method for preparation of terminal aldehydes, from which acids, alcohols, amines, and other derivatives may easily be derived.

Analysis of Products. A. From Methyl Methacrylate.—The two aldehydes, methyl α-formyl isobutyrate and the corresponding β-formyl isomer, were separated by distillation in a 3-ft spinning band column. The former distilled at 50–53° (6–8 mm), the latter at 60–63° (7 mm). The α-isomer was characterized by a singlet aldehydic hydrogen at 9.7 ppm (relative to tetramethylsilane, spectrum obtained on a Varian A-60). The β isomer was characterized by a triplet at 9.8 ppm.

After the original separation and identification of the individual constituents, which provided authentic samples of both forms, most subsequent analyses were made directly on the crude reaction mixture, by vpc techniques. A Barber–Colman Model 20 instrument fitted with a hydrogen flame detector was used, with a 200-ft capillary column coated with Dow-Corning 550 silicone fluid, at an oven temperature of 100°. The α isomer was eluted first; aldehyde ratios were determined directly by the areas under the respective peaks. Aldehyde yields were determined by distillation in a few cases, although loss by polymerization was always encountered. A representative yield is 74% with <5% loss to methyl isobutyrate.

B. From Oct-1-ene.—As in the previous case, distillation was used to provide authentic reference samples of nonanals. The linear isomer distilled at 100° (37 mm), the isononanal(s) distilled a few degrees lower but pure samples of the latter were never obtained. The linear aldehyde was characterized by the triplet nmr absorption at 9.77 ppm; samples rich in α-methyloctanal showed a doublet at 9.65 in addition to the triplet.

In the earliest work, vpc analyses were made on the Barber–Colman Model 20 instrument fitted with the column and detector described in the previous section. At 100°, all of the individual isomeric aldehydes present were resolved. In cases in which the yield of *n*-aldehyde was comparatively low, as in the first example of Table III, three compounds were eluted rapidly in succession followed by the fourth after an appreciable time interval. The fourth peak was identified as being that for *n*-nonanal and in all likelihood the third was 2-methyloctanal, with the other two being 2-ethylheptanal and 2-propylhexanal.

For convenience sake, most analyses were conducted with the use of a Varian Aerograph Series 202 instrument. The column was 0.25 in. × 5 ft, packed with 20% Carbowax 20M on Gas Chrom P 60/80. The oven temperature was 160°, programmed to 225° after elution of hydrocarbon. This gave a rapid determination; all isoaldehydes were under one peak, which was followed immediately by the peak for the linear aldehyde.

The major by-product of the reaction is formed by isomerization of oct-1-ene to oct-2-ene. In a typical case the yield of *n*-nonanal was 80%, of 2-methyloctanal 13%, and 7% oct-2-ene. In the experiments involving methyl methacrylate, the major by-product was the hydrogenation product. In all cases the yields of aldehydes were in the range of 72–84%.

Registry No.—Oct-1-ene, 111-66-0; tris(triphenyl phosphite)rhodium carbonyl hydride, 18346-73-1; methyl methacrylate, 80-62-6.

The Enamine Chemistry of 2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizine. I. Reaction with α,β-Unsaturated Aldehydes and Ketones[1]

ROBERT N. SCHUT, FREDERICK E. WARD, AND T. J. LEIPZIG

Therapeutics Research Division, Miles Laboratories, Inc., Elkhart, Indiana

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The reaction of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (**2**) with various electrophilic olefins has been investigated. With acrolein, the pentacyclic system **4a** is formed. Methyl vinyl ketone, on the other hand, undergoes cycloaddition to give the pentacyclic system **13**.

Our interest in the synthesis of compounds structurally related to the indole alkaloids eburnamine (**1a**) and vincamine (**1b**) led us to investigate the reaction of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (**2**) with various electrophilic agents. In this paper, we wish to describe the results of the reaction of compound **2** with acrolein and methyl vinyl ketone.

It was expected that compound **2** would behave like an enamine derived from a cyclic ketone and reaction would take place at C_1 of the quinolizine system. After the initial 1,4 addition to an electrophilic olefin, the charge on the transient species is dissipated either by proton transfer and generation of a substituted enamine or by cycloaddition.[2] However, in the case of compound **2**, the indole nitrogen could react with the carbonyl group of the intermediate substituted enamine to form a pentacyclic system. In a similar situation, Wenkert and coworkers[3] reported that the intermediate obtained by addition of ethyl iodoacetate to the indole-enamine **3** cyclized on heating to give (after hydrogenation) epieburnamonine (**1c**).

The addition of acrolein to **2** in tetrahydrofuran–benzene solution was slightly exothermic; the product which precipitated in 82% yield was a monoadduct. It has been demonstrated that the reaction of enamines with acrolein can lead to aminodihydropyrans[4,5] (*cf.* compound **5**); however, the infrared spectrum of the adduct showed OH but no indole N–H or carbonyl absorption while the ultraviolet spectrum exhibited a maximum at 315 mμ characteristic of the conjugated system in 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizines.[6] Thus it was apparent that the indole nitrogen had interacted with the aldehyde function to give the pentacyclic system **4a** wherein the newly formed ring is seven membered. Analogous results were obtained when crotonaldehyde or methacrolein were substituted for acrolein (compounds **4b** and **4c**) (Chart I).

(1) Presented in part at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 12, 1967.

(2) For a review of the reactions of enamines with electrophilic olefins, see J. Szmuszkovics, *Advan. Org. Chem.*, **4**, 27 (1963).

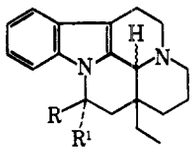
(3) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965).

(4) G. Optiz and I. Löschmann, *Angew. Chem.*, **72**, 523 (1960).

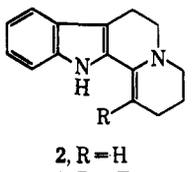
(5) R. N. Schut and T. M. H. Liu, *J. Org. Chem.*, **30**, 2845 (1965).

(6) (a) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965); (b) R. N. Schut and T. J. Leipzig, *J. Heterocycl. Chem.*, **3**, 101 (1966).

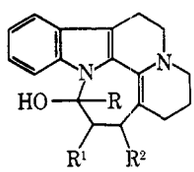
CHART I



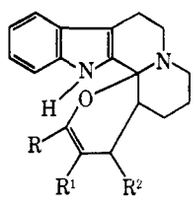
1a, R = H; R¹ = OH; angular H β, equatorial
b, R = CO_2CH_3; R¹ = OH; angular H β, equatorial
c, RR¹ = O; angular H α, axial



2, R = H
3, R = Et

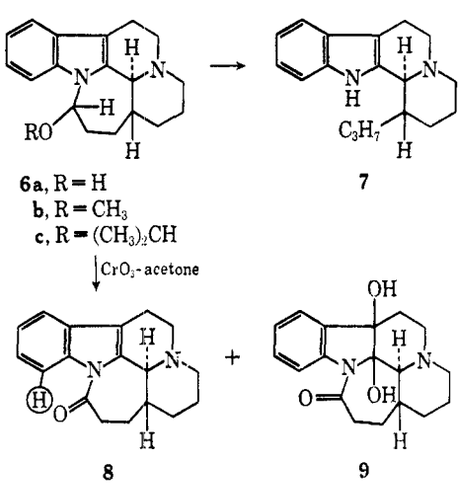


4a, R = R¹ = R² = H
b, R = R¹ = H; R² = CH_3
c, R = R² = H; R¹ = CH_3
d, R = CO_2CH_3; R¹ = H; R² = C_6H_5
e, R = CH_3; R¹ = R² = H



5

SCHEME I



6a, R = H
b, R = CH_3
c, R = $(CH_3)_2CH$

8 9

Catalytic reduction of **4a** in aqueous acidic medium proceeded rapidly with the uptake of 1 mol equiv of hydrogen. Absorption bands at 2755 and 2805 cm^{-1} in the infrared spectrum of the product indicated a *trans*-fused quinolizidine system (rings C and D).[7] Since axial protonation of the β-carbon atom of the enamine system in **4a** should predominate,[8] it follows that rings D and E must also be *trans* fused.[3] When anhydrous alcoholic solvents were used in the hydrogenation, N,O-acetals (*cf.* **6b** and **6c**) were formed. Under Wolff–Kishner reduction conditions ring opening of **6a** occurs and compound **7** is produced (Scheme I).[9]

(7) (a) F. Bohlmann, *Ber.*, **91**, 2157 (1958); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 326.

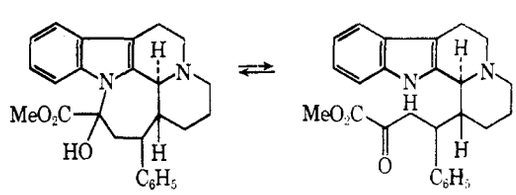
(8) We invoke here the argument used for preferential axial addition of a proton to an enol: E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 241, 242.

(9) The same type of reductive ring scission has been demonstrated for eburnamine: M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, **82**, 5941 (1960).

Oxidation of **6a** with chromic acid–acetone proceeds in poor yield, giving two compounds in about equal amount. The first compound showed carbonyl absorption at 1700 cm^{-1} which was expected for structure **8**, since epieburnamonine (**1c**)[3] also shows carbonyl absorption in this region. An interesting feature of the nuclear magnetic resonance spectrum of **8** is the downfield shift of the indole-C_{11} proton (encircled) to 1.53 ppm. This shift has been noted for similar structures[10] and is apparently due to deshielding by the carbonyl group which is planar with respect to the indole portion of the molecule.

The other product from the oxidation of **6a** exhibited carbonyl absorption at 1650 cm^{-1}; the ultraviolet spectrum (λ_{max} 257 mμ) was not consistent for an indole but rather suggested the presence of an indoline system. The presence of broad absorption at 3400 cm^{-1} in the infrared spectrum as well as two D_2O exchangeable protons (**OH**) at 3.40 and 3.92 ppm in the nuclear magnetic resonance spectrum led to the assignment of structure **9** for the second oxidation product. This type of oxidation is not without precedent since treatment of 9-acetyl-1,2,3,4-tetrahydrocarbazole with nitric acid results in hydroxylation of the indole C_2–C_3 double bond.[11]

In order to obtain a compound more closely related to vincamine (**1b**), compound **2** was allowed to react with methyl benzylidenepyruvate. The expected adduct (**4d**) was formed in 63% yield. The double bond in **4d** was readily reduced catalytically or chemically (1 mol equiv uptake). However, since the OH absorption at 3520 cm^{-1} in the infrared spectrum of **4d** was considerably weaker and typical indole N–H absorption at 3470 cm^{-1} was now present in the spectrum of the hydrogenated product, it was assumed that ring opening had occurred to some extent (*cf.* **10** and **11**).



10 11

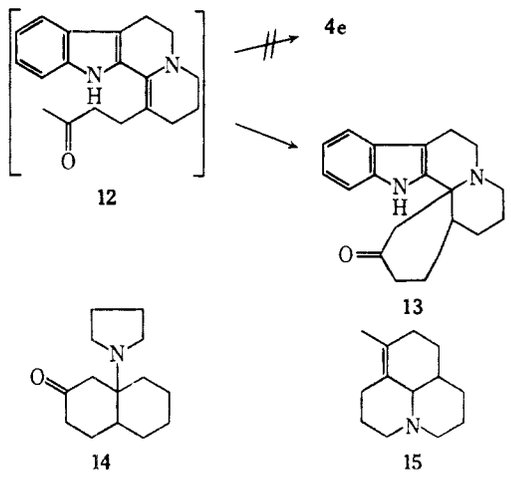
We next turned to the reaction of **2** with methyl vinyl ketone. There are three logical monoadducts which could be formed in this reaction: (1) the open chain compound **12**, (2) the pentacyclic system **4e** analogous to the acrolein reaction product, or (3) the pentacyclic system **13**. The latter pathway is, in fact, that taken in the reaction of methyl vinyl ketone with enamines of cyclic ketones.[12] For example, one of the postulated (but not isolated) intermediates (**14**) in the reaction of methyl vinyl ketone with the pyrrolidine enamine of cyclohexanone is formally analogous to **13** (Scheme II). The product actually isolated in that case was the pyrrolidine enamine of $\Delta^{1,9}$-2-octalone. The reaction of $\Delta^{1,9}$-dehydroquinolizidine with methyl vinyl ketone, however, did not lead to angular alkyla-

(10) E. Winterfeldt, H. Radunz, and P. Strehlke, *Ber.*, **99**, 3750 (1966).

(11) B. Withkop, *J. Amer. Chem. Soc.*, **72**, 614 (1950).

(12) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

SCHEME II



tion.[13,14] Instead the tetrahydrojulolidine derivative **15** was obtained (after sodium borohydride reduction).

The infrared spectrum of the monoadduct obtained from the reaction of methyl vinyl ketone with **2** showed normal ketone carbonyl absorption at 1715 as well as the characteristic indole N–H absorption at 3470 cm^{-1}, thus excluding structure **4e**. The ultraviolet spectrum was consistent for that of a 2,3-disubstituted indole without extended conjugation. Since no uptake of hydrogen occurred on attempted catalytic reduction, it was concluded that the structure of the adduct must be represented by formulation **13**.

Experimental Section[15]

2,3,4,6,7,12-Hexahydro-1,12-(γ-hydroxy)trimethyleneindolo[2,3-*a*]quinolizine (4a).—To a stirred solution of 22.4 g (0.10 mol) of **2**[6b] in 100 ml of THF was added dropwise 20 ml of acrolein in 50 ml of benzene over a 15-min period. Stirring was continued 3 hr at room temperature, then the product was collected and washed with benzene–ether: yield 22.8 g (82%); mp 183–185°. Two recrystallizations from acetone produced the analytical sample: mp 185–186°; uv max (MeOH, neutral) 232 mμ (ε 21,800), 315 (18,200); ir ($CHCl_3$) 3590 cm^{-1} (OH); nmr (DMSO, 10%), τ 2.3–3.6 (4, aromatic), 4.05 (2, –N–CHOH); shaking with D_2O produced one-proton peak at τ 3.92 (–N–CHO–).

Anal. Calcd for $C_{18}H_{20}N_2O$: 77.10; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.27; N, 10.00.

2,3,4,6,7,12-Hexahydro-1,12-(α-methyl-γ-hydroxy)trimethyleneindolo[2,3-*a*]quinolizine (4b) was prepared from **2** and crotonaldehyde in the manner described above: yield 63%; mp 165–166° (acetone).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.52; H, 7.65; N, 9.45.

2,3,4,6,7,12-Hexahydro-1,12-(β-methyl-γ-hydroxy)trimethyleneindo[2,3-*a*]quinolizine (4c) was prepared from **2** and methacrolein; yield 82%; mp 171–173° (benzene).

Anal. Calcd for $C_{19}H_{22}H_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.58; H, 7.81; N, 9.59.

2,3,4,6,7,12-Hexahydro-1,12(α-phenyl-γ-carbomethoxy-γ-hydroxy)trimethyleneindolo[2,3-*a*]quinolizine (4d).—A solution of 15.2 g (0.0792 mol) of methyl benzylidenepyruvate[16] in 60 ml of benzene was added to a stirred solution of 17.7 g (0.0792 mol) of **2** in 100 ml of dry THF over a 20-min period. The reaction mixture was stirred for 1 hr, then concentrated *in vacuo*. The residue was stirred with ether to give 20.7 g (63%) of tan solid, mp 110–112°. An analytical sample was prepared by recrystallization from ether–pentane: mp 114–115°; ir ($CHCl_3$) 3520 cm^{-1} (OH), 1730 (ester C=O); uv (MeOH, neutral) 213 mμ (ε 35,000), shoulder 227 (27,800), 305 (30,000) and 316 (26,000).

Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.33; H, 6.32; N, 6.76. Found: C, 75.04; H, 6.65; N, 6.71.

1,2,3,4,6,7,12,12b-Octahydroindolo-1,12-(γ-hydroxy)trimethyleneindolo[2,3-*a*]quinolizine (6a).—An 18.1-g sample (0.064 mol) of **4a** was dissolved in 125 ml of *i*-PrOH, 25 ml of 3.2 *N* HCl–*i*-PrOH and 50 ml of H_2O; 0.3 g of PtO_2 was added and the mixture was hydrogenated at 50 psi, room temperature. Hydrogen (1 mol equiv) was absorbed within 1 hr; no further uptake was observed. The catalyst was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 1500 ml of hot water and the solution was neutralized with 20% NaOH. The precipitate was collected, washed with water and dried to give 17.0 g of **6a**: yield 94%; mp 200–205°. An analytical sample was prepared by recrystallization from acetone–benzene–ether: mp 206–207°; ir ($CHCl_3$, 5%) 3590 cm^{-1} (OH), 2755, 2805 (12b axial H, *trans*-fused quinolizidine); nmr (DMSO, 10%) τ 3.81 (1, >NCHOH), 3.89 (1, >NCHOH).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.59; H, 7.86; N, 9.92. Found: C, 76.37; H, 7.78; N, 9.99.

1,2,3,4,6,7,12,12b-Octahydro-1,12(γ-methoxy)trimethyleneindolo[2,3-*a*]quinolizine (6b) was prepared as described above except that the hydrogenation was carried out under anhydrous conditions using methanol as solvent. The product was purified as the hydrochloride: yield 63%; mp 258–260° (methanol–ethyl acetate). The free base was generated using saturated $NaHCO_3$ solution and the white crystalline solid which formed was recrystallized from ether–pentane: mp 129–130°; ir ($CHCl_3$) no absorption at 3200–3600 cm^{-1}; 2755 cm^{-1} (12b axial H, *trans*-fused quinolizidine).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.17; N, 9.45. Found: C, 76.99; H, 8.12; N, 9.36.[17]

1,2,3,4,6,7,12,12b-Octahydro-1,12(γ-2-propoxy)trimethyleneindolo[2,3-*a*]quinolizine (6c) was prepared in the same manner using 2-propanol as the solvent. The product was purified as the hydrochloride: yield 37%; mp 181–182° (ether–2-propanol). The free base was generated and recrystallized from ether–pentane, mp 153–154°.

Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; 8.70; N, 8.63. Found: C, 77.45; H, 8.64; 8.51.

Hydrogenation of 4d.—An 8.07-g sample of **4d** was dissolved in 50 ml of H_2O and 175 ml of 2-propanol containing 25 ml of 2 *N* HCl–2-propanol. Catalyst (0.3 g of PtO_2) was added and the mixture was hydrogenated at 50 psi and room temperature. The hydrogenation was complete within 2 hr (1 mol equiv uptake). The crude free base obtained (5.7 g) was chromatographed on 100 g of Florisil using 1 l. of acetone as eluent. The free base thus obtained was treated with ethereal oxalic acid to give 3.6 g of salt, mp 130–150°.

Anal. Calcd for $C_{26}H_{28}N_2O_3 \cdot (CO_2H)_2$: N (basic), 2.76; N (total), 5.53. Found: N (basic), 2.71;[18] N (total), 5.66.

The free base regenerated from the oxalate was an oily material; its infrared spectrum ($CHCl_3$) indicated a mixture of cyclic and open-chain forms **10** and **11** at 3520 (OH) and 3470 cm^{-1} (indole N–H).

1,2,3,4,6,7,12,12b-Octahydro-1,12-(γ-oxo)trimethyleneindolo[2,3-*a*]quinolizine (8).—A 15.0-ml aliquot of chromic acid reagent[19] was added to 7.07 g of **6a** in 900 ml of acetone at 10°. The mixture was stirred at 10–15° for 10 min, then 30 g of Na_2CO_3 in 100 ml of H_2O was added. The inorganic salts were filtered and the filtrate was concentrated *in vacuo*. A chloroform extract of the residue was chromatographed on 150 g of

(13) F. Bohlmann and O. Schmidt, *Ber.*, **97**, 1354 (1964).

(14) F. Bohlmann, D. Schumann, and E. Bauerschmidt [*ibid.*, **100**, 542 (1967)] reported that angular substitution did occur in the Diels–Alder-type addition of 1-acetyl-1,3-butadiene to $\Delta^{1,9}$-dehydroquinolizidine.

(15) Melting points were taken on a Büchi melting point determination apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating infrared spectrophotometer and ultraviolet spectra were recorded on a Perkin-Elmer Model 202 or Beckmann DB-G spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer and resonance peak positions are given in τ units, relative to tetramethylsilane at τ 10.

(16) E. D. Stecher and H. F. Ryder, *J. Amer. Chem. Soc.*, **74**, 4392 (1952)

(17) The Dumas method gave low values for this compound, therefore it was necessary to use the micro-Kjeldahl procedure.

(18) Basic nitrogen determined by titration with standard perchloric acid using acetic acid as solvent.

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Florisil. Elution with chloroform gave 1.0 g of syrup which soon crystallized. After one recrystallization from acetone–ether, the product melted at 142–143°: ir ($CHCl_3$) 1700 cm^{-1} (indole N—C=O); nmr ($CDCl_3$) τ 2.5–2.9 (3, aromatic), 1.53 (1, indole C_{11}–H deshielded by C=O).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.27; N, 10.17.

1,2,3,4,6,7,7a,12,12a,12b-Decahydro-7a,12-dihydroxy-1,12(γ-oxo)trimethyleneindolo[2,3-*a*]quinolizine (9).—Further development of the Florisil column described above using acetone as eluent gave 0.8 g of material which was purified by recrystallization from acetone: mp 244–245°; ir (KCl) 1650 (amide C=O); uv (MeOH) 212 mμ (ε 9800), 257 (10,900); nmr (pyridine-d_5), τ 3.40 (s, 1, C_{12}–OH), 3.92 (m, 1, C_{7a}–OH); shaking the pyridine solution with D_2O caused almost complete removal of these signals.

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91. Found: C, 68.61; H, 7.23; N, 9.01.

1,2,3,4,6,7,12,12b-Octahydro-1-propylindolo[2,3-*a*]quinolizine (7).—A mixture of 2.82 g (0.010 mol) of **6a**, 50 ml of ethylene glycol, 20 ml of hydrazine hydrate and 2 g of KOH was heated under a nitrogen atmosphere at 130–132° for 2 hr. The temperature was then raised to 180° and maintained for 1 hr. The thick solution was shaken with 500 ml of ether and the extract washed with 1 l. of cold water. The aqueous extracts were counter-extracted with ether and the combined extract then concentrated *in vacuo* to give 2.9 g of thick syrup. The material was chromatographed on 100 g of neutral alumina using chloroform as eluent. The product (1.69 g) was a yellow syrup which failed to crystallize; ir ($CHCl_3$) 3480 cm^{-1} (indole N–H); uv_{max} (MeOH) 227 mμ (ε 28,000), 283 (6400). Treatment of the free base with 0.6 g of oxalic acid in ether gave an ivory-colored salt (1.95 g) which after two recrystallizations from ether–methanol melted at 177–178° (bubbling); the salt resolidified and melted again at 244–245°.

Anal. Calcd for $C_{18}H_{24}N_2 \cdot (CO_2H)_2$; N, 7.82. Found: N, 7.69.

1,2,3,6,11,12,13,14,15,15a-Decahydro-13-oxo-5H-benz[*i*]indolo[2,3-*a*]quinolizine (13).—To a stirred solution of 11.2 g (0.050 mol) of **2** in 100 ml of dry THF was added a solution of 3.50 g (0.050 mol) of methyl vinyl ketone in 50 ml of benzene over a 30-min period. The solution was stirred for 5 hr, then the solvent was removed *in vacuo*. The crude product (10.7 g) was dissolved in a little $CHCl_3$ and chromatographed on 200 g of Florisil. Elution with USP ether and concentration of the fractions gave 3.9 g of material, which on stirring with anhydrous ether gave 1.4 g of crystalline product, mp 172–177°. Recrystallization from benzene–ether–hexane gave analytically pure **13**: mp 175–176°; ir ($CHCl_3$) 3470 cm^{-1} (indole N–H), 1715 (ketone C=O), no bands in the 2700–2800-cm^{-1} region; uv (MeOH, neutral) 226 mμ (ε 32,000), 283 (7900).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.55; H, 7.55; N, 9.52. Found: C, 77.46; H, 7.53; N, 9.43.

Acknowledgment.—The authors wish to thank Dr. Dale A. Stauffer and associates for the analytical services.

Registry No.—**2**, 5912-12-9; **4a**, 18039-47-9; **4b**, 18039-48-0; **4c**, 18067-03-3; **4d**, 18039-49-1; **6a**, 18031-30-6; **6b**, 18031-31-7; **6b**·HCl, 18031-32-8; **6c**, 18031-33-9; **6c**·HCl, 18031-34-0; **7**, 18039-51-5; **7** oxalate, 18031-35-1; **8**, 18031-36-2; **9**, 18031-37-3; **10** oxalate, 18031-38-4; **11** oxalate, 18031-39-5; **12**, 18039-50-4.

Steric Inhibition of Intramolecular Cyclizations by *ortho* Substituents. The Synthesis of 1H,3H-Thieno[3,4-*c*]thiophene, Its 2,2-Dioxide, and 5-Ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole[1]

D. J. ZWANENBURG AND HANS WYNBERG

Department of Organic Chemistry of the University, Bloemsingel 10, Groningen, The Netherlands

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During our study of the synthesis of anellated five-membered rings on thiophene, we discovered that some intramolecular cyclizations are adversely affected by *ortho* substituents in the aromatic ring. Reaction of 2,5-dibromo-3,4-bis(bromomethyl)thiophene with sodium sulfide furnished 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene and ring closure of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with sodium sulfide gave the 4,6-dichloro derivative. On the other hand, reaction of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with ethylamine in acetonitrile does not form a thienopyrrole derivative, while cyclization to 5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole was successful when the chlorine atoms on the thiophene nucleus of the tetrachloride were removed prior to the reaction with ethylamine. Our explanation of the steric inhibition of intramolecular cyclization by *ortho* substituents is given.

In an earlier publication[2] we have described the synthesis of 1H,3H-thieno[3,4-*c*]thiophene (**4**) by ring closure of dimethyl 3,4-bis(bromomethyl)thiophene-2,5-dicarboxylate with sodium sulfide, followed by removal of the carbomethoxy groups. In view of the current interest in thienothiophenes,[3,4] we wish to describe here an improved preparation of thienothiophene **4**. Cyclization of 2,5-dibromo-3,4-bis(bromomethyl)thiophene (**1**)[5] with sodium sulfide gave 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene (**2**) in 60% yield; the latter could be reduced to 1H,3H-thieno[3,4-*c*]thiophene (**4**) in 75% yield (Scheme I). The cyclization reaction also yielded the dimeric compound 1,3,7,9-tetrabromo-4H,6H,10H,12H,dithieno[3,4-*c*:3′,4′-*h*][1,6]dithiecin (**3**) in 18% yield. Oxidation of sulfide **2**, followed by zinc in acetic acid reduction, furnished 1H,3H-thieno[3,4-*c*]thiophene 2,2-dioxide (**6**) in 60% over-all yield.

As we have described, reaction of methyl 2,3-bis-

(1) Abstracted in part from the Doctoral Thesis of D. J. Z., Groningen, 1967.

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(5) D. J. Zwanenburg and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, in press.