Registry No.—**3**, 17628-44-3; **4a**, 17628-45-4; **4b**, 17628-46-5; **5**, 17628-47-6; **6**, 17628-48-7; **7**, 17692-13-6; **8**, 17628-99-8; **9**, 17628-94-3; **10**, 17628-95-4; **11**, 17628-49-8; **12**, 17652-45-8; **13**, 17628-50-1; **14**, 17628-96-5; **15a, b**, 17628-51-2; **17a, b**, 17628-52-3; **18**, 17628-53-4; **19**, 17628-54-5; **20**, 17628-97-6; **21**, 17628-98-7.

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Azecino[2,1-*a*]tetrahydroisoquinolines and Related Compounds. II. Preparation of Isoquino[2,1-*a*][1,5]diazacycloundecine and Benzazacyclotetradecine Derivatives, Transannular N → O Acyl Migration, and Other Reactions

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Conversions of azecino[2,1-*a*]tetrahydroisoquinolines into isoquino[2,1-*a*][1,5]diazacycloundecine and benzazacyclotetradecine derivatives *via* Beckmann rearrangement and by intramolecular β elimination, respectively, are recorded. Transannular N → O acyl migration leading to the formation of a 1-isoquinolineoctanoic acid γ-lactone derivative and other reactions are described.

In the preceding paper[1] we have described the preparation of azecino[2,1-*a*]tetrahydroisoquinolines by the reaction of nonenolizable β diketones with 3,4-dihydroisoquinolines. In the course of the transformations carried out to prove the structure of I,[2] its chemical properties were explored in some detail.

KBH_4 reduction of I (Scheme I) gave an epimeric mixture of amido alcohols (IIa, b)[3] which had a broad melting point and was inseparable on tlc. However, on treatment of this mixture with acid, one of the alcohols (IIa) underwent N → O acyl migration to give the labile amino lactone III, whereas the other alcohol (IIb) was recovered in pure form. Under the reaction conditions (HCl in chloroform), lactone III reacted immediately with the ethanol present in the commercial chloroform to give the ethyl ester IV. The sensitivity of lactone III toward traces of water or alcohol thwarted all attempts at its preparation in pure form. The presence of a lactone, however, was indicated by a 1710-cm^{-1} band in the ir spectrum of the crude product obtained from the reaction in washed and dried chloroform. The high reactivity of the lactone is apparently due to the proximity of the carboalkoxy group to the amine function, which may promote intramolecular base catalysis of transesterification with alcohols. Tosylation of IIa, b eliminated this proximity effect and gave a mixture of a stable lactone V (from IIa) along with the expected O-tosylation product VI (from IIb). When IIb alone was allowed to react with TsCl, under identical conditions, complete conversion into VI took place indicating that the lactone-forming reaction is stereoselective in that it requires a favorable orientation of the hydroxy group in the amido alcohol II.

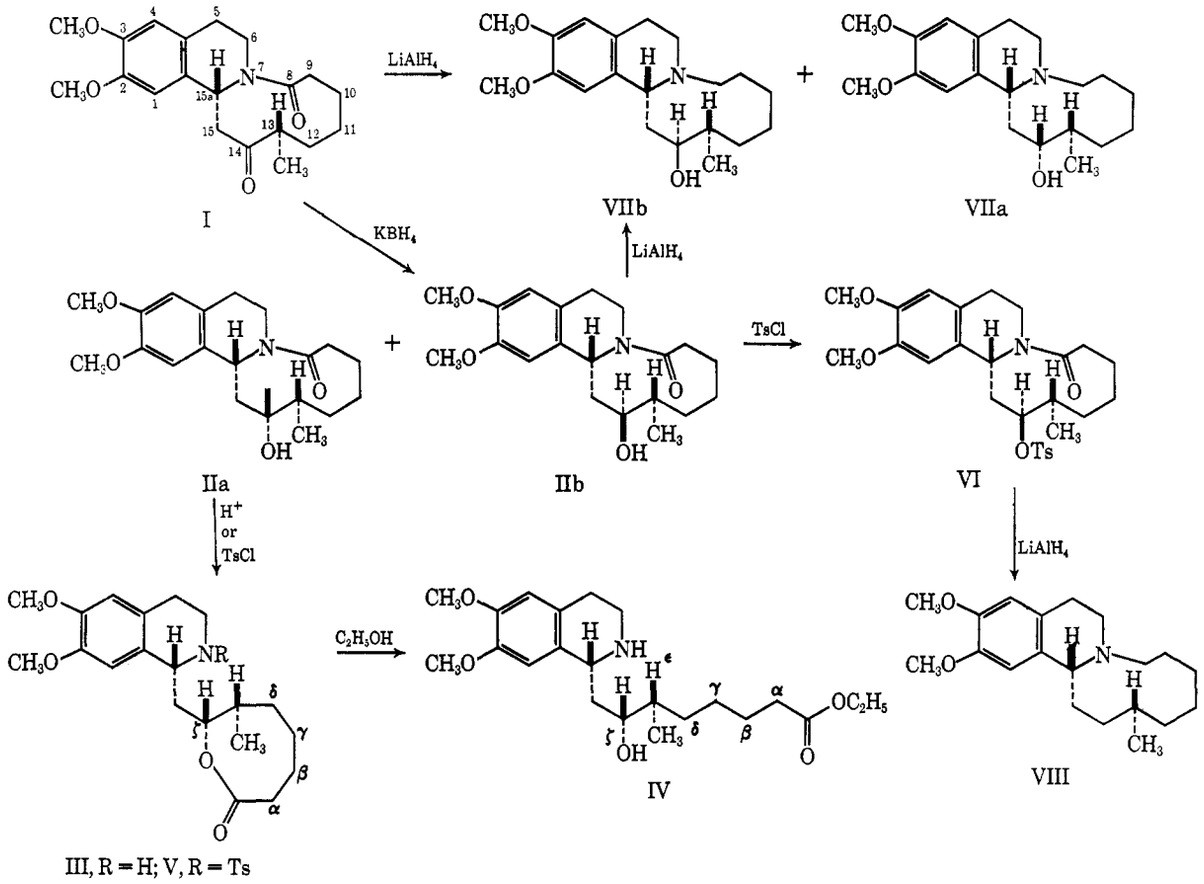
$LiAlH_4$ reduction of I gave two amino alcohols (VIIa and VIIb) which were separable on tlc and by column chromatography. One of the alcohols VIIb was shown to be identical with the alcohol prepared by the $LiAlH_4$ reduction of the amido alcohol IIb. Reduction of the tosyloxy amide VI with $LiAlH_4$ gave the amine VIII.

Treatment of I with base (Scheme II) caused an intramolecular β elimination of the amide group resulting in the formation of an unsaturated 14-membered-ring compound IX. The structure of IX was assigned on the basis of the following evidence. The uv spectrum [λ_{max} 222 mμ (ϵ 11,700), 246 (11,200), 305 (11,700) plateau, and 339 (16,000)] resembles that of veratralacetone [λ_{max} 224 mμ (ϵ 7500), 244 (9500), 298 (10,500) shoulder, and 335 (17,500)]. The ir spectrum showed bands characteristic of amide carbonyl (1640), amide NH (3330), and α,β-unsaturated ketone (1662 cm^{-1}). In contrast to I, the pmr spectrum of IX displays no signals in the 5–6.5-ppm region, indicating that position 15a was involved in the chemical transformation. In the low-field region, in addition to the signals of the two aromatic protons (6.87 and 7.27 ppm), there is now displayed an AB quartet (6.56, 6.83, 7.54, and 7.81 ppm) indicative of the two olefinic hydrogens.

With hydroxylamine I readily formed the oxime X, which on treatment with polyphosphoric acid underwent the Beckmann rearrangement to give the 11-membered cyclic diamide XI. That the nitrogen was inserted between the carbonyl carbon and the carbon carrying the methyl group was confirmed by identification of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid among the fragments resulting from a vigorous acid hydrolysis of XI. Reduction of XI by $LiAlH_4$ at room temperature gave the amine amide XII. That the tertiary amide was reduced, in preference to the secondary, was indicated by the ir spectrum of XII which displayed an amide NH at 3280 cm^{-1}. The $LiAlH_4$ reduction at room temperature of the amide oxime X gave an amine oxime XIII which, according to its ir spectrum, had no carbonyl functions. The near-ir spectrum indicated absence of NH and presence of OH. The latter was confirmed by O acetylation (XIIIa). The assumption that the amide group was reduced in preference to the oxime was confirmed by

(1) M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 4010 (1968).
(2) Compound **8** of preceding paper.[1]
(3) Compounds **15a, b** of preceding paper.[1]

SCHEME I[a]



[a] The configurational assignments are tentative.

the Beckmann rearrangement of XIII to XII. On treatment with HCl, XIII readily gave compound XIV, the uv spectrum of which [λ_{max} 220 mμ (ε 13,250), 242 (12,250), 295 (16,100), and 325 (17,250)] closely resembles the veratralacetone chromophore of IX. The presence of OH and NH groups, indicated by near-ir spectroscopy, was confirmed by the preparation of diacetyl derivative XIVa. The uv spectrum of the latter compound [λ_{max} 224 mμ (ε 13,500), 242 (14,250), 305 (13,250), and 335 (16,900)] was nearly identical with the spectrum of IX. In agreement with the assigned structure, the pmr spectra of XIV and XIVa showed signals corresponding to four protons in the low-field region.

Stereochemical Considerations.—In the preceding paper[1] compound I was tentatively assigned the *cis* (C-13,C-15a) configuration. Therefore, its derivatives VIII, X, XIII, and XIIIa are presumably also *cis*. Since the Beckmann rearrangement is known to proceed with retention of configuration of the migrating carbon,[4] the *cis* configuration is assigned to XI and XII.

The configuration assignment of the amido alcohols II is based on the ability of one of the isomers (IIa) to form a lactone. Consideration of Dreiding models indicates that both the *threo* and the *erythro* forms (the *threo* and *erythro* prefixes refer to the spatial arrangement at positions 13 and 14) appear *a priori* to be capable of lactone formation. However, lactone formation from the *erythro* isomer appears more facile because (in one of the preferred conformations) its hydroxyl points in the direction of the amide N–C bond and, on conformational inversion around the N–C-15a axis, can approach the carbonyl carbon within bonding distance, at a favorable angle and without serious interactions. The model of the intermediate is free of crowding. On this basis the *cis,threo* [(C-13,C-15a),-(C-13,C-14)] configuration may tentatively be assigned to IIb, VI, and VIIb and the *cis,erythro* [(C-13,C-15a),-(C-13,C-14)] configuration to IIa, VIIa, V, and IV. (The configuration of the alcohols VII follows from the conversion of IIb into VIIb by $LiAlH_4$ reduction.)

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," pp 618–621, M. Holt and Co., New York, N. Y., 1959.

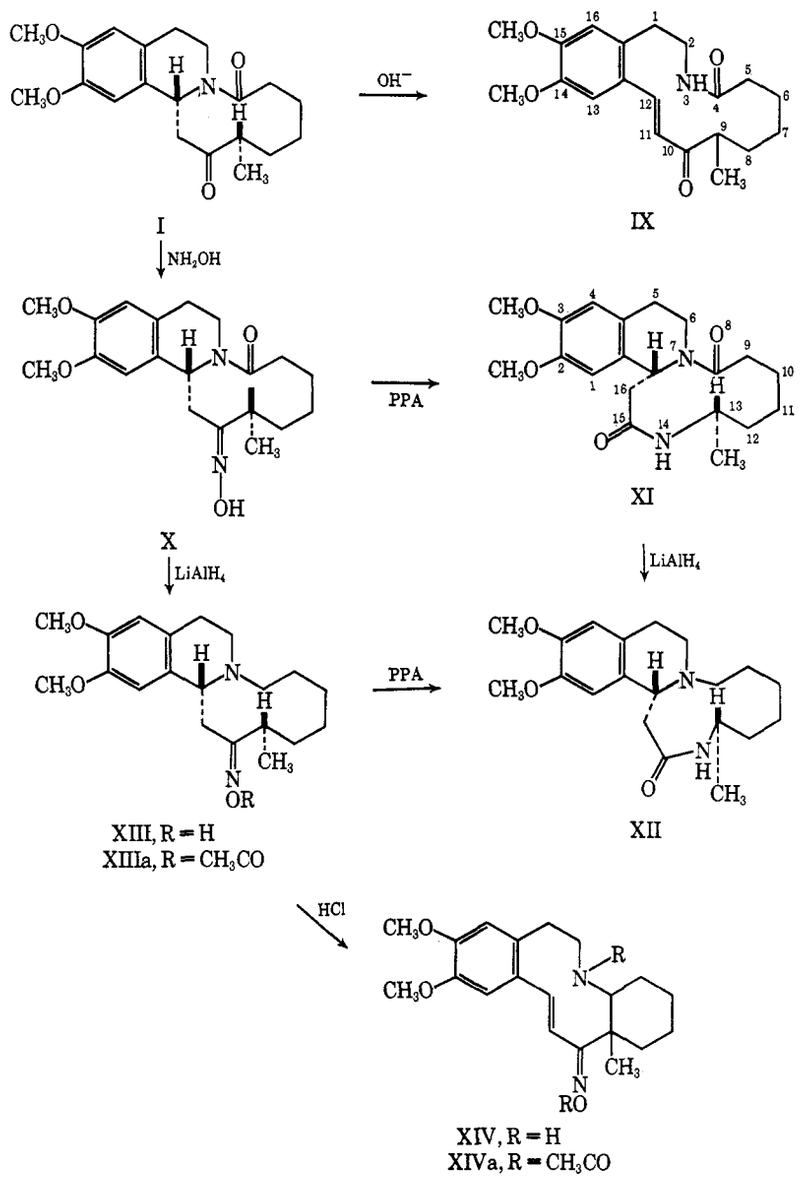
Experimental Section[5]

Treatment of Amido Alcohols IIa, b with HCl.—A slow stream of dry HCl was passed for 40 min through a solution of 7.2 g of IIa, b[1] in 350 ml of chloroform. The mixture was allowed to stand overnight, and the solvent was removed *in vacuo* at room temperature (rotary evaporator). Chloroform was added, and the evaporation was repeated. The glossy residue was treated with 200 ml of ethyl acetate. The crystalline precipitate was filtered off, and the filtrate was extracted with three 70-ml portions of water.

The aqueous extracts were combined, made basic with saturated sodium bicarbonate solution, and extracted with chloroform. The chloroform extracts were dried and evaporated, and

(5) Melting points were determined using the Thomas–Hoover capillary melting point apparatus. The uv and ir spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The nmr spectra were determined in deuterated chloroform using a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Tlc was carried out on silica gel G according to Stahl (Merck, Darmstadt), using ethyl acetate as the eluent. The chromatograms were developed by spraying with either dilute aqueous $KMnO_4$ or ethanolic iodine (4%) solutions.

SCHEME II



the residue was recrystallized from ethyl acetate to give 2.68 g (39%) of **ethyl 1,2,3,4-tetrahydro-ζ-hydroxy-6,7-dimethoxy-ε-methyl-1-isoquinoline octanoate (IV)**: mp 82–83°; ν_{max} 1520 (vs), 1610 (ms), 1730 (vs), 3100 (m), and 3300 cm^{-1} (m); λ_{max} shoulder 223 mμ (ε 3100), 282 (3800), and 286 (3800); δ 0.88 (d, CH_3–CH), 1.22 (t, CH_3–CH_2), 3.83 (CH_3O), 4.12 (q, CH_3CH_2), 4.39 (t, isoquinoline H-1), and 6.56, 6.60 ppm (aromatic H).

Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.14; H, 8.97; N, 3.56. Found: C, 67.42; H, 9.02; N, 3.63.

The initial crystalline precipitate and the concentrated ethyl acetate solution (marked with asterisk) yielded 3.17 g (44%) of **5,6,9,10,11,12,13,14,15,15a-decahydro-14-hydroxy-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinolin-8-one (IIb)**: mp 211–216°; ν_{max} 3430 (m), and 1600 cm^{-1} (s); δ 1.01 (d, CH_3–CH), 3.86 (CH_3O), 4.8–5.3 (2 H, m, H-15a and equatorial H-6), and 6.60, 6.68 ppm (aromatic H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.02; H, 8.52; N, 4.00.

Reaction of IIa, b with *p*-Toluenesulfonyl Chloride.—A solution of 10 g (0.029 mol) of IIa, b in 250 ml of pyridine was treated dropwise (45 min) with a solution of 11.4 g (0.06 mol) of *p*-toluenesulfonyl chloride in 100 ml of pyridine and was stirred at room temperature for 22 hr. The reaction mixture was concentrated under reduced pressure at temperatures not exceeding 40°. The residue was dissolved in 250 ml of chloroform and was washed consecutively with dilute HCl, 5% sodium hydroxide solution, and H_2O. Drying and evaporation of the chloroform solution gave 13.2 g of residue. Crystallization from 100 ml of 2-propanol afforded 3 g (21%) of **5,6,9,10,11,12,13,14,15,15a-decahydro-14-hydroxy-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinoline-8-one *p*-toluenesulfonate (VI)**. Crystallization from ethyl acetate yielded analytical material: mp 165–166°; R_f 0.5; ν_{max} 1635 (s), 1520 (m), and 915 cm^{-1} (vs).

Anal. Calcd for $C_{27}H_{35}NO_6S$: C, 64.65; H, 7.03; N, 2.79. Found: C, 64.70; H, 7.15; N, 3.06.

A second crop of crystalline material from the 2-propanol mother liquor of VI gave on recrystallization from ethyl acetate 0.88 g (6%) of **1,2,3,4-tetrahydro-ζ-hydroxy-6,7-dimethoxy-ε-methyl-2-(*p*-tolylsulfonyl)-1-isoquinolineoctanoic acid ζ-lactone (V)**: mp 189–190°; R_f 0.8; ν_{max} 1720 cm^{-1} (s); δ 0.93 (d, CH_3–CH), 2.27 (CH_3–C_6H_4), 3.73, 3.84 (CH_3O), 4.3–4.8 (2 H, m, equatorial H-3, ζ-H), 5.15 (H-1, q, J_{ab} = 12 cps, J_{ab} = 3.5 cps), 6.28, 6.57 (dimethoxybenzene aromatic H's), and 6.98, 7.12, 7.48, 7.63 ppm (toluene aromatic H's).

Anal. Calcd for $C_{27}H_{35}NO_6S$: C, 64.65; H, 7.03; S, 6.30. Found: C, 64.88; H, 7.05; S, 6.28.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinolin-14-ols (VIIa and VIIb).—A solution of 8.7 g of IIa,b in 500 ml of tetrahydrofuran was treated with 8 g of $LiAlH_4$, refluxed for 8 hr, and allowed to stand overnight. Excess $LiAlH_4$ was destroyed with water, and the solids were filtered off and washed with tetrahydrofuran. Combined filtrate and washings were concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 3 *N* HCl. The acid solution was made basic with

10% NaOH and extracted with chloroform. Evaporation of the chloroform solution gave 6.32 g (80%) of crude isomeric mixture.

Chromatography of a portion of the crude product on Florisil (40 g/g) with ethyl acetate afforded isomer VIIa (R_f 0.7) which was dissolved in dilute HCl and treated with an excess of 17% perchloric acid. The precipitated perchloric acid salt was recrystallized from 2-propanol: mp 160°; ν_{max} 3400 (m), 3100 (w), 1610 (w), and 1525 cm^{-1} (m).

Anal. Calcd for $C_{20}H_{31}NO_3 \cdot HClO_4$: C, 55.36; H, 7.43; N, 3.23; Cl, 8.17. Found: C, 55.62; H, 7.33; N, 3.47; Cl, 8.39.

Chromatography of a portion of the crude product on silica gel (100 g/g) with ethyl acetate afforded chromatographically pure VIIb as a gum (R_f 0.85). The hydrochloride salt, prepared by dissolving the gum in ethyl acetate and treating it with ethereal hydrogen chloride, was crystallized from 2-propanol three times to give the analytical sample: mp 183–185°; ν_{max} 3300 (s), 2550 (m), 1610 (w), and 1520 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{31}NO_3 \cdot HCl$: C, 64.94; H, 8.72; N, 3.79; Cl, 9.58. Found: C, 65.06; H, 8.88; N, 4.09; Cl, 9.35.

Preparation of VIIb from IIb.—A mixture of $LiAlH_4$ (2.7 g) and IIb (2.74 g) in 125 ml of tetrahydrofuran was refluxed for 6.5 hr. Excess reagent was destroyed with water. The mixture was filtered, and the solids were washed with tetrahydrofuran. Combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was extracted with 2 *N* HCl. The aqueous extracts were made basic with 10% NaOH and extracted with chloroform. On drying and evaporation of the chloroform solution VIIb base was obtained (R_f 0.85). The gummy product was dissolved in ether, and the solution was treated with ethereal HCl. The precipitated hydrochloride was filtered off and recrystallized from acetonitrile to yield 1.9 g (65%), mp 181–183°.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-*a*]isoquinoline Perchlorate (VIII).—A solution of 3 g of VI in 250 ml of tetrahydrofuran was treated with 3 g of $LiAlH_4$ and refluxed for 4 hr. Excess $LiAlH_4$ was destroyed by addition of water. The solids were filtered off and washed with hot tetrahydrofuran. Combined filtrate and washings were concentrated under reduced pressure. The oily residue was dissolved in ether and extracted with 2 *N* HCl. The acid solution was made basic with 10% NaOH and extracted with $CHCl_3$. Drying and evaporation of the $CHCl_3$ solution yielded the crude product. Chromatography on 30 g of Florisil with ethyl acetate as the eluent afforded chromatographically pure material (R_f 0.9), which was dissolved in 10 ml of methanol and treated with 2 ml of 70% perchloric acid. After evaporation of the methanol, the residue was triturated with cold water and crystallized from 2-propanol to yield 1.42 g (51%) of product, mp 161–163°. Recrystallization from 2-propanol afforded analytical material, mp 162–165° [dried at 140° (0.1 mm) for 5 hr].

Anal. Calcd for $C_{20}H_{31}NO_2 \cdot HClO_4$: C, 57.48; H, 7.72; N, 3.35; Cl, 8.48. Found: C, 57.24; H, 7.88; N, 3.61; Cl, 8.60.

1,2,5,6,7,8-Hexahydro-14,15-dimethoxy-9-methyl-3-benzazacyclotetradecine-4,10(3H,9H)-dione (IX).—A solution of 5 g of I in 125 ml ethanol was treated with 6.5 ml of a 0.17 *N* solution of sodium in ethanol and was refluxed for 1.5 hr with exclusion of moisture. The solvent was removed *in vacuo*, and the residue was dissolved in 125 ml of $CHCl_3$ and washed twice with H_2O. Drying and concentration of the solution yielded crude IX. Crystallization from 95% ethanol and recrystallization from ethyl acetate afforded 0.56 g (11.2%) of analytical material: mp 188–189°; λ_{max} 222 mμ (ε 11,700) plateau, 246 (11,200), 305 (11,700) shoulder, and 339 (16,000); ν_{max} 3330 (m), 1660 (s), 1640 (s), 1600 (s), 1535 (m), and 1525 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.77; H, 8.02; N, 4.13.

5,6,10,11,12,13,15,15a-Octahydro-2,3-dimethoxy-13-methyl-9H-azecino[2,1-*a*]isoquinoline-8,14-dione 14-Oxime (X).—A solution of 10 g of I in 750 ml of 95% ethanol was combined with a solution of 25 g of $NH_2OH \cdot HCl$ in 150 ml of H_2O, treated with 100 ml of 10% NaOH, and refluxed for 15 hr. After evaporation of the ethanol *in vacuo*, the residue was treated with 500 ml of H_2O, made acid with concentrated HCl, and extracted three times with 300-ml portions of chloroform. The chloroform solution was dried and concentrated to dryness *in vacuo*. Crystallization of the crude oxime from methanol afforded 9.1 g (87%) of product. Recrystallization from methanol gave the analytical material: mp 217–220°; λ_{max} 282 mμ (ε 4500) and 286 (4500); ν_{max} 3200 (m), 1615 (s), 1590 (s), and 1520 cm^{-1} (ms).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.60; H, 7.80; N, 7.51.

5,6,9,10,11,12,13,14,16,16a-Decahydro-2,3-dimethoxy-13-methylisoquino[2,1-*a*][1,5]diazacycloundecine-8,15-dione (XI).—Powdered X (5 g) was added to polyphosphoric acid (100 g) and heated on a steam bath (95–100°) with occasional stirring for 0.5 hr. After cooling and dilution with 1 l. of ice water with vigorous stirring, the mixture was extracted with $CHCl_3$. Evaporation of combined and dried extracts yielded the crude product, which was crystallized from 100 ml of ethyl acetate to give 4.05 g (81%) of chromatographically pure material. Recrystallization from acetonitrile gave analytical material: mp 252–255°; λ_{max} 282 mμ (ε 4550) and 286 (4590); ν_{max} 3450 (w), 3350 (ms) 3300 (w), 1660 (s), 1630 (s), 1545 (s), and 1515 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.73; H, 7.69; N, 7.63.

Hydrolysis of XI.—A mixture of 0.5 g of XI and 25 ml of 4 *N* HCl was refluxed for 17 hr, cooled, washed with chloroform, and evaporated to dryness. The residue was dissolved in pyridine, treated with 2 ml of acetic anhydride, and heated on a steam bath for 15 min. Ice–water was added; the mixture was made strongly basic with NaOH solution and was washed with chloroform and ethyl acetate. Acidification gave 0.2 g of product which was identified as N-acetyl-1,2,3,4-tetrahydroisoquinoline-1-acetic acid by comparison with the authentic sample: ν_{max} 1710 (–COOH) and 1620 cm^{-1} ($NCOCH_3$).

5,6,8,9,10,11,12,13,14,15,16,16a-Dodecahydro-2,3-dimethoxy-13-methylisoquino[2,1-*a*][1,5]diazacycloundecin-15-one (XII). A. $LiAlH_4$ Reduction of XI.—A solution of 3.68 g of XI in 500 ml of tetrahydrofuran was chilled, treated with 3.6 g of $LiAlH_4$, and stirred at room temperature for 3 hr. Excess $LiAlH_4$ was destroyed with water with external cooling. The reaction mixture was filtered and the cake was washed several times with tetrahydrofuan. The combined filtrate and washings were dried and evaporated under reduced pressure. The residue was crystallized from aqueous ethanol to give 2.5 g (71%) of analytically pure material: mp 173–175°; λ_{max} 282 mμ (ε 4400) and 286 (4400); ν_{max} 3300 (m), 1630 (s), 1540 (m), and 1515 cm^{-1} (ms).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.12; H, 9.03; N, 7.99.

B. Beckmann Rearrangement of XIII.—A mixture of 0.5 g of XIII and 18 g of polyphosphoirc acid was heated on the steam bath for 40 min with frequent stirring. The reaction mixture was cooled and dissolved in 100 ml of ice–water. The solution was made basic with 40% KOH and extracted with $CHCl_3$. Drying and evaporation of the chloroform solution and crystallization of the residue from ethyl acetate yielded 0.11 g of XII: mp 172–174.5°; with XII prepared by reduction of XI, mmp 173–175°.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-*a*]isoquinolin-14-one Oxime (XIII).—A solution of 10 g of X in 1 l. of tetrahydrofuran was cooled, treated with 5 g of $LiAlH_4$, and stirred at room temperature for 3.5 hr. Excess $LiAlH_4$ was destroyed with water; the inorganic material was filtered off and washed with hot tetrahydrofuran. Combined and dried filtrate and washings were evaporated to dryness. The oily residue (10 g) was dissolved in ethyl acetate and adsorbed on a 250-g Florisil column. Elution with ethyl acetate then chloroform gave 7.7 g (80%). When this was dissolved in hot "Skelly B" and the solution allowed to cool, a glassy product was obtained which liquified at 65–90°: δ 1.05 (d, CH_3–CH), 3.84 (CH_3O), 3.8-4.2 (m, H-15a, equatorial H-6), and 6.60, 7.07 (aromtic H); λ_{max} 281 mμ (ε 4160); ν_{max} 3200 (m), 1605 (w), and 1510 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.25; H, 8.65; N, 8.19.

5,6,8,9,10,11,12,13,14,15a-Decahydro-2,3-dimethoxy-13-methyl-14H-azecino[2,1-*a*]isoquinolin-14-one O-Acetyl Oxime (XIIIa).—A solution of 2 g of oxime XIII in 50 ml of pyridine was treated with 5 ml of acetic anhydride and allowed to stand at room temperature overnight. The reaction was concentrated on a rotary evaporator below 60°. The solution of the residue in 50 ml of ethyl acetate was washed with 5% NaOH then with water and was evaporated under reduced pressure. Trituration of the residue with petroleum ether (bp 37–47°) yielded 1.86 g (83%) of crude XIII. A twofold crystallization from anhydrous ether afforded analytical material: mp 131–133°; ν_{max} 1750 cm^{-1}; δ 1.12 (d, CH_3–CH), 2.23 (CH_3CO), 3.85 (CH_3O), 3.8–4.2 (m, H-15a, equatorial H-6), and 6.58, 6.85 (aromatic H).

Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.27. Found: C, 68.07; H, 8.39; N, 7.51.

1,2,3,4,5,6,7,8-Octahydo-14,15-dimethoxy-9-methyl-3-benzazacyclotetradecin-10(9H)-one Oxime (XIV).—A solution of XIII (3.6 g) in 50 ml of 3 *N* HCl was stirred at room temperature for 1 hr. The acidic suspension was made basic with 10% NaOH and extracted with $CHCl_3$. The dried chloroform solution was evaporated *in vacuo*. The residue was crystallied from 50 ml of ethyl acetate to give 1 g (28%) of product. Evaporation of the ethyl acetate mother liquor and treatment of the residue with 20 ml of 6 *N* HCl for 2 hr at room temperature afforded an additional 0.9 g (25%) of XIV. An analytical sample was prepared by a single crystallization from methanol: mp 199–202° dec; δ 1.15 (d, CH_3–CH), 3.82 (CH_3O), and 6.88, 7.20 7.29 (*ca.* 1:1:2, H-11, H-12, H-13, H-16); λ_{max} 221 mμ (ϵ 13,500), 238 (12,400), 295 (15,800), 325 (16,800); ν_{max} 3300 (m), 2650 (m), 1600 (m), 1510 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.28; H, 8.85; N, 8.32.

3-Acetyl-1,2,3,4,5,6,7,8-octahydro-14,15-dimethoxy-9-methyl-3-benzazecyclotetradecin-10 (9H)-one O-Acetyl Oxime (XIVa).—A solution of 1.8 g of XIV in 50 ml of pyridine was treated with 5 ml of acetic anhydride and allowed to stand overnight. Concentration under reduced pressure yielded an oily residue which was triturated with cold H_2O and dissolved in chloroform. The solution was washed with water, dried, and concentrated *in vacuo* to yield 1.16 g (52%) of XIVa. Twofold crystallization from ethyl acetate gave analytical material: mp 59–62°; λ_{max} 224 mμ (ϵ 14,500) shoulder, 242 (14,900), 303 (13,800) plateau, and 336 (17,700); ν_{max} 1750 (s) and 1635 cm^{-1} (s); δ 1.32 (d, CH_3–CH), 2.12 (CH_3CON), 2.23 (CH_3COO), 3.93 (CH_3O), and 6.75, 6.87, 7.15, 7.28 (4 H, AB quartet superimposed on two singlets, H-11, H-12, H-13, H-16).

Anal. Calcd for $C_{24}H_{34}N_2O_5$: C, 66.95; H, 7.96; N, 6.51. Found: C, 67.22; H, 7.96; N, 6.65.

Registry No.—IIb, 17628-55-6; IV, 17628-56-7; V, 17628-67-0; VI, 17628-57-8; VIIa, 17628-58-9; VIIb, 17628-59-0; VIII, 17628-60-3; IX, 17658-47-8; X, 17628-61-4; XI, 17628-62-5; XII, 17658-46-7; XIII, 17628-63-6; XIIIa, 17628-64-7; XIV, 17628-65-8; XIVa, 17628-66-9.

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Rearrangement of Azidoquinones. Reaction of Thymoquinone and 2,5-Dimethyl-1,4-benzoquinone with Sodium Azide in Trichloroacetic Acid

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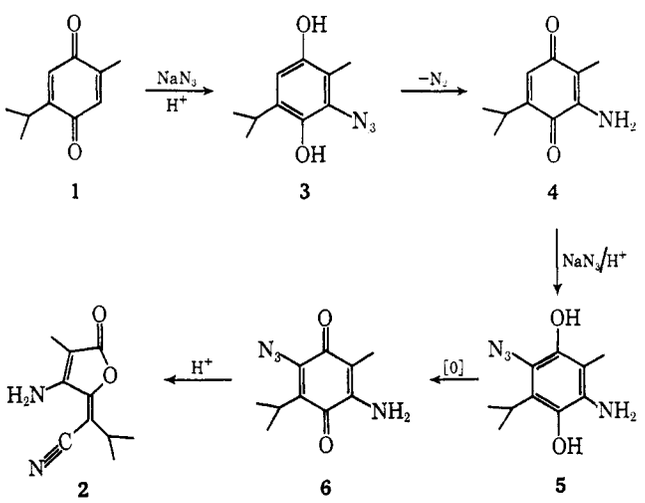
The rearrangements of thymoquinone (**1**) and 2,5-dimethyl-1,4-benzoquinone (**18**) to the γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides (**2**) and (**19**), respectively, upon reaction with sodium azide in trichloroacetic acid has been studied. In the case of thymoquinone a mechanism for this rearrangement is presented based upon the synthesis of the proposed intermediates **3**, **4**, and **6** and their subsequent conversion into **2** under the reaction conditions. By analogy, the rearrangement of **18** is also explained. Two new rearrangements of azidoquinones to ring-contracted compounds are also described: an acid-catalyzed rearrangement to γ-lactones and a thermal rearrangement to 5-cyanocyclopentene-1,4-diones.

The rearrangement of thymoquinone (**1**) to the γ-lactone, **2**, was recently reported by Rees[1,2] who observed this transformation when the quinone was treated with excess sodium azide in trichloroacetic acid at 65°. Described here is an investigation which indicates that this reaction proceeds as shown in Scheme I. The intermediates **3**, **4**, and **6** have been synthesized and found to give the lactone, **2**, when subjected to the reported reaction conditions.[1,2] In addition to the mechanistic implications concerning the rearrangement of **1** to **2** this study includes the following results of particular interest: (i) demonstration that azidohydroquinones undergo an intramolecular oxidation–reduction reaction to yield aminoquinones, and (ii) establishment of two interesting rearrangements of azidoquinones, an acid-catalyzed rearrangement to γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides and a thermal rearrangement to 5-cyano-cyclopentene-1,4-diones.

The azidohydroquinone, **3**, proposed as an intermediate in Scheme I, was prepared in 92% yield by dithionite reduction of an aqueous ethanolic solution of the corresponding azidoquinone, **7**. The quinone, **7**, was prepared by displacement of chloride by azide from 3-chloro-2-methyl-5-isopropyl-1,4-benzoquinone[3] according to the method reported by Fieser and Hartwell.[4] The spectral data for the new compounds, **3** and **7**, are reported in Table I.

SCHEME I



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