2,3,4,5,6*-d_5)-2-spiro[2-oxo-3-(benzylidene-α,*2,3,4,5,6*-d_6]cyclobutyl)bicyclo-[3.2.0]heptan-*3,4,5*-d_3-6-one (5e).—2,4-Di(benzylidene-α,*2,3,4,-5,6*-d_6)cyclobutanone (**2h**, 0.50 g, 1.94 mmol) was dissolved in a solution prepared by dissolving 20 mg of sodium in 30 ml of ethanol-*O*-*d* and 2 ml of D_2O and the solution was kept at 45° for 10 min. The clear orange solution was allowed to cool to 25° during 50 min; D_2O (10 ml) and *N*-deuteriosulfuric acid in D_2O (10 ml) were added and the mixture was allowed to stand overnight. Filtration gave 0.45 g of solid, mp 122–130°, which was crystallized from acetonitrile to yield 80 mg (16%) of dimer **5e**, mp 191–192°, as clusters of pale-yellow spear-shaped crystals.

2,4-Bis(4-methylbenzylidene)cyclobutanone (2b).—A solution of cyclobutanone (1.0 g, 0.0143 mol) and *p*-tolualdehyde (3.5 g, 0.029 mol) in 16 ml of 95% ethanol was added dropwise, with stirring, to 80 ml of 0.1% sodium hydroxide in 70% ethanol during 4 hr, keeping the temperature at 18–20°; stirring was continued at 20° for an additional 4 hr. The mixture was filtered and washed with 70% ethanol to yield 3.19 g of ketone **2b**, mp 191–201°; recrystallization from acetone gave long yellow needles, 1.95 g (61%), mp 205–207° (lit.[6] mp 200–202°) (43%); ν (KBr) 1720 (C=O), 1670, 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.37, 7.17 (q, J = 8.0 Hz, 8, aryl), 7.12 (t, J = 2.5 Hz, 2, =CH), 3.71 (t, J = 2.5 Hz, 2, CH_2), 2.37 (s, 6, CH_3).

7-(4-Methylbenzylidene)-3,4-di(4-methylphenyl)-2-spiro[2-oxo-3-(4-methylbenzylidene)]bicyclo[3.2.0]heptan-6-one (5f).—3,4-Di(4-methylbenzylidene)cyclobutanone (**2b**, 0.50 g, 1.82 mmol) was dissolved in 50 ml of absolute ethanol and heated to 45°. Aqueous sodium hydroxide solution (4 ml of 1% solution) was added and the solution was kept at 50° for 30 min and at 68° for 20 min. The clear orange solution was allowed to cool to 25° during 1 hr; it was then treated with 20 ml of 2 *N* sulfuric acid and diluted with water. The following day the solid was filtered, 0.48 g, mp 98–100°. Recrystallization from acetonitrile gave 0.23 g of crude crystalline dimer **5f**, mp 204–207°; one recrystallization gave small prisms, 0.16 g (32%), mp 213–217°. Further recrystallization from acetonitrile raised the melting point to 215–218°: ν (KBr) 1740 (C=O), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.0–7.4 (m, 17, aryl and =CH), 6.67 (m, 1, =CH), 4.0–4.3 (m, 4, ring CH), 2.78 (m, 2, CH_2), 2.30 (s, 6, CH_3), 2.22 (s, 6, CH_3).

Anal. Calcd for $C_{40}H_{36}O_2$: C, 87.56; H, 6.61; mol wt 548.7. Found: C, 87.52; H, 6.62; mol wt 548 (mass spectrum).

The above procedure applied to 2,4-bis(4-methoxybenzylidene)-cyclobutanone[6] (**2c**, 0.5 g) gave recovered reactant (10%) and an amorphous product, mp 105–108°. Fractional crystallization of the product from acetonitrile ultimately gave 2 mg of amorphous product which forms tiny crystals near the melting point, 240–260° [ν (KBr) 1725 cm^{-1} (s, C=O), 1635 (s, C=C)]. With 2,4-bis(4-chlorobenzylidene)cyclobutanone (**2d**)[6] the procedure gave an amorphous product, mp 125–138° [ν (KBr) 3500 (w, OH), 1770 (m), 1740 (s, C=O), 1640 cm^{-1} (C=C)]; no crystalline material could be isolated from this product.

2,4-Bis(3,4-dimethoxybenzylidene)cyclobutanone (2e).—Cyclobutanone (1.0 g, 0.0143 mol) and 3,4-dimethoxybenzaldehyde (4.82 g, 0.029 mol) were condensed employing the procedure used in preparation of **2b**; crude crystalline product, 3.38 g, mp 174–178°, was obtained. Recrystallization from acetone gave 2.23 g (52%) of **2e**, mp 182–186°; two more recrystallizations gave long yellow needles, mp 191–193°; ν (KBr) 1710 (C=O), 1650, 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.3–7.8 (m, 8, aryl and =CH), 3.90 (s, 12, CH_3O), 3.75 (t, J = 2.5 Hz, 2, CH_2).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05; mol wt 366.4. Found: C, 71.91; H, 6.10; mol wt 370 (osmometry).

Dimerization of **2e** (0.50 g) employing the procedure used in the preparation of dimer **5f** gave an amorphous product, mp 109–120°, from which 5 mg (1%) of dimer **5g** was isolated by fractional crystallization from acetonitrile, small prisms, mp 232–235°; ν (KBr) 1740 (C=O), 1635 cm^{-1} (C=C).

Anal. Calcd for $C_{44}H_{44}O_{10}$: C, 72.11; H, 6.05; mol wt 732.8. Found: C, 71.98; H, 5.95; mol wt 741 (osmometry).

2,4-Bis(4-dimethylaminobenzylidene)cyclobutanone (2f).—A solution of cyclobutanone (1.0 g, 0.0143 mol) and 4-dimethylaminobenzaldehyde (4.32 g, 0.029 mol) in 16 ml of 95% ethanol was added dropwise, with stirring, during 2 hr to 80 ml of 0.1% sodium hydroxide in 70% ethanol, keeping the temperature below 20°; stirring was continued at 20° for 5 hr. After standing at 25° for 10 days there was obtained in several crops a total of 2.50 g of scarlet needles, mp 171–180°. The filtrate on standing at 25° for 4 weeks deposited 0.07 g of **2f**, mp 271–273°. Crystallization of the first crop from 250 ml of boiling acetone gave 0.60 g of **2f**, mp 270–275°; total yield, 0.67 g (14%). Recrystallization from dimethylformamide gave flat, dark-red prisms, mp 274–275°; ν (KBr) 1680 (C=O), 1640 cm^{-1} (C=C). The material is only very slightly soluble in most organic solvents (hot), including acetone, acetonitrile, dimethyl sulfoxide, ethylene dichloride, pyridine, chloroform and nitromethane; nmr (CF_3CO_2H) δ 7.85, 8.02 (m, 8, aryl), 7.68 (t, poorly resolved, 2, J = 2.5 Hz, =CH), 4.22 (m, 2, CH_2), 3.60 (s, 12, CH_3).

Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43; mol wt 332.4. Found: C, 79.32; H, 7.27; N, 8.30; mol wt 332 (mass spectrum), 342 (vapor osmometry in dimethylformamide).

2-(4-Dimethylaminobenzylidene)cyclobutanone (19).—The filtrate (acetone solvent) remaining from crystallization of **2f** above was concentrated to *ca.* 60 ml and filtered hot to remove additional **2f** (0.05 g, mp 269–270°). Chilling the filtrate to 0° de-

---

[25] Procedure of R. Pappo D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Amer. Chem. Soc.*, **21**, 478 (1956).

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-Δ⁸-naphthyridine and 2-Keto-8-methyl-7-oxa-Δ⁵-1-azabicyclo[4.3.0]nonane[1]

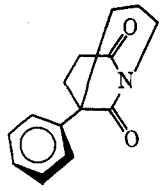
EDWARD E. SMISSMAN* AND JAMES W. AYRES

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

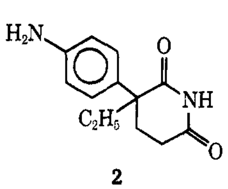
Received November 23, 1970

The synthesis of 2-keto-4a-phenyloctahydro-Δ⁸-naphthyridine (**10**) and 2-keto-8-methyl-7-oxa-Δ⁵-1-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**).

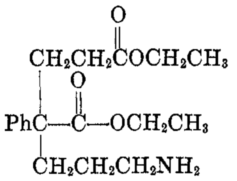


1



2

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

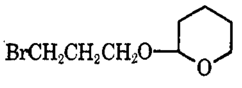


$$PhC(CH_2CH_2COOCH_2CH_3)(COOCH_2CH_3)(CH_2CH_2CH_2NH_2)$$

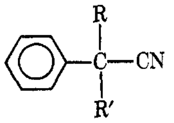
3

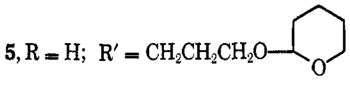
intramolecular attack by the amino group on the ester functions would produce **1**.

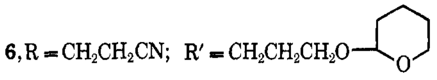
Phenylacetonitrile was allowed to react with 2-(3-bromopropoxy)tetrahydropyran (**4**) to yield 2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**). The latter compound (**5**) was converted to 2-cyanoethyl-2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**6**) *via* cyanoethylation. 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



4



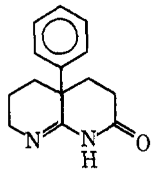




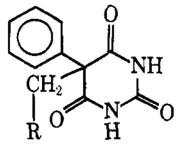
7, R = CH_2CH_2CN; R' = $CH_2CH_2CH_2OH$

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

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

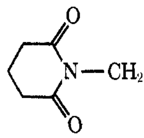


10



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).