A New General Synthesis of Benzo[a]quinolizines, Dibenzo[a,f]quinolizines, and Related Compounds

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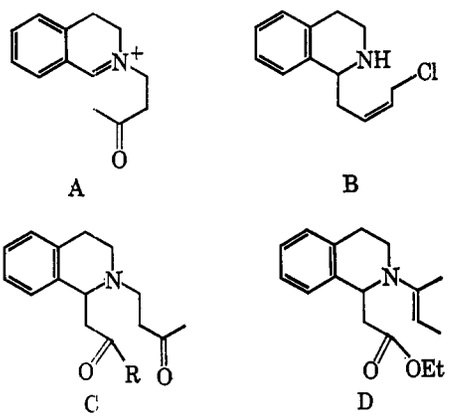
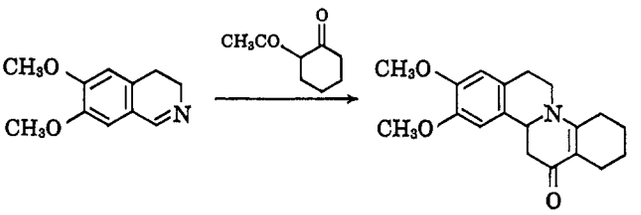
Condensation of β-diketones with 3,4-dihydroisoquinolines provides a facile one-step route to benzo[a]quinolizines, dibenzo[a,f]quinolizines, and related compounds having 8-azasteroid and 8- (or 9-) aza-D-homosteroid nuclei. The spectral data and the reaction mechanism are discussed. Configurations and conformations of benzo[a]quinolizines substituted at C-1 and of dibenzo[a,f]quinolizines substituted at C-12 are assigned on the basis of nmr and chemical evidence.

In view of the biological implication of emetine and azasteroids, there has recently been considerable interest in syntheses of benzo[a]quinolizine-type compounds.[1-9] With few exceptions,[6,9] these syntheses utilize a hydroisoquinoline as the starting material; the most common route involves the cyclization of an intermediate of type A obtained by β acylethylation of a 3,4-dihydroisoquinoline with an α,β-unsaturated ketone,[1,10] β-trialkylammonium ketone,[3] or a β-hydroxymethylene ketone.[3,11,12] Alternatively, a 1,2,3,4-tetrahydroisoquinoline may be used as starting material; in this case the β-acylethylation step is followed by dehydrogenation of the C-1–N linkage.[3] Other commonly used paths proceed through cyclization of intermediates of type B,[13] C,[2,4,14] or D.[7]



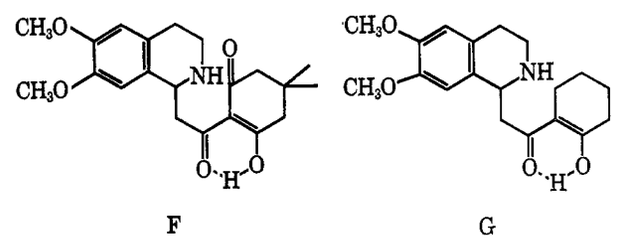
The present paper describes a novel one-step synthesis of benzo[a]quinolizines, as well as dibenzo[a,f]quinolizines and related compounds having 8-azasteroid and 8- (or 9-) aza-D-homosteroid nuclei, using 3,4-dihydroisoquinolines and enolizable β-diketones as (readily available) starting materials. For example, condensation of 2-acetylcyclohexanone and



6,7-dimethoxy-3,4-dihydroisoquinoline yielded the crystalline product, XVII, whose identity was established by an independent synthesis[7,15] from 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and excess cyclohexanone (method D).

Extension of this reaction to other β-diketones and dihydroisoquinolines led to the preparation of the compounds listed in Tables I and II. The only triketone used, 2-acetyldimedone,[16] behaved in the same manner (XXVI, Table II) except for a much greater rate of reaction.[17]

The ultraviolet spectra of the products are in agreement with those of known compounds containing the vinylogous amide chromophore.[18] Tricyclic compounds which are unsubstituted at C-3 (I–VII, Table I) display an absorption maximum at 319 mμ. Compounds with a substituent both at C-3 and C-4 (VIII–XIII, Table I), including the tetracyclic types (Table II), absorb in the 333–336-mμ region. The bathochromic



be explained by the presence of an additional carbonyl group which is located in a position favorable to cyclization. In contrast, hydrogen bonding in β-diketones such as G results in deactivation of the carbonyl toward amine addition and holds it in a position that is spatially unfavorable to ring closure.

(1) A. Brossi, L. H. Chopard-dit-Jean, J. Wuersch, and O. Schnider, *Helv. Chim. Acta*, **43**, 583 (1960).

(2) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *ibid.*, **41**, 119 (1958).

(3) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1449 (1963).

(4) A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *ibid.*, 2463 (1953).

(5) R. F. K. Meredith, A. C. Ritchie, T. Walker, and K. D. E. Whiting, *ibid.*, 2672 (1963).

(6) R. I. Meltzer, D. M. Lustgarten, P. J. Stanaback, and R. E. Brown, *Tetrahedron Letters*, **No. 23**, 1581 (1963).

(7) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *ibid.*, **No. 4**, 255 (1965).

(8) Imperial Chemical Industries Ltd., Belgian Patent 642,060 (1964).

(9) N. A. Nelson and Y. Tamura, *Can. J. Chem.*, **43**, 1323 (1965).

(10) D. Beke and C. Szantay, *Chem. Ber.*, **95**, 2132 (1962).

(11) K. Lenard and P. Bite, *Acta Chim. Acad. Sci. Hung.*, **38**, 57 (1963).

(12) J. R. Tretter, U. S. Patents 3,095,419 and 3,105,079 (1963).

(13) D. Schoepf and R. Klug, U. S. Patent 3,132,147 (1964).

(14) D. H. R. Barton, *et al.*, U. S. Patent 3,121,720 (1964).

(15) This synthesis is an adaptation of H. Tiedke's [*Ber.*, **42**, 621 (1909)] preparation of acridones from anthranilic acid and cyclohexanone.

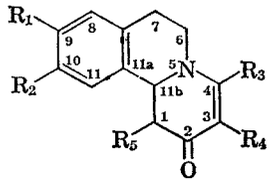
(16) W. Dieckmann and R. Stein, *ibid.*, **37**, 3370 (1904).

(17) The condensation of 2-acetyldimedone with 6,7-dimethoxy-3,4-dihydroisoquinoline in ethanol was completed within 25 min, whereas the analogous reaction of 2-acetylcyclohexanone required 72 hr. In the light of the proposed mechanism (Scheme I), the fast reaction of compound F can

(18) (a) K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon [*J. Chem. Soc.*, 45 (1946)] have found that the N—C=C—CO— group shows a maximum at 308 mμ. (b) J. Romo and A. Romo de Vivar [*J. Am. Chem. Soc.*, **81**, 3446 (1959)] described an example of a β-amino-α,β-unsaturated ketone which was characterized by an ultraviolet absorption band at 314 mμ. (c) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Rensche, *Chem. Ber.*, **94**, 1774 (1961).

TABLE I

PHYSICAL AND ANALYTICAL PROPERTIES OF 1,6,7,11b-TETRAHYDRO-2H-BENZO[*a*]QUINOLIZIN-2-ONES

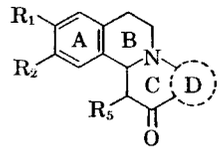


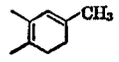
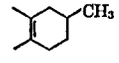
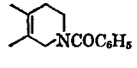
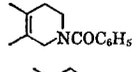
Compd	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	$\nu_{C=O}$ cm^{-1}	λ_{max},[a] mμ (ϵ)	H-11b, ppm	J, cps ax,ax	J, cps eq,ax	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
I	H	H	CH_3	H	H	131–133	23	1540 1628	319 (17,200)	4.76 q[b]	14	6	$C_{14}H_{15}NO$	78.84	7.09	6.57	78.88	7.17	6.78
II	H	H	CH_3	H	OCH_3	153–155	10	1540 1615	323 (14,900)		Nd[c]		$C_{15}H_{17}NO_2$	74.05	7.04	5.76	74.27	7.08	5.75
III	OCH_3	H	CH_3	H	H	106–109	68	1540 1625	287 (5200) (sh)[d] 319 (16,000)	4.70 q	13	6	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	73.96	7.08	5.69
IV	OCH_3	OCH_3	CH_3	H	H	189–193	58	1550 1615	294 (8000) (sh) 319 (16,600)	4.68 q	15	6	$C_{16}H_{19}NO_3$	70.31	7.01	5.12	70.48	7.14	5.34
V	OCH_3	OCH_3	C_6H_5	H	H	169–170	28	1530 1622	285 (5900) 331 (13,500)	4.97 q	12	8	$C_{21}H_{21}NO_3$	75.20	6.31	4.18	75.13	6.50	4.45
VI	OCH_3	OCH_3	CH_3	H	α-OCH_3[e]	183–186	2.5	1550 1620	292 (7200) (sh) 323 (16,000)	4.68 d[f]		4.5[g]	$C_{17}H_{21}NO_4$	67.31	6.98	4.62	67.25	7.06	4.90
VII	OCH_3	OCH_3	CH_3	H	β-OCH_3	166–168	16.5	1550 1635	290 (6150) 324 (14,000)	4.68 d	12		$C_{17}H_{21}NO_4$	67.31	6.98	4.62	67.02	7.20	4.65
VIII	OCH_3	OCH_3	CH_3	CH_3	H	169–172	68	1540 1600	285 (5320) 335 (15,700)	4.53 q	14	5	$C_{17}H_{21}NO_3$	71.06	7.37	4.87	71.29	7.55	4.63
IX	OCH_3	OCH_3	CH_3	C_2H_5	H	176–179	54	1550 1610	286 (4850) 333 (14,200)		Nd		$C_{18}H_{23}NO_3$	71.73	7.69	4.65	72.02	7.81	4.51
X	OCH_3	OCH_3	CH_3	C_3H_7	H	138–139	65	1550 1625	285 (5000) 334 (14,900)	4.53 q	14	5	$C_{19}H_{23}NO_3$	72.35	7.99	4.44	72.63	8.23	4.35
XI	OCH_3	OCH_3	CH_3	*n*-Bu	H	107–110	33	1545 1610	285 (4900) 334 (14,900)		Nd		$C_{20}H_{27}NO_3$	72.92	8.26	4.25	73.18	8.40	4.45
XII	OCH_3	OCH_3	CH_3	*i*-Bu	H	126–130	50	1535 1610	286 (5000) 333 (14,500)		Nd		$C_{20}H_{27}NO_3$	72.92	8.26	4.25	72.93	8.48	4.34
XIII	OCH_3	OCH_3	CH_3	C_5H_{11}	H	129–131	52	1545 1615	287 (5050) 335 (15,100)	4.54 q	14	5	$C_{21}H_{22}NO_3$	73.43	8.51	4.08	73.22	8.67	4.02

[a] Additional bands at lower wavelengths, characteristic of the respective aromatic chromophores, are not included. [b] q = quartet. [c] Nd = not determined. [d] sh = shoulder. [e] The prefixes α and β are used in analogy to steroid convention, β meaning on the same side as the angular hydrogen and α meaning on the opposite side. (See E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 89.) [f] d = doublet. [g] Band width at half-peak height.

TABLE II

PHYSICAL AND ANALYTICAL PROPERTIES OF 13H-DIBENZO[a,f]QUINOLIZIN-13-ONES AND RELATED COMPOUNDS[a-f]



Compd	R_1	R_2	R_5	Ring D	Mp, °C	Yield, %	$\nu_{C=O}$ cm^{-1}	λ_{max},[a] mμ (ε)	Angular proton, ppm	J, cps ax,ax	J, cps eq,ax	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
XIV[g]	H	H	H		171–173	55	1560 1620	333 (14,300)	4.57 q[b]	15	5	$C_{17}H_{19}NO$	80.60	7.56	5.53	80.44	7.55	5.78
XV	OCH_3	H	H		154–156	50	1545 1618	285 (3750) 333 (14,300)	4.55 q	14	5	$C_{18}H_{21}NO_2$	76.29	7.47	4.94	76.56	7.59	5.07
XVI	OCH_3	OCH_3	H		246–255	18	1565 1620	288 (5300) 330 (16,600)	4.66 q	14	5	$C_{18}H_{21}NO_3$	72.22	7.07	4.68	72.00	7.29	4.38
XVII	OCH_3	OCH_3	H		211–214	73	1555 1615	286 (5100) 332 (14,350)	4.53 q	14	5	$C_{19}H_{23}NO_3$	72.82	7.40	4.47	72.94	7.50	4.50
XVIII	OCH_3	OCH_3	H		186–188	38	1555 1620	286 (4750) 336 (14,700)		Nd[c]		$C_{20}H_{25}NO_3$	73.37	7.70	4.28	73.23	7.78	4.52
XIX	OCH_3	OCH_3	H		201–203	27	1525 1605 1640 1665	235 (18,500) 265 (14,300) 381 (7850)	4.62 q	13	6	$C_{20}H_{23}NO_2$	73.82	7.12	4.30	73.66	7.10	4.54
XX	OCH_3	OCH_3	H		193–196	85	1552 1618	285 (4950) 334 (13,000)		Nd		$C_{20}H_{25}NO_3$	73.37	7.70	4.28	73.53	7.84	4.18
XXI	OCH_3	OCH_3	β-CH_3[e]		142–143	37	1550 1610	287 (4680) 336 (13,000)	4.33 d[f]	9		$C_{20}H_{25}NO_3$	73.37	7.70	4.28	73.46	7.84	4.58
XXII	OCH_3	OCH_3	β-OCH_3		158–160	7	1545 1630	285 (4560) 339 (12,500)	4.57 d	11		$C_{20}H_{25}NO_4$	69.96	7.33	4.08	70.04	7.54	3.96
XXIII	H	H	H		186–189	13	1560 1630	328 (13,200)		Nd		$C_{23}H_{22}N_2O_2$	77.07	6.19	7.82	77.11	6.28	7.80
XXIV	OCH_3	OCH_3	H		203–208	20	1565 1627	287 (5690) 329 (13,750)		Nd		$C_{25}H_{26}N_2O_4$	71.75	6.26	6.69	71.86	6.50	6.95
XXV	OCH_3	OCH_3	H		227–231	55	1560 1612	290 (5600) 330 (14,000)		Nd		$C_{18}H_{22}N_2O_3$	68.77	7.05	8.91	68.94	7.16	9.17
XXVI	OCH_3	OCH_3	H		267–274	62	1510 1675	266 (15,750) 303 (19,200)	4.82 q	13	6	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	70.91	7.01	4.01

[a-f] See Table I for footnotes a–f. [g] The preparation of this compound (mp 170–171°) by method D (Figure 1) has been recently described[7] without preparative detail.

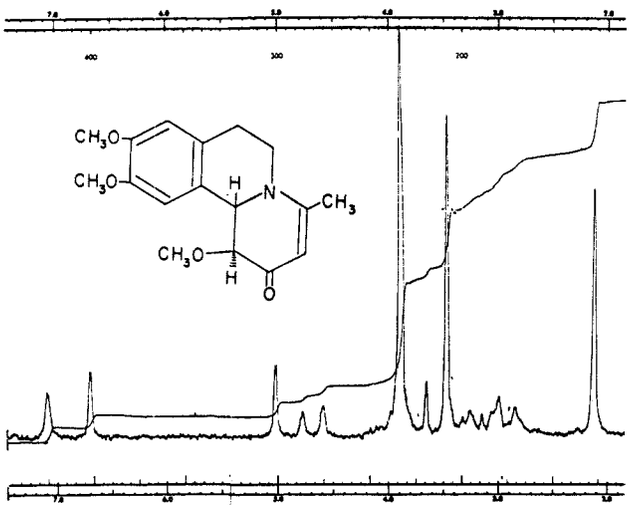
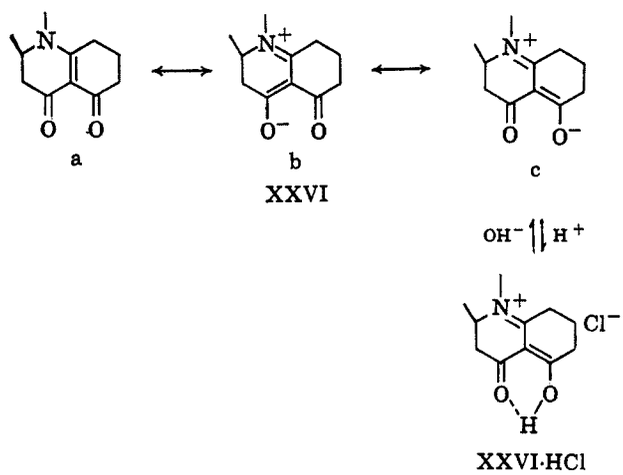


Figure 1.—The nmr spectrum of *trans*-1,6,7,11b-tetrahydro-1,9,10-trimethoxy-4-methyl-2H-benzo[*a*]quinolizin-2-one (VII).

shift, caused by the additional substituent, resembles the substitutional effects[19] on the location of the K band of α,β-unsaturated ketones. Substitution by a methoxy group at the methylene carbon next to the carbonyl (as in compounds II, VI, VII, and XXII) shifts the maximum by 4–6 mμ to longer wavelengths. The isoquinonaphthyridines XXIII–XXV, the phenyl-substituted benzo[*a*]quinolizine V, the ring-D unsaturated dibenzo[*a*,*f*]quinolizine XIX, and the dicarbonyl compound XXVI deviate from the above absorption patterns because of the modifying influence of an additional chromophore.

The infrared spectra display two strong bands in the 1530–1565- and 1610–1635-cm^{-1} regions which are considered to be indicative of a vinylogous amide moiety.[20]

The infrared spectrum of XXVI is markedly different from that of other vinylogous amides; instead of the bands at 1530–1565 and 1610–1635 cm^{-1}, it displays strong absorption at 1510 and 1677 cm^{-1}. This difference, coupled with the high melting point and low ethanol solubility of XXVI, suggests a strongly contributing dipolar resonance form (probably the *s-trans* form c) in which one C–O bond (presumably the one at 1510 cm^{-1}) has enhanced single-bond character and the other (1677 cm^{-1}) is ketonic in nature. While the infrared spectra of the ordinary vinylogous amides are not greatly affected by acid,[21] the hydrochloride of XXVI (not characterized but reconverted to XXVI upon treatment with base) has, in addition to the 1510-cm^{-1} peak, a band at 1578–1590 cm^{-1} (broad), in lieu of the 1677-cm^{-1} band, possibly due to hydrogen-bonded carbonyl (XXVI·HCl). The ultraviolet spectrum of XXVI does not greatly change with pH, the chromophoric group apparently being unaffected by O-protonation.[21]



The proton nmr spectra of the vinylogous lactams are in agreement with assigned structures. Those of the tricyclic compounds show the signal of the methyl group at C-4 in the 2.12–2.14-ppm region and that of the vinyl proton (when present) in the 5.02–5.10-ppm region. The most characteristic feature in all of the spectra is the resonance of the angular benzylic proton which occurs between 4.5 and 4.7 ppm, usually as a quartet (see Table I and II). Spectra of the compounds which are substituted at the methylene carbon next to the carbonyl (C-1 in VI and VII, C-12 in XXI and XXII) display this signal, depending on the dihedral angle,[22] as a doublet[23] (J = 9–12 cps; see, for example, Figure 1) or a broad band (width at half-height = 4.5 cps, Figure 2). The nmr evidence alone does not permit configuration assignments to these compounds, since opposite conclusions are reached depending whether ring C is considered to be in the half-boat or half-chair conformation.[24] The solution of this problem was sought by comparison of elimination rates of methanol from the epimers VI and VII. According to a well-established concept,[25] the *cis* epimer, having the CH_3O group and the 11b-H in a *trans* arrangement, would be expected to undergo ionic elimination with much greater ease than the *trans* epimer. Indeed, it was found that, on refluxing in methanol in the presence of base, isomer VI eliminated methanol to give XXVII at a rate which was at least 10 times as fast as that observed for isomer VII. The structure of XXVII was confirmed by an alternate synthesis, consisting of dehydrogenation of IV with mercuric acetate. Its characteristic ultraviolet spectrum [λ_{max}, mμ (ϵ), 217 (18,700), 237 (24,000), 257

(19) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 72, 76 (1942).

(20) G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).

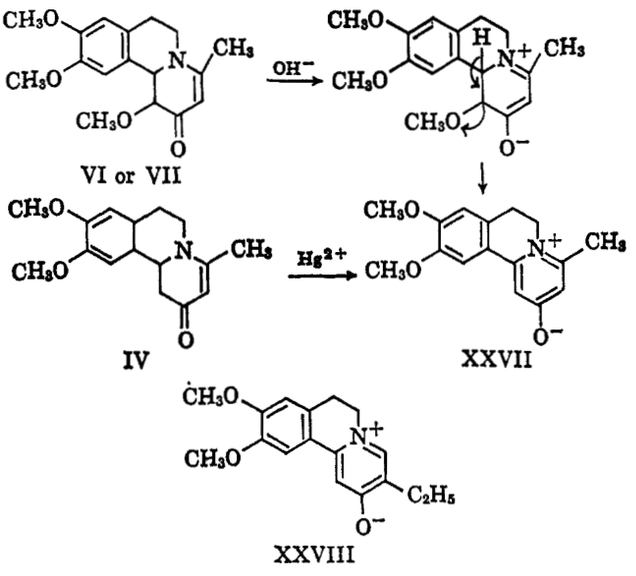
(21) The protonation of vinylogous amides takes place at the oxygen atom: (a) N. J. Leonard and J. A. Adamcik *J. Am. Chem. Soc.*, **81**, 595 (1959); (b) H. E. A. Kramer and R. Gomper, *Tetrahedron Letters*, 969 (1963); (c) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965).

(22) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

(23) The corresponding doublet of the hydrogen on the carbon bearing the methoxy group (H-1) can be seen at 3.53 ppm in the 100-Mc spectrum only. The 60-Mc spectrum of VII (Figure 1) displays, however, one-half of this signal at 3.67 ppm, the other half being buried under the aliphatic methoxy group. Comparison of the spectra of VI and VII (Figures 1 and 2) shows that this signal shifts from 3.53 ppm in VII (H-1, axial) to 3.50 in VI (H-1, equatorial). This observation is in line with the frequent experience that an axial proton adjacent to a carbonyl group in a cyclohexanone ring will appear at a downfield position relative to its equatorial counterpart. See, for example, N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Am. Chem. Soc.*, **87**, 302 (1965).

(24) Study of the models suggests that only small energy difference exists between the possible conformations of ring C. While little is known about the conformation of such systems, it has been reported that 1,3-cyclohexadiene appears to exist in the half-chair form: (a) A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4661 (1961); (b) A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *ibid.*, **83**, 4660 (1961).

(25) For a recent review of the application of elimination reactions to configurational studies, see B. Belleau and S. McLean, "Elucidation of Structures by Physical and Chemical Methods," Part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 921.



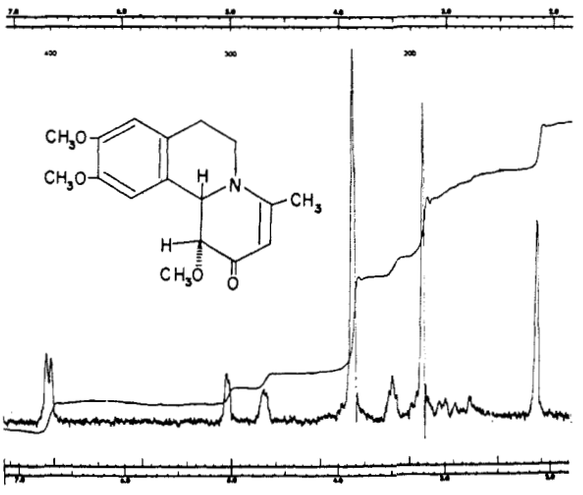


Figure 2.—The nmr spectrum of *cis*-1,6,7,11b-tetrahydro-1,9,10-trimethoxy-4-methyl-2H-benzo[*a*]quinolizin-2-one (VI).

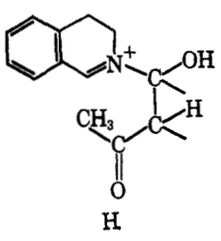
(23,200), and 313 (17,200)] closely resembles the spectrum recorded for XXVIII by Brossi, *et al.*[2]

The assignment of the *cis* configuration to the isomer VI and the *trans* configuration to the isomer VII, on the basis of the above-presented chemical evidence, permitted the determination of the conformation of both isomers from their nmr spectra. The "large" coupling constant of 12 cps of the doublet at 4.68 ppm in compound VII is compatible only with the *trans*-diaxial arrangement of two hydrogens (H-11b, H-1) as found in the half-chair conformation of ring C. The band width at half-peak height of 4.5 cps shown by the 4.68-ppm band in the spectrum of VI indicates a *gauche* arrangement of the half-chair conformation. The tetracyclic compounds XXI and XXII are presumably also in the half-chair conformation, since the addition of the fourth ring would not appear to alter the relative conformational stabilities of the parent tricyclic vinylogous lactam system. The observed "large" coupling constant (9 cps for XXI and 11 cps for XXII) of the angular protons would then indicate the *trans* configuration for both compounds. The proximity of the pseudo-equatorial methoxy group to the aromatic nucleus in compounds VII and XXII is reflected in the downfield shift (7.03 ppm for VII and 7.08 ppm for XXII) of the aromatic proton at C-11.[26] Spectra of the unsubstituted compounds, as well as those of VI and XXI, substituted by a pseudo-axial methoxy group and a methyl group, respectively, display this band together with the second aromatic proton signal in the 6.65–6.75-ppm region.

With two exceptions, all of the β-diketones used as starting materials in this investigation are known compounds. The two new diketones, 2-(methoxyacetyl)cyclohexanone (XXIX) and 3-acetyl-N-benzoyl-4-piperidone (XXX), were prepared by acylation of cyclohexanone pyrrolidine enamine[27] with methoxyacetic anhydride[28] and by acylation of N-benzoyl-4-piperidone pyrrolidine enamine (not isolated) with acetic anhydride. Condensation of XXX with 3,4-dihydroisoquinoline and its 6,7-dimethoxy derivative led to the diaza-D-homosteroid derivatives XXIII, XXIV, and XXV. The latter was prepared by hydrolysis of XXIV.

1,2,7,11b-Tetrahydro-9,10-dimethoxy-3-methyl-6H-dibenzo[*a*,*f*]quinolizin-13(12H)-one (XIX) was obtained not only from 6-acetyl-3-methyl-2-cyclohexen-1-one but also (in lesser yield) from 3-acetyl-2,6-heptanedione by condensation with 6,7-dimethoxy-3,4-dihydroisoquinoline. Hydrogenation of the double bond in the cyclohexadiene ring of XIX gave the hexahydro derivative XX.

The principal question with regard to the mechanism of the present quinolizidine synthesis is whether attachment of the diketone takes place initially at the nitrogen atom or at the carbon atom of the dihydroisoquinoline. (A simultaneous attack appeared most unlikely on *a priori* grounds of entropy.) The analogous question has been recently raised[29] in connection with the reaction of dihydroisoquinoline with α,β-unsaturated ketones; in that case, isolation of enammonium salt adduct (type A) indicates primary reaction at nitrogen. In contrast, in the present work, ultraviolet analysis of the progress of the reaction suggests the absence of an analogous intermediate in appreciable concentration, as evidenced by lack of absorption bands above 332 mμ (immonium ions of type A absorb in the region of 362 mμ). Thus, there can be no appreciable stationary state concentration of an intermediate of type H or its dehydration product.



H

The following alternatives are consistent with this finding. (1) H is an intermediate but cyclizes very rapidly. (2) H is an intermediate formed in a highly unfavorable reversible equilibrium process which greatly

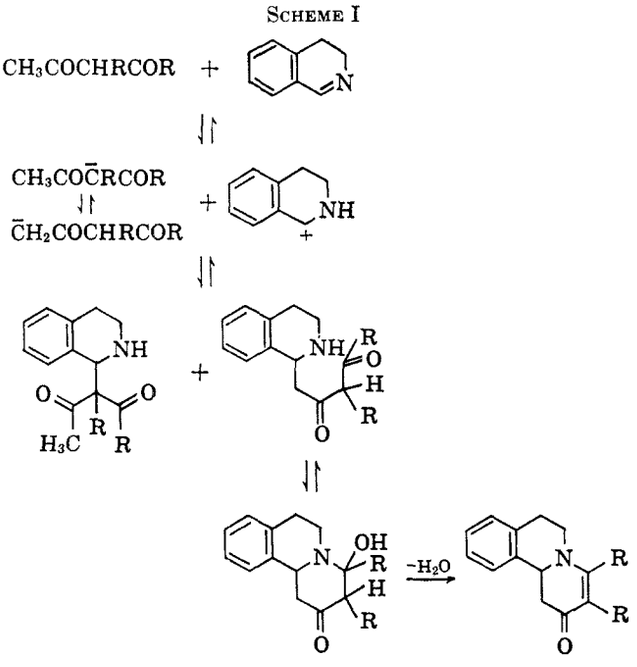
(26) A similar effect of the methylenedioxy group upon an aromatic proton in dicentrine has been observed by S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.*, 306 (1958).

(27) G. Stork, A. Brizzolara, J. Szmuszkovicz, and R. Terrel, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(28) C. J. Malm and C. R. Fordyce, U. S. Patent 2,017,182 (1935).

(29) C. Szantay and J. Rohaly, *Chem. Ber.*, **98**, 557 (1965).

SCHEME I



favors the starting material. (3) H is not an intermediate, but the reaction proceeds by primary addition at carbon (Scheme I).

The pH dependence (similarly to the Mannich reaction,[30] the condensation is strongly retarded by alkali and completely inhibited by strong acid) and the solvent dependence of the reaction (no reaction in benzene and ether, rate increases with solvent polarity: ethanol < dimethyl sulfoxide < water)[31] are most clearly compatible with mechanism 3 (Scheme I) which we consider the most likely at the present time.

Experimental Section

Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared 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 the Varian A-60 spectrometer with tetramethylsilane as an internal standard. Thin layer chromatography 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. The drying agent used throughout was Na_2SO_4.

General Procedure.—A solution of 0.1 mole of a 3,4-dihydroisoquinoline and 0.1 mole of a β-diketone in 100 ml of ethanol was refluxed for 72 hr (25 min for XXVI). After cooling, the crystalline product was filtered off, washed with cold absolute ethanol, and recrystallized for analysis from ethanol or ethyl acetate.

2-(Methoxyacetyl)cyclohexanone (XXIX).—A solution of 10 g of cyclohexanone pyrrolidine enamine[27] and 12 g of methoxyacetic acid anhydride[28] in 25 ml of dioxane was allowed to stand at 25–30° for 18 hr. The mixture was treated with 5 ml of water, refluxed for 30 min, and concentrated *in vacuo*. The oily residue was extracted with four 50-ml portions of ether. The combined extracts were dried and, after evaporation of the solvent, distilled *in vacuo:* yield 3 g (25%); bp 143–145° (19 mm); λ_{max}, mμ (ε), 288 (8350); ν_{max} 1120, 1190, 1590, 1625 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.38; H, 8.30.

3-Acetyl-N-benzoyl-4-piperidone (XXX).—A solution of 19 g of N-benzoyl-4-piperidone and 13.5 g. of pyrrolidine in 500 ml of benzene was refluxed with azeotropic water entrainment through a Dean–Stark trap for 18 hr. Benzene and excess pyrrolidine were removed *in vacuo* and the remaining gum was dissolved in 125 ml of dioxane. Acetic anhydride (19 ml) was added and the solution was allowed to stand overnight, treated with 19 ml of water, refluxed for 30 min, and evaporated *in vacuo*. The residue was extracted with ether and the combined extracts were washed with 5% HCl, dried, and evaporated to give 9 g (37%) of oily residue which crystallized on prolonged standing. The analytical sample was obtained by recrystallization from ethanol: mp 84–86.5°; λ_{max}, mμ (ε), 283 (8100); ν_{max} 710, 1250, 1580, 1600, 1630 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.31; H, 6.46; N, 5.91.

1,6,7,11b-Tetrahydro-1,9,10-trimethoxy-4-methyl-2H-benzo[*a*]quinolizin-2-ones (VI and VII).—A solution of 38.2 g (0.2 mole) of 6,7-dimethoxy-3,4-dihydroisoquinoline and 26 g (0.2 mole) of methoxyacetylacetone in 200 ml of absolute ethanol was refluxed for 96 hr and evaporated *in vacuo*. The solution of the residual gum in boiling ethyl acetate was treated with charcoal and filtered. On cooling, 30 g of crystalline product was obtained: mp 142–180°. This was dissolved in 2 l of warm ethyl acetate and passed through a 700-g activated magnesium silicate ("Florisil") column using ethyl acetate as the eluent. The first fractions gave 1.6 g of the *cis* isomer VI (OCH_3 is axial and *trans* to the angular hydrogen), and the later fractions yielded 11 g of the *trans* isomer VII (OCH_3 is equatorial and *cis* to the angular hydrogen).

1,2,3,4,7,11b-Hexahydro-9,10-dimethoxy-6H-dibenzo[*a*,*f*]quinolizin-13(12H)-one (XVII). Alternate Method.—A mixture of 0.6 g of ethyl 6,7-dimethoxyisoquinolinylacetate and 2 ml of cyclohexanone was refluxed for 3 hr. The solvent was removed with the aid of a stream of nitrogen, and after trituration with ether, the residue was recrystallized from ethanol.

1,2,7,11b-Tetrahydro-9,10-dimethoxy-3-methyl-6H-dibenzo[*a*,*f*]quinolizin-13(12H)-one (XIX). Alternate Method.—A mixture of 0.95 g (0.005 mole) of 6,7-dimethoxy-3,4-dihydroisoquinoline and 0.85 g (0.0053 mole) of 3-acetyl-2,6-heptanedione in 25 ml of water was refluxed for 22 hr, cooled, and extracted with chloroform. The extracts were washed with dilute NaOH, dried, and evaporated *in vacuo*. The residue crystallized from ethyl acetate.

1,2,3,4,7,11b-Hexahydro-9,10-dimethoxy-3-methyl-6H-dibenzo[*a*,*f*]quinolizin-13(12H)-one (XX).—A solution of 0.5 g of XIX in 50 ml of absolute ethanol was hydrogenated at room temperature and 1 atm in the presence of 150 mg of 10% palladium on carbon. The mixture was filtered and the filtrate was evaporated. The crystalline residue was recrystallized from ethanol.

2,3,4,6,7,11b,12,13-Octahydro-9,10-dimethoxy-1H-isoquino[2,1-*a*][1,6]naphthyridin-13-one (XXV).—A suspension of 5.5 g of XXIV in 250 ml of 3 *N* HCl was refluxed for 3 hr. The solution was cooled and the precipitated benzoic acid was removed by filtration. The filtrate was washed with three 100-ml portions of ether and made basic to pH 12 with 40% KOH in the cold. The precipitate was filtered off, washed with water, and recrystallized from acetonitrile.

6,7-Dihydro-2-hydroxy-9,10-dimethoxy-4-methylbenzo[*a*]quinolizinium Hydroxide Inner Salt (XXVII). A. Dehydrogenation of IV.—A mixture of 1 g of IV and 5.08 g of mercuric acetate in 80 ml of 5% acetic acid was heated on a steam bath for 4 hr, chilled, and filtered. The filtrate was brought to boiling, saturated with H_2S, cooled, treated with a few drops of concentrated HCl, and filtered. The filtrate was adjusted to pH 8 with concentrated NH_4OH and extracted several times with chloroform. Combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The crystalline residue was recrystallized from CH_3CN, and dried *in vacuo* for 24 hr at 140°: mp 254–256°; yield 0.2 g (20%); λ_{max}, mμ (ε), 217 (18,700), 237 (24,000), 257 (23,200), 313 (17,200); ν_{max} 1150, 1210, 1260, 1510, 1550, 1600, 1630 cm^{-1}.

(30) E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949).

(31) In practical application, however, the gain in reaction time resulting from the use of a more polar solvent is outweighed by mechanical difficulties such as the removal of dimethyl sulfoxide and the insolubility of some of the reactants in water. For example, the use of water in place of ethanol in the preparation of XVII caused a 25% decrease in yield.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.94; H, 6.22; N, 5.41.

B. Elimination of CH_3OH from VI and VII.—A solution of 0.1 g of VI in 10 ml of methanol and an analogous solution of VII were each treated with 0.2 g of Na_2CO_3 and allowed to stand at room temperature. After 2 hr, analysis by thin layer chromatography (silica gel G, 2:1 acetone–benzene) indicated 50% conversion of VI into XXVII and less than 5% of the corresponding conversion of VII. Sodium ethoxide (0.1 g) was added to the mixtures and the reactions were completed by refluxing the solution of VI for 10 min and that of VII for 3.5 hr. The mixtures were concentrated under a stream of nitrogen, diluted with cold water, neutralized, and extracted with chloroform. The extracts were dried and evaporated to give crystalline residues which were recrystallized from acetonitrile. Both products were found to possess identical melting points, ultraviolet, infrared, and pmr spectra with the compound XXVII prepared by the above described mercuric acetate dehydrogenation of IV.

Study of the Solvent and pH Dependence of the Reaction of 6,7-Dimethoxy-3,4-dihydroisoquinoline with 2-Acetylcyclohexanone.—Mixtures of 0.96 g of 6,7-dimethoxy-3,4-dihydroisoquinoline and 0.7 g of 2-acetylcyclohexanone were dissolved in 10 ml each of (a) water, (b) dimethyl sulfoxide, (c) ethanol, (d) benzene, (e) 2% NaOH, (f) 1 *N* HCl, and (g) 1 *N* acetic acid, and the batches were heated to 78–82° (a variation of batch d was provided with a Dean–Stark trap for possible azeotropic water entrainment). Samples taken from the vigorously stirred reaction mixtures after 2, 4, and 24 hr were analyzed by thin layer chromatography using silica gel G and benzene–acetone (1:1) mixture. The progress of the reactions was estimated by a visual comparison of the intensities of the product spot (R_f 0.49).

Acknowledgment.—We wish to thank Professor E. L. Eliel for his helpful discussions. The authors are indebted to Mr. C. Puchalski and Mr. A. Caro for technical assistance in the phase of this work concerned with structure proof and reaction mechanism. We wish to express our gratitude to Mr. A. Lewis and his associates, Mrs. U. Zeek, Mr. R. Puchalski, and Mr. R. DeSimone, for analytical and spectral data. We thank Dr. A. W. Ruddy and his associates, Messrs. F. McMillan, R. Novack, and O. Kukla, for large-scale preparation of intermediates.

3-Aryl-1,2-dihydroquinoxalines

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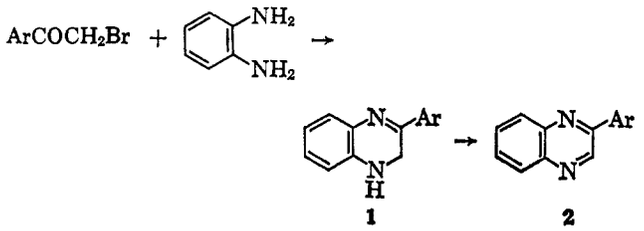
Under sufficiently mild conditions, 2-haloacetophenones react with *o*-phenylenediamine to give 3-aryl-1,2-dihydroquinoxalines in good yield. The structure of these compounds is established by acetylation, oxidation to quinoxalines, and physical methods.

Hinsberg[1,2] reported that 2-bromoacetophenone gave directly 2-arylquinoxalines (**2**) in reaction with *o*-phenylenediamine or *m*-toluylenediamine in boiling alcohol. He suggested that the dihydroquinoxaline

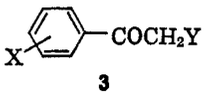


1 **2**

(**1**) was an intermediate product readily oxidized by air to the corresponding quinoxaline (**2**). Buu-Hoï and Khoi[3] reported quantitative yields of 2-arylquinoxalines (**2**) directly from the reaction of 2-bromo-3′-nitroacetophenone and 2-bromo-4′-nitroacetophenone with *o*-phenylenediamine in the presence of sodium acetate under conditions of gentle warming. In an attempt to repeat Buu-Hoï's procedure, it has been found that the dihydroquinoxalines (**1**) may be obtained in good yield if reaction is allowed to occur at room temperature, preferably under a nitrogen atmosphere. Compounds of this type have been previously prepared by partial reduction of 2,3-diphenylquinoxaline or by condensation of benzoin with *o*-phenylenediamine.[4]

(1) O. Hinsberg, *Ann.*, **237**, 327 (1887).
(2) O. Hinsberg, *ibid.*, **292**, 245 (1896).
(3) N. P. Buu-Hoï and N. H. Khoi, *Bull. Soc. Chim. France*, **15**, 753 (1950).
(4) Y. T. Pratt, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 485 ff.

Substituted α-haloacetophenones (**3**, X = H, 4-OCH_3, 4-Br, 4-NO_2, and Y = Br; X = 3-NO_2 and Y = Cl) were allowed to react with *o*-phenylenediamine to give dihydroquinoxalines corresponding to structure **1**. The assigned structure is supported by several pieces of evidence: the dihydroquinoxalines give monoacetyl derivatives with acetic anhydride (see Table I), indicating the presence of one reactive N–H group; they are readily oxidized by a variety of agents (see Experimental Section) to quinoxalines; they show an absorption band in the infrared region at 3300–3400 cm^{-1}, characteristic of the N–H group. The infrared absorption band disappeared after acetylation or oxidation of the dihydro compounds.



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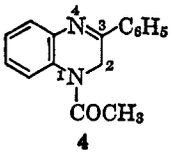
The nmr spectra of 3-phenyl-1,2-dihydroquinoxaline (**1**, Ar = C_6H_5) and its acetyl derivative (**4**) are in



4

agreement with the assigned structures. In particular both spectra contain peaks characteristic of the methylene protons at C-2 (3-phenyl-1,2-dihydroquinoxaline, singlet at δ = 4.44 ppm; 1-acetyl-3-phenyl-1,2-dihydroquinoxaline, singlet at 4.82 ppm), verifying the assignment of the double bond in the