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The annelation of α-pyridones to five membered ring systems is demonstrated by the synthesis of a series of 2-azafluorenones. These tricyclic heterocycles could be optionally substituted with methyl or phenyl groups by varying the orthoester reagent in the cyclization reaction. The conversion of the resultant cyanopyridones to pyridonecarboxamides and their *N*-methyl homologs is also described.

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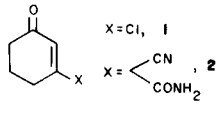
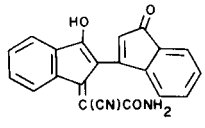
In our earlier reports (1,2) we described the synthesis of a cyclohexanone annelated α-pyridone which was readily converted to 7-aza-6-methoxy-1-tetralone, a valuable precursor of biologically interesting molecules (2,3). We have since examined the scope of this novel pyridone-annelation reaction and wish to report on this work as it applies to the title series. These members of the 2-aza-fluorenone family were of interest because their preparation demonstrated the applicability of this reaction to five-membered ring systems and enabled us to synthesize a variety of heretofore unknown 2-azafluorenones, optionally substituted at the 1- and 4-positions. While other methods for the preparation of 2-azafluorenones are known (4), the method described herein provides a versatile alternative.

Our previous work had utilized 3-chlorocyclohex-2-en-1-one (**1**) as a precursor for the necessary 3-cyanoacetamidoadduct **2**. While **1** is readily obtained from dihydro-



resorcinol *via* chlorination, the 3-chloroindenone analog **5** is not nearly as accessible from indan-1,3-dione *via* halogenation due to the propensity of this compound to undergo self-condensation. To circumvent this problem in the synthesis of **5**, we resorted to modification of a procedure by Straus, *et al.* (5), for the preparation of polyhalogenated indanes using hypohalite-base solution. Thus, prolonged stirring of indene (**3**) in the presence of sodium hypochlorite-sodium hydroxide solution followed by mild hydrolysis of the unstable 1,1,3-trichloroindene (**4**) afforded the desired chlorinated ketone **5** in modest yield.

In the cyclohexenone series, conjugate addition of anions derived from malonate derivatives to the chloroenone system required warming to provide adducts like **2** (2). In contrast, the indenone system requires low temperatures for the preparation of the desired adduct **6** in high yields. Thus, when **5** was contacted with the sodium salt of 2-cyanoacetamide in DMF at *ca.* -40°, the adduct **6** was isolated from the red reaction mixture in 80% yield. When the reaction was run at temperatures above 0°, a deep-purple reaction mixture resulted which



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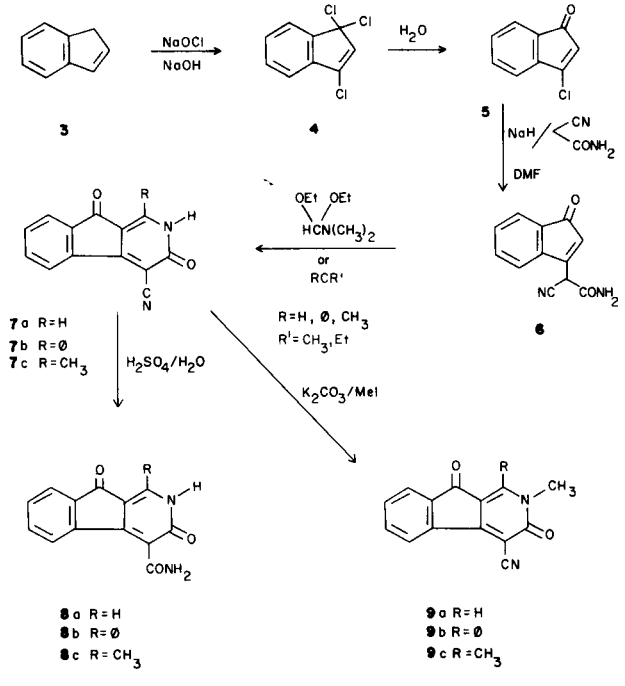
afforded the condensation product **10**. This compound, which resulted from the reaction of the desired product with the starting material **5**, was also prepared by treatment of the sodium salt of the desired product **6** with **5** in DMF at room temperature in a separate experiment.

The tricyclic system **7a** was initially prepared by treatment of **6** with dimethylformamide diethyl acetal in DMF at room temperature over a three hour period as in the previous series (1,2). It was later found that ortho-



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esters though requiring higher reaction temperatures, would also convert **6** to the tricyclic heterocycles. In these cases, steam bath temperature and heating times of one to three hours were generally sufficient. Yields were good with the orthoformate ester, moderate with the orthobenzoate ester and poor with the orthoacetate ester.

The tricyclic cyanopyridones could then be hydrolyzed to the corresponding amides **8** by treatment with concentrated sulfuric acid containing a trace of water at elevated temperatures. The *N*-methylated pyridones **9** were also prepared by treatment of **7** with potassium carbonate and methyl iodide in DMF at elevated temperatures (6).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were taken on Varian A-60A or T-60 spectrometers using TMS as an internal standard. Uv spectra were obtained in methanol on a Beckman DK-2A. The spectra were run by the group of Mr. A. J. Damascus and the microanalyses were performed by the group of Mr. E. Zielinski. Mass spectra were recorded by Dr. J. Hribar and associates using an AEI MS-30.

1,1,3-Trichloro-2-indene (**4**).

To 1.5 liters of commercially available 5.25% sodium hypochlorite solution containing 120 g. of sodium hydroxide was added 60 g. of indene in 600 ml. of Skelly B and the heterogenous reaction mixture was stirred at room temperature for 72 hours. The two layers were then separated and the aqueous phase was extracted with one 200 ml. portion of Skelly B. The combined extracts were then treated with an additional portion of basic sodium hypochlorite solution in the above proportions and again stirred for 72 hours at room temperature. After separation and extraction with Skelly B, the process was repeated a third time for 72 hours. The layers were then separated and the organic phase was washed with saturated sodium chloride solution, and dried over magnesium sulfate. Solvent removal *in vacuo* left an oily residue which solidified into a yellow solid after exposing the oil to a steady stream of nitrogen for 1 to 2 hours. The crude solid, 31.6 g. (*ca.* 27%), was used for the subsequent hydrolysis without further purification; nmr (deuteriochloroform): δ 6.32 (1H, s, vinyl-H).

3-Chloro-2-inden-1-one (**5**).

A solution of 35 g. of **2** in 750 ml. of aqueous acetone (1:1) was refluxed overnight in a nitrogen atmosphere. Most of the acetone was then removed *in vacuo* with the heating bath kept below 35°. The aqueous mixture was then extracted with three portions of ether and the combined extracts were washed with saturated salt solution and dried (magnesium sulfate). Solvent removal *in vacuo* gave an oily residue which crystallized from pentane to give 10.4 g. (40%) of orange solid. Recrystallization from ether-isopropanol gave the pure compound, m.p. 53-59°; uv (methanol): 232 nm (ε 28000), 239 (ε 28000); nmr (deuteriochloroform): δ 5.98 (1H, s, vinyl H), 7.07-7.67 (4H, m, aromatic H's).

Anal. Calcd. for C_9H_5ClO: C, 65.68; H, 3.06. Found: C, 65.51; H, 3.30.

2-Cyano-2-(1-oxo-1*H*-inden-1-yl)acetamide (**6**).

To 4.6 g. of 57% sodium hydride/mineral oil dispersion (0.11 mole) washed twice with Skelly B to remove the oil in 100 ml. of DMF in an atmosphere of nitrogen was added in portions 8.2 g. (0.1 mole) of 2-cyanoacetamide. After addition the reaction mixture was stirred for 30 minutes before cooling to *ca.* -50°. To the cooled solution was then added 8.0 g. (0.0485 mole) of **5** in 30 ml. of DMF dropwise over a 20 minute period. After addition the deep red solution was stirred at *ca.* -45° for an additional 30 minutes before 50 ml. of glacial acetic acid was added to the reaction mixture and the cooling bath was removed. After the reaction mixture warmed to -10°, 100 ml. of 1*N* hydrochloric acid solution was added which caused the red color to discharge and a precipitate to form which was collected. After washing with water then methanol and drying, 8.2 g. (80%) of **6** was obtained. Recrystallization from acetic acid gave the pure compound, m.p. 221-222°; uv (methanol): 292 nm (ε 17,700), 253 (14,600), 245 (16,500), 238 (16,000), 229 (15,300); ir (potassium bromide): 4.50, 5.80, 5.88, 5.98, 6.23, 6.32 nm.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.96; H, 3.87; N, 13.06.

3,9-Dihydro-3,9-dioxo-2*H*-indeno[2,1-*c*]pyridine-4-carbonitrile (**7a**) *via* the Dimethylformamide Diethyl Acetal Method.

To 3.2 g. (0.0151 mole) of **6** in 50 ml. of DMF was added 5.0 g. (0.034 mole) of ketal reagent at room temperature. After stirring the reaction mixture for 3 hours, sufficient 1*N* hydrochloric acid solution was added to acidify the solution. Further addition of water caused formation of a precipitate which was collected and dried affording 2.95 g. (88%) of product. Recrystallization from DMF-water gave pure **5a**, m.p. > 300°; uv (methanol): 290, 278, 260 nm (7); nmr (DMSO-d_6): δ 7.73-8.00 (3H, m, aromatic H's), 8.10-8.25 (1H, m, 5-H), 8.33 (1H, s, 1-H).

Anal. Calcd. for $C_{13}H_6N_2O_2$: C, 70.27; H, 2.72; N, 12.61. Found: C, 70.29; H, 2.80; N, 12.57.

Compound **7a** *via* the Orthoester Method.

To 3.0 g. (0.0142 mole) of **6** in 20 ml. of DMF was added 3.0 g. (0.0202 mole) of triethylorthoformate and the reaction mixture was heated on a steam bath for 1 hour. The reaction mixture was then cooled to 5° and the solid present was collected, washed with ether, and dried to afford 2.65 g. (84%) of product identical to that obtained by the previous method; ms: m/e 222 (M^+).

Compound **7b** *via* the Orthoester Method.

To 2.0 g. (0.0094 mole) of **6** in 30 ml. of DMF was added 3.0 g. (0.0165 mole) of trimethyl orthobenzoate and the reaction mixture was heated at 100-105° for 3 hours. After cooling the precipitate present was collected, washed with ethyl acetate, then ether and dried to give 1.35 g. (48%) of analytically pure product: m.p. > 300°; uv (methanol): 274 (brd), 296 (sh), 350 (brd) nm (7); ms: m/e 298 (M^+).

Anal. Calcd. for $C_{19}H_{10}N_2O_2$: C, 76.50; H, 3.38; N, 9.39. Found: C, 76.63; H, 3.66; N, 9.55.

Compound **7c** *via* the Orthoester Method.

To 1.0 g. (0.0047 mole) of **6** in 6.5 ml. of DMF was added 1.0 g. (0.0062 mole) of triethyl orthoacetate and the reaction mixture was heated on a steam bath for 2 hours. The volume of the solution was then reduced to *ca.* 2/3 with a stream of nitrogen and the solid present was collected, washed with ethyl acetate and dried to give 0.4 g. (36%) of product. Recrystallization from acetic acid and then ethyl acetate gave the pure compound, m.p.

>300°; uv (methanol): 292, 280, 270 nm (7); ms: m/e 236 (M^+).

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 70.80; H, 3.47; N, 11.49.

General Procedure for the Preparation of the Carboxamides **8a**, **8b**, and **8c**.

To 2 ml. of concentrated sulfuric acid at room temperature was added 1-2 mmoles of tricyclic nitrile (**7**). After the pyridones went into solution, 2 drops of water were added and the reaction mixture was heated on the steam bath for 3 hours. After cooling, water was cautiously added and the precipitate which formed was collected. Recrystallization from glacial acetic acid gave **8a** (80%), m.p. >300°; uv (methanol): 260 nm (7).

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.04; H, 3.44; N, 11.61.

Recrystallization from DMF/water gave **8b** (81%), m.p. > 300°; uv (methanol): 262 nm (7).

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.14; H, 3.82; N, 8.86. Found: C, 71.84; H, 4.03; N, 8.93.

Recrystallization from DMF/water (2 x) gave **8c** (60%) as the hemihydrate, m.p. >300°; uv (methanol): 259 nm (7).

Anal. Calcd. for $C_{14}H_{10}N_2O_3 \cdot 1/2H_2O$: C, 63.88; H, 4.21; N, 10.64. Found: C, 64.14; H, 3.79; N, 10.47.

General Procedure for the Preparation of the *N*-Methylpyridones **9a**, **9b**, and **9c**.

To 1 mmole of tricyclic pyridone **7** in 5 ml. of DMF was added 1.1 mmoles of anhydrous potassium carbonate and 3 mmoles of methyl iodide and the reaction mixture was heated at 60-80° for 1-2 hours. Water was then added followed by a sufficient amount of 5% sodium hydroxide solution so that aqueous solution became basic. After stirring for a few minutes to allow any unreacted starting material to dissolve into the basic solution, the precipitate was collected. The parent tricyclic **9a** was obtained in > 95% crude yield and was recrystallized from ethanol/acetic acid, m.p. > 300°; nmr (trifluoroacetic acid/deuteriochloroform): δ 3.73 (3H, s, $-CH_3$), 6.75-7.20 (3H, m, aromatic H's), 7.42 (1H, s, 1-H), 7.35-7.65 (1H, m, 5-H).

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 71.13; H, 3.43; N, 11.87.

The phenylsubstituted tricyclic **9b** was also isolated in >95% crude yield. Recrystallization from chloroform/Skelly B gave the pure compound, m.p. 255-256°; nmr (deuteriochloroform): δ 3.32 (3H, s, $-CH_3$), 7.2-7.8 (8H, m, aromatic H's), 8.1-8.6 (1H, m, 5-H).

Anal. Calcd. for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 77.00; H, 4.03; N, 8.96.

The methyl-substituted tricyclic **9c** was isolated in 77% crude yield. After trituration with ethyl acetate/toluene the remaining solid was recrystallized from DMF/methanol to give the pure compound, m.p. 271-273.5°; nmr (DMSO-d_6): δ 2.78 (3H, s, 1-CH_3), 3.45 (3H, s, N-CH_3), 7.6-8.3 (aromatic H').

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.68; H, 3.94; N, 11.09.

Preparation of **10**.

To 1.0 g. of 57% sodium hydride/mineral oil dispersion (0.0238 mole) washed twice with Skelly B to remove the oil in 40 ml. of DMF was added 4.24 g. (0.02 mole) of **6** in 20 ml. DMF dropwise in a nitrogen atmosphere. After addition, the reaction mixture was stirred for an additional 10 minutes before 3.3 g. (0.02 mole) of **5** in 15 ml. of DMF was added dropwise at room temperature. After stirring for 2 hours the reaction was quenched with 25 ml. of acetic acid, poured into water and the solid present was collected, washed with water and dried. Recrystallization from acetic acid gave 2.8 g. (41%) of pure **10**, m.p. 253-256° dec.; uv (methanol): 229, 240 (sh), 220 nm (7); ms: m/e 340 (M^+).

Anal. Calcd. for $C_{21}H_{12}N_2O_3$: C, 74.11; H, 3.55; N, 8.23. Found: C, 73.86; H, 3.57; N, 7.94.

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(7) Due to the extreme insolubility of these compounds accurate ε-values were not obtained.