20.9 ml (0.4 mole) of sulfuric acid (sp. gr. 1.87 g/ml)], and the mixture was stirred at 0-5°C for 3 h. It was then poured over ice, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized from toluene to give 1.6 g of trinitrobenzo[g]isoquinoline XI. The aqueous solution was neutralized (pH 10) with sodium carbonate, and the resulting precipitate was washed with water, dried, and crystallized from benzene to give 0.15 g of dinitrobenzo[g]isoquinoline XII.

Data on VII-XIII are presented in Tables 1 and 2.

LITERATURE CITED

1. I. Braun and I. Nelles, Chem. Ber., 70, 1760 (1937).
2. I. Lindner and M. Stanfer, Monatsh. Chem., 40, 231 (1926).
3. N. S. Prostakov, L. M. Kirillova, Dharvar Phalgumani, L. A. Shakhparonova, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 6, 1068 (1967).
4. N. S. Prostakov and V. V. Dorogov, Khim. Geterotsikl. Soedin., No. 3, 373 (1971).
5. N. S. Prostakov, V. I. Kuznetsov, V. F. Zakharov, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 8, 1077 (1976).
6. N. S. Prostakov, V. I. Kuznetsov, and H. Datta Rai, Khim. Geterotsikl. Soedin., No. 5, 673 (1980).
7. M. J. C. Dewar and N. Trinajstic, J. Chem. Soc., A, No. 9, 1220 (1971).

SYNTHESIS AND STEREOCHEMISTRY OF BENZO[a]CYCLOHEXANO[f]QUINOLIZIDINES OF THE 8-AZA-D-HOMOESTRANE SERIES

E. N. Rozhkov, B. I. Bryantsev,
E. P. Prokof'ev, A. Ya. Strakov,
and A. M. Moiseenkov

UDC 547.837:541.63

A mixture of trans,anti, cis- and cis,anti,cis-quinolizidines in a ratio of ∿1:4, respectively, was obtained (in ∿10% yield) in the thermal condensation of 4-methyl-4-acetylcyclohex-2-en-1-one with 3,4-dihydroisoquinoline.

Recently in a preliminary communication [1] we described the simple synthesis of analogs of 8-aza-D-homoestrane that contain a methyl substituent attached to C_{13} by means of the thermal condensation of cyclohexenone (I) with 3,4-dihydroisoquinoline (II) (to give the product in ∿10% yield). We also accomplished this reaction at a pressure of 14000 atm [2], which made it possible to increase the yields of the desired products significantly. In all cases stereoisomers Va, b are formed in a ratio of 1:4, which evidently reflects the difference in the ease with which the plane of the immonium fragment in intermediate IV, which arises from initial betaine III [1], undergoes attack by the acetyl carbanion. The results of a study of the structures and stereochemistries of the indicated isomers are examined in the present communication.

It follows from the data from the IR and ^{1}H NMR spectra that benzo[a]cyclohexano[f]quinolizidines Va, b have different stereochemistries, which are due primarily to differences in the fusion of the B and C rings. Thus, in conformity with the known criterion [3, 4], trans-B/C fusion should be assigned to minor reaction product Va, since intense Bohlmann bands at 2760 and 2810 cm^{-1} are present in its IR spectrum, while a resonance signal (the X part of the ABX spectrum) of the benzyl 11b-H proton is found at 3.71 ppm (in $CDCl_3$). Bohlmann bands are absent in the IR spectrum of preponderant isomer Vb, and the signal of the benzyl proton has a chemical shift of 4.16 ppm (in $CDCl_3$); this indicates cis-B/C fusion in this isomer. It is apparent from the data in Table 1 that the vicinal

---

Riga Polytechnic Institute, Riga 226355. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1662-1668, December, 1981. Original article submitted December 29, 1980.

0009-3122/81/1712-1220$07.50

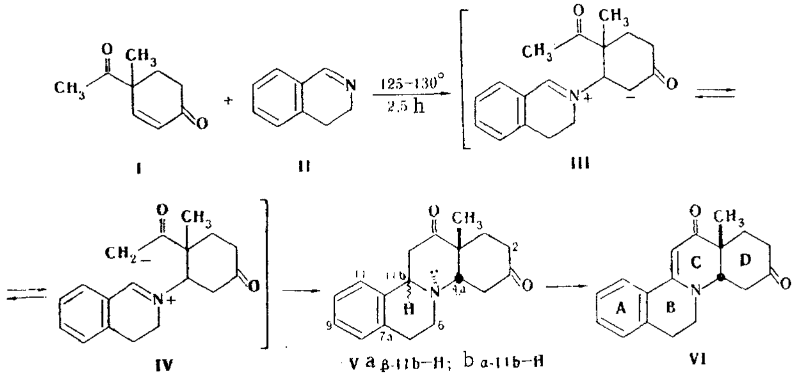
TABLE 1. Parameters of the ^1H NMR Spectra of Va, b in C_6D_6

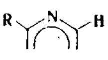
Proton *	Va		Vb	
	δ, ppm	J, Hz *, †	δ, ppm	J, Hz *, †
1 (*a*)	2,18	15,0 [2 (*a*), 2 (*e*)]; 12,5 [1 (*a*), 1 (*e*)]; 12,5 [1 (*a*), 2 (*a*)]; 7,0 [1 (*e*), 2 (*a*)]; 5,5 [1 (*a*), 2 (*e*)]; 2,0 [1 (*e*), 2 (*e*)]; 2,0 [1 (*e*), 4a (*e*)]; 2,0 [2 (*e*), 4 (*e*)]	0,81	14,0 [2 (*a*), 2 (*e*)]; 13,5 [1 (*a*), 1 (*e*)]; 13,5 [1 (*a*), 2 (*a*)]; 6,5 [1 (*e*), 2 (*a*)]; 5,0 [1 (*a*), 2 (*e*)]; 2,5 [1 (*e*), 2 (*e*)]; 2,0 [2 (*e*), 4 (*e*)]
1 (*e*)	0,96		2,30	
2 (*a*)	1,81		2,42	
2 (*e*)	1,99		2,04	
4 (*a*)	1,98	15,0 [4 (*a*), 4 (*e*)]; 4,0 [4 (*a*), 4a (*e*)]; 3,0 [4 (*e*), 4a (*e*)]; 6,0 (broad lines)	1,93	13,0 [4 (*a*), 4 (*e*)]; 12,5 [4 (*a*), 4a (*a*)]; 4,5 [4 (*e*), 4a (*a*)]
4 (*e*)	2,35		2,11	
4a ‡	2,11		2,66	
6 (*qa*)	1,69	16,0 [7 (*qa*), 7 (*qe*)]; 12,0 [6 (*qa*), 7 (*qa*)]; 11,0 [6 (*qa*), 6 (*qe*)]; 5,0 [6 (*qe*), 7 (*qa*)]; 3,0 [6 (*qa*), 7 (*qe*)]; 2,5 [6 (*qe*), 7 (*qe*)]	2,19	16,0 [7 (*qa*), 7 (*qe*)]; 12,0 [6 (*qa*), 6 (*qe*)]; 12,0 [6 (*qa*), 7 (*qa*)]; 6,0 [6 (*qe*), 7 (*qa*)]; 4,0 [6 (*qa*), 7 (*qe*)]
6 (*qe*)	3,21		2,35—2,25	
7 (*qa*)	2,77		2,81	
7 (*qe*)	2,25		2,35—2,25	
11b (*a*)**	3,17	15,0 [12 (*a*), 12 (*e*)]; 11,5 [11b (*a*), 12 (*a*)]; 4,0 [11b (*a*), 12 (*e*)]	3,62	14,5 [12 (*a*), 12 (*e*)]; 11,5 [11b (*a*), 12 (*a*)]; 4,0 [11b (*a*), 12 (*e*)]
12 (*a*)	2,35		2,26	
12 (*e*)	2,65		2,60	
CH_3 ††	1,05	—	0,97	—

---

*The spatial orientation of the protons is indicated in parentheses. †The interacting protons are indicated in brackets. ‡Relative to the D ring, equatorial in Va and axial in Vb. **Relative to the C ring. ††Relative to the D ring, axial in Va and equatorial in Vb.

spin–spin coupling constant (SSCC) of this proton with respect to one of the protons attached to C_{12} in both isomers has a value of 11.5 Hz, which is characteristic for an axial–axial interaction. In the case of dehydrogenation with chloranil in refluxing tert-butyl alcohol both epimers of V are converted in high yield to the same vinylogous lactam VI; on the basis of the presence of an intense absorption band at 367 nm in its UV spectrum it may be assumed [5, 6] that cis-C/D fusion of the rings exists in VI and consequently in Va, b.





This assumption was confirmed by an analysis of the ^1H NMR spectra obtained for Va, b in solution in C_6D_6 at 360 MHz and in solution insolution in $CDCl_3$ at 200 MHz for the completely deuterated (at C_2, C_4, and C_{12}) derivatives of these compounds, as well as the ^{13}C NMR spectra in solution in $CDCl_3$ at 20.1 MHz. Various possible variants of the three-dimensional structures of these substances that follow from their molecular models were taken into account in the analysis of the spectral data.

In conformity with the types of spin–spin systems formed by the protons of V, for Va in the spectrum obtained at 360 MHz we isolated two spectra of a three-spin system (δ 3.17, 2.65, and 2.35 ppm and J = 15.0, 11.5, and 4.0 Hz; δ 2.35, 2.11, and 1.98 ppm and J = 15.0,

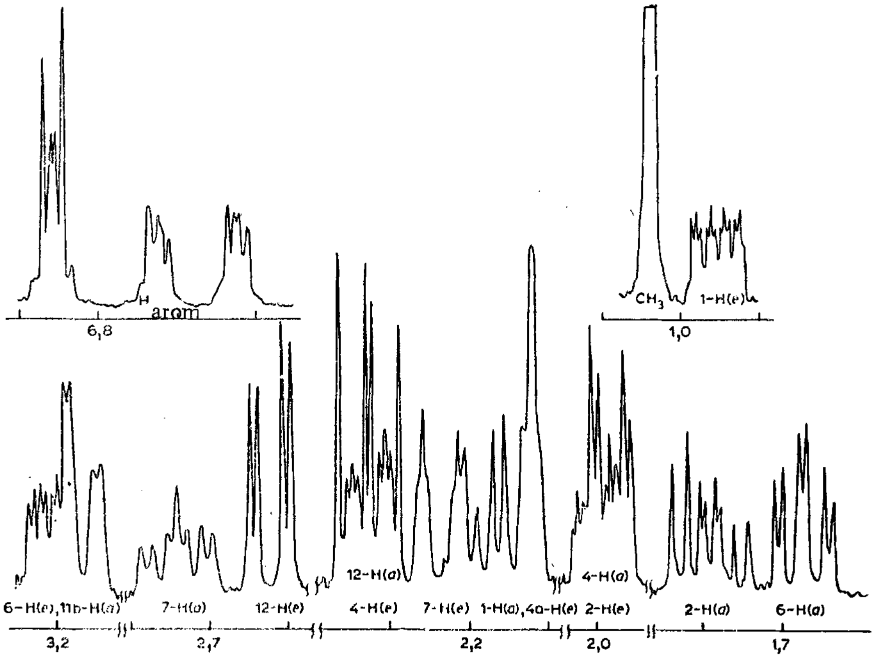


Fig. 1. ^1H NMR spectrum (360 MHz) of Va in C_6D_6.

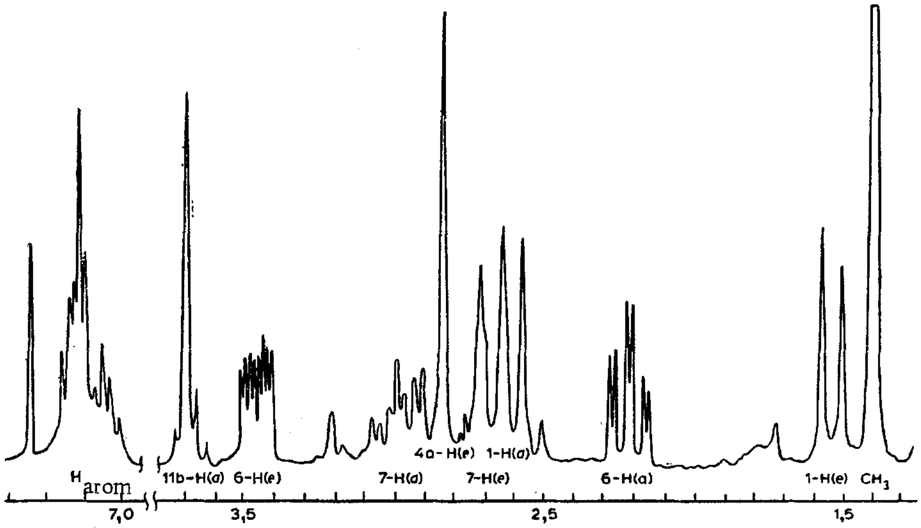


Fig. 2. ^1H NMR spectrum (200 MHz) of 2,2,4,4,12,12-hexadeutero-Va in $CDCl_3$.

4.0, and 3.0 Hz) and two spectra of a four-spin system (δ 2.18, 1.99, 1.81, and 0.96 ppm and J = 15.0, 12.5, 12.5, 7.0, 5.5, and 2.0 Hz; δ 3.21, 2.77, 2.25, and 1.69 ppm and J = 16.0, 12.0, 11.0, 5.0, 3.0, and 2.5 Hz) (Fig. 1 and Table 1). Taking into account the axial (relative to the C ring) orientation of the proton attached to C_{11b} [4], we assigned the first of the spectra of the three-spin system, in which two relatively large SSCC are observed, to the 11b (a), 12 (a), and 12 (e) protons and the second, in which there is only one such constant, to the 4 (a), 4 (e), and 4a protons. The definitive assignment within each of these two spectra, which is presented in Table 1, was made with allowance for the chemical shifts [4] and SSCC and a comparison with the spectrum of this compound after it was deuterated completely in the 2, 4, and 12 positions (Fig. 2).

The assignment presented in Table 1 shows that the proton attached to C_{4a}, the signal of which is a broad singlet with a width of ≈6 Hz, experiences equatorial—axial and equatorial—equatorial coupling with 4-H (a) and 4-H (e) (J = 4.0 and 3.0 Hz) and coupling through four σ bonds with 1-H (e) (J = 2.0 Hz). Thus 4a-H is equatorially oriented relative to the D ring, which, in conformity with the assumptions of conformational analysis,

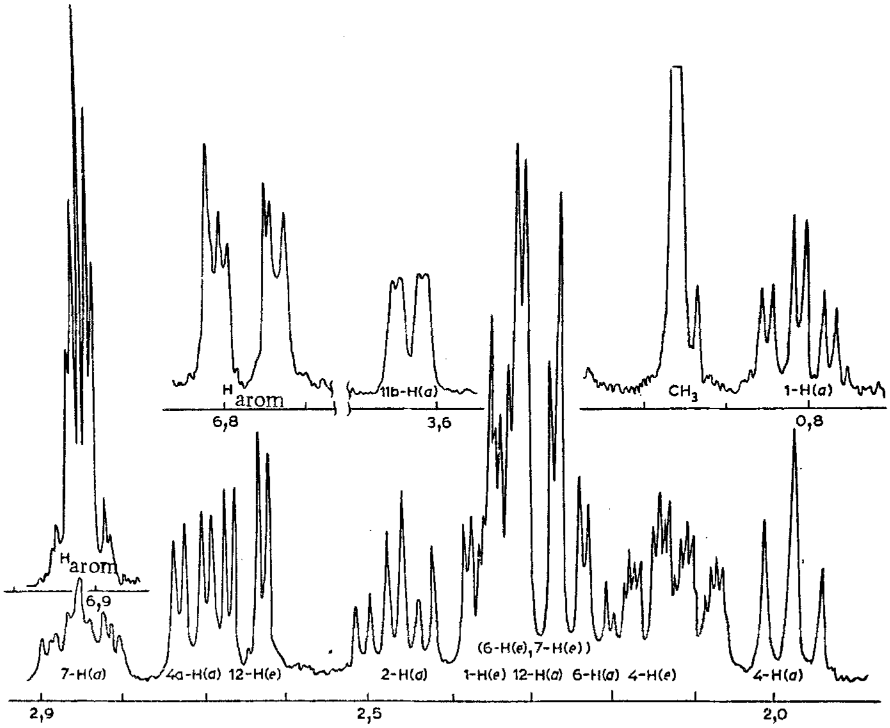


Fig. 3. ^1H NMR spectrum (360 MHz) of Vb in C_6D_6.

is a direct indication of cis-C/D fusion of the rings and simultaneously indicates an axial orientation of the methyl substituent relative to the same ring in the Va molecule.

The two four-spin systems were identified by comparison with the spectrum of the hexadeutero derivative of Va, in which the spectrum of the protons attached to C_1 and C_2 is simplified substantially, which simultaneously made it possible to assign the signals of the 1-H (a), 1-H (e), 2-H (a), and 2-H (e) protons. Within the second four-spin system the signals of the protons attached to C_7 are easily detected from the large value of the geminal SSCC [7] and the broadening of the signal of the pseudoaxial proton due to allylic coupling with the proton of the aromatic ring.

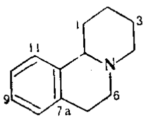
Two spectra of a three-spin system (δ 3.62, 2.60, and 2.26 ppm and J = 14.5, 11.5, and 4.0 Hz; δ 2.66, 2.11, and 1.93 ppm and J = 13.0, 12.5, and 4.5 Hz) and one spectrum of a four-spin system (δ 2.42, 2.30, 2.04, and 0.81 ppm and J = 14.0, 13.5, 13.5, 6.5, 5.0, and 2.5 Hz) were isolated in the spectrum (Table 1 and Fig. 3) of isomer Vb. For the second four-spin system we were able to isolate only signals of axial protons (δ 2.81 ppm and J = 16.0, 12.0, and 6.0 Hz; δ 2.19 ppm and J = 12.0, 12.0, and 4.0 Hz); the signals of two equatorial protons are overlapped by other signals and, as demonstrated by the integral intensities, are found at 2.25-2.35 ppm.

The existence of an axial—axial SSCC in each three-spin system is apparent from the data presented above. Axial orientation of the proton attached to C_{4a} relative to the D ring hence follows unambiguously; for the established cis-C/D fusion in isomer Vb this means an equatorial orientation of the angular CH_3 group relative to the same ring. Taking into account the data obtained for isomer Va, we assigned the first of the spectra of the three-spin system to the 11b (a), 12 (a), and 12 (e) protons and the second to the 4 (a), 4 (e), and 4a (a) protons. The assignment of the signals within these spectra, which is presented in Table 1, was made by means of the chemical shifts [4] and the SSCC. The identification of the two four-spin systems and the assignment of the 1-H (a), 1-H (e), 2-H (a), and 2-H (e) signals were made on the basis of the chemical shifts and the SSCC. The existence of allylic coupling of the quasi-axial proton with the proton of the aromatic A ring, which is observed for the 7-H signal (qa), and the difference in the geminal SSCC [7] made it possible to distinguish 7-H (qa) from 6-H (qa).

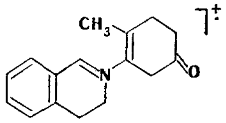
The V structures were confirmed by their ^{13}C NMR spectra. The chemical shifts (in $CDCl_3$) of the carbon atoms with an indication of the multiplicity of the lines obtained in the spectra with incomplete suppression of the ^{13}C—^1H spin—spin coupling are presented below for Vb: 26.4 (q, CH_3); 30.6 and 31.7 (t, C_1 and C_7); 37.7, 38.7, and 44.9 (t, C_2, C_4, and C_{12}); 48.8 (t, C_6); 50.3 (s, C_{13a}); 54.8 and 70.5 (d, C_{4a}, C_{11b}); 125.3 (d, C_{11}); 126.6 (d, C_{10}); 126.8 (d, C_9); 129.4 (d, C_8); 134.6 (s, C_{7a}); 137.6 (s, C_{11a}); 206.7 and 208.0 ppm (s, C_3, C_{13}). The ^{13}C NMR spectrum of the hexadeuterated (in the 2, 4, and 12 positions) analog of Vb, in which the C_2, C_4, and C_{12} signals are absent, made it possible to distinguish from them the C_1, C_6, and C_7 signals. The assignment of C_6 is confirmed by the data in [8, 9], according to which this carbon atom has δ values below 46 ppm for all of the investigated benzo[a]quinolizidines with cis-B/C fusion. The assignment of the carbon atoms of the aromatic A ring was made with allowance for known (for benzo[a]quinolizidine VII) values of the chemical shifts of the analogous atoms, which, for C_{7a}, C_8, C_9, C_{10}, C_{11}, and C_{11a}, are, respectively, 134.4, 128.7, 125.8, 125.5, 124.6, and 138.4 ppm [8].

Starting from the multiplicity of the signals, as well as from the data obtained for Vb, one can propose the following assignment of the lines in the ^{13}C NMR spectrum of stereoisomer Va: 18.2 (q, CH_3); 30.3 and 32.2 (t, C_1 and C_7); 37.3, 40.8, 45.3 or 45.5 (t, C_2, C_4, C_{12}); 45.5 or 45.3 (t, C_6); 49.6 (s, C_{13a}); 62.7 and 69.8 (d, C_{4a} and C_{11b}); 125.2 (d, C_{11}); 126.4 (d, C_{10}); 126.8 (d, C_9); 128.9 (d, C_8); 135.0 (s, C_{7a}); 137.0 (s, C_{11a}); 205.2 and 207.2 ppm (s, C_3 and C_{13}).

The significant decrease in the chemical shift of the carbon atom of the CH_3 group (by ∿8 ppm) on passing from Vb to stereoisomer Va is in good agreement with the above-expressed assertion of cis-C/D fusion, as well as the axial (relative to the D ring) orientation of the angular CH_3 group in Va and the equatorial orientation in Vb. It follows from an examination of the models that precisely in this three-dimensional structure the CH_3 group in Va experiences significant γ coupling with the axial protons attached to C_2 and C_4, while the CH_3 group in Vb experiences γ coupling with the axial proton attached to C_{12} and δ coupling with the protons attached to C_6. The existence of both couplings also evidently leads to the observed substantial difference in the chemical shifts of the CH_3 groups [10-12]. The ∿3.5 ppm decrease in the shielding of C_6 in the Vb molecule as compared with Va is also in agreement with their three-dimensional structures. In fact, in Va this carbon atom experiences only γ coupling with C_4, whereas in Vb, in addition to γ coupling with C_{12}, it should experience appreciable δ coupling with the CH_3 group, a consequence of which should be the above-noted deshielding [12].



VII



VIII

In conclusion, it should be noted that the mass spectra of the isomeric quinolizidines V and their hexadeutero derivatives constitute evidence for the extremely similar fragmentation patterns of these substances, which do not make it possible to form a reliable judgment regarding the fine peculiarities of their three-dimensional structures. The reason for this is the fact that the C_{11}–C_{12} bond undergoes preferred cleavage in both cases under electron impact. As a result, fragment VIII with m/z ($M^+ - 43$) is formed, evidently as a consequence of detachment of C_{12} and C_{13} together with a proton attached to C_{4a}.

We thank Professor O. S. Chizhov and A. S. Shashkov for their fruitful discussion of the material set forth above.

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ were obtained with a UR-10 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The ^1H NMR spectra of solutions of the compounds were recorded with Varian DA-60-IL (in $CDCl_3$), Bruker WH-360 (in C_6D_6), and Bruker WP-200 (hexadeuterated derivatives in $CDCl_3$) spectrometers with tetramethylsilane (TMS) as the standard. The ^{13}C NMR spectra were measured with a Bruker WP-80 spectrometer relative to TMS. The mass spectra were obtained with an LKB chromatographic mass spectrometer (with a glass capillary column filled with 1% SE-30).

trans,anti,cis- (Va) and cis,anti,cis-13aβ-Methyl-3,13-dioxo-2,3,4,4a,6,7,11b,12,13,13a-hexahydro-1H-dibenzo[a,f]quinolizine (Vb). A) A mixture of 0.46 g (3.5 mmole) of dihydroisoquinoline II and 0.67 g (4.4 mmole) of diketone I was heated in a sealed glass ampul in an oil bath at 125-130°C for 1.5 h, after which it was chromatographed on 50 g of SiO_2. Gradient elution with hexane—ether (up to 30% of the latter) gave 80 mg (8%) of Vb, 20 mg (2%) of Va, and 130 mg of unchanged I. Compound Va was obtained as colorless prisms with mp 153-155°C (from ether—hexane). IR spectrum: 1708 (CO); 2760, 2810 cm^{-1} (Bohlmann bands [3]). ^1H NMR spectrum (in $CDCl_3$): 1.42 (s, 3H, CH_3) and 3.71 ppm (dd, J_1 = 11.5, J_2 = 4.0 Hz, 1H, 11b-H). Found: C 76.0; H 7.5; N 5.0%; M 283. $C_{18}H_{21}NO_2$. Calculated: C 76.3; H 7.5; N 4.9%; M 283.4. Compound Vb was obtained as colorless prisms with mp 143-145°C (from ether—hexane). IR spectrum: 1707 cm^{-1} (CO). ^1H NMR spectrum (in $CDCl_3$): 1.42 (s, 3H, CH_3) and 4.16 ppm (dd, J_1 = 11.5, J_2 = 4.0 Hz, 1H, 11b-H). Found: C 76.2; H 7.5; N 4.6%; M 283. $C_{18}H_{21}NO_2$. Calculated: C 76.3; H 7.5; N 4.9%; M 283.4.

B) A solution of 0.15 g (0.99 mmole) of diketone I and 0.26 g (2.0 mmole) of dihydroisoquinoline II in 2 ml of acetonitrile was maintained at 80°C and 14,000 atm for 6 h, after which it was worked up as indicated above to give 90 mg (32%) of Vb and 22 mg (8%) of Va, which were identical to the samples described above with respect to their IR, mass, and ^1H NMR spectra. No melting-point depressions were observed for mixtures of samples of the products.

cis-13aβ-Methyl-3,13-dioxo-2,3,4,4a,6,7,13,13a-octahydro-1H-dibenzo[a,f]quinolizine (VI). A) A mixture of 0.1 g (0.4 mmole) of Va and 0.09 g (0.4 mmole) of chloranil in 10 ml of tert-butyl alcohol was refluxed for 1 h, after which the precipitate was removed by filtration and washed on the filter with tert-butyl alcohol. The alcohol was removed by distillation *in vacuo*, and the residue was chromatographed on 10 g of SiO_2. Gradient elution with hexane—ether (up to 90% of the latter) gave 80 mg (80%) of VI in the form of light-yellow prisms with mp 173-175°C (from tetrahydrofuran—hexane). IR spectrum: 1615, 1630 (C=CH—C=O); 1708 cm^{-1} (CO). UV spectrum, λ_{max}, nm (log ε): 207 (4.27), 262 (4.19), and 367 (4.09). ^1H NMR spectrum (in $CDCl_3$): 1.24 (s, 3H, CH_3) and 5.64 ppm (s, 1H, 12-H). Found: C 76.5; H 6.6; N 5.0%; M 281. $C_{18}H_{19}NO_2$. Calculated: C 76.8; H 6.8; N 5.0%; M 281.4.

B) A mixture of 0.21 g (0.74 mmole) of Vb and 0.18 g (0.74 mmole) of chloranil in 20 ml of tert-butyl alcohol was refluxed for 1 h, after which it was worked up as described above to give 0.18 g (85%) of VI, which was identical to the sample obtained from Va with respect to the IR, UV, mass, and ^1H NMR spectra. No melting-point depressions were observed for mixtures of the products.

2,2,4,4,12,12-Hexadeutero-Va. A mixture of 0.1 g (0.4 mmole) of Va, 2 mg (0.04 mmole) of sodium methoxide, and 4 ml of CD_3OD was heated at 50°C for 8 h, after which it was evaporated *in vacuo*. After two changes of the solvent and maintenance of the mixture under the indicated conditions, the reaction mixture was neutralized with 2 mg (0.02 mmole) of D_2SO_4 and evaporated *in vacuo*, and the residue was dissolved in 5 ml of $CHCl_3$. The solution was filtered, the filter was washed with 1 ml of $CHCl_3$, and the filtrate was evaporated *in vacuo* to give 80 mg (80%) of d_6-Va in the form of colorless crystals with mp 153-155°C. Found: M 289. $C_{18}H_{15}D_6NO_2$. Calculated: M 289.4.

2,2,4,4,12,12-Hexadeutero-Vb. This compound was similarly obtained (in 80% yield) as colorless crystals with mp 143-145°C. Found: M 289. $C_{18}H_{15}D_6NO_2$. Calculated: M 289.4.

LITERATURE CITED

1. A. M. Moiseenkov, E. N. Rozhkov, and A. Ya. Strakov, J. Prakt. Chem., 322, 554 (1980).
2. A. Ya. Strakov, E. N. Rozhkov, A. M. Moiseenkov, and B. S. Él'yanov, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 3, 372 (1980).
3. F. Bohlmann, Chem. Ber., 91, 2157 (1958).
4. M. Usković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, J. Am. Chem. Soc., 86, 3364 (1964).
5. R. Clarkson, J. Chem. Soc., No. 9, 4900 (1965).
6. C. Szántay, A. Vedres, and G. Tõth, Heterocycles, 6, 1793 (1977).
7. M. Barfield and D. M. Grant, J. Am. Chem. Soc., 85, 1899 (1963).
8. M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, Chem. Pharm. Bull., 26, 1168 (1978).
9. M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, Chem. Pharm. Bull., 26, 1901 (1978).
10. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
11. B. V. Cheney and D. M. Grant, J. Am. Chem. Soc., 89, 5319 (1967).
12. J. G. Batchelor, J. Magn. Reson., 18, 212 (1975).