bath. Recrystallization from ether gave a white powder, m.p. 138–139°.

Anal. Calcd. for $C_{27}H_{33}O_4P$: C, 71.6; H, 7.31; P, 6.86. Found: C, 72.2, 71.9; H, 7.58, 7.11; P, 6.75, 6.92.

Acknowledgment.—The author thanks Mr. Howard Margulies for technical assistance and Dr. John Lancaster for the n.m.r. spectra.

Some New Tricyclic Compounds Containing the Bispidine Moiety

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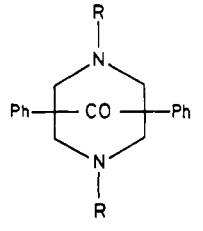
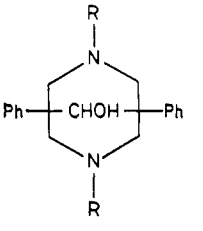
The reaction of 1,5-diphenyl-3,7-bis(chloroacetyl)-9-bispidinone (Ic) with ammonia and primary amines has resulted in the formation of a new series of triazatricyclotetradecanes (III). The tertiary amino nitrogen in the 4-position of the new ring system has been shown to be weakly basic. The same behavior of N-4 is observed with the tricyclic compounds, IV, obtained from the reaction of 1,5-diphenyl-3,7-bis(chloroacetyl)-9-bispidinol (IIb) with primary amines. This lack of basicity coupled with n.m.r. studies has permitted a conformational assignment of these tricyclic compounds.

Both the chemical and the pharmacological interest of compounds related to 1,5-diphenyl-9-bispidinone (Ia) and 1,5-diphenyl-9-bispidinol (IIa) have led us to undertake the synthesis of new substances belonging to this class of compounds. In a recent publication,[2] we described the synthesis of a series of 1,5-diphenyl-3,7-bis(aminoacetyl)-9-bispidinones from the reaction of the corresponding bis(chloroacetyl) compound, Ic, with secondary amines. These compounds displayed the expected physical and chemical properties of tertiary amines including solubility in weak acids and formation of bisquaternary salts.[3] However, when the corresponding reaction was carried out with ammonia or primary amines, the resulting products were only sparingly

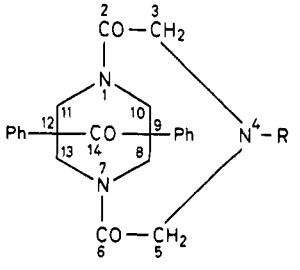


I a, R = H
b, R = $COCH_3$
c, R = $COCH_2Cl$

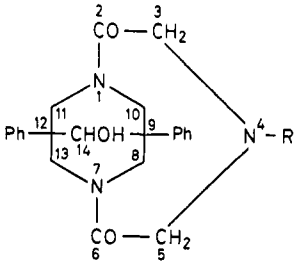


II a, R = H
b, R = $COCH_2Cl$

soluble in most organic solvents, melted or decomposed at temperatures about 250–300°, and displayed only weakly basic properties. These physical properties coupled with the microanalytical data and molecular weight determinations (see Table I) suggested the formation of the tricyclic system III.



III a, R = H; b, R = CH_3; c, R = C_2H_5; d, R = CH_2CH_2OH; e, R = $CH_2C_6H_5$; f, R = $COCH_3$



IV a, R = H; b, R = CH_3; c, R = C_2H_5; d, R = CH_2CH_2OH; e, R = $CH_2C_6H_5$; f, R = $COCH_3$

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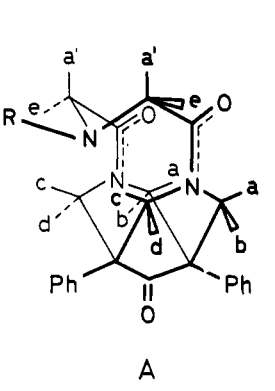
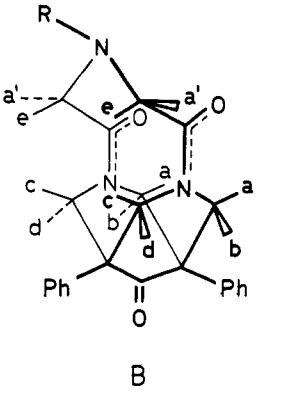
This new tricyclic system has a very rigid and compact steric structure. Dreiding models show that rotation is allowed only about the C-3–N-4–C-5 bridge resulting in two possible conformations, A and B. The tertiary amines, compounds IIIb–e, form hydrochlorides which hydrolyze immediately in the presence of water. Attempted preparation of the methiodide in Methyl Cellosolve with excess methyl iodide failed. These properties indicated that conformation A is preferred since axial substitution to form a quaternary salt should result in strong steric interaction with the two



A



B

H_c hydrogens. As expected, equatorial substitution, both alkylation and acylation, of the secondary amino function of compound IIIa was readily effected. Methylation with excess methyl iodide in refluxing Methyl Cellosolve gave as the exclusive product the same tertiary amine, IIIb, as was obtained by the cyclization reaction with methylamine. Acetylation under mild conditions led to the N-acetyl derivative, IIIf, in high yield. An examination of Dreiding models lends additional support to this assignment. The model of conformation B reveals a strong steric interaction between protons H_c and H_e which lie in the same plane at a calculated distance of 1.5 Å.

A close analysis of the n.m.r. spectrum[4] of compound IIIb (Figure 2) completely justifies the above interpretation. In order to better understand this spec-

(2) S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1253 (1958).

(3) S. Chiavarelli and G. Settimj, unpublished results.

(4) Spectra were taken in deuteriochloroform using a Varian Model A60 spectrometer. Decoupling experiments were performed with the Varian Model HR60 spectrometer. Tetramethylsilane (TMS) served as internal standard.

TABLE I

PREPARATIVE DATA OF 4-ALKYL-9,12-DIPHENYL-1,4,7-TRIAZATRICYCLO[5.3.3.1^{9,12}]TETRADECANE-2,6,14-TRIONES

Compd.	Yield, %[a]	M.p., °C.[b]	Recrystn. solvent	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
IIIa[c]	37.2	320–321 dec.	DMF–water	$C_{23}H_{23}N_3O_3$	70.93	5.95	10.79		70.68	6.02	10.82	
Hydrochloride		275–277 dec.	Abs. ethanol					8.42				8.25
Picrate		227–228	Ethanol		56.31	4.24	13.61		56.34	4.34	13.35	
IIIb[d]	55.5	312–313	DMF–water	$C_{24}H_{25}N_3O_3$	71.44	6.25	10.42		71.69	6.19	10.54	
Hydrochloride		238–239	Abs. ethanol–abs. ether					8.06				7.95
IIIc	34.5	254–255	DMF–water	$C_{25}H_{27}N_3O_3$	71.92	6.52	10.07		71.85	6.60	10.15	
IIId	30.0	255–256	DMF–water	$C_{25}H_{27}N_3O_4$	69.26	6.28	9.69		69.27	6.47	9.45	
IIIe	36.0	254–255	Ethanol	$C_{30}H_{29}N_3O_3$	75.13	6.10	8.76		75.13	6.37	8.77	
IIIf	100.0	348 dec.	Dioxane–water	$C_{25}H_{25}N_3O_4$	69.59	5.84	9.74		69.28	5.95	9.67	

[a] Based on crude product. [b] Determined after recrystallization. [c] *Anal.* Calcd.: mol. wt., 389. Found: mol. wt., 382 (thermoelectrical method). [d] *Anal.* Calcd.: mol. wt., 403. Found: mol. wt., 403 (mass spectroscopy).

TABLE II

PREPARATIVE DATA OF 4-ALKYL-14-HYDROXY-9,12-DIPHENYL-1,4,7-TRIAZATRICYCLO[5.3.3.1^{9,12}]TERADECANE-2,6-DIONES

Compd.	Yield, %[a]	M.p., °C.[b]	Recrystn. solvent	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
IVa	12.0[c]	279–281 dec.	DMF–water	$C_{23}H_{25}N_3O_3$	70.57	6.44	10.74		70.28	6.17	10.67	
IVb[d]	45.6	335–336 dec.	DMF–water	$C_{24}H_{27}N_3O_3$	71.09	6.71	10.36		71.14	6.92	10.13	
Hydrochloride		306–307 dec.	Abs. ethanol–abs. ether					8.02				7.94
Picrate		274 dec.	Ethanol		56.78	4.77	13.24		56.47	4.61	13.42	
IVc	31.0	330–331	DMF–water	$C_{25}H_{29}N_3O_3$	71.57	6.97	10.02		71.68	6.93	10.18	
IVd	34.4	347–348 dec.	DMF–water	$C_{25}H_{29}N_3O_4$	68.94	6.71	9.65		68.84	6.72	9.58	
IVe[e]	31.0	314 dec.	Dioxane–water	$C_{30}H_{31}N_3O_3$	74.82	6.49	8.73		74.55	6.44	8.85	
IVf	100.0	380 dec.	DMF–water	$C_{25}H_{27}N_3O_4$	69.26	6.28	9.69		69.12	6.37	9.75	

[a] Based on crude product. [b] Determined after recrystallization. [c] Based on recrystallized product obtained through catalytic hydrogenation of IIIa. [d] *Anal.* Calcd.: mol. wt., 405. Found: mol. wt., 405 (mass spectroscopy). [e] *Anal.* Calcd.: mol. wt., 481. Found: mol. wt., 481 (mass spectroscopy).

trum, it is first necessary to examine the spectrum of 1,5-diphenyl-3,7-diacetyl-9-bispidinone[5] (Ib, Figure 1).

The eight hydrogens H_{a-d} of the bispidine moiety are represented by the characteristic pattern of two AB systems. These were readily identified by decoupling experiments. The low-field doublet at 339 c.p.s. has been assigned to the two equatorial protons H_a, since they lie in the plane of the magnetically anisotropic carbonyl groups and experience their long-range deshielding.[6] The two axial protons H_b are coupled with the H_a hydrogens (J = 13.5 c.p.s.) to give a doublet at 209 c.p.s. The two remaining doublets at 267 and 234 c.p.s. have been assigned to the two equatorial hydrogens H_c and the two axial hydrogens H_d (J = 13.0 c.p.s.), respectively. The further splitting (J = 2.5 c.p.s.) of each peak of the two AB systems is due to long-range spin–spin couplings between H_a and H_c, and H_b and H_d, as was unambiguously established by decoupling experiments.

Returning now to the spectrum of the tricyclic compound IIIb, the two low-field peaks at 325 c.p.s. integrate for four protons, the A-protons of two AB systems with the same chemical shift. We have assigned this doublet to the four protons H_a and $H_{a'}$, which, as was previously observed for the H_a hydrogens in the spectrum of Ib, are shifted to lower magnetic fields because they lie in the planes of the two amidic carbonyl groups, at calculated distances from the carbonyl bonds of 2.4 and 2.0 Å., respectively. The identification of the related B-protons was aided by decoupling experiments. Saturation of the low-field hydrogens at 97 and 117 c.p.s. downfield from the two doublets appearing at 228 and 208 c.p.s. collapsed the latter ones to sharp singlets, thus identifying these as the B-protons of the two AB systems. We have assigned the two peaks at 208 c.p.s. to the two H_b protons because they have the same chemical shift as the corresponding H_b protons of Ib (209 c.p.s.). Consequently, the signals at 228 c.p.s. must be due to the two H_e protons.

These data are consistent only with conformation A in which there are four hydrogens coplanar with the carbonyl groups and in a *cis* relationship with them. In conformation B, one should find only two such hydrogens. The remaining four protons, H_c and H_d, give the two doublets of an AB system at 224 and 196 c.p.s. with J = 14.0 c.p.s., as found for the other two AB systems. It is also of interest to note that the aromatic hydrogens of the two benzene rings are not perfectly equivalent.

The same steric situation as in the 2,6,14-triones, IIIa–e, occurs in the related 14-hydroxy-2,6-dione series, compounds IVa–e (see Table II). These compounds, with the exception of IVa, were prepared in a similar manner from 1,5-diphenyl-3,7-bis(chloroacetyl)-9-bispidinol[7] (IIb) and primary amines. Attempted quaternization in this series also failed and the hydrochlorides could be kept only under anhydrous conditions.

Attempts to prepare the N-4–H compound, IVa, by the cyclization with ammonia and by hydrogenolysis of the N-4–benzyl compound, IVe, were unsuccessful. The

(5) Z. Yoong-Kyi and W. Wilson, *J. Chem. Soc.*, 1706 (1951).

(6) L. M. Jackman in "Application of N.m.r. Spectroscopy in Organic Chemistry," D. H. R. Barton and W. Doering, Ed., Pergamon Press Ltd., London, 1959, p. 124.

(7) S. Chiavarelli and G. Settimj, *Farmaco, Ed. Sci.* (Pavia), **16**, 313 (1961).

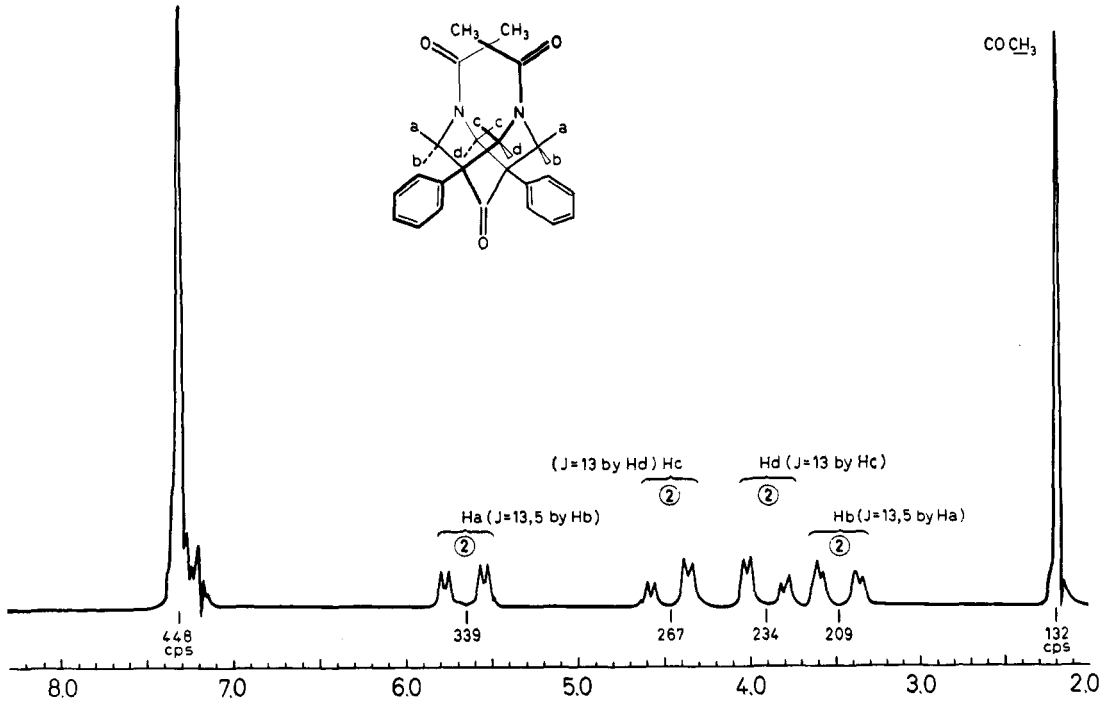


Figure 1.—The proton n.m.r. spectrum of 1,5-diphenyl-3,7-diacetyl-9-bispidinone (Ib).

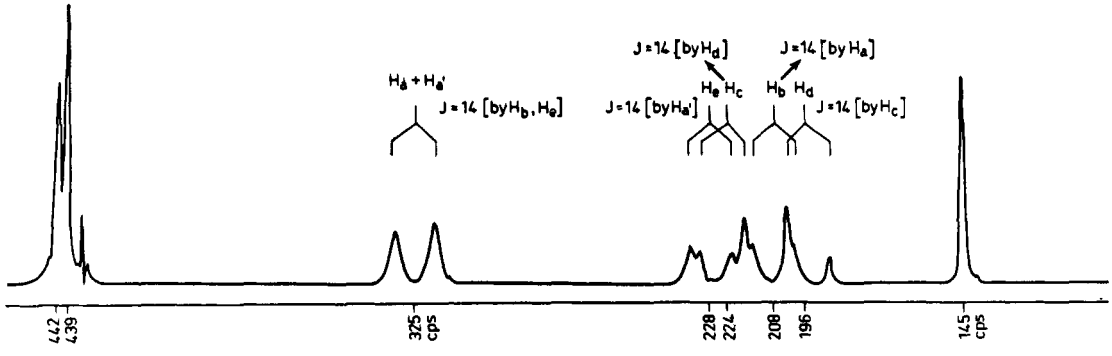


Figure 2.—The proton n.m.r. spectrum of 4-methyl-9,12-diphenyl-1,4,7-triazatricyclo[5.3.3.1^{9,12}]tetradecane-2,6,14-trione (IIIb, conformation A).

preparation of IVa was finally accomplished by catalytic hydrogenation of the corresponding ketone, IIIa. As for the latter, methylation and acetylation of IVa to give IVb (also obtained from the cyclization reaction) and IVf, respectively, proceeded smoothly.

These two series of compounds were easily related to each other by sodium borohydride reduction (of IIIb) or catalytic hydrogenation (of IIIe) of the 14-keto group to give the corresponding 14-hydroxy compounds already prepared by the cyclization reaction.

Experimental[8]

4-Alkyl-9,12-diphenyl-1,4,7-triazatricyclo[5.3.3.1^{9,12}]tetradecane-2,6,14-triones (IIIa–e, Table I).—In general, the preparation of these compounds was effected by allowing a mixture of the bis(chloroacetyl)bispidinone[9] (Ic, 44.5 g., 0.1 mole) and 17% aqueous ammonia or primary amine (0.3 mole) in dioxane (200 ml.) to react at room temperature with occasional shaking for several days. During the course of the reaction the amine hydrochloride, formed from the excess amine present and the liberated HCl, separated. At the end of the reaction period, the reaction mixture was filtered and, in the case of compound IIIa[10] and IIIb, the crude product was obtained from the precipitate by washing well with water to remove the ammonium or methylamine hydrochloride. To isolate compounds IIIc and IIIe, the filtered dioxane solution was evaporated to dryness under vacuum, and the yellowish residue was suspended in acetone. The acetone-insoluble material was then crystallized to give the pure product. Compound IIId was obtained in the following manner. After 2 days, the oily ethanolamine hydrochloride layer was separated from the upper dioxane solution. After standing an additional 2 days at room temperature, white crystals were obtained from the dioxane solution which melted at 150–160°. On continued heating to about 190°, the solvent of crystallization was lost, and the compound solidified again. This solvent-free material melted at 245–246°.

These compounds all displayed infrared bands at 1725 (ketone) and 1670 and 1650 cm.$^{-1}$ (amide). In addition to these bands, compound IIIa showed absorption at 3350 cm.$^{-1}$ (NH stretching) and compound IIId at 3570 cm.$^{-1}$ (OH stretching).

The hydrochloride of IIIa was obtained by adding anhydrous ethanolic HCl to a solution of the base in DMF–absolute ethanol. After 30 min., the white silky needles were filtered and crystallized from hot absolute ethanol. The picrate resulted by

(8) Melting points are uncorrected; the infrared spectra were taken in Nujol with a Perkin-Elmer Model 21 double-beam spectrometer. Microanalyses were performed by the Laboratorio di Microanalisi of the Istituto Superiore di Sanità, directed by Professor M. Marzadro.

(9) This compound was obtained with minor modifications as described earlier: S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1257 (1958).

(10) The molecular weight determination of this compound was carried out with the thermoelectrical method, as described by W. Simon and C. Tomlison [*Chimia*, **14**, 301 (1960)].

addition of ethanolic picric acid to a hot solution of the base in Methyl Cellosolve.

The hydrochloride of IIIb was obtained by addition of saturated etheral HCl (10 ml.) diluted with an equal volume of absolute ethanol to a solution of the base (0.5 g.) in dioxane (70 ml.). It was then dried 2 hr. at 20° (30 mm.). When dried for 6 hr. at 20° (0.2 mm.), 12.5% of its HCl was lost and the melting point was raised to 275°. When dissolved in aqueous media, as for the hydrochloride of IIIa, the starting base was recovered.

Methylation of IIIa.—A solution of the tricyclic secondary amine IIIa (1 g., 2.55 mmoles) and methyl iodide (4 ml.) in Methyl Cellosolve (20 ml.) was refluxed for 1.5 hr. After cooling, the resulting yellow solid was filtered and crystallized twice from ethanol to give 0.6 g. (58%) of the N-methyl compound, IIIb, identical in all respects with that obtained from the cyclization reaction.[11]

Acetylation of IIIa.—A solution of IIIa (1 g., 2.55 mmoles) in acetic anhydride (20 ml.) was maintained at 40° for 4 days. During this period crystalline solid separated. The acetic anhydride was removed under vacuum and the residue was purified by crystallization from dioxane–water (1:1) to give an almost quantitative yield of the N-acetyl derivative, IIIf.

4-Alkyl-14-hydroxy-9,12-diphenyl-1,4,7-triazatricyclo[5.3.-3.1^{9,12}]tetradecane-2,6-diones (IVa–e, Table II).—The general preparation of these compounds, except IVa, was effected by adding to a previously cooled solution of 1,5-diphenyl-3,7-bis-(chloroacetyl)-9-bispidinol (IIb, 4.5 g., 10 mmoles) in dioxane (90 ml.) 30 mmoles of the primary amine. Except for compound IVe, the reaction mixture was allowed to stand at room temperature for 15 days and the resulting solid was filtered and washed with dioxane and then thoroughly with water. After drying at 100°, purification of the crude product was achieved by crystallization from DMF–water (1:1). To obtain the N-benzyl tricyclic compound IVe, the reaction mixture, after standing 5 days at room temperature, was filtered free from the benzylamine hydrochloride. The filtrate was then evaporated to dryness and the residue was suspended in acetone. The acetone-insoluble material was crystallized from 50% aqueous dioxane to give the pure product.

These compounds all displayed infrared bands at 3350–3400 (OH stretching) and at 1660 and 1620 cm.$^{-1}$ (amide); compound IVa showed a broad band at 3400 cm.$^{-1}$ for the NH and OH stretching, while its N-acetyl derivative, IVf, had a band at 3300 cm.$^{-1}$ (OH stretching).

The hydrochloride of IVb was obtained in colorless needles by adding to a filtered solution of the base in absolute ethanol an equal volume of saturated ethereal HCl. When dissolved in 50% aqueous dioxane, the starting base was recovered.

Hydrogenation of IIIa.—A solution of compound IIIa (10 g., 25 mmoles) in acetic acid (200 ml.) was hydrogenated 6 hr. at room temperature under 3 atm. with Adams catalyst (0.5 g.). Charcoal was then added and the filtered solution was evaporated to dryness under vacuum on a steam bath. To the resulting viscous residue, warm dioxane (50 ml.) was added and a white solid was obtained. The latter was dissolved in cold DMF and an equal volume of water was added. After standing for 1 day, the solid material was collected and resubjected to the same procedure, four times in total, to remove the less-soluble amorphous material. The combined mother liquors were then diluted with an equal amount of water and filtered and, after standing several days in the refrigerator, compound IVa (1.2 g., 12%) separated in thin, colorless needles, m.p. 279–281° dec.

Methylation of IVa.—A mixture of compound IVa (200 mg., 0.51 mmole) and methyl iodide (1 ml.) in methanol (20 ml.) was refluxed for 3 hr. The solution was then evaporated under vacuum to dryness, and acetone (10 ml.) was added to the yellow residue to give 120 mg. (58%) of crude product. Crystallization from DMF–water gave the pure compound identical in all respects with IVb obtained from the cyclization reaction.[12]

Acetylation of IVa.—A suspension of IVa (200 mg., 0.51 mmole) in acetic anhydride (4 ml.) was heated for 2 min. on a steam bath. Before solution was complete, separation of a white precipitate occurred. After the mixture was kept overnight, water (4 ml.) was added, and the resulting suspension was heated for a few minutes to complete hydrolysis of the acetic anhydride. The precipitated crude product weighed 220 mg. (100%). After crystallization from DMF–water, the pure compound melted with decomposition at 380°.

Reduction of Compound IIIb with Sodium Borohydride.—Compound IIIb (4 g., 10 mmoles) was treated with $NaBH_4$ (0.5 g., 13 mmoles) in anhydrous pyridine (100 ml.) at room temperature for 5 hr. The excess hydride was then decomposed with methanol (20 ml.) and, after the addition of water (200 ml.), the resulting solution was evaporated to dryness under vacuum. Suspension of the residue in warm methanol gave 2.6 g. (65%) of a white crystalline powder which, on crystallization from DMF–water, gave prisms (m.p. 335–336°) whose infrared spectrum was identical with that of compound IVb obtained from the cyclization reaction.

Hydrogenation of IIIe.—A solution of compound IIIe (2 g., 4.2 mmoles) in acetic acid (15 ml.) was hydrogenated at room temperature under 3 atm. for 6 hr. with Adams catalyst (0.2 g.). After treating with charcoal, the solution was filtered and water (15 ml.) was added. The crude product (1.1 g., 55%), after crystallization from aqueous dioxane, was identical in all respects with compound IVe obtained from the cyclization reaction.

Acknowledgment.—The authors are indebted to and wish to thank Dr. A. Melera and the Varian A. G. Zürich for the n.m.r. spectra and Dr. J. Seibl, E. T. H. Zürich, for the mass spectra.

(11) An attempted iodomethylation run with IIIb gave only the hydroiodide (m.p. 232–234°), which was completely hydrolized to the starting material after two crystallizations from 95% ethanol.

(12) Attempted iodomethylation of IVb (0.5 g.) with excess methyl iodide (4 ml.) in refluxing methanol (20 ml.) for 6 hr. gave only 0.4 g. (80%) of recovered starting material.