Triazino[4,3-*f*]phenanthridine Derivatives *via* a Novel Nucleophilic Cyclization[1]

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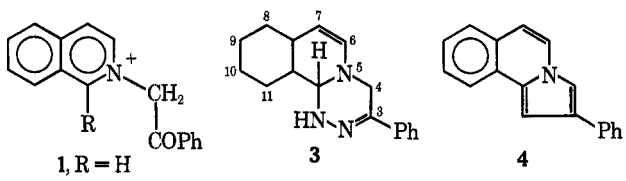
2-Phenacylisoquinolinium bromide reacts with hydrazine to afford an unstable triazino[3,4-*a*]isoquinoline derivative (**3**). More stable products were formed by the reaction of 5-phenacyl- and 5-acetonylphenanthridinium bromides (**5** and **6**) with hydrazines. Those 1,13b-dihydro-4*H*-*as*-triazino[4,3-*f*]phenanthridines which were prepared by use of unsubstituted hydrazine underwent dehydrogenation at positions 1 and 13b.

The ability of aromatic quaternary salts to undergo a large number of nucleophilic reactions[2] involving attack on the aromatic ring suggests that such reactions might form the basis of several hitherto unexplored cyclization reactions.[3]

When 2-phenacylisoquinolinium bromide (**1**) was allowed to react with approximately 2 equiv of hydrazine the result was not a salt but the unstable cyclized base **3**, as evidenced in the uv by strongly diminished absorption in the 340-mμ region and in the nmr by indication of the transformation of three aromatic protons to protons of the vinyl or benzyl type. Efforts to re-



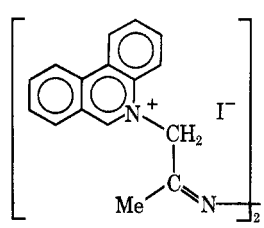
1, R = H
2, R = Me

3 **4**

aromatize the isoquinone ring of **3** by use of oxidants such as iodine failed, evidently because of the labile nature of the cyclic system.

Since the loss of aromatic character in one ring of a phenanthridinium salt produces a smaller fractional loss in the total resonance energy than does the corresponding change in a quinolinium salt, it seemed likely that phenanthridinium salts (**5**) analogous to **1** might undergo the new cyclization reaction more readily than isoquinolinium salts and give more stable products. The validity of this prediction is demonstrated by the results recorded in Table I. 5-Phenacylphenanthridinium bromide gave the cyclization reaction with hydrazine and methylhydrazine but failed with hydrazobenzene, 2,4-dinitrophenylhydrazine, and acethydrazide. 5-Acetonylphenanthridinium bromide also reacted with hydrazine and methylhydrazine. It was soon discovered that, when a tetrahydrofuran solution of 1,13b-dihydro-3-phenyl-4*H*-*as*-triazino[4,3-*f*]phenanthridine (**7**, R′ = H) was treated with mineral acids, it underwent dehydrogenation, and the salt obtained (**9**, R = Ph) could be neutralized to afford a new base having two hydrogen atoms less than **7** (R′ = H). The oxidation could be effected more readily by the action of iodine or 1-chlorobenztriazole. It is interesting that, when position 1 is blocked by a methyl group (**7**, R′ = CH_3), reaction with iodine fails to give an isolable product, while reaction with hydrobromic acid yields the original phenacyl salt (**5**).

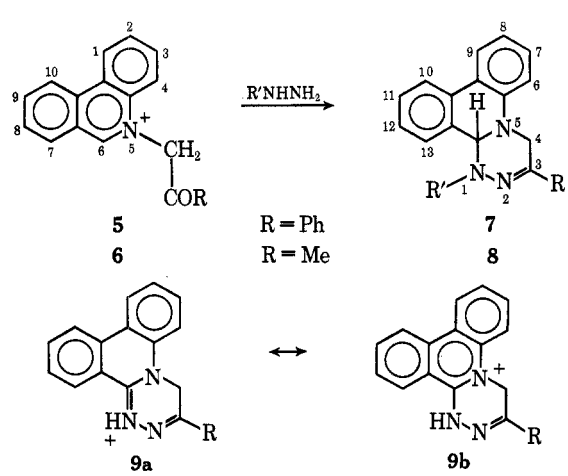
When the reaction product (**8**, R′ = H) of 5-acetonylphenanthridinium ion with hydrazine was allowed to react with iodine at temperatures from −30 to 60°, the product was always a mixture of about equal parts of the expected 3-methyl-4*H*-*as*-triazino[4,3-*f*]phenanthridine hydriodide (**9**, R = CH_3) and the azine (**10**) of



10

5-acetonylphenanthridinium ion. The triazine derivative (**9**, R = CH_3) may be purified by selective hydrolysis of the azine **10** to the 5-acetonylphenanthridinium ion (**6**). The azine **10** on treatment with hydrazine affords the triazino derivative **8**.

A further observation of interest is that when 1-methyl-2-phenacylisoquinolinium ion (**2**) was allowed to react with hydrazine the result was a Tschitschibabin cyclization[4] affording **4**. In this case the hydrazine functions merely to abstract a proton.



5 **6** R = Ph, R = Me **7** **8**

9a ↔ **9b**

Experimental Section

All melting points were taken in capillaries using the Thomas–Hoover apparatus and are uncorrected. The uv spectra were taken on a Beckman DB-G grating spectrometer using 1-cm quartz cells. The mass spectra are courtesy of the Research Triangle Center for Mass spectrometry, where they were ob-

(1) This research was supported by U. S. Public Health Service Grant No. CA-05509 from the National Cancer Institute.

(2) (a) C. K. Bradsher and J. H. Jones, *J. Amer. Chem. Soc.*, **81**, 1938 (1959), in particular ref 5–17; (b) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953); (c) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955); (d) N. Campbell in "Chemistry of Organic Compounds," Vol. IVa, E. H. Rodd, Ed., Elsevier, Amsterdam, 1957, pp 597, 653; (e) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958).

(3) For a recent example of a nucleophilic cyclization of a salt, see C. K. Bradsher, W. S. Burnham, and M. F. Zinn, *J. Heterocycl. Chem.*, **7**, 779 (1970).

(4) A. E. Tschitschibabin, *Fortsch. Teerfarbenfabrication*, **16B**, 2651 (1931).

TABLE I

TRIAZINO DERIVATIVES (7 AND 8) PRODUCED BY ADDITION OF HYDRAZINES TO PHENACYL- (5) AND ACETONYLPHENANTHRIDINIUM (6) BROMIDES

R	R′	Time, hr	Temp, °C	Yield, %	Mp, °C	Formula[a]	Nmr, δ[b]
Ph	H	0.08	23	62[c]	185–186	$C_{21}H_{17}N_3$[d]	4.7 (m, 2, CH_2), 5.72 (s, 1, CH)
Ph	Me	0.25	23	11.5[e]	155–156	$C_{22}H_{19}N_3$	2.62 (s, 3, CH_3), 4.70 (d, 2, J = 7 Hz, CH_2), 5.18 (s, 1, CH)
Me	H	4	23	51[c]	159–160	$C_{16}H_{15}N_3$	1.87 (s, 3, CH_3), 3.96 (s, 2, CH_2), 5.39 (s, 1, CH)
Me	Me	24	23	41[f]	156–157	$C_{17}H_{17}N_3$	1.90 (s, 3, CH_3C), 2.44 (s, 3, CH_3N), 4.05 (d, 2, J = 4 Hz, CH_2), 4.83 (s, 1, CH)

[a] Acceptable analyses (±0.20% for C, H, and N) were submitted for all compounds in this table. Ed. [b] Signals for aromatic protons (at δ <6.5 ppm) have been omitted. [c] The product was collected and slurried with water before final recrystallization. [d] Mass spectrum m/e (rel intensity) 311 (77), 295 (59), 281 (11), 194 (100), 179 (100), 165 (65), 151 (32). [e] The crude product was collected and heated with 30 ml of methanol per gram of product. The mixture was filtered hot, rejecting the undissolved solid, and the product was recovered by cooling the filtrate. [f] After the reaction mixture was cooled and any solid was removed by filtration, the resulting solution was diluted with water and cooled. The product thus obtained was recrystallized from tetrahydrofuran–heptane.

served at low resolution with a MS 902 mass spectrometer. All nuclear magnetic resonance data were obtained with 60-MHz instruments. Elemental analyses were by M-H-W Laboratories, Garden City, Mich., or by Jannsen, Pharmaceutica Research Laboratories, Beerse, Belgium.

1,11b-Dihydro-3-phenyl-4*H*-*as*-triazino[3,4-*a*]isoquinoline (3).—To a solution of 5.0 g of 2-phenacylisoquinolinium bromide in 40 ml of redistilled anhydrous acetonitrile, 1.53 g of hydrazine hydrate was added, affording a colorless precipitate. After 10 min the precipitate was collected and recrystallized from tetrahydrofuran by forming a saturated solution at 23°, filtering to remove salts, then cooling to −15°. The product was obtained as a colorless, fibrous solid: mp 123–125°; yield 1.8 g (45%); nmr [$(CD_3)_2SO$] δ 4.53 (br s, 2, CH_2), 5.23 (d, 1, J = 8 Hz, C-7 H), 5.6 (m, 2, NH and C-11b H), 6.33 (d, 1, J = 8 Hz, C-6 H), 6.7–7.9 (m, 9, aromatic); ir 1634 cm^{-1} (C=N–).

Anal. Calcd for $C_{17}H_{15}N_3 \cdot H_2O$: C, 73.08; H, 6.14; N, 15.04. Found: C, 73.29; H, 5.99; N, 14.76.

One gram of **3** was dissolved in 20 ml of tetrahydrofuran and 0.945 g of iodine was added. A tan precipitate formed and after 5 min was collected. The product was crystallized from methanol, affording 0.5 g (33%) of 2-phenacylisoquinolinium iodide, mp 178–179° (lit.[5] 178–180°).

1,13b-Dihydro-4*H*-*as*-triazino[4,3-*f*]phenanthridines (Table I).—The quaternary salt (**5** or **6**) was dissolved in 10 ml of anhydrous acetonitrile per gram of solute and mixed with 2 equiv of the hydrazine. At the end of the reaction the product was isolated and except as indicated crystallized from methanol–tetrahydrofuran.

3-Phenyl-4*H*-*as*-triazino[4,3-*f*]phenanthridine Hydriodide (9, R = Ph).—To a solution of 2.5 g of **7** (R′ = H) in 40 ml of reagent grade tetrahydrofuran, 1.9 g of elemental iodine was added over a 5–10 min period. The mixture was stirred for an additional 15 min and the product was collected and recrystallized from hot methanol, affording 1.5 g (44%) of yellow solid: mp 270–271°; uv max (100% C_2H_5OH) 256 mμ (sh), 264 (log ε 5.27), 292 (5.01), 324 (4.39), 370 (4.91), 388 (5.07), 410 (4.85); nmr [$(CD_3)_2SO$] δ 5.5 (s, 2, CH_2), 7.5–9.0 (m, 13, aromatic).

Anal. Calcd for $C_{21}H_{16}N_3I$: C, 57.67; H, 3.68; N, 9.61. Found: C, 57.69; H, 3.65; N, 9.55.

The free base was obtained by dropwise addition of triethylamine to a suspension of the hydriodide in acetonitrile. The product crystallized from tetrahydrofuran–methanol as bright yellow needles: mp 160–161°; nmr ($CDCl_3$) δ 4.72 (s, 2, CH_2), 7.0–8.3 (m, 13, aromatic); mass spectrum m/e (rel intensity) 309 (66), 281 (100), 204 (10), 179 (73), 151 (39).

Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.52; H, 4.89; N, 13.59. Found: C, 81.40; H, 4.92; N, 13.43.

3-Methyl-4*H*-*as*-triazino[4,3-*f*]phenanthridine Hydriodide (9, R = CH_3).—The dehydrogenation of 3.5 g of 13b-dihydro-3-methyl-4*H*-*as*-triazino[4,3-*f*]phenanthridine (**8**, R′ = H) was carried out essentially as in the case of the phenyl analog (**7**, R′ = H) except that the crude product which crystallized from the tetrahydrofuran was heated at 80° for 1 hr with 40 ml of 48% hydriodic acid. The resulting colorless solid was collected and recrystallized from hot methanol, affording 1.1 g (22%) of product: mp 297–298°; uv max (100% C_2H_5OH) 240 mμ (log ε 5.43), 250 (5.43), 260 (5.37), 344 (4.92), 362 (4.97), 380 (4.82); nmr [$(CD_3)_2SO$] δ 2.32 (s, 3, CH_3), 5.19 (s, 2, CH_2), 7.6–9.4 (m, 8, aromatic).

The free base was obtained by treating the salt (**9**, R = CH_3) with triethylamine as in the case of the phenyl analog (**9**, R = Ph). The product crystallized from tetrahydrofuran–hexane as a light tan solid: mp 155–156°; nmr ($CDCl_3$) δ 2.19 (s, 3, CH_3), 4.29 (s, 2, CH_2), 6.7–9.7 (m, 8, aromatic); mass spectrum m/e (rel intensity) 247 (100), 219 (50), 204 (19), 179 (63) 151 (28).

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.70; H, 5.30; N, 17.01. Found: C, 77.75; H, 5.10; N, 16.87.

Azine 10 of 5-Acetonylphenanthridinium Iodide.—If in the dehydrogenation of **8** (R = H) the crude product was not heated with hydriodic acid, but was simply recrystallized from methanol–ethyl acetate, it afforded orange-yellow needles: mp 215–216° dec; yield 44%; nmr [$(CD_3)_2SO$] δ 1.62 (s, 3, CH_3), 6.16 (s, 2, CH_2), 6.3–7.8 (m, 8, aromatics), 10.04 (s, 1, H at C-6).

Anal. Calcd for $C_{32}H_{28}N_4I_2$: C, 53.20; H, 3.87; N, 7.70. Found: C, 53.19; H, 3.87; N, 7.44.

1-Methyl-2-phenacylisoquinolinium Bromide (2).—A mixture of 3.0 g of 1-methylisoquinoline, 5.2 g of phenacyl bromide, and 7 ml of tetramethylene sulfone was heated at 80° for 10 min. After the resulting green melt had cooled, acetone was added and the resulting solid was collected from methanol–ethyl acetate, yield 5 g (69%), mp 215°.

Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09. Found: C, 62.95; H, 4.57; N, 3.91.

2-Phenylpyrrolo[2,1-*a*]isoquinoline (4).—When 1-methyl-2-phenacylisoquinolinium bromide was treated with hydrazine hydrate as was **1** in the preparation of **3**, a colorless solid was obtained, mp 160°, in a yield of 56%: nmr ($CDCl_3$) all signals δ >6.5.

Anal. Calcd for $C_{18}H_{13}N$: C, 88.84; H, 5.39; N, 5.76. Found: C, 88.57; H, 5.36; N, 5.76.

Registry No.—**2**, 30589-42-5; **3**, 30589-43-6; **4**, 7496-93-7; **7** (R′ = H), 30589-45-8; **7** (R′ = Me), 30589-46-9; **8** (R′ = H), 30589-47-0; **8** (R′ = Me), 30589-48-1; **9a** (R = Ph), 30589-49-2; **9a** (R = Ph) hydriodide, 30589-50-5; **9a** (R = CH_3), 30589-51-6; **9a** (R = CH_3) hydriodide, 30589-52-7; **9b** (R = Ph), 30589-53-8; **9b** (R = Ph) hydriodide, 30589-54-9; **9b** (R = CH_3), 30589-55-0; **9b** (R = CH_3) hydriodide, 30589-56-1; **10**, 30589-57-2.

(5) L. C. King and M. McWhirter, *J. Amer. Chem. Soc.*, **68**, 717 (1946).