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.

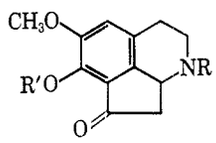
Intramolecular Cyclization of N-Formyl-1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

ROBERT M. CARLSON[1] AND RICHARD K. HILL

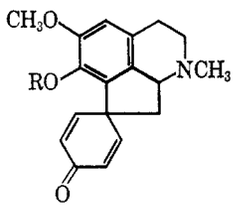
Frick Chemical Laboratory, Princeton University, Princeton, New Jersey

Received March 4, 1966

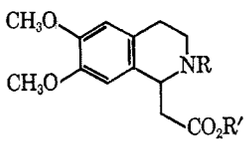
The announcement[2] of the total synthesis of the spirodienone alkaloid pronuciferin, utilizing an intermediate of type I (R = R′ = CH_3), prompts this report of an independent effort to prepare derivatives of the tricyclic ketone I.



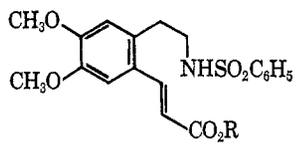
Ia, R = CHO; R′ = CH_3
b, R = CHO; R′ = H



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).
(4) B. Gilbert, M. Gilbert, M. M. DeOliverira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 694 (1964).
(5) We are indebted to Dr. A. Brossi of Hoffmann-La Roche, Inc., Nutley, N. J., for a generous sample of this compound.

ethanol gave the analytical sample: mp 203.5–205°; λ_{max} 295, 328 mμ; ν 1695, 3230 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.29; H, 5.41; N, 3.58; S, 8.20. Found: C, 58.36; H, 5.51; N, 3.43; S, 8.42.

N-Formyl-1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IId).—Compound IIa (27.93 g) was mixed with 350 ml of ethyl formate and heated under reflux for 1 hr. Removal of the solvent under reduced pressure left the N-formyl derivative as a yellow oil which readily crystallized. Trituration with ether gave a pale yellow solid (28.03 g, 91%), mp 104–107°. The colorless analytical sample, obtained by recrystallization from ether, had mp 107.5–108°; λ_{max} 285 mμ; ν 1725, 1655 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.55; H, 6.97; N, 4.53.

N-Formyl-1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIe).—To a solution of IId (10 g) in 75 ml of 50% aqueous ethanol was added 7.5 g of potassium hydroxide, and the solution was refluxed for 30 min. The solution was cooled, diluted with 200 ml of water, and washed with chloroform, then acidified with 30% sulfuric acid, and saturated with sodium chloride. Extraction with chloroform (3 × 50 ml) and concentration of the extracts gave a viscous oil which slowly solidified (5.3 g, 58%). Three recrystallizations from absolute ethanol gave a pure sample of IIe: mp 153–155° with gas evolution; λ_{max} 285 mμ; ν 1740, 1625 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.11; H, 6.18; N, 5.00.

1-Formyl-1,2,3,7,8,8a-hexahydro-5,6-dimethoxy-7-oxocyclopent[*ij*]isoquinoline (Ia). A.—A mixture of IId (5.00 g) in 50 g of polyphosphoric acid was stirred and heated at 100–110° for 80 min. The red-brown solution was cooled, decomposed with ice, and extracted with chloroform (4 × 50 ml). The extracts were dried over sodium sulfate, filtered through charcoal, and concentrated at reduced pressure. The residue was dissolved in 50 ml of benzene and stirred for 10 min with 3 g of alumina, then filtered, and concentrated. The residue was recrystallized from benzene–heptane to afford 0.20 g (4.7%) of a pale yellow solid, mp 138–144°, whose infrared spectrum was identical with that of the ketone prepared in part B.

B.—A solution of 100 mg of Ib in 20 ml of a 1:1 mixture of benzene and tetrahydrofuran was warmed while an ethereal solution of diazomethane was added over 15 min. Most of the solid material dissolved during the addition. The solvents were evaporated in a stream of nitrogen, and the light brown residue was recrystallized from benzene–heptane. The pale yellow plates of Ia (0.05 g), mp 145–146°, were recrystallized twice more to give the analytical sample: mp 146–147°; ν 1705, 1655 cm^{-1}; λ_{max} 236, 263, 346 mμ.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.44; H, 5.93; N, 5.15.

1-Formyl-1,2,3,7,8,8a-hexahydro-5-methoxy-6-hydroxy-7-oxocyclopent[*ij*]isoquinoline (Ib).—A mixture of 1.00 g of IId and 10 g of polyphosphoric acid was heated at 140–150° for 30 min. The red-brown solution was poured over ice and extracted with chloroform. The orange extracts were dried over sodium sulfate, filtered through charcoal, and concentrated, yielding an oil which readily crystallized. The solid was washed with a few milliliters of benzene, leaving 170 mg (21%) of light brown ketone. Recrystallization from benzene–heptane gave the analytical sample: mp 203–205° dec; λ_{max} 265, 344 mμ; ν 1722, 1651 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.08; H, 5.43; N, 5.50.

Heating the acid IIc in polyphosphoric acid at 90–100° for 16 hr and working up as described gave a 2% yield of Ib.

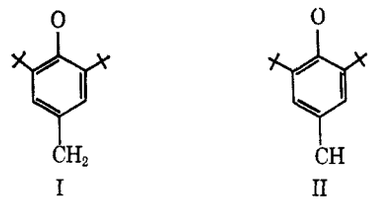
On the Decomposition of Hindered Quinone Methides

B. R. LOY

Dow Chemical Company, Physical Research Laboratory, Midland, Michigan 48641

Received November 5, 1965

The esr spectrum of a 3,5-di-*t*-butyl-*p*-quinone methide has previously been interpreted by Coppinger, *et al.*,[1,2] to consist of equal parts of two free-radical species One is a triplet of triplets with approximate splitting constants of 9 and 2 gauss. These are said to represent the partial structures I and II. Our interest

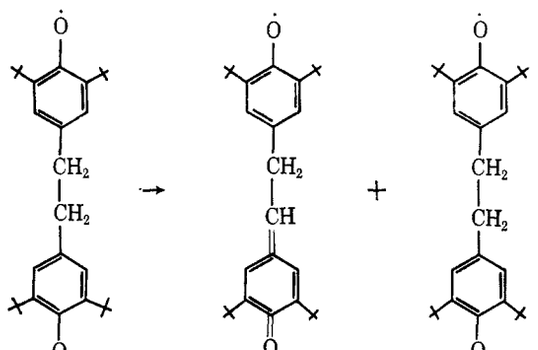


I II

in the reaction mechanisms of polymerization inhibitors[3–6] and the revival[7] of an earlier proposal[8] that the 2,6-di-*t*-butyl-4-methyl phenoxyl radical rearranged to form the 3,5-di-*t*-butyl-4-hydroxybenzyl radical has prompted a repetition of the above experiment.

The esr spectra obtained from varied concentrations of quinone methide indicate that the interpretation leading to radical II was an error which was probably due to low signal/noise ratio.

For the 0.25 *M* solution of 3,5-di-*t*-butyl-*p*-quinone methide, Figure 1 shows only a triplet of triplets with splitting constants of 7.67 and 1.67 gauss. From the experimental splittings in several phenoxy radicals,[9] it is reasonable to assign this spectrum, "A," to structure I in agreement with Coppinger. However, it is interesting that partial structure I can include such forms as the ones that are shown below (III–V).



III IV V

These should give nearly identical spectra since the π systems in the biradical III may be treated as separate entities.[9] Of course, esr cannot differentiate between any of these, but the presence of III is strongly inferred from a series of experiments by Neureiter.[10] Hydrogen abstraction from IV and/or III by V and/or III could lead to the final products, VI, 3,3′,5,5′-tetra-*t*-butylstilbene-4,4′-quinone, and VII, 1,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane. This step is suggested from experiments by Brodskii, *et al.*,[7] who found that

(1) G. M. Coppinger, *J. Am. Chem. Soc.*, **86**, 4385 (1964).
(2) R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963).
(3) R. H. Hoskins and B. R. Loy, *J. Chem. Phys.*, **28**, 2461 (1955).
(4) R. H. Hoskins, *ibid.*, **25**, 788 (1956).
(5) R. H. Hoskins, *ibid.*, **23**, 1975 (1955).
(6) R. H. Hoskins and B. R. Loy, unpublished Dow Chemical report, PRL No. 54126-3.
(7) A. I. Brodskii, V. D. Pokhodenko, and L. N. Ganyuk, *Roczniki Chemii*, **38**, 105 (1964).
(8) C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955).
(9) See, for example, "Free Radicals," D. J. E. Ingram, Ed., Academic Press Inc., New York, N. Y., 1958, p 230.
(10) N. P. Neureiter, *J. Org. Chem.*, **28**, 3486 (1963).