product (36.4%). 3.0 g. of the starting material, b.p. 104–106°; $n^{20}D$ 1.4732, was recovered; the intermediary fraction, boiling between 93 and 104°, amounted to 10.8 g.

The greater part of this investigation was carried out in the Research Laboratories of Publicker Industries, Inc., Philadelphia, Pa.

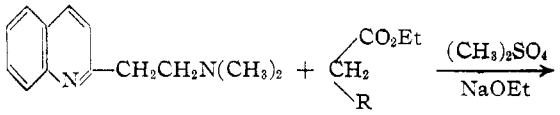
DANIEL SIEFF RESEARCH INSTITUTE
WEIZMANN INSTITUTE OF SCIENCE
REHOVOTH, ISRAEL RECEIVED DECEMBER 11, 1950

A Study of the Alkylation of Active Methylene Compounds Using 2-(β-Dimethylaminoethyl)-quinoline[1,2]

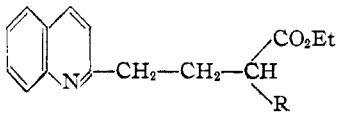
BY V. BOEKELHEIDE AND G. MARINETTI

In previous publications,[3,4] we have reported on the synthesis of various quinolizidine derivatives by the condensation of 2-vinylpyridine with active methylene compounds followed by reductive cyclization. Because some of the compounds prepared in this work showed activity as muscular relaxant agents,[5,6] it seemed of value to examine some of the corresponding compounds in the quinoline series.

For the synthesis of the quinoline derivatives, it was necessary to modify the previous approach due to difficulties experienced in the laboratory preparation of 2-vinylquinoline. Thus, instead of attempting to convert 2-(β-dimethylaminoethyl)-quinoline (I) to 2-vinylquinoline by a Hofmann decomposition, the base was employed directly as an alkylating agent using the procedure developed by Albertson, Archer and Suter for similar alkylations with other Mannich bases.[7] As is shown below, the alkylation of diethyl malonate, ethyl acetoacetate and ethyl benzoylacetate proceeded smoothly to give the corresponding γ-(2-quinolyl)-butyric esters in yields of 33 to 44%.



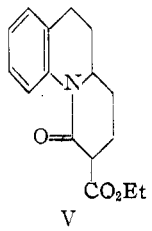
I



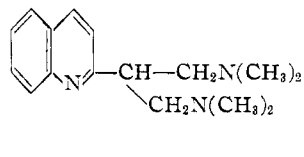
II, R = $-CO_2Et$
III, R = $-COCH_3$
IV, R = $-COC_6H_5$

As would be expected, when III and IV were boiled with 20% hydrochloric acid, hydrolysis and decarboxylation occurred to give in good yield the corresponding ketones, 1-(2′-quinolyl)-4-pentanone and γ-(2-quinolyl)-propiophenone, respectively.

Although it would be anticipated that the quinoline esters and ketones obtained in this work should undergo reductive cyclization to give benzoquinolizidine derivatives in an analogous fashion to the corresponding compounds of the pyridine series, only one example of this has thus far been studied. When II was subjected to high pressure hydrogenation using Raney nickel catalyst at 100°, approximately two molar equivalents of hydrogen were absorbed and a neutral compound, $C_{16}H_{19}NO_3$, resulted. This has been assigned structure V by analogy with the reductive cyclization of diethyl β-(2-pyridyl)-ethylmalonate.[3]



V



VI

The preparation of the starting material, 2-(β-dimethylaminoethyl)-quinoline, was accomplished by a modification of the procedure previously used by Bartholomaus.[8] The use of an excess of quinaldine in this Mannich base condensation is essential for, when equimolar quantities of quinaldine, dimethylamine hydrochloride and formaldehyde were employed, the principal product of the reaction was the di-Mannich base, VI. Since it seemed possible that VI could be used for preparing some interesting branched chain quinoline esters, we investigated the reaction of VI with diethyl malonate. Unfortunately, this alkylation proved to be rather complex in character. Provisional formulas for two of the products isolated are indicated in the experimental section.

The only compound in this series to show muscular relaxant activity was 1-(2′-quinolyl)-4-pentanone and this was much less active than previous compounds of the pyridine series.[9]

Experimental[10]

2-(β-Dimethylaminoethyl)-quinoline (I).—A solution of dimethylamine hydrochloride (28.6 g., 0.35 mole) in 30 ml. of formalin was added dropwise with stirring to quinaldine (100 g., 0.70 mole). After the heterogeneous reaction mixture was heated for one-half hour at 50°, it became homogeneous. The reaction mixture was then cooled, diluted with 50 ml. of water, and extracted with ether to remove unreacted quinaldine. When the aqueous layer was made basic, the oil which separated was taken up in ether and dried over sodium sulfate. After removal of the ether, distillation of the residue gave 27.5 g. (39%) of a light yellow oil; b.p. 120–129° at 0.7 mm., $n^{25}D$ 1.5821. The styphnate of I was obtained from acetone as yellow crystals, m.p. 148–149° (lit.,[8] 148°); the mercuric chloride double salt of I crystallized from alcohol as white needles, m.p. 160–161°, dec. (lit.,[8] m.p. 165° dec.). In our hands boiling the reaction mixture under reflux, as indicated by Bartholomaus,[8] caused considerable tar formation and resulted in very poor yields of the desired product.

1,3-Di-(dimethylamino)-2-(2′-quinolyl)-propane (VI).—To a solution of dimethylamine hydrochloride (65.2 g., 0.8 mole) in 69 ml. of a 35% formalin solution maintained at 50°, quinaldine (114 g., 0.8 mole) was added dropwise with stirring. After the mixture had been heated at 50° for two hours, it changed from an emulsion to a clear orange solu-

(1) Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

(2) Abstracted from the B.S. thesis of G. Marinetti.

(3) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(4) V. Boekelheide and E. J. Agnello, *ibid.*, **72**, 5005 (1950).

(5) V. Boekelheide and J. Mason, *ibid.*, **73**, 2356 (1951).

(6) J. F. O'Leary, D. E. Leary and I. H. Slater, *Proc. Soc. Exp. Biol. and Med.*, in press.

(7) N. F. Albertson, S. Archer and C. M. Suter, THIS JOURNAL, **67**, 6 (1945); see also W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **69**, 1698 (1947); N. J. Leonard and E. H. Burk, Jr., *ibid.*, **72**, 2543 (1950).

(8) E. Bartholomaus, German Patent 497,907, May 8, 1927.

(9) We are indebted to Dr. I. H. Slater, University of Rochester, School of Medicine and Dentistry, Rochester, New York, for the physiological testing.

(10) Analyses by Miss C. King and the Micro-tech Laboratories.

tion. The solution was then cooled and extracted with ether to remove unchanged quinaldine. The aqueous layer was made basic and the oil which separated was extracted with ether and dried over sodium sulfate. After removal of the ether, the residue was distilled using a Fenske column. In addition to a small forerun of I, there was obtained 68.5 g. (38%) of a light yellow oil; b.p. 139–145° at 2 mm., $n^{21}D$ 1.5653.

Anal. Calcd. for $C_{16}H_{23}N_3$: C, 74.66; H, 9.01. Found: C, 74.20; H, 8.95.

The mono-styphnate of VI crystallized from an alcohol-water mixture as yellow needles, m.p. 160–161° dec.

Anal. Calcd. for $C_{22}H_{26}N_6O_8$: C, 52.58; H, 5.22. Found: C, 52.90; H, 5.45.

The di-methiodide of VI was obtained from absolute alcohol as white crystals, m.p. 230–231° dec.

Anal. Calcd. for $C_{18}H_{29}N_3I_2$: C, 39.94; H, 5.40. Found: C, 39.52; H, 5.71.

Diethyl β-(2-Quinolyl)-ethylmalonate (II).—A solution, prepared by adding 9.7 g. of dimethyl sulfate in the cold to 15.4 g. of I dissolved in 50 ml. of absolute alcohol, was added dropwise with stirring to a mixture of 49.3 g. of diethyl malonate dissolved in a solution prepared by adding 1.8 g. of sodium to 100 ml. of absolute alcohol. When the reaction mixture was warmed, rapid evolution of trimethylamine occurred. The reaction mixture was held at 50° for twenty hours and then at 110° for another 21 hours. After removal of the alcohol, 100 ml. of dilute hydrochloric acid was added and the solution was extracted with ether. When the aqueous layer was made basic, an oil separated which was extracted with ether and dried over sodium sulfate. The ether was removed and the residue, on distillation, gave 9.5 g. (43%) of an orange-yellow oil; b.p. 184–185° at 0.3 mm., $n^{20}D$ 1.5419.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71. Found: C, 68.62; H, 6.83.

The picrate of II was obtained from alcohol as yellow crystals, m.p. 93–94°.

Anal. Calcd. for $C_{24}H_{24}N_4O_{11}$: C, 52.94; H, 4.44. Found: C, 53.17; H, 4.65.

Ethyl β-(2-Quinolyl)-ethylacetoacetate (III).—This was prepared in the same manner as described for II. From 20.0 g. of 2-(β-dimethylaminoethyl)-quinoline, using ethyl acetoacetate in fourfold excess, there resulted 12.5 g. (44%) of an orange-yellow oil; b.p. 185–196° at 0.4 mm., $n^{21}D$ 1.5620. The infrared absorption spectrum of III showed absorption peaks at 5.76 and 5.87 μ corresponding to the ester and ketone carbonyl groups, respectively. The picrate and styphnate of III formed as oils.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.79; H, 6.93.

1-(2′-Quinolyl)-4-pentanone.—A solution of 7.8 g. of III was boiled under reflux for four hours with 30 ml. of 20% hydrochloric acid. The mixture was then neutralized with base and extracted with ether. After the ethereal solution had been dried over sodium sulfate, the ether was removed *in vacuo* and the residue was distilled to yield 3.2 g. (55%) of a yellow oil; b.p. 130–149° at 0.1 mm., $n^{21}D$ 1.5858. A sample of the oil, which was purified through the picrate for analysis, gave a value of $n^{21}D$ 1.5800. The infrared absorption spectrum of the purified oil showed an absorption peak at 5.87 μ but none at 5.76 μ.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 79.00; H, 7.29.

The picrate of 1-(2′-quinolyl)-4-pentanone was obtained from alcohol as yellow crystals, m.p. 125–126°.

Anal. Calcd. for $C_{20}H_{18}N_4O_8$: C, 54.30; H, 4.10. Found: C, 54.60; H, 4.29.

Ethyl β-(2-Quinolyl)-ethylbenzoylacetate (IV).—This was prepared in the same manner as II and III. From 20.0 g. of 2-(β-dimethylaminoethyl)-quinoline there was obtained 11.5 g. (33%) of a viscous orange oil; b.p. 180–200° at 0.01 mm., $n^{22}D$ 1.5920. Because of its high boiling point IV was difficult to purify and the analytical sample ($n^{23}D$ 1.5958) was obtained by repeated molecular distillation. The infrared absorption spectrum showed an ester carbonyl peak at 5.77 μ and a phenyl conjugated carbonyl peak at 5.96 μ. IV gave only oily picrates and styphnates.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.05; H, 6.09. Found: C, 75.16; H, 6.49.

When 14.1 g. of IV was subjected to hydrolysis and decarboxylation by boiling with hydrochloric acid in the procedure described for the preparation of 1-(2′-quinolyl)-4-pentanone, there was obtained 7.2 g. (64%) of a crude orange oil; b.p. 170–190° at 0.1 mm., $n^{21}D$ 1.6132. The infrared spectrum of the oil showed a peak at 5.97 μ (phenyl carbonyl) but none in the region of 5.70 to 5.80 μ. Treatment of the oil with picric acid in ethanol gave yellow crystals, m.p. 171–172°.

Anal. (picrate). Calcd. for $C_{25}H_{20}N_4O_8$: C, 59.52; H, 4.00. Found: C, 59.35; H, 4.12.

Reaction of VI with Diethyl Malonate.—This was carried out on a 0.1 molar scale using the same reaction conditions as for the preparation of II and using the same molar ratio of reactants. From the distillation of the reaction product two main fractions were taken and a fair amount of high-boiling material remained in the pot. Although the relative amounts of the two fractions varied in separate runs, the following is typical.

The lower boiling oil amounted to 4.5 g. of a pale yellow oil; b.p. 120–127° at 0.1 mm., $n^{20}D$ 1.6058. The infrared absorption spectrum of this oil showed an absorption peak at 11.07 μ which is in the region typical of terminal methylene absorption. This in conjunction with the composition of the material and its instability has led us to assign it structure VII.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60. Found: C, 79.21; H, 7.47.

The picrate of VII formed readily in ethanol as yellow crystals, m.p. 164–165°.

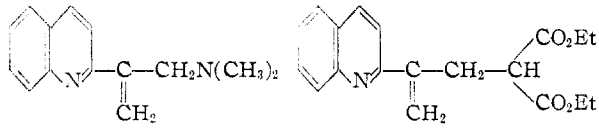
Anal. Calcd. for $C_{20}H_{19}N_5O_7$: C, 54.42; H, 4.34. Found: C, 54.30; H, 4.47.

The styphnate of VII was likewise obtained from ethanol as yellow crystals, m.p. 174–175° dec.

Anal. Calcd. for $C_{20}H_{19}N_5O_8$: C, 52.52; H, 4.09. Found: C, 52.44; H, 4.25.

The higher boiling oil amounted to 9.1 g. of a greenish-yellow oil; b.p. 160–180° at 0.04 mm., $n^{21}D$ 1.5558. The infrared absorption spectrum of the oil showed peaks at 5.76 and at 10.94 μ, as would be expected for an ester carbonyl and a terminal methylene group. Structure VIII is suggested for this oil.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47. Found: C, 69.78; H, 6.75.



VII VIII

3-Carbethoxy-4-keto-5,6-benzoquinolizidine (V).—A mixture of 5.5 g. of II, 2.0 g. of Raney nickel catalyst and 20 ml. of absolute ethanol was subjected to hydrogenation at 100° under 150 atm. pressure of hydrogen. At the end of four hours, the hydrogen uptake roughly corresponded to two molar equivalents. After removal of the catalyst and solvent, the residual oil was distilled yielding 2.0 g. (42%) of a viscous oil; b.p. 188–190° at 0.2 mm., $n^{21}D$ 1.5551. The oil crystallized on prolonged standing and gave white crystals, m.p. 99–101°, from a benzene–hexane mixture.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.01. Found: C, 70.22; H, 7.22.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK

RECEIVED MARCH 2, 1951

Fluorocarbon Chemistry. IV. The Preparation and Some Reactions of Silver Undecafluorocyclohexanecarboxylate

BY THOMAS J. BRICE[1a] AND J. H. SIMONS[1b]

The preparation of fluorocarbon derivatives, including carboxylic acids, by the electrochemical

(1) (a) Central Research Department, Minnesota Mining & Manufacturing Company, St. Paul 1, Minnesota. (b) Department of Chemical Engineering, University of Florida, Gainesville, Florida.