scribed for the preparation of **9** from **7**. The yield was quantitative, and the purification procedure was analogous to that described for **9** (R = Cl; R^1 = H). Elemental analysis is given in Table III.

Dibenzo[*b*,*g*][1,8]naphthyridine-11,12(5,6H)-dione (14), Isomer of Epindolidione.—To 250 ml of boiling Dowtherm A was added 25 g of diethyl dianilinomethylenemalonate[27] in small portions over a period of 15 min. By the use of a Dean–Stark tube, provision was made for the removal of product ethanol. After completion of the addition, reflux was continued for 1 hr. After the mixture cooled to room temperature, the product was removed by filtration, washed with ethanol, and dried at 60°. The yield was 17.4 g (96.5%). A sample was recrystallized from acetic acid and found not to melt up to 400°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.30; H, 4.00; N, 10.84.

3-(2-Carboxyphenylamino)-4-quinolone (16).—A mixture of 30.4 g (0.19 mol) of 3-amino-4-quinolone, 38.0 g (0.19 mol) of *o*-bromobenzoic acid, 50.5 g (0.38 mol) of potassium carbonate, 0.5 g of spongy copper,[28] and 500 ml of amyl alcohol was refluxed for 4 hr and then steam distilled to remove the amyl alcohol. The resultant mixture was filtered hot, and the cooled filtrate was acidified with concentrated hydrochloric acid. The product was collected by filtration, then extracted with 500 ml of boiling water, filtered, washed free of acid, and dried at 80°. The yield was 34.7 g (69%). After recrystallization from methanol the melting point was 255–256° (lit.[4] mp 255°). Calcd: neut equiv, 280. Found: neut equiv, 278.

Epindolidione *via* 16. Aluminum Chloride Method I.—An intimate mixture of 70 g of aluminum chloride and **7** g of sodium chloride was heated to 130–135°. To the stirred molten mass was added 5.6 g of **16** in small portions. The mixture was heated at 200° for 3 hr, cooled to 130–135°, and cautiously poured over a mixture of 500 g of ice and 100 ml of concentrated hydrochloric acid. The slurry was heated at 95–100° for 15 min, and the yellow product was collected by filtration and washed free of acid and chloride ion with water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 5.0 g (96.3%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

Epindolidione *via* 16. Polyphosphoric Acid Method II.—A mixture of 50 g of polyphosphoric acid and 5.0 g of **16** was heated with stirring at 200° for 6 hr. After it cooled to 40–50°, water was slowly added, maintaining the temperature at 50°, until the vigorous hydrolysis reaction had ceased, after which an excess of water was added. The mixture was heated to boiling and filtered hot. The product was washed free of acid with hot water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 3.0 g (64.2%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

(27) W. Traube and A. Eyme, *Ber.*, **32**, 3176 (1899).

(28) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 446.

Registry No.—**2**, 17352-37-3; **5a** (Table I), 17540-23-7; **5b**, 17540-24-8; **5c**, 17540-25-9; **5d**, 17540-26-0; **5e**, 17540-27-1; **5f**, 17540-28-2; **5g**, 17540-29-3; **7a** (Table II), 16377-52-9; **7b**, 16479-61-1; **7c**, 17540-32-8; **7d**, 17540-33-9; **7e**, 16377-54-1; **7f**, 16427-99-9; **7g**, 16377-56-3; **8** (R = OCH_3; R′ = H), 16377-61-0; **9b** (Table III), 17352-38-4; **9c**, 17540-39-5; **9d**, 17341-72-9; **9e**, 17470-44-9; **9f**, 17352-60-2; **9g**, 17341-73-0; **14**, 3048-67-7.

Acknowledgment.—We are indebted to Dr. G. S. Hammond, Dr. R. C. Lord, and Dr. J. C. Sheehan for helpful comments.

Azecino[2,1-*a*]tetrahydroisoquinolines and Related Compounds. I. Reaction of 3,4-Dihydroisoquinolines with Nonenolizable β Diketones

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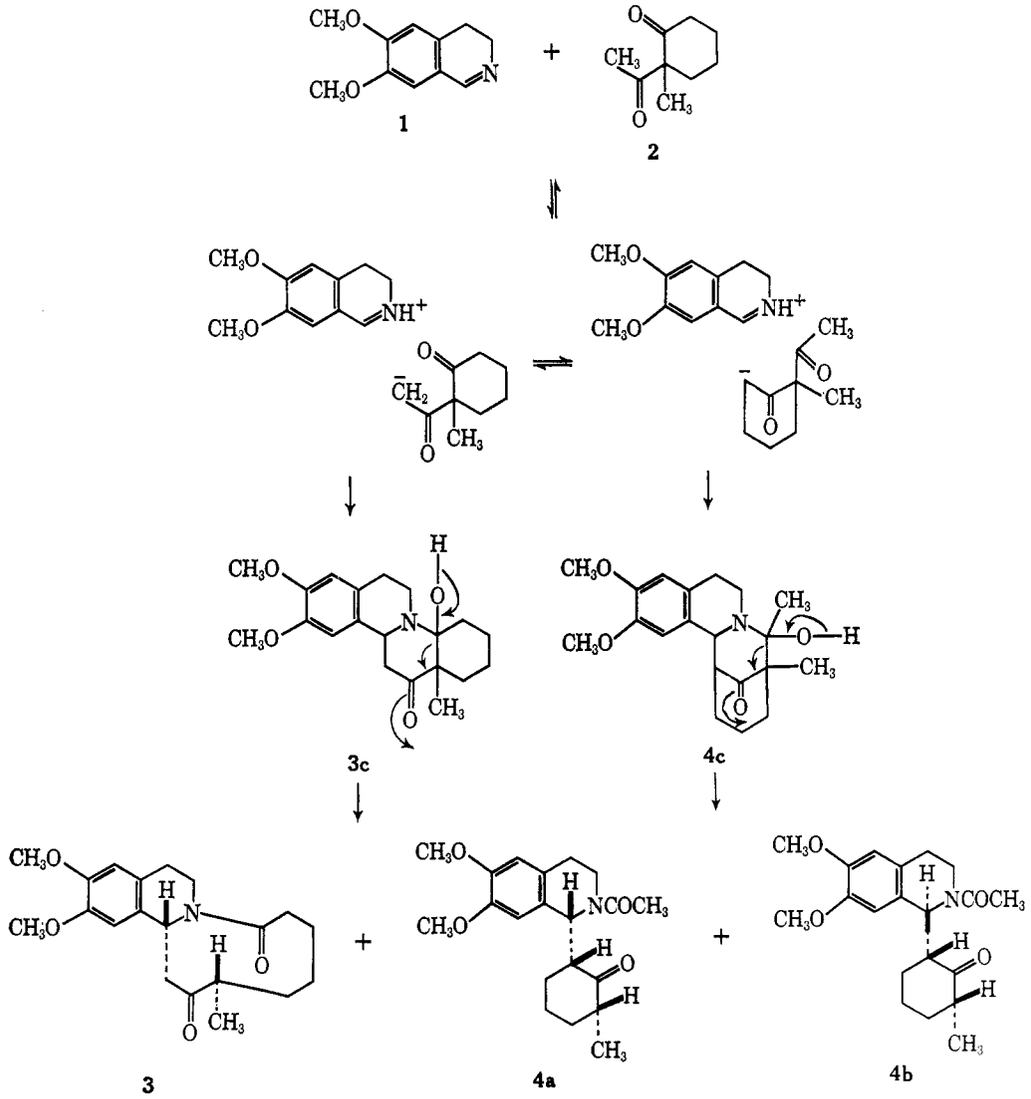
3,4-Dihydroisoquinolines react with nonenolizable β diketones to give 1-(2-oxoalkyl- or -cycloalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (type **4** and **9**), and azecino[2,1-*a*]isoquinolines (type **3**), or other related large-ring compounds (**8**).

Recently, we have described the synthesis of benzo[*a*]quinolizines and dibenzo[*a*,*f*]quinolizines by the condensation of 3,4-dihydroisoquinolines with enolizable β diketones.[1] The present communication is concerned with the reaction of 3,4-dihydroisoquinolines with nonenolizable β diketones (Scheme I). In the course of this reaction the β diketone is cleaved, and the resulting oxoalkyl (or oxocycloalkyl) and acyl fragments alkylate and acylate the isoquinoline reactant at C-1 and N, respectively. Linear β diketones yield 1-(2-oxoalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (**9**, **10**), whereas β diketones of the acylcycloalkanone type give 1-(2-oxocycloalkyl)-N-acyltetrahydroisoquinolines (type **4a**, **b**) and azecino[2,1-*a*]isoquinolines (type **3**), or other related, large-ring compounds (**8**). For example, the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) with 2-acetyl-2-methylcyclohexanone (**2**) gave 5,6,10,11,12,13,15,15a-octahydro-2,3-dimethoxy-13-methyl-9H-azecino[2,1-*a*]-isoquinoline-8,14-dione (**3**) and two of the four possible stereoisomeric 2-acetyl-1-(3-methyl-2-oxocyclohexyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines (**4a**, **b**). The pH dependence (the reaction is inhibited by alkali and strong acid) and the solvent dependence (rate increases with solvent polarity) are analogous to those observed in the reaction of 3,4-dihydroisoquinolines and enolizable β diketones.[1] This suggests that both reactions proceed by related mechanisms. Extension of this reaction to other dihydroisoquinolines and to 3,4-dihydro-β-carboline is summarized in Table I. The table also includes 3-phenyl-2,4-pentanedione (**10**), which in contrast to the other enolizable β diketones did not yield a benzo[*a*]quinolizine. Instead, it was cleaved analogously to nonenolizable β diketones. This may be a consequence of stabilization of the resulting anion by the phenyl group.

The structure of the large-ring compounds is based on the following evidence. The ultraviolet spectra are characteristic of the parent tetrahydroisoquinoline chromophores. The infrared spectra show bands typical of a ketone (1700–1705-cm^{-1} region) and an amide carbonyl (1620–1633-cm^{-1} region). The mono-

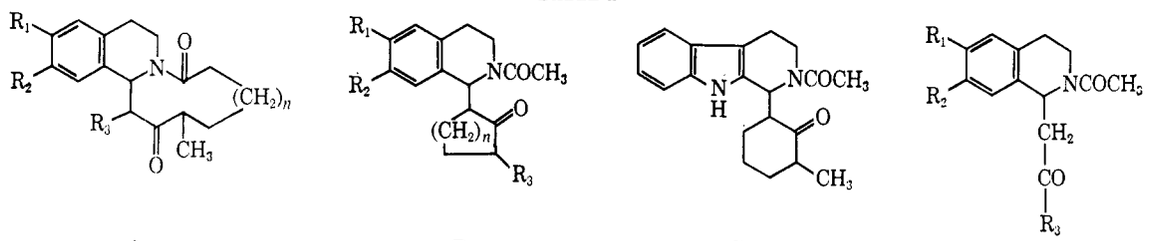
(1) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1965).

SCHEME I[a]



[a] The configurational assignments are tentative.

TABLE I



Compound	Starting β diketone	Type	Product R1	Product R2	Product R3	n	Mp, °C	% yield	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
3	2-Acetyl-2-methylcyclohexanone	A	CH_3O	CH_3O	H	2	240–244	35	69.54	7.88	4.05	69.52	7.96	4.24
4a	2-Acetyl-2-methylcyclohexanone	B			CH_3	2	158–158.5	3.5	69.54	7.88	4.05	69.72	8.06	4.35
4b	2-Acetyl-2-methylcyclohexanone	B	CH_3O	CH_3O	CH_3	2	135–137	1	69.54	7.88	4.05	69.77	7.95	4.34
5	2-Acetyl-2-carbethoxycyclohexanone	B	CH_3O	CH_3O	$COOC_2H_5$	2	144–152	5	65.49	7.25	3.47	65.34	7.04	3.30
6	2-Acetyl-2-methylcyclopentanone	B	CH_3O	CH_3O	CH_3	1	134–139	28	68.86	7.60	4.23	69.03	7.64	4.47
7	2-Methoxyacetyl-2-methylcyclohexanone	A	CH_3O	CH_3O	CH_3O	2	161.5–163	12	67.18	7.79	3.73	67.09	7.68	4.00
8	2-Acetyl-2-methylcyclododecanone	A	CH_3O	CH_3O	H	8	129–130	25	72.69	9.15	3.26	72.88	9.10	3.18
9	3,3-Diethyl-2,4-pentanedione	D	CH_3O	CH_3O	$(C_2H_5)_2CH$		139–140	6.5	69.13	8.41	4.03	69.39	8.63	4.27
10	3-Phenyl-2,4-pentanedione	D	CH_3O	CH_3O	$C_6H_5CH_2$		124–126	68	71.92	6.86	3.81	71.79	6.92	3.97
11	2-Acetyl-2-methylcyclohexanone	A	CH_3O	H	H	2	189–191	14	72.35	7.99	4.44	72.44	8.01	4.53
12	2-Acetyl-2-methylcyclohexanone	B	CH_3O	H	CH_3	2	168–171	1	72.35	7.99	4.44	72.26	7.73	4.56
13	2-Acetyl-2-methylcyclohexanone	A	H	H	H	2	151–153	2	75.75	8.12	4.91	75.60	8.03	4.80
14	2-Acetyl-2-methylcyclohexanone	C					250–252	50	74.04	7.46	8.64	73.91	7.43	8.57

molecular formula was confirmed by Rast molecular weight determination. A Kuhn–Roth assay indicated the presence of one C–CH_3 group. The corresponding pmr signals are found as a doublet in the 1.10–1.13-ppm region. In addition, the spectra show four signals corresponding to one proton in the 5.63–5.80-ppm region constituting the X part of the H-15a–H_2-15 ABX system. (Compound **7** having only one hydrogen

TABLE II

THE PMR OF KETO AMIDES (TABLE I)

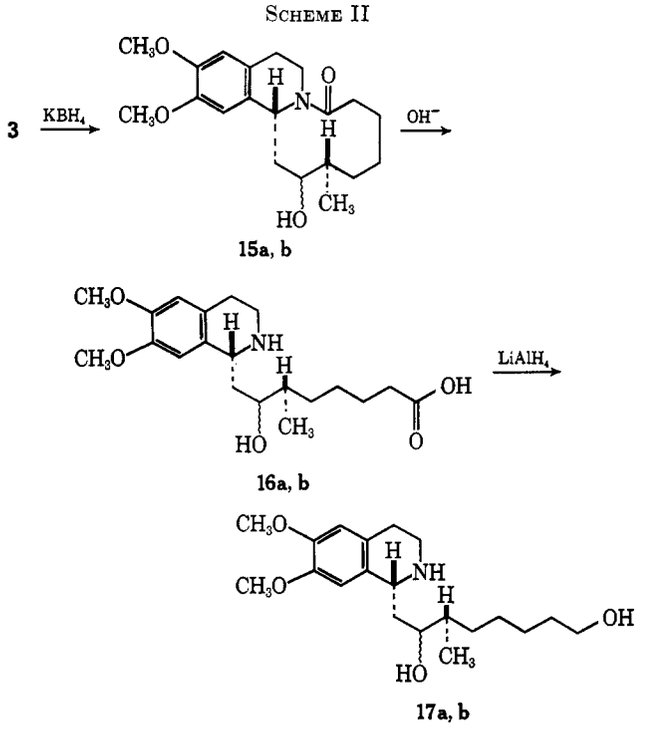
Compound	>CH–CH₃[a]	Ar–CH–N	Multiplicity of Ar–CH–N (*J*, cps)	CH₃CON<	Solvent
3	1.13	5.63	Quadruplet (12, 6)		$CDCl_3$
7	1.13	5.15	Doublet (9)		$CDCl_3$
8	1.10	5.6–6.1	Multiplet		$CDCl_3$
11	1.10	5.78	Quadruplet (12, 5)		$CDCl_3$
13	1.12	5.80	Quadruplet (12, 5)		$CDCl_3$
4a	1.02, 0.96	5.50, 6.24	Two doublets (10)	2.13	$CDCl_3$
4a	0.95	5.78	Doublet (9)	2.02	$(CD_3)_2SO$, 140°
4b	0.98	6.04	Doublet (12)	2.03	$CDCl_3$
5	1.14	5.77, 5.10	Two doublets (9)	1.98	$(CD_3)_2SO$
6	1.0	5.78, 5.32	Two doublets (5)	2.09	$(CD_3)_2SO$
6	1.0	5.63	Doublet (5)	2.10	$(CD_3)_2SO$, 130°
9	0.83	6.00, 5.51	Two triplets (6)	2.22 (2.12)	$CDCl_3$
10		5.88, 5.42	Two triplets (7)	2.15 (2.24)	$CDCl_3$
10		5.63	Triplet (7)	2.03	$(CD_3)_2SO$, 140°
12	0.88	6.08, 5.38	Two doublets (10)	2.02	$(CD_3)_2SO$
14	1.2	5.98	Doublet (7)	2.6	CF_3COOH

[a] Shifts expressed in parts per million (δ) from tetramethylsilane (TMS).

at C-15 gives this signal as a doublet at 5.15 ppm.) The cyclic nature of the amide was established by the fact that no carbon was lost upon hydrolysis of the amide bond.

Since attempted hydrolysis of **3** itself was attended by β elimination,[2] it was decided to reduce the carbonyl function prior to hydrolysis. KBH_4 reduction of the ketone amide **3** gave a stereoisomeric mixture of amide alcohols **15a, b**[2] which was hydrolyzed to a noncrystalline mixture of amino acids **16a, b**. The latter was characterized by its amphoteric properties, by the

SCHEME II



ir spectrum of the derived mixture of hydrochlorides which displayed a carboxyl band at 1710 cm^{-1}, as well as by reduction to the crystalline aminodiol mixture **17a, b** (Scheme II above).

(2) The elimination reactions as well as the separation of the mixture of epimers **15a, b** is described in the accompanying paper: M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 4015 (1968).

The structure of compounds of type **4** is based on the following evidence. Similarly, as in the large-ring compounds, the uv and the ir spectra are characteristic of the parent tetrahydroisoquinoline chromophore (tetrahydro-β-carboline in the case of **14**), and of the amide and ketone functions. The Kuhn–Roth assay indicates the presence of two C–CH_3 groups. The pmr spectra display the signals of these groups as a singlet ($CH_3CON<$) in the 1.98–2.22-ppm region and a doublet (>CH–CH_3) in the 0.88–1.03-ppm region. In place of the latter signal, the spectrum of the carbethoxy-substituted compound **5** shows a triplet at 1.14 ppm. In contrast to the finding in the large-ring compounds, the proton at the tetrahydroisoquinoline C-1 is shown as a doublet (rather than a quartet) in the 5.50–6.24-ppm region. Hydrolysis of the amido alcohol **18**, prepared by the KBH_4 reduction[3] of the keto amide **4a**, gave the amino alcohol **19**. The loss of the acetyl group in the course of hydrolysis proves the noncyclic nature of the amide. Compounds not subjected to the reduction–hydrolysis sequence were classified as cyclic (type **3**) or noncyclic (type 4) amides on the basis of their pmr spectra, using as criteria the presence or absence of the N-acetyl proton signals, and the multiplicity (doublet or quartet) of the tetrahydroisoquinoline H-1 signal. (See Table II.)

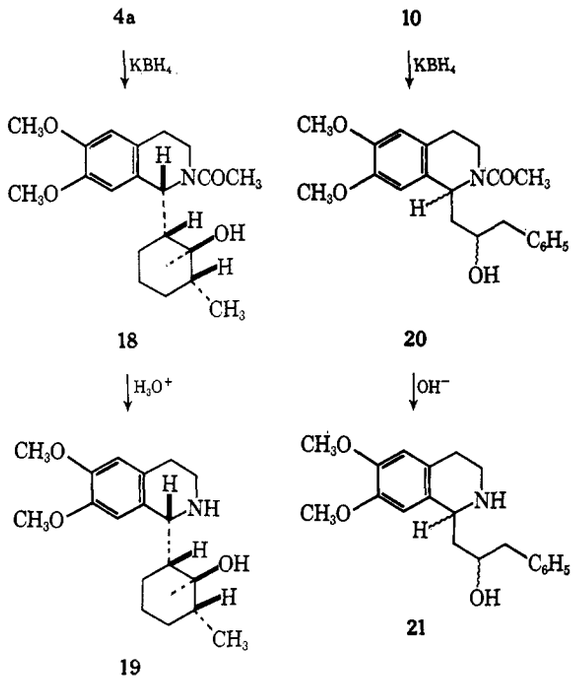
The structures of compounds **9** and **10** are based on their uv (6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline chromophore), ir (ketone and amide carbonyl bands), and pmr spectra (tetrahydroisoquinoline H-1 triplet; N-acetyl) and on the hydrolysis of the amido alcohol **20**[3] to the amino alcohol **21** (Scheme III).

Stereochemical Considerations.—The assignments of configurations were based upon consideration of Dreiding models and pmr spectra. Because of lack of basic knowledge in the literature[4] about relative conforma-

(3) (a) The KBH_4 reduction gave predominantly one of the two expected epimers, the small amount of the second one being lost upon crystallization. (b) The reduction prior to hydrolysis was necessary because, under the reaction conditions, **4a** suffered β elimination as evidenced by the isolation of 3,4-dihydro-6,7-dimethoxyisoquinoline.

(4) For discussion of stereochemistry of ten-membered rings, see J. Sicher in "Progress in Stereochemistry," part 3, de la Mare and Klyne, Ed., Butterworth and Co. Ltd., London, 1962, p 202; J. Sicher, M. Svoboda, J. Zavada, R. B. Turner, and P. Goebel, *Tetrahedron*, **22**, 659 (1966); R. M. Moriarty, *J. Org. Chem.*, **29**, 2748 (1964); L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965).

SCHEME III



tional stabilities of azecines having an amide and a keto function, *these assignments must be considered as tentative.*

Analogies in the pmr spectra (Table II) of the azecino-[2,1-*a*]isoquinolines indicate a common stereochemistry for **3**, **11**, and **13** (Figure 1). The following discussion of the pmr spectrum of **13** is therefore pertinent to the other compounds of this series. The H-15a signal appears as the X part of an ABX system at 5.8 ppm, (four equally intense signals with observed splittings of 12 and 5 cps). The large chemical shift of this proton indicates its position in the plane of the aromatic ring as well as in the plane of the amide group.[5] Consequently, the 15a–15 bond is pseudoaxial with respect to the tetrahydropyridine ring. The splitting pattern of the H-15a signal and magnitude of the coupling constants are best explained by assumption of approximately 180 and 60° dihedral angles with the two protons at C-15.[6] Spin decoupling of the methyl group hydrogens permits the location of the H-13 signal at 3.28 ppm. This unusual low-field position cannot be explained by proximity of the carbonyl group alone (H-2 in 2-methylcyclohexanone resonates at *ca.* 2.5 ppm). Inspection of models suggests that, in the *trans* configuration (referring to the H-15a,H-13 relationship), H-13 may be located either in the diamagnetic zone of the amide group or outside of its magnetic field. In contrast, in the *cis* configuration, the conformation with the least amount of interactions (Figure 1), H-13 appears to be located in the paramagnetic zone of the amide.[7] The *cis* configuration is therefore assigned to **3**, **11**, and **13**.

(5) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965), report a chemical-shift difference of 2.4 ppm for the geminal protons at C-6 of 4-oxoquinolizidine. The low-field resonance (4.63 ppm) of the equatorial H-6 is attributed to its position in the plane of the lactam group.

(6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(7) (a) The argument is crucially dependent on the assumption that H-15a is axial and the C-15a–C-15 bond is equatorial. A referee has suggested that there may actually be fast ring inversion at C-15a and that we may be observing an averaged conformation in the nmr. However, our C-15a proton signals in **3**, **11**, and **13** at 5.63–5.80 ppm are uniquely compatible with the *equatorial* proton signals (5.60–5.65 ppm) reported in ref 8b. (b) For a detailed study of the magnetic anisotropy of the amide group see H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967). (c) No evidence is available regarding the configuration at C-13 in **7**. In contrast to the spectrum of **3**, that of **7** displays the aromatic protons at different fields (H-1, 7.08; H-4, 6.67 ppm) indicating that H-1 is in the field of the aliphatic methoxy group. (For correlation of chemical shifts of the aromic hydrogens with the spatial arrangement of the aliphatic methoxy group in a similar molecule, see ref 1.) The signal of H-15 is a sharp doublet (J = 9 cps) at 3.7 ppm and the corresponding H-15a doublet is displayed at 5.15 ppm. The magnitude of the coupling constant[6] as well as the H-1–CH_3O-15 interaction suggest an *anti*-periplanar arrangement for H-15 and H-15a. The smaller chemical shift of the H-15a signal, compared with the corresponding resonance of **3**, suggests that H-15a, while being in the deshielding zones of the aromatic ring and the amide carbonyl, is not in their plane. This finding, as well as the H-1–CH_3O-15 interaction, points to a pseudoequatorial arrangement of the C-15a–C-15 axis with respect to the tetrahydropyridine ring.

(8) (a) D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Lett.*, 2687 (1965). (b) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, **89**, 329 (1967). These authors observe Ar–CH–N signals at 4.72–4.77 and 5.60–5.65 ppm which they ascribe to axial and equatorial protons at C-1, respectively, the benzyl substituent at C-1 flipping slowly from the equatorial to the axial position. The signals observed by us are at lower field; in view of this difference, as well as the different geometry, at least of our series B, we feel that the two conformations observed by us are due to a different change, probably a rotation of the amide ($CH_3CON<$) grouping.

(9) The terms *threo* and *erythro* refer to spatial arrangement around the tetrahydroisoquinoline C-1–cyclohexanone C-2 axis. The *threo* configuration has the ketone carbonyl and the amide group on opposite sides of the plane dissecting the eclipsed hydrogens; the *erythro* configuration has these groups on the same side.

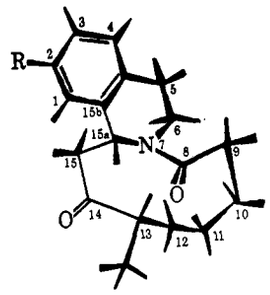


Figure 1.—Suggested conformation of azecino[2,1-*a*]isoquinolines **3**, **11**, and **13**. [The model is viewed approximately perpendicular to the 15b–15a–15–14–(H-13) segment.]

The pmr spectra of the compounds of type **4a** (including **9** and **10**) show a double set of signals. For example, the spectrum of **4a** in $CDCl_3$ displays two overlapping doublets at 0.96 and 1.02 ppm (CH–CH_3), two half-proton doublets at 5.50 and 6.24 ppm (tetrahydroisoquinoline H-1), one proton singlet at 6.62 ppm, and two half-proton singlets at 6.7 and 7.11 ppm (aromatic hydrogens). This doubling is explained by the presence of two conformations, in relatively slow equilibrium similar to those observed by Dalton, *et al.*,[8] in the case of 2-acetyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines. Upon heating to 130–140° in $(CD_3)_2$-SO solution the two sets of signals coalesce to a simple spectrum: a doublet at 0.95 ppm (CH–CH_3), a doublet at 5.87 ppm (tetrahydroisoquinoline H-1), and two singlets at 6.67 and 6.87 ppm (aromatic hydrogens).

The difference in the chemical shifts of the two aromatic hydrogens suggests that the tetrahydroisoquinoline H-8 is deshielded by the carbonyl group. Examination of the models shows that the proximity of the tetrahydroisoquinoline H-8 to the carbonyl group is possible only in the *erythro*[9] configuration, providing that the tetrahydroisoquinoline H-1 and the cyclohexanone H-2 are predominantly *anti* periplanar, as suggested by their coupling constant (J = 10 cps). The *erythro* configuration is therefore assigned to **4a** and the *threo* configuration to **4b** which has both aro-

matic hydrogens resonating at approximately the same field (6.74 and 6.77 ppm). Since formation of compounds of type **4** from the cage intermediate (**4c**) probably involves enolization at cyclohexanone C-6, the end product is likely to have the preferred *cis* (diequatorial) configuration of the two cyclohexanone substituents.[10] This was confirmed by equilibration of **4a** and **4b** by Na_2CO_3 in methanol. Since this equilibration involves epimerization at C-2, it is likely that it also leads to labilization of the chiral center at C-6; consequently, the relative configuration of C-2 and C-6 in both **4a** and **4b** is the more stable one, *i.e.*, *cis*. At equilibrium, **4a** (*erythro*) predominated over **4b** (*threo*) in a ratio of about 10:1 (by tlc estimations) presumably because of steric (or dipolar) repulsion of the cyclohexanone carbonyl and acetamide functions in the preferred (H-1,H-2 *anti*) conformation of **4b**.[11]

The greater crowding of the N-acetyl group in **4b** apparently restricts the amide to a single conformation, since the pmr spectrum of **4b** does not show the doubling of signals, observed with compounds of type **4a**.

In summation, *erythro,cis* configuration is assigned to **4a** and compounds with analogous pmr spectra **5**, **6**, and **12**, and *threo,cis* configuration is assigned to **4b**.

Since KBH_4 reduction of **4a** might be expected to give as the major product, the more stable alcohol,[3a,12] the *erythro,cis,trans* [*erythro* (isoquinoline C-1,cyclohexanol C-2), *cis* (cyclohexanol C-2,C-6), and *trans*(cyclohexanol C-2, C-1)] configuration is assigned to **18** and **19**.

The configurations of compounds **8**, **14**, **20**, and **21** were not determined.

The separation of the alcohols **15a** and **15b** together with the assignments of their configurations were carried out within the study of the chemical reactions of azecino[2,1-*a*]isoquinolines and are described in part II of this series.

Experimental Section[13]

Preparation of Keto Amides (Table I).—A mixture of 0.1 mol of a 3,4-dihydroisoquinoline (or 3,4-dihydro-β-carboline) and 0.1 mol of a suitable β diketone in 500 ml of water (100 ml of ethanol for **10**, and 900 ml of 75% ethanol for **14**) was refluxed for 20 hr (34 hr for **8**, 7.5 hr for **9**, and 48 hr for **10**). In the case of **10** and **14**, the product crystallized on chilling. In the case of **3**, after chilling of the reaction mixture, the aqueous layer was decanted, and the oily residue was crystallized by boiling in 100 ml of acetonitrile. In all other cases, the mixture was extracted with chloroform. The extracts were freed from basic material by washing with 2 *N* HCl, dried over Na_2SO_4, and evaporated at reduced pressure. The residual gum was crystallized directly (**5**, **8**, **11**, and **13**) or chromatographed on Florisil (1 g:40 g) using ethyl acetate as the eluent (**6**, **7**, and **9**). Concentration of mother liquors of **3** gave **4a**. Chromatography of mother liquors of **4a** and **11** gave **4b** and **12**, respectively. The products were crystallized from acetonitrile (**3**), ethyl acetate (**6**, **7**, **9**, **10**, **11**, **4a**, and **4b**), 2-propanol (**5**, **13**), ethanol (**8**), 95% ethanol (**12**), and acetic acid (**14**). The analytical and the pmr data of the keto amides are listed in Tables I and II, respectively.

KBH_4 Reduction of Keto Amides.—A solution of 2 g of a keto amide (**3**, **4a**, **10**) in 100 ml of 1:1 methanol–chloroform was treated portionwise with 2 g of KBH_4 and stirred for 6 hr at room temperature. The solvents were evaporated at reduced pressure, and the residue was dissolved in 25 ml of chloroform and 10 ml of water. The organic layer was separated, dried over Na_2SO_4, and evaporated to yield 90–95%. The analytical samples were obtained by a twofold crystallization from ethyl acetate.

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-ones (15a, b)[2] had mp 163–194°; ν_{max}^{Nujol} 1515 (s), 1605 (s), 3350 (w), and 3500 (w) cm^{-1}; λ_{max}^{EtOH} 282 mμ (ε 4300).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 68.92; H, 8.54; N, 4.03.

2-(2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-6-methylcyclohexanol (18)[3a] had mp 199–200.5°; λ_{max}^{EtOH} 283 mμ (ε 4000); ν_{max}^{Nujol} 1515 (s), 1615 (vs), and 3470 (s), cm^{-1}.

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.36; H, 8.48; N, 3.90

α-[(2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-methyl]phenethyl alcohol (20)[3a] had mp 157–159°; ν_{max}^{Nujol} 1510 (m), 1620 (s), and 3400 (m) cm^{-1}; λ_{max}^{EtOH} 281 mμ (ε 4000).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.38; H, 7.38; N, 3.59.

Hydrolysis of the Amido Alcohols. 2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)-6-methylcyclohexanol (19).—A solution of 1.5 g of **18** in 15 ml of concentrated HCl was heated on a steam bath for 1 hr. After dilution with 85 ml of water, the reaction mixture was washed with ethyl acetate, made basic with 10% NaOH, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to give 0.81 g (61%) of **19**. The analytical sample was obtained by crystallizations from ether and from ethyl acetate: mp 137–142°.

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.49; H, 8.95; N, 4.72.

2-[(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)methyl]-phenethyl Alcohols (21).—A solution of 1 g of **20** in 10 ml of 95% ethanol was treated with 3 g of KOH, refluxed for 2 hr, diluted with 85 ml of water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to give 0.7 g (80%) of **21**: mp 123.5–125.5; ν_{max}^{Nujol} 1515 (s), 1610 (w), and 3300 (m) cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.42; H, 7.81; N, 4.33.

6-Methyl-8-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-1,7-octanediol (17a, b).—A solution of 0.78 g of **15a, b** and 2.1 g of KOH in 25 ml of 95% ethanol was refluxed for 3.5 hr, chilled, acidified with ethanolic 3 *N* HCl, filtered, and concentrated *in vacuo* to give the hydrochloride of the amino acids (**16a, b**).

A solution of the latter in 50 ml tetrahydrofuran was treated with 1 g of $LiAlH_4$ and refluxed for 4.5 hr. Excess $LiAlH_4$ was destroyed by dropwise addition of water. The mixture was filtered and the collected solids were extracted with tetrahydrofuran. The combined filtrate and extracts were evaporated *in vacuo*. The residue was dissolved in chloroform, and the resulting solution was extracted with 2 *N* HCl. The aqueous portion was made basic with 10% NaOH and extracted with chloroform. The chloroform extracts were dried over Na_2SO_4 and evaporated to give 0.65 g (67%) of **17a, b**. The analytical sample was prepared by a twofold crystallization from CH_3CN: mp 97–99°; ν_{max}^{Nujol} 3300 (s) cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.56; H, 9.49; N, 4.01.

(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 52.

(11) The *anti*-periplanar (H-1,H-2) conformation is confirmed by the observation that J = 12 cps for the protons. An attempt was made to confirm the equatorial conformation of the C-6 methyl group in **4a** and **4b** by studying the effect of benzene on the chemical shifts. According to N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 165, the resonance of an axial methyl group adjacent to carbonyl suffers an upfield shift of 0.2–0.3 ppm on passing from $CDCl_3$ to benzene solution, whereas the resonance of an equatorial methyl suffers a small downfield shift. Our results ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$ = 0.02 for **4a** and −0.2 ppm for **4b**) were not conclusive probably because of effects of the amide and the aromatic ring. If anything, they suggest the equatorial conformation [hence *cis* (cyclohexanone C-2,C-6) configuration] of the methyl group in **4b**.

(12) D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.*, **75**, 6005 (1953); D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(13) Melting points were determined using the Thomas–Hoover capillary melting point apparatus. The uv and ir spectra were recorded, 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 obtained 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 or 95% ethanol as the eluent. The chromatograms were developed by spraying with either dilute aqueous $KMnO_4$ or ethanolic iodine (4%) solutions.

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]