2-Acetylbenzo[*f*]quinoline by Direct Synthesis of a β-Acylpyridine Structure (1)

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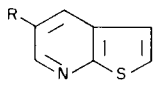
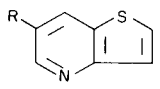
In a recent paper (3), we reported the reaction of 2- and 3-thienylammonium salts with acetoacetaldehyde dimethyl acetal (ADMA) at 75-80° to give 5-acetylthieno-[2,3-*b*]pyridine (Ib) and 6-acetylthieno[3,2-*b*]pyridine (IIb), respectively. Compound Ib served as a convenient intermediate for syntheses of other 5-substituted thieno-



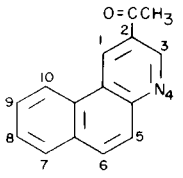
I

a: R = H; b: R = Ac; c: R = NO_2

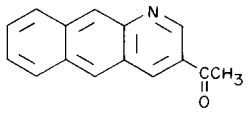


II

[2,3-*b*]pyridines (4). In consideration of the fact that β-acylpyridines and β-acylquinolines are usually made by indirect methods (5), we attempted to extend the ADMA reaction (6) to use of salts of aniline, 1-naphthylamine, and 2-naphthylamine as reactants under the same conditions. Only 2-naphthylamine gave an isolable product, A (86% yield). Preliminary spectral data were consistent with the assignment to A of the structure of either 2-acetylbenzo[*f*]quinoline (III) or its isomer 3-acetylbenzo-[*g*]quinoline (IV). Thus, the ultraviolet spectrum of A



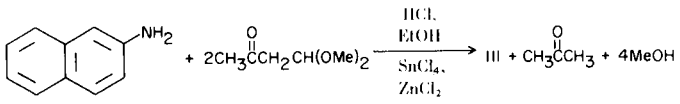
III



IV

exhibited a strong long-wavelength absorption maximum at 380 nm in ethanolic hydrochloric acid, while the infrared spectrum had a carbonyl band. Electron bombardment of A caused loss of methyl, acetyl, and hydrogen cyanide fragments. An nmr spectrum at 60 MHz showed (amongst the various signals) a singlet for acetyl protons, plus a low-field doublet of doublets (J = 2 Hz) for α and γ protons in a β-acylpyridine structure. Final assignment of structure III to A was based on observation of a strong absorption band for two vicinal aromatic hydrogen atoms at 830 cm^{-1} and an nmr spectrum at 100 MHz which showed (in addition to the previously assigned signals) a doublet of doublets (J = 8.6 Hz) for H-5 and H-6, a one-proton multiplet for H-10, and two multiplets for H-7 to H-9.

Identified as a second product of the reaction was acetone, formed in approximately equimolar amount to that of III (see stoichiometric equation 1). Cyclization occurs only at a ring position where electrophilic substi-



equation 1

tution is facile. Thus, no IV was isolated from the present reaction mixture and the yield of IIb (54%, from cyclization into the α position of the thiophene ring) was higher than that of Ib (32%, from cyclization into the β position of the thiophene ring). Moreover, cyclization into the 2-position of naphthalene or into the benzene ring did not take place (*vide supra*).

There is evidence that a colored intermediate, perhaps an anil such as 1-(2-naphthylimino)-3-butanone (V), first forms. Thus, on addition of ADMA to the other components of the reaction mixture, a yellow solid precipitates from the clear solution. Progress of the reaction can then be followed qualitatively by visual disappearance of this color and quantitatively by analysis of the acetone formed in the effluent from slow distillation of the ethanol solvent. Compound V was previously obtained as a yellow solid from reaction of 2-naphthylammonium chloride with a slight excess of sodium acetoacetaldehyde in refluxing methanol (7). However, no formation of III was reported from that process. In fact cyclization of V to the linear molecule 4-methylbenzo[*g*]quinoline was effected in the presence of anhydrous hydrogen fluoride (7). In our process, any V formed might well condense with a second molecule of acetoacetaldehyde and then cyclize to III (with attendant loss of acetone in a reverse Michael reaction) in the manner described previously (3).

The ADMA reaction bears a formal resemblance to that of an amine with malondialdehyde tetraalkyl acetal in the presence of alcoholic zinc chloride (MDTA reaction) to give a fused pyridine ring; see syntheses of the parent thienopyridines Ia and IIa from aminothiophene salts (3), the conversion of aminopyrazoles into pyrazolo[3,4-*b*]-pyridines (8), and the two-step transformations 3-nitrobenzo[*b*]thiophene → thianaphtheno[2,3-*b*]pyridine (9) and 3-nitrothieno[2,3-*b*]pyridine → dipyrido[2,3-*b*; 2′, 3′-*d*]thiophene (10). Analogously, a 2-thienylammonium salt condensed with sodium nitromalondialdehyde hydrate to give 5-nitrothieno[2,3-*b*]pyridine (Ic) in low yield (4). Uhle and Jacobs (11) isolated crystalline anils from aniline plus nitromalondialdehyde or cyanomalondialdehyde, as well as from 2-naphthylamine plus nitromalondialdehyde. These intermediates were cyclized by means of anhydrous zinc chloride at 200-300° to give 3-substituted quinolines (in the first two cases) and 2-nitrobenzo[*f*]quinoline (58% overall yield) in the third one.

Based on the malondialdehyde reactions it is conceivable that the ADMA reaction proceeds by an alternative mechanism which involves initial, rapid self-condensation of free acetoacetaldehyde to form acetone plus acetylmalondialdehyde. Cyclization would then proceed *via* the acetylmalondialdehyde anil. However, in consideration of the slow evolution of acetone during the ADMA reaction and of the drastic reaction conditions employed by Uhle and Jacobs to effect cyclization of their anils, we are inclined to favor reaction *via* V as a more likely route to III (*vide supra*).

EXPERIMENTAL (12)

2-Acetylbenzo[*f*]quinoline (III).

A mixture of 71 g. (0.5 mole) of 2-naphthylamine (Aldrich) (13), 500 ml. of 95% ethanol, 87 g. of stannic chloride pentahydrate, and 20 g. of fused zinc chloride was stirred until solution was complete. Then 150 ml. of concentrated hydrochloric acid was added slowly and the resultant slurry was cooled to 45°. After displacement of air by nitrogen, 140 g. (1.06 moles) of acetoacetaldehyde dimethyl acetal (Aldrich) was added all at once. The yellow solution, which first formed, deposited a yellow precipitate. The mixture was refluxed with partial distillation for *ca.* 8 hours, whereupon evolution of acetone was complete (as determined by a test with 2,4-dinitrophenylhydrazine reagent) (14). The precipitate from filtration (15) of the cold (10°) reaction mixture was dispersed in 800 ml. of 13% sodium hydroxide solution and extracted three times with 100 ml. portions of chloroform. The residue from evaporation of the extract was crystallized from carbon tetrachloride (1 l.) to give light tan III (94.5 g., 86%), m.p. 130-131°.

Sublimation of a sample of crude III at 125° (0.4 mm.) and recrystallizations from ethanol and carbon tetrachloride gave cream-colored needles, m.p. 128-129°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.31; H, 5.23; N, 6.49.

A *picrate* formed a fluorescent, yellow powder from ethanol, m.p. 219-220°.

Anal. Calcd. for $C_{21}H_{14}N_4O_8$: C, 56.00; H, 3.13; N, 12.44. Found: C, 56.02; H, 3.11; N, 12.70.

A *methiodide* gave orange needles from ethanol, m.p. 280-281°.

Anal. Calcd. for $C_{16}H_{14}INO$: C, 52.91; H, 3.89; N, 3.86. Found: C, 52.92; H, 3.85; N, 3.75.

Spectral Investigations of III.

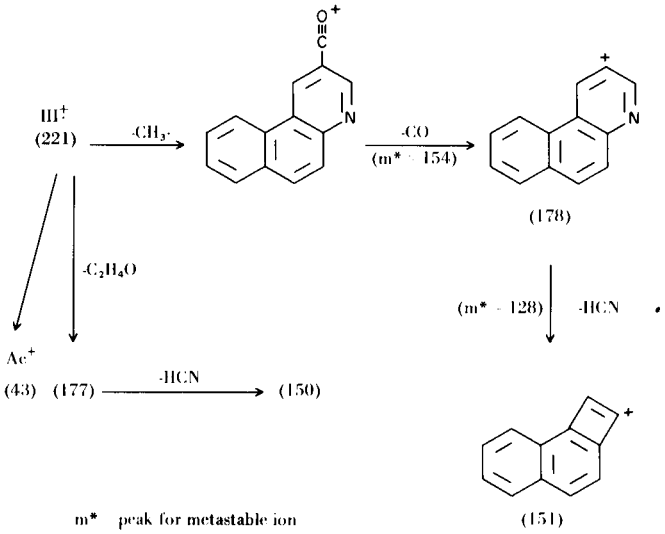
Ultraviolet absorption spectra were determined by means of a Cary model 11 spectrophotometer; λ max (ethanol) 217 nm (log ε 4.38), 239 (4.62), 265 (4.28), 274 (4.22), 318 (3.98), 339 (3.79), 356 (3.67); λ max (ethanol + HCl) 238 nm (log ε 4.55), 283 (4.30), 335 (3.67), 380 (3.90). The latter spectrum bears a general resemblance to spectra of 3-acetylphenanthrene (16) and 2-acetylanthracene (17).

The infrared spectrum (potassium bromide pellet) was determined by means of a Beckman IR-5A instrument; very strong bands at 1670 cm^{-1} (carbonyl), 830 (two vicinal aromatic hydrogens), and 750 (four vicinal aromatic hydrogens) (18). In carbon tetrachloride the carbonyl absorption occurred at 1690 cm^{-1}.

The nmr spectrum (deuteriochloroform) was determined by means of a Varian Associates A-60 instrument with tetramethylsilane as internal standard; δ 2.68 (s, 3, Ac), 7.4-7.9 [m, 5 (including a singlet at δ 7.83 for 2 protons), H-5 to H-9], 8.3-8.7 (m, 1, H-10), 9.21 ppm (d of d, $\Delta\delta$ = 6.9 Hz, J = 2 Hz, H-1 and H-3) (19). In carbon tetrachloride the signal for H-1 and H-3 appeared as a two-proton singlet. Use of a Varian Associates HA-100 instrument (deuteriochloroform) with hexamethyldisiloxane as external standard gave; δ 3.08 (s, Ac), 7.7-8.1 (m, H-8 and H-9), 8.25 (d of d, $\Delta\delta$ = 5.8 Hz, J = 8.6 Hz, H-5 and H-6) (19) which partially overlaps 8.1-8.25 (m, H-7), 8.7-9.0 (m, H-10), 9.59 (d, sharp, $J_{1,3}$ = 2 Hz, H-1), 9.63 ppm (d, broadened, H-3) (20).

The relative magnitudes of the chemical shifts of H-1 and H-3 may be considered to result from the varying effects of three contributing factors, *viz* (a) the 2-acetyl group (expected to affect H-1 and H-3 equally). (b) the ring current (greater downfield shift for H-1), and (c) the hetero nitrogen atom (greater downfield shift for H-3). In carbon tetrachloride, effects of factors (b) and (c) must just counterbalance such that $\delta_1 = \delta_3$. In

SCHEME I



m* peak for metastable ion

deuteriochloroform, on the other hand, hydrogen bonding by the solvent to the nitrogen atom may make $\delta_3 > \delta_1$ through an enhanced inductive effect on H-3. The coincidence that $\delta_5 \simeq \delta_6$ may result from operation of the same factors whereby (a) gives greater downfield shift of H-6 (through electron withdrawal by resonance) then of H-5, (b) affects H-5 and H-6 essentially equally, and (c) gives greater downfield shift of H-5 (through action of the non-bonding electrons on nitrogen) than of H-6.

The mass spectrum was determined by means of a CEC Model 21-110 instrument at 70 eV, m/e (relative abundance) (21); 222 (15), 221 (90), 207 (16), 206 (100), 179 (9), 178 (55), 177 (13), 152 (12), 151 (65), 150 (22), 75.5 (6), 75 (8), 43 (15). A fragmentation scheme which accounts for the more pertinent peaks is indicated in Scheme I.

Acknowledgments.

We gratefully acknowledge assistance by Dr. David R. McCoy, Dr. Danny White, Mrs. Mary Mitchell, and Mr. James R. Koskinen in some of the studies. Thanks are extended to the National Science Foundation and to the National Institutes of Health for providing financial support for purchase (respectively) of the mass spectrometer and the 100 MHz nmr instrument used.

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(15) Basification of the filtrate and extraction with chloroform gave 0.6 g. of recovered 2-naphthylamine.

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(20) Singlets ascribed to the presence of chloroform in the solvent occur at δ 7.30 in the 60 MHz spectrum and at δ 7.58 in the 100 MHz spectrum.

(21) Only peaks of relative abundance $>$ 5% of the 206 peak are reported.

Received April 4, 1970 Eugene, Oregon 97403