was maintained at 20° by means of an external ice bath. The purple product precipitated from the solution and was collected to give 426 mg (62% yield) of 2,5-diamino-1,4-benzoquinone (**5**), mp >360° (lit.[4] mp 325–330°). The spectral data (ir, nmr, and mass spectra), *vida infra*, are in complete agreement with structure **5**.

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.35. Found: C, 51.94; H, 4.53.

2,5-Diamino-1,4-benzoquinone (**5**) was also prepared in 31% yield from 2-amino-5-azido-1,4-benzoquinone (**4**) according to the above procedure. The compounds prepared by both methods were shown to be identical in all respects.

2,5-Diazido-1,4-benzoquinone (**7**).—A solution of 5 g (0.028 mol) of 2,5-dichloro-1,4-benzoquinone in 60 ml of dimethylformamide and 20 ml of acetone was cooled to 15°. An aqueous solution of 4 g (0.061 mol) of sodium azide in 20 ml of water was slowly added keeping the temperature below 18°. The bright orange diazide, **7**, precipitated from the reaction solution in 94% yield. Recrystallization from warm ethanol gave pure 2,5-diazido-1,4-benzoquinone (**7**), mp 93–94° dec. The nmr spectrum of **7** ($CDCl_3$) shows only one peak at δ 6.20. The ir spectrum (Nujol) shows characteristic absorptions at 2150 and 2110 (azide) and 1660 cm^{-1} (quinone carbonyl). The mass spectrum of **7** showed a molecular ion at *m/e* 190 in accord with the molecular formula $C_6H_2N_6O_2$. Reliable combustion analysis could not be obtained owing to the instability of the diazide.

β-Amino-γ-cyanomethylene-$\Delta^{\alpha,\beta}$-butenolide (**6**).—2-Amino-5-azido-1,4-benzoquinone (**4**, 0.02 g, 0.0013 mol) was added in small portions to 3 g of trichloroacetic acid at 65° over a period of 30 min. During this time the solution became dark and nitrogen was evolved. The reaction solution was then poured into 10 ml of ice–water and cooled; the product was collected by filtration giving 0.08 g (44% yield) of β-amino-γ-cyanomethylene-$\Delta^{\alpha,\beta}$-butenolide (**6**), mp 201–204°. Recrystallization from aqueous ethanol gave an analytical sample of **6** as a white crystalline solid, mp 204°.

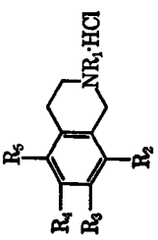
Anal. Calcd for $C_6H_4N_2O_2$: C, 52.94; H, 2.94; N, 20.59. Found: C, 52.93; H, 2.99; N, 20.68.

The ir spectrum of **6** shows characteristic absorptions at 3490, 3200 and 3300 (NH_2), 2250 (CN), and 1780 and 1760 cm^{-1} (C=O). The mass spectrum of **6** shows a molecular ion at *m/e* 136 (59%) in accord with the formulation $C_6H_4N_2O_2$.

Registry No.—1,4-Benzoquinone, 106-51-4; sodium azide, 12136-89-9; **2**, 19462-75-0; **3**, 19462-76-1; **4**, 19462-77-2; **6**, 19459-07-5; **7**, 19462-78-3.

Acknowledgment.—The authors are grateful to the National Science Foundation for partial support of this work from Grant G.P. 8706.

TABLE I
1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd	R_1	R_2	R_3	R_4	R_5	Yields,[a] %	Mp, °C	Lit. mp, °C	Caled, % C	H	N	Cl	Found, % C	H	N	Cl
5	CH_3	OH	OCH_3	H	H	68	212–214	*b*	57.47	7.02	6.09	15.43	57.03	6.74	6.22	15.36
6	CH_3	H	OCH_3	OH	H	26	286–288	285–290[c]								
7	CH_3	OH	OCH_3	OCH_3	H	63	236–238	*d*	55.49	6.96	5.39	13.68	55.37	6.71	5.83	13.83
8	CH_3	OH	OH	H	H	30	228–230		60.11	7.06	7.01	17.75	59.78	7.09	6.64	17.25
9	H	OH	OCH_3	H	H	42	281–283	282–283[e]								
10	H	OH	OCH_3	OCH_3	H	63	257–258	258[f]								
11	CH_3	OH	OCH_2	H	CH_3	50	282–284		59.14	7.45	5.74	14.55	59.13	7.44	5.90	14.94

[a] Yields are calculated on the basis of the starting phenols. [b] Compound **5** was prepared in 70% over-all yield by our published procedure[5] and was identical with this sample. [c] J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *J. Org. Chem.*, **32**, 2225 (1967). [d] Free base prepared by neutralization, mp 130–132° [E. Späth and A. Becke, *Ber.*, **68**, 944 (1935)] reported mp 131–133°). [e] See ref 3. [f] E. Kauder, *Arch. Pharm.*, **237**, 190 (1899); A. Heffter, *Ber.* **34**, 3004 (1901) (as cited in ref 9 of the former).

Synthesis of Isoquinolines. IX. 1,2,3,4-Tetrahydroisoquinolines *via* the Mannich Condensation[1]

J. M. BOBBITT AND C. P. DUTTA[2]

Department of Chemistry, the University of Connecticut, Storrs, Connecticut 06268

Received November 18, 1968

In recent years, we have developed and explored a facile synthesis of simple oxygenated isoquinolines, based upon modifications of the Pomeranz–Fritsch reactions.[3] These modifications have involved the

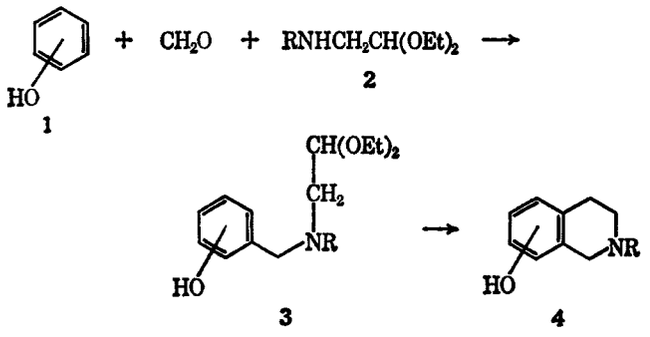
(1) Paper VIII: J. M. Bobbitt and T. E. Moore, *J. Org. Chem.*, **33**, 2958 (1968). This work was sponsored, in part, by Contract DA-49-193-MD-2948 from the U. S. Army Medical Research and Development Command, Publication 513 from the Army Research Program on Malaria.

(2) Recipient of a Fullbright Travel Grant, 1966.

(3) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965). See also preceeding papers in this series.

acid-catalyzed cleavage, ring closure, and reduction of benzyl amino acetals formed by reductive alkylation of aminoacetaldehyde acetal with suitable aromatic aldehydes. We have now been able to prepare the benzyl amino acetals by a simple Mannich reaction on suitable phenols.[4] The method has been especially useful for preparation of 6,7,8-trioxygenated isoquinolines.

The appropriate phenols (**1**) were allowed to react with formaldehyde and suitably substituted amino acetals (**2**, R = H or CH_3) to yield the benzyl amino



acetals (**3**) which were converted into isoquinolines (**4**) by acid treatment followed by hydrogenation over palladium on carbon.[3] The Mannich bases were not isolated. The results are given in Table I. Two products (**5** and **6**) were obtained when the reaction was carried out with guaiacol, but they were easily separable by crystallization and the combined yield was nearly quantitative. The Mannich condensations with methyl amino acetal were carried out at room temperature,[5] but those with amino acetal required reflux temperature in ethanol.

Two of the compounds, **7** and **10**, are known alkaloids, anhalidine and anhalamine, respectively.[6] Methylation of **10** with diazomethane led to the alkaloid, anhalinine (6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline). All three alkaloids were synthesized by a more laborious method by Späth and his coworkers.[7,8] Anhalamine and anhalidine have been prepared more recently by Brossi and his coworkers.[9] Compound **11** was prepared from vanillin. The 5-methyl group was formed by reduction of the aldehyde group during the hydrogenation step. The nmr spectra of all of the compounds, known and unknown, were measured and are in agreement with the assigned structures.

Experimental Section[10]

Reaction of Guaiacol to Yield 5 and 6.—A mixture of guaiacol (2.48 g, 0.02 mol), 3.00 g of 40% aqueous formaldehyde (0.04 mol), and 3.60 g of methylaminoacetaldehyde dimethyl acetal (0.03 mol) in 25 ml of ethanol was stirred at room temperature for 24 hr. The solvent was removed on a rotary evaporator and the resulting thick oil was dissolved in 50 ml of cold 6 *N* HCl and washed with ether. The acidic solution was stirred at room temperature for 15 hr. The last traces of ether were removed on a rotary evaporator and the solution was hydrogenated over 4 g of 5% palladium on carbon at room temperature and atmospheric pressure until no more hydrogen was absorbed (about 0.02 mol). The catalyst was removed by filtration and the solution was concentrated on a rotary evaporator to a yellow syrup. The syrup was treated with 50 ml of hot ethanol and cooled. Crystals formed and were collected to yield 1.20 g of the crude hydrochloride of **6**, (26%) mp 281–284°. The compound was recrystallized from methanol.

The mother liquor after the removal of **6** was concentrated and cooled to yield the crystalline crude hydrochloride of **5** (3.12 g, 68%), mp 208–212°. The analytical sample, mp 212–214°, was crystallized from absolute ethanol.

Preparation of Mannich Bases (3). General Procedure.[5]—The tertiary bases (**3**, R = CH_3) were prepared by stirring a mixture of the phenol (0.02 mol), formaldehyde (0.04 mol of 40% aqueous), and methylaminoacetaldehyde dimethyl acetal[11] (0.03 mol) in 25 ml of ethanol for 24 hr at room temperature. The secondary amines (**3**, R = H) were prepared by stirring similar mixtures (with aminoacetaldehyde dimethyl acetal[11]) at reflux temperature for 6–8 hr. In each case, the solvent was removed on a rotary evaporator and the crude Mannich bases were not purified.

1,2,3,4-Tetrahydroisoquinolines (4).—The crude Mannich bases were dissolved in 50 ml of cold 6 *N* HCl, washed three times with ether, and stirred at room temperature for 15 (leading to **9**) or 36 hr (leading to **7**, **8**, **10**, and **11**). The last traces of ether were removed, and the acid solutions were hydrogenated as described above. The catalyst was removed by filtration, and the solutions were evaporated on a rotary evaporator to yield slightly colored syrups. The syrups were treated with hot absolute ethanol (50 ml) and evaporated again. In some cases, this procedure was repeated twice more. The products crystallized during the evaporation or upon alcohol addition. They were collected by filtration and washed with cold absolute ethanol. Analytical samples were prepared by recrystallization from ethanol.

6,7,8-Trimethoxy-1,2,3,4-tetrahydroisoquinoline (Anhalinine).—Compound **10** (0.3 g) was treated with the diazomethane from 5 g of nitrosomethylurea. The mixture was allowed to stand in a refrigerator for 5 days and was evaporated to a syrup. The sryup was taken up in ether again, washed with 5% aqueous NaOH, dried over Na_2SO_4, and saturated with gaseous HCl. The crude hydrochloride (0.18 g) precipitated and was collected and recrystallized from absolute ethanol to yield anhalinine hydrochloride, mp 248–250° (lit.[7] mp 248–250°).

Registry No.—**5**, 19462-72-7; **8**, 19462-73-8; **11**, 19462-74-9.

(4) This research was suggested during a lecture given at Connecticut by Professor J. H. Burckhalter of the University of Michigan.

(5) E. L. Eliel, *J. Amer. Chem. Soc.*, **73**, 43 (1951).

(6) See L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, New York, N. Y., 1954, p 7.

(7) E. Späth and I. Roder, *Monatsh.*, **42**, 97 (1921); **43**, 93 (1922); *Chem. Abstr.*, **16**, 100, 3303 (1922).

(8) See footnote *d*, Table I.

(9) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).

(10) Melting points were measured on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich and the Baron Consulting Co. of Orange, Conn.

(11) Sometimes the diethyl acetal was used with similar results.

The Formation of Tetramethylpyrazine and 2-Isopropyl-4,5-dimethyl-3-oxazoline in the Strecker Degradation of DL-Valine with 2,3-Butanedione

GEORGE P. RIZZI

Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received November 13, 1968

The Strecker degradation is a well-documented reaction in which an α-amino acid is simultaneously decarboxylated and deaminated to yield a structurally related aldehyde containing one less carbon atom.[1] The reaction is usually observed when α-amino acids are heated in the presence of 1,2-di- or 1,2,3-tricarbonyl

(1) A. Schönberg and R. Moubacher, *Chem. Rev.*, **50**, 261 (1952).