($MgSO_4$), and the solvent was removed to yield 1.28 g of **25**, a yellowish oil, ir (neat) 2110 cm^{-1} (azide). A soln of LAH (0.570, 15.0 mmoles) in 25 ml of anhyd Et_2O was refluxed for 2 hr after which the crude azide **25** in 50 ml of anhyd Et_2O was added at such a rate as to maintain reflux. The reaction mixt was refluxed for 2 hr after which "wet" Et_2O followed by H_2O was added to decomp the excess LAH. The aq layer was extd several times with Et_2O and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the solvent was removed to yield a colorless oil, 1.525 g. Chromatog on silica gel, eluting with 5% MeOH–$CHCl_3$, afforded a colorless oil, 0.850 g. Formation of the HCl salt and recrystn (EtOH–Et_2O) afforded 0.567 g (51%) of **23**, mp 132–134°.

erythro-**2-Amino-3-(3,4-dihydroxyphenyl)butane·HCl (3).**—To *erythro*-2-amino-3-(3,4-dibenzyloxyphenyl)butane·HCl (**23**) (0.200 g, 0.5 mmole) in 5 ml of anhyd MeOH was added 50 mg of 10% Pd/C under N_2. The reaction mixt was hydrogenated at 25° under 1 atm of H_2. The reaction was stopped after consumption of the theoretical amt of H_2. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The resulting solid was crystd (MeOH–Et_2O) to yield 83 mg (79%) of **3**: mp 254–258°; nmr CD_3OD δ 6.83–6.63 (m, 3 H, arom), 3.39 (m, 3 H, C-2 C**H**), 2.85 (m, 1 H, C-3 C**H**), 1.35 (d, 3 H, C-1 C**H**$_3$), 1.15 (d, 3 H, C-4 C**H**$_2$). *Anal.* ($C_{10}H_{16}ClNO_2$) C, H, N.

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Acenaphthene Chemistry. 2. Synthesis and Antiinflammatory Activity of 1-[2-(Dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarboxamide[1]

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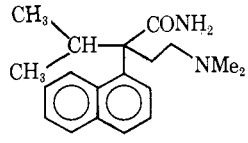
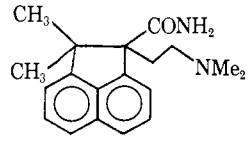
Received January 11, 1971

The synthesis and antiinflammatory activity of 1-[2-(dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarboxamide (**2**) are presented. The nature of the products obtained during attempted cyanide displacement reactions on 1-bromo-2,2-dimethylacenaphthene (**14**) under a variety of conditions is described.

The synthesis and antiinflammatory activity of α-isopropyl-α-[2-(dimethylamino)ethyl]-**1**-naphthylacetamide (**1**) has been reported.[2] If one envisions formation of a bond between the central C atom of the side-chain *i*-Pr group and the C-8 position of the naphthalene ring of **1**, then the acenaphthene **2** is derived. In this paper, we describe the synthesis and antiinflammatory activity of this "bridged" compound, as well as the chemistry of some intermediates.

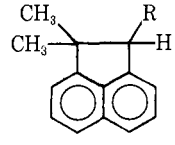


1

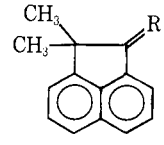


2

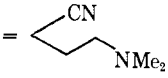
Our successful approach utilized the alcohol **3** as starting material.[3] Sarett[4] or Cornforth oxidation[5] of **3** led to the recovery of **3** as the major product. MnO_2 (active) oxidation[6] of **3** gave a mixture of **3** and the ketone **5**.[3] Oxidation of **3** with Jones reagent[7] gave the carboxylic acid **4**, along with **5**. The ketone may arise from oxidative cleavage of the benzylic C–C bond of **3** or by further oxidation of **4**. The acid was converted into a nitrile (**8**) in the usual manner, and then alkylated with dimethylaminoethyl bromide to give **9**. When **9** was treated under the same drastic acidic conditions employed for the hydrolysis of the corresponding nitrile in the synthesis of **1**,[2] a multicomponent mixture (6 spots, tlc) was obtained in 25% yield. Attempted hydrolysis of **9** with H_2O_2 in NH_4OH was also unsuccessful.[8] While PPA is an excellent reagent for the hydrolysis of unhindered aromatic nitriles, it has been found unsuitable for use with sterically hindered nitriles.[9] Nevertheless, exposure of our hindered nitrile **9** to PPA gave the amide **2** in over 70% yield.



3, R = CH_2OH
4, R = CO_2H
6, R = COCl
7, R = $CONH_2$
8, R = CN



5, R = O

9, R = 

We had originally sought to prepare **8** in a more direct manner by displacement of a suitable acenaphthyl derivative with CN^-. Reduction of **5** with $NaBH_4$ gave the alcohol **10** that was treated with TsCl in pyridine to afford **11**. The formation of such salts from aryl carbinols and allylic hydroxy steroids has been reported recently.[10,11] Treatment of **10** with TsCl in DMF

(1) For part 1, see A. I. Cohen, I. T. Harper, and S. D. Levine, *Chem. Commun.*, 1610 (1970).

(2) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 594 (1965).

(3) A. Bosch and R. K. Brown, *Can. J. Chem.*, **46**, 715 (1968).

(4) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(5) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *Tetrahedron*, **18**, 1351 (1962).

(6) I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

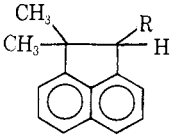
(8) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **91**, 2102 (1969).

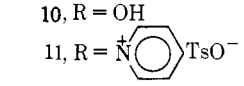
(9) H. R. Snyder and C. T. Elston, *ibid.*, **76**, 3039 (1954).

(10) K. L. Nagpal, P. C. Jain, P. D. Srivastava, M. M. Dhar, and N. Anand, *Indian J. Chem.*, **6**, 762 (1968).

(11) S. B. Laing and P. J. Sykes, *J. Chem. Soc. C*, 421 (1968).

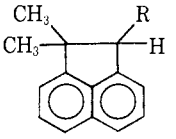
afforded the chloro compound **12**, while reaction with 80% AcOH gave the acetate **13** without any rearrangement to 1,2-dimethylacenaphthylene. Treatment of **13** with KCN in refluxing MeCN, KCN in DMF at 110°, or NaCN in refluxing DMF all led to recovery of starting material.



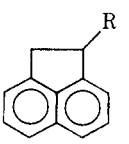
10, R = OH
11, R = 
12, R = Cl
13, R = OAc

We next investigated cyanide displacement reactions on the bromo compound **14** prepared from **10** with PBr_3. Treatment of **14** under the conditions used for the high-yield conversion of 1-bromobenzocyclobutene to 1-cyanobenzocyclobutene,[12] did not afford **8**, but **5** and **10** were isolated after chromatography. The ketone **5** is thought to arise by Kornblum oxidation[13] of **14**. The isolation of **10** is not surprising, since chromatography of pure **14** on silica gel results in its reconversion, in part, to **10**. This product may also arise by simple hydrolysis of **14** during the reaction itself (see below). The alcohol **10** and the formate ester **15** were isolated by chromatography from the reaction of **14** with NaCN in DMF. The reaction of steroidal tosylates with DMF to afford formates has been reported.[14,15] When **14** was refluxed with NaCN in MeCN for an extended period, a product more polar than either **10** or **14** slowly accumulated. Preparative tlc gave an amide formulated as **16** in 40% yield along with **10**. Subsequent experiments showed that this reaction takes place in MeCN alone as well, but that no **16** is formed from the reaction of **10** with NaCN in MeCN. Thus, the reaction resembles a Ritter reaction in an overall fashion, though no acid is present. Reaction of **10** under Ritter conditions proceeded as expected to give **16**. The reaction of **17**[16] with NaCN in MeCN has been reported to give the alcohol **18**[17] as the main product.[18] We were curious to determine whether an amide analogous to **16** was also formed in this reaction. Reaction of **17** with NaCN in MeCN gave **18** as the major product, along with a small amount (*ca.* 1%) of 1-acetamidoacenaphthene (**19**).[19] The greater yield of amide obtained in the 2,2-dimethylacenaphthene series probably reflects the increased stability of the corresponding carbonium ion (carbonium ion like intermediate).

Antiinflammatory Activity.[20]—The compounds were



14, R = Br
15, R = OCHO
16, R = NHAc



17, R = Br
18, R = OH
19, R = NHAc

administered orally as a suspension in 1% CMC to prestarved (16–18 hr), 180–200 g, young adult male Sprague–Dawley rats, that were allowed H_2O *ad libitum*. Two hours later, the left hind paw vol was measured by Hg displacement and 0.05 ml of a 1% soln of carrageenin in sterile pyrogen-free 0.9% NaCl soln was injected into the paw. Three hours later the vol of the paw was again measured by Hg displacement.

A 150 mg/kg dose of **2** inhibited carrageenin-induced edema by 56% and 40% in 2 separate tests. A 6 mg/kg dose of indomethacin generally inhibits edema by 50 ± 10% in this assay.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary mp apparatus. Ir spectra were detd using Perkin-Elmer IR-137 and IR-21 spectrometers, and nmr spectra on a Varian A-60 spectrometer in $CDCl_3$ (Me_4Si). All org solns were dried (Na_2SO_4) and all evapns carried out *in vacuo*. Silica gel HF-254 and alumina (Merck, AG, neutral) were used for chromatogr and the compds were detected by uv. Where analyses are indicated only by the symbols of the elements, anal. results obtd for those elements were within 0.4% of the theoretical values; IPE = isopropyl ether.

Oxidation of 2,2-Dimethyl-1-hydroxymethylacenaphthene (3).[5]—A soln of **3** (70.9 g) in Me_2CO (3.55 l.) was cooled to −5° in an Me_2CO–Dry Ice bath, and treated rapidly with 355 ml of Jones reagent through a dropping funnel. When the addn was complete (T = 13°), MeOH was added and the resulting green suspension was filtered through Hy-Flo. The filtrate was evapd and the residue was dissolved in $CHCl_3$ and washed with H_2O. The $CHCl_3$ soln was extd with 10% aq NaOH, washed with 8% NaCl soln, dried, and evapd to give **5**[3] (27.9 g), which was identified by ir and tlc (silica gel–$CHCl_3$).

The alk exts were acidified with concd HCl and extd with $CHCl_3$. The $CHCl_3$ exts were washed with 8% NaCl soln, dried, and evapd to give the crude acid (**4**, 31.7 g), which was suitable for conversion to the acid chloride. A small portion of **4** was distd *in vacuo* (tube to tube) to afford a slightly yellow oil: nmr τ 8.57 (s, 2-CH_3), 8.35 (s, 2-CH_3), 5.68 (s, 1-H), and −0.2 (broad s, 1-CO_2H).

2,2-Dimethyl-1-acenaphthenecarboxamide (7).—A soln of the crude acid (**4**, 680 mg) in $SOCl_2$ (5 ml) was refluxed for 1 hr and evapd; the residue was then dissolved in $CHCl_3$ (10 ml) and treated with NH_3 for 5 min. The reaction mixt was washed with H_2O and 8% NaCl soln, dried, and evapd. Plate chromatogr of the residue on silica gel using EtOAc as the developing solvent gave a major band that was eluted with EtOAc. Evapn and crystn from Et_2O–IPE gave **7** in two polymorphic forms: 208 mg (mp 108–110°) and 57 mg (mp 122.5–124.5°). Recrystn from Me_2CO–IPE gave the anal. sample: mp 108–110°; nmr τ 8.53 (s, 2-CH_3), 8.39 (s, 2-CH_3), and 5.82 (s, 1-H). *Anal.* ($C_{15}H_{15}NO$): C, H, N.

2,2-Dimethyl-1-acenaphthenecarbonitrile (8).—A mixt of **7** (9.25 g) and P_2O_5 (20 g) in $PhCH_3$ (500 ml) was refluxed for 1.75 hr and cooled, then the $PhCH_3$ was decanted. The residue was dissolved in H_2O and extd with $CHCl_3$. The exts and toluene fraction were combined, washed with 8% NaCl soln, dried, and evapd to give **8** (8.0 g) as an oil. A small portion of **8** was distd (tube to tube) at 100° (0.25 mm) to afford the anal. sample: nmr τ 8.41 (s, 2-CH_3), 8.38 (s, 2-CH_3), and 5.63 (s, 1-H). *Anal.* ($C_{15}H_{13}N$): C, H, N.

1-[2-(Dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarbonitrile (9).—A mixt of **8** (2.85 g) and NaH (650 mg) in DMF

(12) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2257 (1958).
(13) N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959).
(14) F. C. Chang and R. T. Blickenstaff, *ibid.*, **80**, 2906 (1958).
(15) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 2883 (1961).
(16) W. E. Bachmann and J. C. Sheehan, *J. Amer. Chem. Soc.*, **63**, 204 (1941).
(17) L. F. Fieser and J. Cason., *ibid.*, **62**, 432 (1940).
(18) M. Julia and M. Baillarge, *Bull. Soc. Chim. Fr.*, 1065 (1952).
(19) H. Lettre and M. Stratmann, *Hoppe-Seyler's Z. Physiol. Chem.*, **288**, 25 (1951).
(20) Modification of the method described by C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(20 ml) was stirred under N_2 for 1 hr. A soln of dimethylaminoethyl bromide (2.62 g) in $PhCH_3$ (75 ml) was added and the reaction mixt was stirred overnight under N_2. It was poured into H_2O, the $PhCH_3$ sepd and the aq portion was extd with Et_2O The combined org layers were extd with 2 *N* HCl. The acidic fraction was made alk with 10% aq NaOH and extd with Et_2O. The Et_2O exts were washed with 8% NaCl soln, dried, and evapd to give **9** (2.89 g) as an oil. A small portion of **9** was distd (tube to tube) at 140° (0.10 mm) to give a viscous oil that was crystd from petr ether to afford the anal. sample: mp 69–70°; nmr τ 8.49 (s, 2-CH_3), 8.42 (s, 2-CH_3) and 7.91 (s, Me_2N). *Anal.* ($C_{19}H_{22}N_2$): C, H, N.

1-[2-(Dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarboxamide (2).—A mixt of **9** (5.21 g) and PPA (150 ml) was stirred vigorously (blade) for 1.5 hr in a preheated 120° oil bath. The mixt was poured into ice water and made alk with KOH pellets. The alk soln was extd with Et_2O, and the Et_2O exts were washed with 8% NaCl soln, dried, and evapd. The oil was distd (210–230°) *in vacuo* to give **2** (4.0 g), which solidified on standing (mp 61–63°). The anal. sample was prepd by distn (tube to tube) at 180° (0.17 mm): nmr τ 8.74 (s, 2-CH_3), 8.37 (s, 2-CH_3), and 7.87 (s, Me_2N). *Anal.* ($C_{19}H_{24}N_2O$): C, H, N.

2,2-Dimethyl-1-acenaphthenol (10).—A soln of **5**[3] (4.2 g) in MeOH (50 ml) was cooled in an ice bath and treated with $NaBH_4$ (1.3 g). It was stirred at room temp for 2.5 hr, treated with AcOH, concd, and dild with H_2O. The aq phase was extd with $CHCl_3$, and the exts were washed with 8% NaCl soln, dried, and evapd. The residue was crystd from Et_2O–hexane to give **10** (3.48 g, mp 87–88°). Recrystn from Et_2O–hexane gave the anal. sample: mp 89–90°; nmr τ 8.63 (s, 2-CH_3), 8.55 (s, 2-CH_3), 8.18 (s, 1-OH), and 4.80 (s, 1-H). *Anal.* ($C_{14}H_{14}O$): C, H.

1-(2,2-Dimethyl-1-acenaphthenyl)pyridinium Tosylate (11).—A soln of **10** (355 mg) and TsCl (355 mg) in pyridine (5 ml) was left at room temp overnight. The mixt was dild with H_2O and extd with $CHCl_3$. The $CHCl_3$ exts were washed with 8% NaCl soln, dried, and evapd. Crystn of the residue from Me_2CO gave **11** (254 mg, mp 191.5–192.5° dec). The anal. sample was prepd by recrystn from Me_2CO: mp 193–194° dec; nmr τ 9.05 (s, 2-CH_3), 8.39 (s, 2-CH_3), and 7.72 (s, $CH_3C_6H_4$). *Anal.* ($C_{26}H_{25}NO_3S$): C, H, N, S.

1-Chloro-2,2-dimethylacenaphthene (12).—A soln of **10** (500 mg) and TsCl (525 mg) in DMF (5 ml) was left at 60° overnight, dild with H_2O, and extd with $CHCl_3$. The $CHCl_3$ exts were washed with satd $NaHCO_3$ soln and 8% NaCl soln, dried, and evapd. Plate chromatogr of the residue on silica gel, utilizing $CHCl_3$ as the developing solvent, gave two bands. Elution of the more polar band with EtOAc and evapn gave **10** (210 mg, ir). This hydrolysis took place during chromatogr. The less polar band was eluted with EtOAc and evapd to give **12** (180 mg) as an oil. The anal. sample was prepd by distn (tube to tube) at 100° (0.15 mm): nmr τ 8.52 (s, 2-CH_3) and 4.57 (s, 1-H); mass spectra, $M^+ = 216$. *Anal.* ($C_{14}H_{13}Cl$): C, H.

2,2-Dimethyl-1-acenaphthenol Acetate (13).—A soln of **10** (70 mg) in 80% AcOH (5 ml) was refluxed for 6.5 hr, dild with H_2O, and extd with $CHCl_3$. The $CHCl_3$ exts were washed with 8% NaCl soln, dried, and evapd. Plate chromatogr of the residue on silica gel, using $CHCl_3$ as the developing solvent, and elution of the least polar band with EtOAc after evapn gave **13** (40 mg) as an oil. Tube-to-tube distn at 100° (0.01 mm) gave the anal. sample: nmr τ 8.60 (s, 2-CH_3), 8.50 (s, 2-CH_3), 7.85 (s, OAc), and 3.63 (s, 1-H). *Anal.* ($C_{16}H_{16}O_2$): C, H.

1-Bromo-2,2-dimethylacenaphthene (14).—A mixt of **10** (1.0 g) and PBr_3 (0.2 ml) in Et_2O (10 ml) was left at room temp overnight, satd $NaHCO_3$ soln was added, and the Et_2O layer was sep. The Et_2O layer was washed with 8% NaCl soln, dried, and evapd to give **14** (1.0 g) as an oil. Tube-to-tube distn at 100° (0.2 mm) gave the anal. sample: nmr τ 8.55 (s, 2-CH_3), 8.42 (s, 2-CH_3), and 4.38 (s, 1-H). *Anal.* ($C_{14}H_{13}Br$): C, H, Br.

2,2-Dimethyl-1-acenaphthenol Formate (15).—A mixt of **14** (780 mg) and NaCN (500 mg) in DMF (10 ml) was warmed at 100° for 3.5 hr. It was dild with H_2O and extd with $CHCl_3$. The $CHCl_3$ exts were washed with 8% NaCl soln, dried, and evapd. Plate chromatogr of the residue using $CHCl_3$–hexane (3:2) as the developing solvent gave 2 major bands. Elution of the more polar band with EtOAc and evapn gave **10** (232 mg, ir). The less polar band was eluted with EtOAc and evapd to give **15** (257 mg) as an oil. Tube-to-tube distn at 100° (0.1 mm) gave the anal. sample: nmr τ 8.59 (s, 2-CH_3), 8.49 (s, 2-CH_3), 3.55 (s, 1-H), and 1.72 (d, J = 1.5 Hz). *Anal.* ($C_{15}H_{14}O_2$): C, H.

1-Acetamido-2,2-dimethylacenaphthene (16).—(A) A mixt of **14** (0.52 g) and NaCN (0.3 g) in MeCN (15 ml) was refluxed for 5 days, dild with $CHCl_3$, washed with 8% NaCl soln, dried, and evapd. Plate chromatogr of the residue on silica gel, using $CHCl_3$ as the developing solvent, gave 2 bands more polar than **14**. Elution of the less polar band with EtOAc and evapn gave **10** (47 mg, ir). The more polar band was extd with EtOAc and evapd to give **16** (270 mg). Crystn from IPE–Me_2CO gave 193 mg, mp 129–130°. The anal. sample was prepd by recrystn from IPE: mp 130–131°; nmr τ 8.72 (s, 2-CH_3), 8.43 (s, 2-CH_3), 7.93 (s, 1-NAc), and 4.30 (s, 1-H). *Anal.* ($C_{16}H_{17}NO$): C, H, N.

(B) A soln of **14** (1.1 g) in MeCN (50 ml) was refluxed for 3 days and evapd. The dark residue was dissolved in 10 ml of PhH–$CHCl_3$ (3:1) and added to a 30-g, dry-packed alumina column. The column was eluted with PhH–$CHCl_3$ (1:1) and $CHCl_3$. An initial orange-colored band was discarded. The amide-contg fractions were combined, evapd, and crystd from Et_2O–hexane to afford **16** (538 mg, mp 130–131°).

(C) A soln of **10** (1.0 g) in MeCN (10 ml) was treated dropwise with concd H_2SO_4 (3.0 ml) while being stirred. The mixt was then stirred for 70 min, poured into H_2O, and extd with $CHCl_3$. The $CHCl_3$ exts were washed with satd $NaHCO_3$ soln and 8% NaCl soln, dried, and evapd. The residue was purified by alumina chromatogr as described above to give **16** (650 mg, mp 130–131°).

1-Acetamidoaconaphthene (19).—A mixt of **17** (2.32 g) and NaCN (1.54 g) in MeCN (77 ml) was refluxed for 10 days, dild with $CHCl_3$, and decanted, leaving an insol residue. The org fraction was washed with 8% NaCl soln, dried, and evapd to give a 1.06-g residue. Plate chromatogr of a 500-mg portion on silica gel, using $CHCl_3$ as the developing solvent, gave two bands. The less polar band was eluted with EtOAc and evapd; the residue crystd from Et_2O to give **18**[17] (221 mg, mp 143–145°). Elution of the more polar band with EtOAc, followed by evap, and crystn of the residue from Me_2CO, gave **19**[18] (14 mg, mp 201–202.5°).

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