Notes

Reactions of Enamines. IX. Benzoylation of 1-Ethyl-2-methylene-1,2-dihydroquinoline[1]

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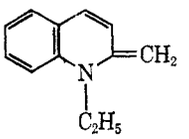
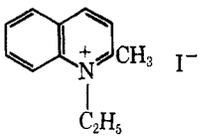
The methylene base I[2,3] obtained by treatment of quinaldine ethiodide (II) with strong aqueous sodium hydroxide has been shown to undergo many reactions characteristic of an enamine.[3,4] Our attention was

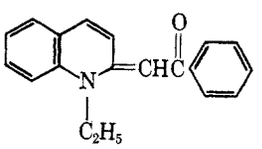


I

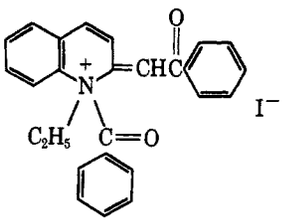


II

drawn to a report[5] that benzoylation of II under Schotten–Baumann conditions[6] gave a salt isolated as the iodide with elemental analyses corresponding most closely to $C_{26}H_{22}INO_2$. On the basis of the empirical formula and its easy hydrolysis to III, the compound was assigned structure IV.



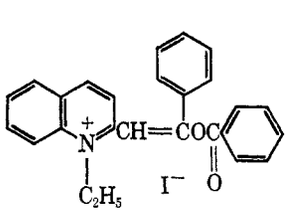
III



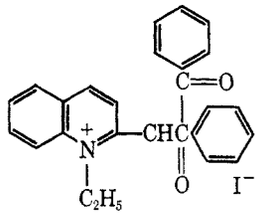
IV

It seemed to us in view of the well-known acylation reactions of enamines[7,8] and enamino ketones[8,9] that structure IV was probably not correct. Presumably the reaction proceeded by benzoylation of the enamine I to the enamino ketone III and by further benzoylation of III to give the isolated compound. Structures V and VI which correspond to O- and C-benzoylation of III are in better accord with the known behavior of enamino ketones.

On repeating the previous work a compound having the reported properties was isolated and elemental analysis confirmed the empirical formula $C_{26}H_{22}INO_2$. The compound showed infrared absorption at 5.72 μ consistent with the carbonyl absorption of an enol ester. An enol ester structure is also in accord with the previously noted facile acid hydrolysis. The compound may, therefore, be assigned structure V. Structure VI or its enol may be excluded as they would be expected to exhibit infrared carbonyl absorption above 6 μ and to resist acid hydrolysis.



V



VI

The intermediacy of III in the formation of V from II was established by benzoylation of III by 1 mole of benzoyl chloride to give a hygroscopic salt which was converted to V by treatment with sodium iodide. This product was identical with the benzoylation product of II under Schotten–Baumann conditions. Thus it appears that II is indeed converted to the enamino ketone III which then undergoes further benzoylation.[10]

Experimental Section[11]

Reaction of Quinaldine Ethiodide with Benzoyl Chloride and Base.—Quinaldine ethiodide (10.0 g, 0.0335 mole) in water (50 ml) was treated successively with 200 ml of 4% sodium hydroxide solution and 9.4 g (0.067 mole) of benzoyl chloride keeping the temperature below 20° by external cooling. The reaction mixture was stirred vigorously for 2 hr and allowed to stand overnight. The tarry solid which had separated was allowed to settle and the aqueous layer was removed by decantation. The solid was taken up in 30 ml of glacial acetic acid and a solution of 10 g of sodium iodide in 20 ml of water was added. Addition of water induced a yellow-green solid to crystallize which was removed by filtration and washed with ethanol to give 5 g of V: mp 195–197° dec. Recrystallization from ethanol gave analytically pure V as gold-yellow plates: mp 200–202° dec; λ_{max}^{EtOH} 361 mμ (ϵ 26,500), 245 mμ (ϵ 39,000) (sh) at 298 mμ (ϵ 9000). The nmr spectrum in trifluoracetic acid showed absorption at τ 8.08 (3 H, triplet), τ 4.70 (2 H, quadruplet), and between τ 2.65 and 1.00 (17 H, complex series of multiplets). The compound showed carbonyl absorption at 5.72 μ in the infrared.

Anal. Calcd for $C_{26}H_{22}INO_2$: C, 61.55; H, 4.37; I, 25.01; N, 2.76. Found: C, 61.37; H, 4.36; I, 25.12; N, 2.80.

Vongerichten and Rotta[5] reported mp 197° but no satisfactory analysis.

Acid Hydrolysis of V.—Compound V (2.5 g, 0.005 mole) was heated under reflux with 125 ml of concentrated hydrochloric acid for 1 hr. The reaction mixture was extracted with three 50-ml portions of ether giving 600 mg (98%) of benzoic acid, mp and mmp 122°. The aqueous layer was made alkaline with ammonia. The precipitated yellow solid was isolated by filtration and crystallized from ethanol to give 800 mg of III as yellow plates: mp 137–139° (lit.[5] mp 139°). The nmr spectrum in deuteriochloroform showed absorption at τ 8.57 (3 H, triplet), τ

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(2) E. Vongerichten and C. Höfchen, *Ber.*, **41**, 3054 (1908).
(3) F. M. Hamer, R. J. Rathbone, and B. S. Winton, *J. Chem. Soc.*, 954 (1947).
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(5) E. Vongerichten and W. Rotta, *Ber.*, **44**, 1419 (1911).
(6) C. Schotten and E. Baumann, *ibid.*, **19**, 3218 (1886).
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(8) S. Hünig, E. Benzing, and E. Lücke, *Ber.*, **90**, 2833 (1957).
(9) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 798 (1964).
(10) The only other reported case of O-acylation of an enamino ketone is that of Hünig, *et al.*, ref 8.
(11) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on Perkin-Elmer Infracord Model 137 in chloroform solution. Ultraviolet spectra were taken with a Beckman DK2A spectrophotometer in ethanol solution. Nmr spectra were taken with a Varian A-60 instrument in the solvent stated using tetramethylsilane as internal standard.

5.86 (2 H, quadruplet), τ 4.05 (1 H, singlet), and between τ 2.95 and 1.95 (11 H, complex series of multiplets). The compound showed carbonyl absorption at 6.15 μ in the infrared.

Benzoylation of III.—The enamino ketone III (1.4 g, 0.005 mole) in chloroform (10 ml) was treated with benzoyl chloride (0.8 g, 0.0057 mole) at reflux temperature for 30 min. Evaporation of the chloroform gave a hygroscopic, tarry residue which was taken up in a minimum amount of glacial acetic acid and treated with a concentrated solution of sodium iodide. On standing, 1.2 g (48%) of V, mp 197–199° dec, crystallized. The melting point was not depressed on admixture with authentic material above.

Acknowledgment.—Thanks are due to Dr. A. J. Speziale for many helpful and stimulating discussions.

Intramolecular Cyclization of N-Formyl-1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

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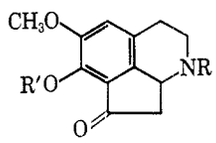
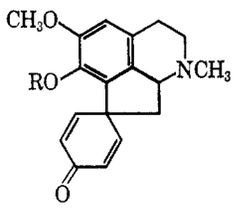
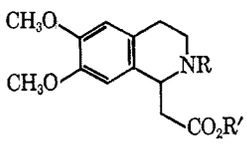
The announcement[2] of the total synthesis of the spirodienone alkaloid pronuciferin, utilizing an intermediate of type I (R = R′ = CH_3), prompts this report of an independent effort to prepare derivatives of the tricyclic ketone I.



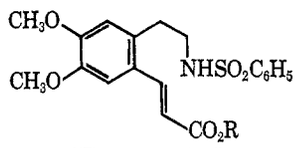
Ia, R = CHO; R′ = CH_3
b, R = CHO; R′ = H



pronuciferin, R = CH_3
glaziovine, R = H



IIa, R = H; R′ = C_2H_5
b, R = $SO_2C_6H_5$; R′ = H
c, R = $SO_2C_6H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CHO; R′ = H



IIIa, R = C_2H_5
b, R = H

Initial attempts to cyclize 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIa) with concentrated sulfuric acid or polyphosphoric acid gave only amphoteric water-soluble products. Cyclization of the benzenesulfonamide IIc with sulfuric acid was attempted, but the only products isolated were the cinnamic acid derivatives IIIa and b, resulting from β elimination. Assignment of structure to IIIa and b was based on elemental analyses, the presence of extended ultraviolet absorption relative to IIa and b, infrared bands corresponding to N–H and conjugated carbonyl stretching vibrations, and the presence of olefinic proton absorption in the nmr spectra. Intramolecular acylation of the acid chloride of IIb, using aluminum chloride or stannic chloride, was also unsuccessful.

However, cyclization could be effected by using the N-formyl derivatives IId or e. Treatment of either IId or e with polyphosphoric acid at 90–100° produced the ketone Ia. Longer reaction times and higher temperatures brought about selective ether cleavage to the monophenol Ib. The lack of sharp O–H absorption in the infrared spectrum of Ib is a familiar property of *o*-hydroxy aryl ketones, and there is ample precedent for selective cleavage of a methoxyl group adjacent to a carbonyl.[3] Methylation of Ib with diazomethane gave Ia.

Further transformations toward the proaporphine skeleton were discontinued because of the close similarity of this approach to the published synthesis. Compounds Ia and b appear well suited for elaboration, using Bernauer's method, to a variety of N- and O-substituted relatives of pronuciferin, or other alkaloids of this series, particularly glaziovine.[4]

Experimental Section

1-Carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Benzenesulfonamide (IIb).—1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIa)[5] (3.00 g) was dissolved in a 10% solution of potassium hydroxide in 25 ml of 2:1 dioxane–water; the solution was refluxed for 3 hr. Excess benzenesulfonyl chloride was added to the cooled solution and the mixture was shaken for several minutes. The mixture was acidified with 1:1 hydrochloric acid and kept for 3 days at room temperature. The colorless sulfonamide was collected; it weighed 1.30 g (26.6%), mp 168–172°. Three recrystallizations from benzene gave the pure sulfonamide, mp 171–172°, λ_{max} 285 mμ.

Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.29; H, 5.41; N, 3.58; S, 8.20. Found: C, 58.55; H, 5.49; N, 3.45; S, 7.95.

1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Benzenesulfonamide (IIc).—To 3.00 g of IIa in 8 ml of pyridine was added 2.5 g of benzenesulfonyl chloride. The solution was kept at room temperature for 15 min, cooled, poured into water, and extracted with ether (3 × 25 ml). The combined extracts were washed with 5% hydrochloric acid. Addition of ice-cold brine caused immediate precipitation of the colorless sulfonamide (3.46 g), mp 70–75°. Recrystallization from absolute ethanol gave pure material, mp 90.5–91.5°, ν 1710 cm.$^{-1}$

Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.00; N, 2.99; S, 7.66. Found: C, 59.89; H, 6.03; N, 3.19; S, 7.80.

Benzenesulfonamide of Ethyl 3,4-Dimethoxy-6-(β-aminoethyl)-cinnamate (IIIa).—Benzenesulfonamide IIc was prepared as before, and the crude product (3.53 g) was added directly to 20 ml of concentrated sulfuric acid. After 10 min at room temperature the mixture was cautiously poured into 200 ml of water, depositing a white oil. The mixture was made basic with 20% sodium hydroxide and extracted with ether (3 × 100 ml). The extracts were dried over sodium sulfate and concentrated *in vacuo*, leaving a colorless oil. Trituration with absolute ethanol gave the crystalline ester IIIa (0.34 g, 7.5%), mp 147–151°. Three recrystallizations from ethanol gave the pure ester: mp 152.5–153°; λ_{max} 297, 232 mμ; ν 1690, 3230 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.00; N, 2.99; S, 7.66. Found: C, 60.17; H, 6.12; N, 3.20; S, 7.79.

Benzenesulfonamide of 3,4-Dimethoxy-6-(β-aminoethyl)cinnamic Acid (IIIb).—The alkaline layer remaining in the above preparation was acidified with concentrated hydrochloric acid to give an oily, white solid. Trituration with absolute ethanol gave 1.80 g (43%), mp 199–203°. Recrystallization from absolute

(1) Public Health Service Predoctoral Fellow, 1963–1965.
(2) K. Bernauer, *Experientia*, **20**, 380 (1964).
(3) (a) G. C. Morrison and J. Shavel, Jr., *J. Org. Chem.*, **29**, 2486 (1964); (b) S. Karady, *ibid.*, **27**, 3720 (1962); (c) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 97 (1945); (d) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).
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(5) We are indebted to Dr. A. Brossi of Hoffmann-La Roche, Inc., Nutley, N. J., for a generous sample of this compound.