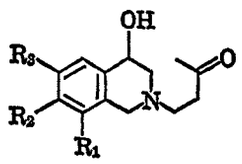
TABLE I

N-(3-OXOBUTYL)-4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINES

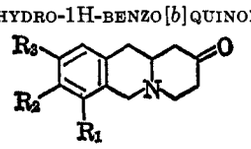


Compd	R_1	R_2	R_3	Yields,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6	H	OH	OCH_3	51	135–137	63.40	7.17	5.28	63.16	7.26	5.50
7	H	OCH_3	OH	53	138–141	63.40	7.17	5.28	63.12	7.14	5.32
8	H	OCH_3	OCH_3	72	128–128.5	64.50	7.58	5.01	64.41	7.67	5.00
9	OH	OCH_3	H	76	136.5–138.5	63.38	7.22	5.28	63.31	7.22	5.13
10[b]	H	OCH_2O		33	184.5–185.5	56.09	6.06	4.67	56.54	6.22	4.41

[a] Yields are based upon starting aldehydes. [b] Isolated and characterized as hydrochloride salt and as picrate. *Anal.* Calcd: Cl, 11.83. Found: Cl, 11.93.

TABLE II

3,4,11,11a-TETRAHYDRO-1H-BENZO[*b*]QUINOLIZIN-2-(6H)-ONES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	H	OH	OCH_3	68 (55)	192.5–193.5	68.00	6.93	5.66	68.31	6.86	5.67
12	H	OCH_3	OH	40 (74)	212–213	68.00	6.93	5.66	67.99	6.86	5.65
13	H	OCH_3	OCH_3	66 (22)	140.5–141.5	68.94	7.33	5.36	68.61	7.58	5.29
14	OH	OCH_3	H	60 (59)	163–164	68.00	6.93	5.66	68.10	7.11	5.51
15	H	OCH_2O		41 (79)	168–169	68.56	6.16	5.71	68.69	6.29	5.65

[a] The yields given refer to the sequence 1 → 2 → 3 → 5. The yields in parentheses refer to the conversions of 4 → 5.

were recrystallized from absolute ethanol; **8** was recrystallized from 95% ethanol; **9** was recrystallized from 1-propanol and **10** was recrystallized from methanol. The picrate of **10** was prepared in ethanol from the hydrochloride and recrystallized from methanol to yield an analytical sample, mp 160° dec.

Anal. Calcd for $C_{20}H_{20}N_4O_{11}$: C, 48.81; H, 4.10; N, 11.39. Found: C, 48.73; H, 4.41; N, 11.20.

3,4,11,11a-Tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones (5). General Procedure.—The oily tertiary amines (**3**), prepared as described above, were dissolved in 50 ml of concentrated hydrochloric acid. The solutions became hot and were cooled and washed with three portions of a 3:2 mixture of ether–benzene. The acid solutions were then heated at 45–50° for 30 min. The cooled solutions were diluted with water and made basic with aqueous ammonia to pH 9–10. In the cases where the amine did not precipitate at this point (**13** and **14**), the basic, aqueous solution was extracted with chloroform. The chloroform extracts were concentrated to an oil which, when cooled and diluted with a little ethanol, crystallized. The products were collected by filtration. The general procedure is valid with the following exceptions: in the preparation of **13**, the acid solution was heated to 88–95° for 15 min before extracting it with ether–benzene; in the preparation of **14**, the best yields were obtained when the acid solution was allowed to stand at room temperature for about 11 hr instead of heating it. Compounds **12**, **13**, and **15** were recrystallized for analysis from 95% ethanol; **11** was recrystallized from absolute ethanol; and **14** was recrystallized from methanol.

The conditions for the conversion of the 4-hydroxyisoquinolines (**4**) into the tricyclic ketones (**5**) are identical with those given for the conversions of **3** into **5**. The yields are given in parentheses in Table II.

Registry No.—**6**, 16675-64-2; **7**, 16675-65-3; **8**, 16675-66-4; **9**, 16675-67-5; **10** HCl, 16675-68-6; **10** picrate, 16675-69-7; **11**, 16675-70-0; **12**, 16675-72-2; **13**, 16675-71-1; **14**, 16675-73-3; **15**, 16675-74-4.

The Reaction of Piperidoneenamines with Methyl β-Vinylacrylate. A Route to Quinolines and Isoquinolines[1]

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Received December 21, 1967

Berchtold and Ciabattoni[2] were the first to report on the cycloaddition reaction of enamines with β-vinylacrylic esters. The synthetic importance of this reaction arises from the subsequent retro Michael elimination of the amine function to produce 1,3-cyclohexadienes not otherwise readily preparable.[3] These systems can in turn be aromatized to produce benzene rings.[4] For example, the reaction of the pyrrolidineenamine of cyclopentanone (**1**) and methyl β-vinylacrylate (**2**) affords the fused bicyclic system **3**, which undergoes an elimination reaction to give **4**, which may subsequently be aromatized to **6**. In a concurrent study in this laboratory,[5] the cycloaddition–retro

(1) This research was supported by a grant from the Petroleum Research Fund of the American Chemical Society.

(2) G. A. Berchtold, J. Ciabattoni, and A. A. Tunick, Abstracts, the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 35.

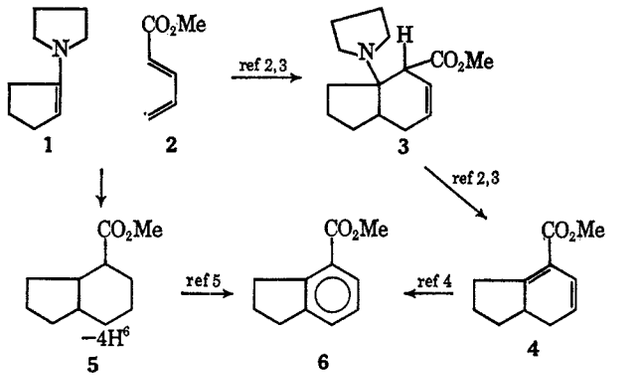
(3) G. A. Berchtold, J. Ciabattoni, and A. A. Tunick, *J. Org. Chem.*, **30**, 3679 (1965).

(4) H. O. House and T. H. Cronin, *ibid.*, **30**, 1061 (1965).

(5) S. Danishefsky and R. Cunningham, *ibid.*, **30**, 3676 (1965).

Michael sequence was also noted, although the product obtained was an isomeric mixture of cyclohexadienes, **5**,[6] which could be aromatized either oxidatively or thermally. These results are summarized in Scheme I.

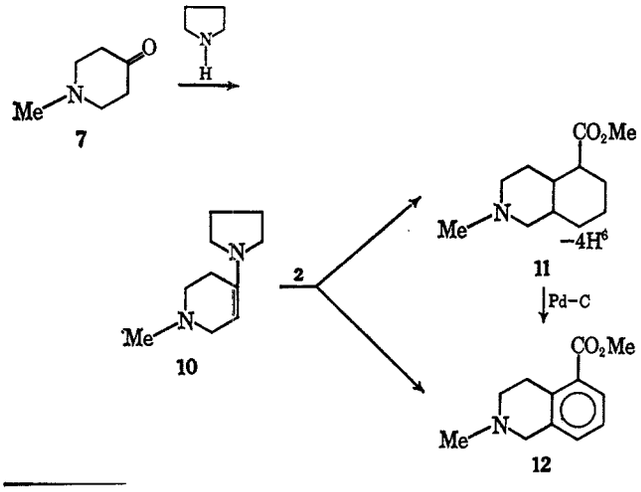
SCHEME I



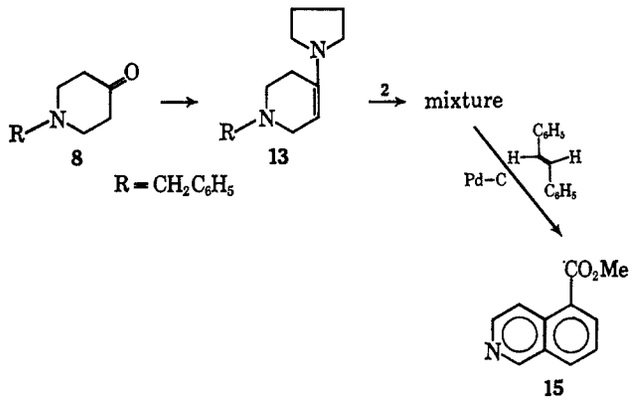
In this paper we report the extension of these reactions to the synthesis of heterocyclic ring systems.[7] Selected for study were the N-substituted piperidones **7**, **8**, and **9**.

Treatment[8] of compound **7** with pyrrolidine afforded the enamine **10** in 91% yield. When this compound was allowed to react with the ester **2**,[9] there was obtained, in 94% yield, a mixture (**11**) of three compounds. Treatment of the mixture with 5% Pd–C in methanol solution under reflux afforded a 93% yield of the 2-methyl-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline (**12**). This compound was one of the three components present in the original mixture, the other two presumably being isomeric hexahydro derivatives which underwent monodehydrogenation to yield **12**. The structure of **12** was established by its combustion analysis, by infrared (ir) and nuclear magnetic resonance (nmr) spectra, and *via* preparation of a picrate (see Experimental Section). The conversion of compound **7** into the isoquinoline **12** is 80% from the starting piperidone. These results are summarized in Scheme II.

SCHEME II



The possibility of using an N-benzyl system with the potentialities inherent in debenzylation was also examined. Thus, compound **8**, upon treatment with pyrrolidine, gave the enamine **13** in 95% yield. Reaction of this enamine with the ester **2** gave an 81% yield of a mixture of 1-benzyl-5-carbomethoxyhydroisoquinolines signified as mixture **14**. Treatment of this mixture with 5% Pd–C in the presence of excess *trans*-stilbene afforded a 72% yield of the previously known[10] 5-carbomethoxyisoquinoline **15**. The exact sequence of steps leading to the noteworthy result of threefold dehydrogenation[11] and onefold hydrogenolysis has not been established.



The reaction of pyrrolidine with 1-benzyl-3-piperidone (**9**) might, in principle, have given either the enamine **16** or its isomer **17** or a mixture of these compounds. In practice, this reaction gave an exceedingly unstable enamine (84% yield) whose structure was clearly **16** since its nmr spectrum contained a singlet encompassing one proton at τ 5.15. While we have not established whether **16** arose from kinetic or thermodynamic control, one might assume that it is the more stable of the two enamines since it contains conjugation of the "lone pair" of the N-benzyl nitrogen atom with the double bond.

The enediamine system **16** offers, in principle, the interesting possibility of ambident nucleophilic activity at C_1 or C_2. Attack of an electrophile at C_1 would be favored on steric grounds. On the other hand, attack at C_1 requires coplanarity of the pyrrolidine and tetrahydropyridine ring systems for maximum overlap of the "lone pair" of the N-pyrrolidino nitrogen with the double bond. Attack at C_2 requires a conformation already present in the ground state, *i.e.*, with the benzyl group quasi-equatorial and the unshared electron pair of the N-benzyl nitrogen quasi-axial and well disposed for overlap.

In practice, reaction of the enamine **16** with compound **2** gave a mixture (**18**) of hydroquinolines. Analysis of the mixture through combined gas chromatography–mass spectrometry[12] showed it to consist of a 4:1 ratio of hexahydro/octahydro isomers.[13] Dehy-

(6) The number under the formula represents the number of hydrogen atoms required for saturation, *e.g.*, −4H is a mixture of bisdehydro compounds.

(7) For some recent applications of this reaction to heterocyclic synthesis, see F. Bohlman, D. Habeek, F. Poetsch, and D. Schumann, *Chem. Ber.*, **100**, 2742 (1967).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(9) E. Adlerova, L. Blaha, M. Borovicka, I. Ernest, J. O. Jilek, B. Kahac, L. Novak, M. Rajsner, and M. Protiva, *Collect. Czech. Chem. Commun.*, **25**, 221 (1960).

(10) F. T. Tyson, *J. Amer. Chem. Soc.*, **61**, 183 (1959).

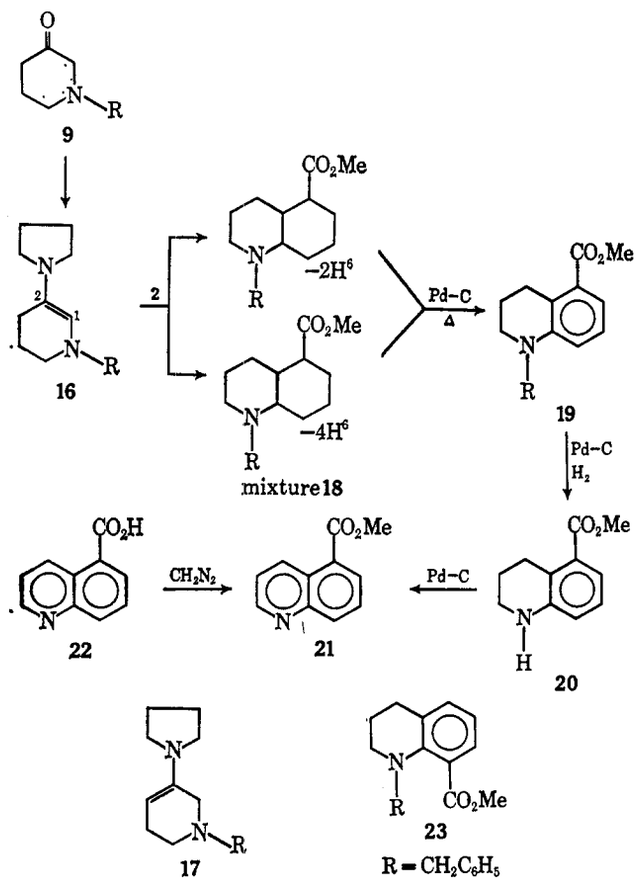
(11) This assumes the major portion of the reaction mixture to be hexahydroquinoline isomers.

(12) The mass spectra were obtained from an LKB 9000 by Mr. J. Nawarol.

(13) The octahydro isomers undoubtedly arose from disproportionation of the hexahydro systems. We were unable to detect any of the corresponding tetrahydro system (**19**) in the reaction mixture at this stage.

drogenation with Pd–C in toluene afforded a 41% yield (based on **16**) of compound **19**. The structure of **19** follows from its debenzylation[14] and dehydrogenation to afford compound **21**. The compound thus obtained was identical with that obtained by treating the known quinoline-5-carboxylic acid (**22**) with diazomethane. These results are summarized in Scheme III.

SCHEME III



Since all cycloaddition reactions of enamines with compound **2** thus far studied are directionally specific in the Michael–Mannich sense, it is clear that the sequence of reactions leading to **19** rather than **23** must have begun with electrophilic attack at C_1 of the ambident enamine **16**. However, since the yield of compound **19** is only 41%, the possibility of the formation of products arising from initial electrophilic attack at C_2 can hardly be excluded.

Experimental Section[15]

Preparation of Enamines.—The following enamines were prepared according to the general procedure of Stork.[8]

N-Methyl-4-piperidonepyrrolidineenamine (**10**) was a yellow oil (91%): bp 78–80° (0.1 mm); ir ($CHCl_3$), 6.10 μ (enamine); nmr (neat), τ 5.93 (t, 1, J = 4 Hz), 6.9–8.4 (m, 17, with a singlet at 7.93).

Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 72.13; H, 11.07; N, 16.96.

N-Benzyl-4-piperidonepyrrolidineenamine (**13**) was a yellow oil (92%): bp 138–140° (0.05 mm); ir (CCl_4), 6.07 (enamine), 14.32 μ; nmr (neat), τ 2.6–2.8 (m, 5), 5.8–6.0 (poorly resolved triplet, 1) 6.50 (s, 2), 6.8–8.5 (m, 14).

Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15. Found: C, 78.96; H, 9.15.

N-Benzyl-3-piperidonepyrrolidineenamine (**16**) was a yellow oil (84%): bp 133–137° (0.06 mm); ir (CH_2Cl_2), 6.10 μ (enamine); nmr ($CDCl_3$), τ 3.15 (broad singlet, 5), 5.15 (s, 1), 6.50 (s, 2), 7.18–8.5 (m, 14).

Reaction of Enamine 10 with Methyl β-Vinylacrylate (**2**).—A solution of 16.5 g (0.147 mol) of the ester **2**, and 24 g (0.144 mol) of the enamine **10** was heated in 50 ml of dry benzene under reflux in a nitrogen atmosphere for 20 hr. After cooling, the solution as extracted with 150 ml of 10% HCl. The aqueous layer was washed with 100 ml of ether, made basic by the cautious addition of excess solid Na_2CO_3 and extracted with three 100-ml portions of ether. The ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue which upon distillation gave 28 g (94%) of a yellow oil (**11**): bp 94–97° (0.05 mm); ir ($CHCl_3$), 5.80 μ (unsaturated ester); vpc (8-ft 20% "FFAP" on Chromosorb W, flow rate 82 ml/min, temperature = 200°), retention time in min (approximate area), 33 (1) 34 (3) 42 (3).

2-Methyl-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline (**12**).—A solution of 1.95 g (9.4 mmol) of the above mixture in 10 ml dry methanol was heated under reflux with 0.3 g of 5% Pd–C for 6 hr. The catalyst was filtered and washed with ether, the filtrates were combined, the solvents were removed at the water pump, and the residue was distilled from an oil-jacketed flask. There was thus obtained 1.8 g (93%) of **12**, bp 110° (0.1 mm). Vpc analysis showed this to be homogeneous and the same as the component with retention time of 42 min in the previous experiment: ir ($CHCl_3$), 5.81, 6.3, 6.4, 6.9 μ; nmr (CCl_4), τ 2.67 (apparent triplet, 1, J = 4 Hz); 3.30 (apparent doublet, 2, J = 4 Hz), 6.42 (s, 3), 6.72 (s, 2), 6.8–7.8 (m, 14), 7.82 (s, 3).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.04; H, 7.53; N, 6.90.

The picrate had mp 166–167° (EtOH).

Anal. Calcd for $C_{18}H_{18}N_4O_9$: C, 49.47; H, 4.18; N, 12.90. Found: C, 49.50; H, 4.13; N, 13.15.

Reaction of Enamine 13 with Methyl β-Vinylacrylate (**2**).—A solution of 13.5 (0.12 mol) of compound **2** and 24.2 g (0.10 mol) of the enamine **13** in 100 ml of benzene was heated under reflux in a nitrogen atmosphere for 18 hr. The solution was cooled and extracted with 150 ml of 10% HCl. The acidic layer was washed with 50 ml of ether, made basic with excess sodium carbonate, and extracted with three 100-ml portions of ether. The ethereal extracts were dried (Na_2SO_4), concentrated under reduced pressure, and distilled to give 24.9 g (81%) of mixture **14**: bp 160–161°; ir (CCl_4), 5.79, 6.7, 14.3 μ.

5-Carbomethoxyisoquinoline (**15**).—A solution of 4.8 g (0.017 mol) of the above mixture with 15 g (0.083 mol) of *trans*-stilbene and 2.0 g of 5% Pd–C in 100 ml of *p*-cymene was stirred and heated under reflux for 42 hr. After cooling, the catalyst was filtered and washed with ether. The washings were combined with the cymene solution and the total solution was extracted with 50 ml of 10% HCl. The acidic layer was washed with 50 ml of ether, made basic with excess sodium carbonate, and extracted with five 20-ml portions of ether. The ether extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue when distilled gave 2.3 g (73%) of **15**, bp 90–120°, which solidified in the receiving flask. Recrystallization afforded **15** as a solid: mp 66° (lit.[10] mp 66°); ir ($CHCl_3$), 5.81, 6.15, 6.20, 8.0, 11.9 μ; nmr ($CDCl_3$), τ 0.79–0.94 (m, 1), 1.24–1.44 (m, 2), 1.54–1.80 (m, 1), 1.84–2.04 (m, 1), 2.34–2.59 (m, 1), 6.00 (s, 3).

Reaction of Enamine 16 with Methyl β-Vinylacrylate (**2**).—A solution (under nitrogen) of 8 g (0.033 mol) of **16** and 8 g (0.071 mol) of compound **2** in 40 ml of dry benzene was heated under reflux for 16 hr. The solution was extracted with 75 ml of 10% HCl. The aqueous layer was washed with 50 ml of ether and made basic with excess sodium carbonate. The emulsion was extracted with three 50-ml portions of ether. The ethereal solution was dried (Na_2SO_4) and concentrated under reduced pressure. The concentrate was distilled to afford 7.5 g (80%) of mixture **18** as a yellow oil: bp 160–165° (0.08 mm); ir ($CHCl_3$), 5.82, 6.15, 14.30 μ; vpc (6.3% OV-17 on "Gas-Chrom G" −215°, 100 ml/min), retention time in min (relative area),

(14) Attempts to isolate the intermediate debenzylation product, **20**, gave irreproducible results.

(15) All melting points are corrected. Infrared spectra were determined with either a Beckman IR-8 or a Perkin-Elmer 137 Infracord. Nmr spectra were determined with a Varian A-60 spectrometer and are reported in parts per million downfield from tetramethylsilane. Combustion analyses were conducted by Galbraith Laboratories, Inc., Nashville, Tenn. Gas chromatograms were obtained on a Varian Associated A-90 P-3 instrument. The piperidones were obtained from the Aldrich Chemical Co. and distilled before use. The 5% Pd–C catalyst was obtained from Englehard Corp. The quinoline-5-carboxylic acid was purchased from K & K Laboratories.

molecular weight in *m/e*, 13 (2), *m/e* 285, 15 (1), *m/e* 285, 21 (5), *m/e* 283, 24 (7), *m/e* 283.

1-Benzyl-5-carbomethoxy-1,2,3,4-tetrahydroquinoline (19).—A solution of 2.5 g (0.009 mol) of mixture **18** in 10 ml of toluene was heated under reflux with 1 g of 5% Pd–C for 26 hr. The catalyst was filtered and washed with ether. The washings were combined with the toluene solution and concentrated *in vacuo*. The residue was chromatographed on 100 g of Woelm neutral alumina. With benzene as the eluent, 1.3 g (51%) of compound **19** was obtained. Recrystallization from ethanol afforded an analytical sample of **19**: mp 77–78°; ir ($CHCl_3$), 5.84, 6.29, 14.4 μ; nmr ($CDCl_3$), τ 2.6–3.5 (m, 8), 5.55 (s, 2), 6.17 (s, 3), 6.5–7.1 (m, 4), 7.8–8.2 (m, 2).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.72; N, 4.99.

5-Carbomethoxyquinoline (21).—A solution of 102 mg of compound **19** in 5 ml of absolute ethanol was treated with 500 mg of 5% Pd–C for 2 hr at atmospheric pressure and room temperature. *An evolution of gas was noted.* The catalyst was filtered and washed with ethanol. The washings were combined with the filtrate and concentrated *in vacuo* whereupon a solid residue was formed. Recrystallization from ether at −70° gave 55 mg (81%) of compound **21**: mp 39–41°; ir ($CHCl_3$), 5.82, 6.64 μ; nmr ($CDCl_3$), τ 0.50–0.70 (m, 1), 1.51–1.75 (m, 1), 2.10–2.30 (m, 2), 2.65–2.74 (m, 2), 6.00 (s, 3).

5-Carbomethoxyquinoline (21) by Known Synthesis.—A solution of 25 mg of quinoline-5-carboxylic acid in 50 ml of methanol was treated with excess diazoamethane. Evaporation of the solvent left a residue which was purified through preparative scale gas chromatography on a 5-ft, 20% SE-30 column at a flow rate of 90 ml/min and a column temperature of 190°. There was thus obtained 16 mg of ester **21**, mp 39–31° (undepressed on admixture with **21** from above).

Registry No.—**2**, 2409-87-2; **10**, 16675-55-1; **12**, 16675-56-2; picrate of **12**, 16675-57-3; **13**, 16675-58-4; **15**, 16675-59-5; **16**, 16675-60-8; **19**, 16675-61-9; **21**, 16675-62-0.

Mass Spectrometry in Structural and Stereochemical Problems. CLX.[1] On the Supposed *peri* Interaction in 4-Isobutylquinoline[2]

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Received March 14, 1968

In a previous publication from this laboratory,[3] the mass spectrum of 4-isobutylquinoline was reported. At 70 eV the base peak appeared at *m/e* 170, corresponding to the loss of a methyl radical. Even at 12 eV, this peak was second only to the molecular ion (*m/e* 185) in intensity, indicative of a highly facile mode of decomposition. Such behavior has been noted in 8-alkylquinolines, *e.g.*, 8-propylquinoline[3] where it has been attributed to ring closure with the suitably situated nitrogen atom. Since the concept of *peri* interactions in mass spectral fragmentations is being recognized more frequently,[4] the preferred loss of a methyl radical was

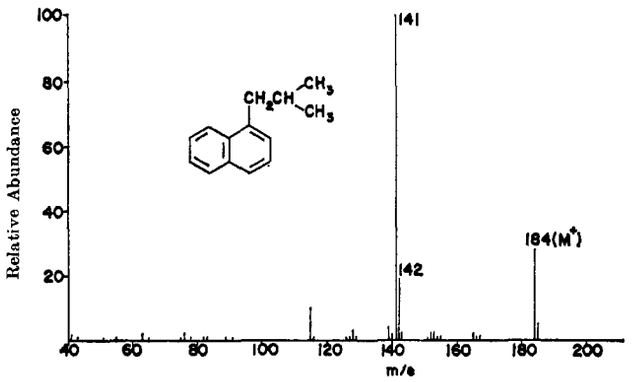

Figure 1.—Mass spectrum of 1-isobutylnaphthalene.

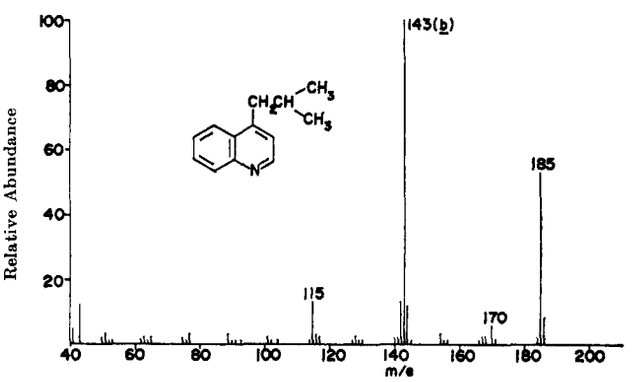

Figure 2.—Mass spectrum of 4-isobutylquinoline.

rationalized in terms of a cyclized structure (a), which would imply that in this instance (contrary to 8-propylquinoline) the presence of the heteroatom played no significant role in promoting this decomposition.

Accordingly, similar behavior would be expected in the hydrocarbon analog, *i.e.*, 1-isobutylnaphthalene. Consequently, this compound was prepared, as well as 1- and 2-butylnaphthalene. The occurrence of *peri* interaction would be expected to produce distinct qualitative differences between the 1- and 2-alkylnaphthalenes. In fact, the spectra of the three butylnaphthalenes are essentially identical. The reproduced spectrum (Figure 1) of 1-isobutylnaphthalene is representative. No evidence of significant *peri* interaction was obtained.

The dichotomy of these results cast suspicion on the original 4-isobutylquinoline spectrum.[3] The sample previously investigated was of commercial origin, and we were unable to determine the synthetic route used for its preparation. Gas chromatographic analysis revealed it to be a mixture of two major components in approximately 2:1 ratio, the greater one being 8-*t*-butylquinoline (as demonstrated by nmr spectroscopy) and the lesser one being quinoline. The presence of the former provides a simple explanation for the facile loss of a methyl radical.[3]

Consequently, authentic 4-isobutylquinoline was prepared by an unambiguous route as described in the Experimental Section. Its mass spectrum (Figure 2) is in marked contrast to that previously reported[3] and is completely consistent with the spectra[3] of other alkylquinolines. Thus the base peak at *m/e* 143 (70 eV) is due to the ubiquitous McLafferty rearrangement (I →

(1) For paper CLIX, see A. V. Robertson, M. Marx, and C. Djerassi, *Chem. Commun.*, 414 (1968).

(2) Support by the National Institutes of Health (Grant No. GM 11309) is gratefully acknowledged.

(3) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 518.