Acknowledgments.—The authors wish to express their gratitude to Drs. M. R. Bell and D. Wood for samples of 2-tropanols. We wish also to acknowledge our gratitude for the technical assistance of Miss D. Fort and Mrs. L. Conklin in the pharmacological experimentation described in this communication.

Synthesis and Analgesic Activity of a New Bridged Heterocyclic System[1]

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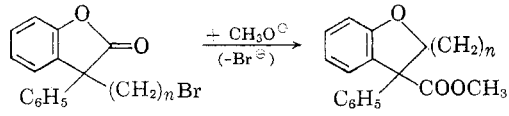
Synthesis of a new bridged heterocyclic system, an aza-benzoxabicyclo-[3.3.1]-nonane derivative (VI) is described. Application of a new methoxide induced rearrangement of 3-(haloalkyl)-3-phenyl-2-benzofuranones which includes preferential and stereospecific displacement of one of two bromine atoms in the molecule, gives methyl *cis*-2-bromomethyl-4-chromancarboxylate (IIa). Heating this intermediate with primary amines produces the lactams V in good yields. The new heterocyclic system thus becomes readily accessible in five steps from phenol and mandelic acid or mandelonitrile. Structural analogy of this system to the analgesically active 6,7-benzomorphane ring system is pointed out, and preliminary pharmacological examination of several examples is reported.

A previous paper[2] described the methoxide ion induced rearrangement of the three homologous benzofuranones A to the corresponding methyl esters B.[3] The first two members of this series (n = 1, 2) rearranged with extreme rapidity (reaction could be accomplished under titration conditions); and, by contrast, the third member



A (n = 1,2,3) B (n = 1,2,3)

(1) Part IV of the series, "Neighboring Group Reactions." For Part III, *cf.* H. E. Zaugg, R. W. DeNet, R. J. Michaels, W. H. Washburn, and F. E. Chadde, *J. Org. Chem.*, **26**, 4753 (1961).

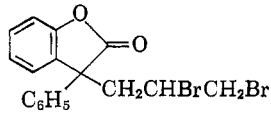
(2) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *ibid.*, **26**, 4821 (1961).

(3) This rearrangement, resulting from preferential nucleophilic attack of methoxide ion at the carbonyl carbon atom followed by intramolecular displacement of bromide ion, bears a formal resemblance to the suggested mode[4] of the rapid base-catalyzed solvolysis of the antibiotic, Antimycin-A.

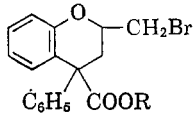
(4) (a) A. J. Birch, D. W. Cameron, Y. Harada, and R. W. Richards, *J. Chem. Soc.*, 889 (1961); (b) E. E. van Tamelen, J. P. Dickie, M. E. Loomans, R. S. Dewey, and F. M. Strong, *J. Am. Chem. Soc.*, **83**, 1639 (1961).

(n = 3) rearranged slowly.[5] Therefore, it seemed likely that, if two bromine atoms were present in the side chain of A, one separated from the quaternary center by two and the other by three carbon atoms, the former might react preferentially on treatment with one equivalent of methoxide ion. This paper reports the realization of this expectation together with some of its preparative and pharmacological consequences.

Bromination of the readily accessible 3-allyl-3-phenyl-2-benzofuranone[7] led to a good yield (> 90%) of a binary mixture which was easily resolved by fractional crystallization into its diastereomeric components Ia and Ib. Treatment of each of these isomers with an



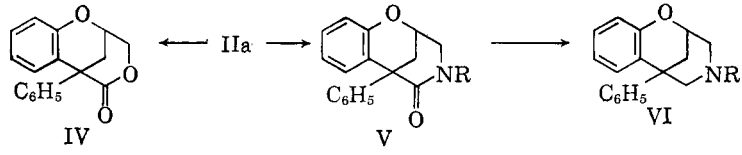
equivalent of sodium methoxide in methanol, resulted in both preferential and stereospecific intramolecular displacement of the secondary bromine atom to give the two bromo esters IIa (from Ia) and IIb (from Ib), in 89% and 96% yields, respectively. Acid



IIa, R = CH_3 (*cis*)
IIb, R = CH_3 (*trans*)
IIIa, R = H (*cis*)
IIIb, R = H (*trans*)

hydrolysis of these esters gave the corresponding isomeric carboxylic acids IIIa and IIIb.

The configurations of the bromomethyl relative to the carbomethoxyl groups in these two esters were established by thermolysis and aminolysis. At elevated temperatures (220°) IIa split out methyl bromide to give the lactone IV while IIb remained unaffected. Heating IIa with benzylamine (at 100°) led to the neutral lactam V (R



(5) Despite the comparatively slow rate of this reaction it proceeded eventually (24 hr.) to virtual completion (90% yield), thus providing a convenient route to the relatively uncommon[6] tetrahydro-1-benzoxepin ring system (B, n = 3).

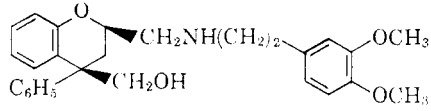
(6) (a) S. G. Powell and L. Anderson, *J. Am. Chem. Soc.*, **53**, 811 (1931); (b) O. Dann and W.-D. Arndt, *Ann.*, **587**, 38 (1954); (c) M. S. Newman and A. B. Mekler, *J. Org. Chem.*, **26**, 336 (1961).

(7) A. Lowenbein and H. Simonis, *Ber.*, **57**, 2040 (1924).

= $C_6H_5CH_2$) in 72% yield. However, identical treatment of IIb gave only the basic amino ester VIIb (R = $C_6H_5CH_2$). Clearly, then, the two functional groups are *cis* to each other in IIa and *trans* in IIb.[8]

Extension of the aminolysis reaction of IIa to several other unhindered primary amines led to corresponding lactams V in 75 to 80% yields (see Table IA). However, at a reaction temperature of 100°, the only product obtained from cyclohexylamine was the *cis* amino ester VIIa (R = cyclohexyl). Vacuum distillation of this ester at 200° was required to effect even partial (25%) cyclization to the lactam V (R = cyclohexyl).

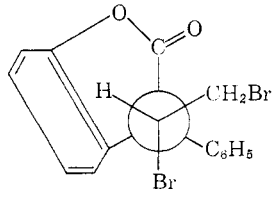
Reduction with excess lithium aluminum hydride of the lactams V generally led to high yields (90–99%) of the related cyclic amines VI (see Table IB). However, in the case of V (R = homoveratryl) a controlled amount of reducing agent was necessary for an optimum yield (85%). Otherwise considerable quantities (40–50%) of the



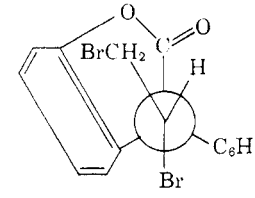
VIII

by-product VIII were formed. Similar amide reductions have been studied by Mićović and Mihailović[9] who noted that use of excessive amounts of reducing agent and substitution of bulky groups on the nitrogen atom were two factors favoring cleavage to alcohols. However, in view of the normal behavior of the phenethyl derivative of V

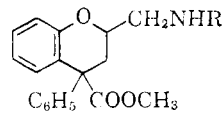
(8) Operating on the reasonable assumption that halide displacement in Ia and Ib occurs with complete inversion, their relative configurations can be assigned as follows, each form representing only one mirror image:



Ia (*d* or *l*)



Ib (*d* or *l*)



VIIa (*cis*)
VIIb (*trans*)

(9) V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

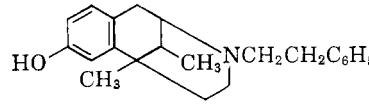
toward lithium aluminum hydride (Table IB), the reason for the anomalous behavior of the related homoveratryl analog observed in this instance is not apparent.

Compound VIII was synthesized independently as an added check on its structure. Treatment of IIa with homoveratrylamine *at room temperature* gave the amino ester VIIa (R = homoveratryl) which then was reduced with lithium aluminum hydride to VIII. The ability to isolate an intermediate of the type VIIa in this instance as well as with cyclohexylamine is clear indication that the formation of V from IIa occurs through initial halide displacement and not by initial ester aminolysis.

Several amines of type VI were prepared by an alternate route. Catalytic debenzylation of VI (R = $C_6H_5CH_2$) gave VI (R = H) (86% yield) which, with a suitable alkylating agent, was reconverted to the desired N-substituted derivative (Table IB).

Pharmacology

The structural resemblance of the bridged compounds of type VI to the potent analgesic phenazocine (NIH 7519)[10] is quite obvious.



Phenazocine

Therefore, they were submitted to a preliminary pharmacological comparison with results summarized in Table II.

Acute Toxicity.—Acute toxicities were determined in female Scientific strain mice, using 10 animals per dose level. With the exception of VI (R = CH_3), which was given as an aqueous solution, all others were given in methylcellulose suspension. The LD_{50} values and their associated confidence limits were calculated according to the method of Litchfield and Wilcoxon.[11]

Analgesic Activity.—Preliminary impressions of analgesic activity were obtained by the hot-plate method of Woolfe and MacDonald.[12] The 2-phenyl-1,4-benzoquinone induced "writhing" method of Siegmund, *et al.*,[13] was used as a secondary test. Both methods were employed substantially as originally described, using 10 mice at each dose level.

(10) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294, 1435 (1959).
(11) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
(12) G. Woolfe and A. D. MacDonald, *ibid.*, **80**, 300 (1944).
(13) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

TABLE I

BRIDGED LACTAMS V AND BRIDGED AMINES VI

Substituent, R	Procedure	Yield, %	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
				A. Bridged Lactams V						
$C_6H_5CH_2$	1	72	151–152	$C_{24}H_{21}NO_2$	81.10	81.06	5.96	6.23	3.95	3.95[a]
$C_6H_5CH_2CH_2$	1	75	95–96	$C_{25}H_{23}NO_2$	81.28	81.11	6.27	6.34	3.79	4.03[b]
$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	1	77	137–138	$C_{27}H_{27}NO_4$	75.50	75.30	6.34	6.22	3.27	3.18[b]
Cyclopropyl	1[c]	80	163–164	$C_{20}H_{19}NO_2$	78.65	78.36	6.27	5.98	4.59	4.41[d]
Cyclohexyl	2	17	170–171	$C_{23}H_{25}NO_2$	79.52	79.57	7.25	7.19	4.04	4.26[e]
				B. Bridged Amines VI						
$C_6H_5CH_2$	3	99	145–147[f]	$C_{24}H_{24}ClNO$	76.27	76.37	6.41	6.46	3.71	3.54
$C_6H_5CH_2CH_2$	3	90	76–77[g] 99–100[h]	$C_{25}H_{25}NO$[i]	84.46	84.10	7.09	7.13	3.95	3.76
$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	3[j]	85	104–105	$C_{27}H_{29}NO_3$[k]	78.05	77.91	7.04	7.00	3.38	3.02
Cyclopropyl	3	97	102–103	$C_{20}H_{21}NO$[e]	82.43	82.50	7.26	7.31	4.81	4.92
H	4	86	129–130	$C_{17}H_{17}NO$	81.25	81.10	6.82	6.70	5.58	5.49[m]
CH_3	5	64	133–134	$C_{18}H_{19}NO$	81.49	81.57	7.22	7.43	5.28	5.17
$C_6H_5CH{=}CHCH_2$	6	67	203–204[f]	$C_{26}H_{26}ClNO$	77.31	77.52	6.49	6.29	3.47	3.53
$C_6H_5OCH_2CH(OH)CH_2$	6[n]	75	193–195[f]	$C_{26}H_{28}ClNO_3$	71.31	71.47	6.44	6.26	3.20	3.49

[a] $\lambda_{max}^{CHCl_3}$ 6.05μ (C=O). [b] $\lambda_{max}^{CHCl_3}$ 6.07μ (C=O). [c] The bromoester IIa was refluxed in cyclopropylamine for one week. [d] $\lambda_{max}^{CHCl_3}$ 6.03μ (C=O). [e] $\lambda_{max}^{CCl_4}$ 6.06μ (C=O). [f] Hydrochloride of the base. [g] Metastable dimorph. [h] Stable dimorph. [i] Base hydrochloride, m.p. 243–245° dec. *Anal.* Calcd. for $C_{25}H_{26}ClNO$: C, 76.61; H, 6.69; N, 3.57. Found: C, 76.86; H, 6.63; N, 3.80. [j] Molar ratio of $LiAlH_4$ to amide V, 2:3. [k] Base hydrochloride, m.p. 223–224° dec. *Anal.* Calcd. for $C_{27}H_{30}ClNO_3$: C, 71.76; H, 6.69; N, 3.10. Found: C, 71.41; H, 6.80; N, 3.25. [l] Base sulfate dihydrate, m.p. 179–180° dec. *Anal.* Calcd. for $2(C_{20}H_{21}NO)\cdot H_2SO_4\cdot 2H_2O$: C, 63.81; H, 6.96; N, 3.73. Found: C, 63.84; H, 6.48; N, 3.96. [m] $\lambda_{max}^{CHCl_3}$ 1.54μ (N—H). [n] No triethylamine was used with the reagent 1,2-epoxy-3-phenoxypropane

TABLE II

PRELIMINARY PHARMACOLOGICAL COMPARISONS

Compound VI, R =	Intraperitoneal LD_{50}—mice mg./kg. (95% C.L.)	Analgesic activity, mg./kg. Hot plate[a] oral	Hot plate[a] i.p.	Hot plate[a] s.c.	Writhing[b] oral	Writhing[b] i.p.	% Increase in barbiturate sleep time
H	182 (135–246)	125	70	1000+	39	12	92
CH_3	120 (110–131)	235	110	500	84	44	58
$C_6H_5CH_2CH_2$	3750 (3130–4500)	1000+	1000+	..	1000+	550	58
Homoveratryl	1050 (990–1100)	1000+	195	130	350	98	182
$C_6H_5CH{=}CHCH_2$	1000 (910–1100)	410	46	53	225	27	41
$C_6H_5OCH_2(CHOH)CH_2$	1300 (1140–1480)	690	76	160	370	220	75
Cyclopropyl	590 (421–826)	1000+	1000+	1000+	210	54	370
Phenazocine	47 (42–53)	5.7	<1	<0.25	4-1/2	<1/2	25

[a] The dose calculated to increase average response time by 100%. [b] The dose inducing 50% reduction in frequency of "writhing" movements.

Other Studies.—Central depressant properties of these chemicals were determined by pretreating groups of 10 male mice intraperitoneally for 30 min. with the drugs at 0.1 of their respective LD_{50} values and then challenging them with an intraperitoneal injection of 60 mg./kg. of sodium pentobarbital. Onset of and duration of sleep were compared with controls run concurrently. Additional analgesic and pharmacodynamic studies are currently in progress.

Results.—The symptoms listed were seen after intraperitoneal administration at or near toxic levels: tremors, ataxia, clonic convulsions and depression. The most water-soluble of these analogs, VI (R = CH_3), showed the highest toxicity, its intraperitoneal LD_{50} being 120 mg./kg. Values for other analogs ranged from 182 to 3750 mg./kg. By contrast, phenazocine showed an intraperitoneal LD_{50} of 47 mg./kg. in our hands. It is interesting to note that the analog VI (R = $C_6H_5CH_2CH_2$) most closely related to phenazocine was the least toxic and least active.

Absence of complete pharmacodynamic data at this moment precludes any definitive statements with respect to the over-all evaluation of these analogs. However, the following impressions are gained from our preliminary studies: (a) none of the analogs approached phenazocine in analgesic activity on a mg./kg. basis when tested by either the hot-plate or by the "writhing" method; (b) calculated in terms of their therapeutic indices, phenazocine again showed the most favorable index; (c) again, based on equivalent fractions of their respective intraperitoneal LD_{50} values, phenazocine was the least depressant when tested by the method previously described.

Experimental[14]

3-(2′,3′-Dibromopropyl)-3-phenyl-2-benzofuranones (Ia) and (Ib).—To a cooled, stirred solution of 3-allyl-3-phenyl-2-benzofuranone[7] (233 g., 0.93 mole) in chloroform (1 l.) was added dropwise over an 8 hr. period a solution of bromine (149 g., 0.93 mole) in chloroform (200 ml.). During the addition, temperature was maintained at 0–5° by means of an ice bath. After standing at room temperature overnight, the chloroform was removed by distillation. Treatment of the residual oil with absolute ethanol (500 ml.) induced crystallization of the product (361 g., 95%) which was isolated in three crops ranging in melting point from 84° to 107°. Further fractional crystallization of these crops from absolute ethanol (5 ml./g. of dibromide) gave 204 g. of pure Ib, m.p. 137–138°, as the less soluble isomer.

Anal. Calcd. for $C_{17}H_{14}Br_2O_2$: C, 49.78; H, 3.44. Found: C, 50.10; H, 3.63. $\lambda_{max}^{CHCl_3}$ 5.53 μ (C=O).

From the mother liquors was obtained a total of 151 g. of a mixture of Ia and

(14) Melting points are uncorrected.

Ib, m.p. 89–91°, shown by thin-layer silica gel chromatographic analysis to consist mainly of Ia (a synthetic mixture of Ia and Ib was readily resolvable by this technique. Using benzene as a developing solvent Ib travelled appreciably faster than Ia). For further synthetic work involving Ia, the mixture, m.p 89–91°, could be used without further treatment. However, some of it was purified by wasteful recrystallization from ethanol, whereby pure Ia, m.p. 99–101°, was obtained.

Anal. Calcd. for $C_{17}H_{14}Br_2O_2$: C, 49.78; H, 3.44. Found: C, 49.89; H, 3.55. $\lambda_{max}^{CS_2}$ 5.54 μ (C=O).

With the exception of strong peaks at 10.25 μ and 12.76 μ (CS_2) in Ib, both of which are absent in Ia, the infrared spectra of the two isomers are virtually identical.

Methyl *cis*-2-bromomethyl-4-phenyl-4-chromancarboxylate (IIa).—To a stirred solution of sodium methoxide prepared from sodium (9.5 g., 0.415 mole) in dry methanol (1 l.) powdered Ia (170 g., 0.415 mole, m.p. 99–101° obtained by crystallization from several large batches of mixed dibromides) was added in one portion at room temperature. After stirring for 1 hr., solution was virtually complete and product began to precipitate. The mixture was stirred at room temperature overnight, cooled in ice for several hr. and the product IIa (133 g., 89%, m.p. 106–107°) was collected on a suction filter. Recrystallization from methanol raised the melting point only to 107–108°; $\lambda_{max}^{CS_2}$ 5.75 μ (C=O).

Anal. Calcd. for $C_{18}H_{17}BrO_3$: C, 59.84; H, 4.74; Br, 22.12; O, 13.30. Found: C, 59.75; H, 4.98; Br, 22.08; O, 13.47.

Methyl *trans*-2-bromomethyl-4-phenyl-4-chromancarboxylate (IIb) was likewise obtained from Ib, m.p. 137–138°, by the above procedure in 96% yield, m.p. 111–112° (mixture with IIa, m.p. 88–90°); $\lambda_{max}^{CS_2}$ 5.77 μ (C=O).

Anal. Calcd. for $C_{18}H_{17}BrO_3$: C, 59.84; H, 4.74; Br, 22.12. Found: C, 59.60; H, 4.89; Br, 21.99.

When the mixture (m.p. 89–91°) of Ia and Ib was treated with sodium methoxide in methanol, a corresponding mixture (m.p. 98–100°) of IIa and IIb resulted. However, thin-layer silica gel chromatographic analysis clearly revealed that IIa (the slower moving component with benzene development) predominated. Therefore, this mixture could be used in further synthetic work in place of the less readily obtainable pure IIa. Both IIa, m.p. 107–108°, and IIb, m.p. 111–112°, appeared homogeneous by thin-layer chromatographic analysis.

***cis*-2-Bromomethyl-4-phenyl-4-chromancarboxylic Acid (IIIa).**—A solution of IIa (5 g., 0.0138 mole) in glacial acetic acid (60 ml.) containing aqueous (48%) hydrobromic acid (15 ml.) was refluxed overnight. Removal of solvent by distillation followed by extraction of the residue with aqueous sodium bicarbonate, filtration from insoluble material, and acidification gave IIIa (2.1 g., 43%), m.p. 150–151°, after several recrystallizations from a benzene-hexane mixture. λ_{max}^{CHCl} (μ) 2.88, 3.82 (OH); 5.73, 5.86 (C=O).

Anal. Calcd. $C_{17}H_{15}BrO_3$: C, 58.80; H, 4.35; Br. 23.02. Found: C, 59.00; H, 4.49; Br. 23.25.

***trans*-2-Bromomethyl-4-phenyl-4-chromancarboxylic acid (IIIb)** was likewise obtained from IIb, m.p. 111–112°, by the above procedure in nearly quantitative yield, m.p. 217–218° (from methanol). $\lambda_{max}^{CHCl_3}$ (μ) 2.87, 3.82 (OH); 5.75, 5.86 (C=O).

Anal. Calcd. for $C_{17}H_{15}BrO_3$: C, 58.80; H, 4.35; Br, 23.02; O, 13.83. Found: C, 58.90; H, 4.20; Br, 22.56; O, 14.27.

cis-**2-Hydroxymethyl-5-phenyl-4-chromancarboxylic Acid Lactone (IV).**—The *cis*-bromoester IIa (3 g., 0.0083 mole) was heated for 3 hr. in an oil bath held at 220–225°. The cooled residue was triturated with cold ether and the resulting solid lactone IV (1.5 g., 68%, m.p. 149–151°) was collected on a filter. One recrystallization raised the melting point to 154–155°; $\lambda_{max}^{CHCl_3}$ 5.75 μ (C=O).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.74; H, 5.53.

Similar thermal treatment of the *trans*-bromoester (IIb) resulted in recovery of starting material (93%).

Methyl *trans*-2-Benzylaminomethyl-4-phenyl-4-chromancarboxylate (VIIb, R = $C_6H_5CH_2$).—A mixture of the *trans*-bromoester IIb (5 g., 0.0138 mole) and benzylamine (20 ml.) was heated on the steam bath overnight. Excess benzylamine was removed by distillation *in vacuo*. The residue was taken up in ether, filtered from insoluble solid (2.5 g., 97% of theoretical for $C_6H_5CH_2NH_2 \cdot HBr$, m.p. 217–219°), and washed with water. After removal of more insoluble material by filtration, the ether layer was extracted with cold dilute hydrochloric acid. The combined aqueous extract and oily insoluble hydrochloride was made alkaline with 10% sodium hydroxide solution, extracted with ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a base (3.8 g.) which could not be crystallized. By treatment with ethereal hydrogen chloride it was converted to its salt which was then recrystallized from ethanol and isopropyl alcohol; yield, 2.8 g., m.p. 229–230° dec.; $\lambda_{max}^{CHCl_3}$ 5.79 μ (C=O).

Anal. Calcd. for $C_{25}H_{26}ClNO_3$ (hydrochloride salt of VIIb): C, 70.81; H, 6.18; N, 3.30. Found: C, 70.46; H, 5.65; N, 3.18.

3-Aza-6,7-benzo-3-benzyl-4-keto-8-oxa-5-phenylbicyclo[3.3.1]nonane (V, R = $C_6H_5CH_2$). Procedure 1.—A mixture of the crude *cis*-bromoester IIa (54 g., 0.149 mole, m.p. 98–100°) and benzylamine (75 ml.) was heated on the steam bath for 24 hr. The excess benzylamine was removed by distillation *in vacuo* and the residue was stirred with dry ether (400–500 ml.). The resulting solid (77 g.) was collected on a suction filter and then slurried in water (300–400 ml.) to dissolve benzylamine hydrobromide. Insoluble product (38 g., m.p. 148–150°) was collected at the filter and a sample was recrystallized from absolute ethanol to give pure V (R = $C_6H_5CH_2$) (see Table IA).

Extraction of the ether filtrate with dilute hydrochloric acid and further treatment as outlined above resulted in the isolation of VIIb (R = $C_6H_5CH_2$) (7.1 g., m.p. 226–228°), identified by infrared spectrum and the melting point of the mixture of compound VIIb with the authentic sample. This resulted from the contaminating *trans*-bromoester IIb present in the crude starting material. The use of pure IIa in this reaction would undoubtedly lead to a much better yield of V (R = $C_6H_5CH_2$) than the 72% obtained from the mixture of IIa and IIb.

By substitution of the appropriate primary amine for benzylamine in the foregoing procedure, other bridged amides of type V were obtained (see Table IA).

3-Aza-6,7-benzo-3-cyclohexyl-4-keto-8-oxa-5-phenylbicyclo[3.3.1]nonane (V, R = cyclohexyl). Procedure 2.—Heating IIa (5 g., 0.0138 mole) with cyclohexylamine (15 ml.) overnight on the steam bath gave 5.5 g. of a viscous base and only a trace of neutral product. Conversion of the base to the corresponding hydrochloride in the usual manner and then recrystallization from an ethanol-ether mixture gave 3.8 g. (60%) of *methyl cis-2-cyclohexylaminomethyl-4-phenyl-4 chromancarboxylate* hydrochloride (VIIa; R = cyclohexyl), m.p. 204–205° dec. $\lambda_{max}^{CHCl_3}$ 5.76 μ (C=O).

This salt (3.8 g.) was reconverted to the free base and distilled *in vacuo* to give 2.6 g. of a clear glassy product, b.p. 200° (1 mm.), the infrared spectrum of which indicated that it was a mixture of a small quantity of the cyclized amide, and a predominant amount of starting material. Removal of the basic ester by acid extraction, followed by recrystallization (ethanol) of the neutral fraction, gave 0.8 g. (25%) of pure V (R = cyclohexyl) (see Table IA).

3-Aza-6,7-benzo-3-benzyl-8-oxa-5-phenylbicyclo[3.3.1]nonane (VI, R = C_6H_5-CH_2). Procedure 3.—To a stirred suspension of lithium aluminum hydride (2.2 g., 0.56 mole) in dry ether (400 ml.), solid V (R = $C_6H_5CH_2$) (8 g., 0.0225 mole) was added portionwise. The mixture was then stirred and refluxed for 24 hr. After cooling to room temperature, excess reducing agent was decomposed by the successive dropwise addition of water (3 ml.), 10% sodium hydroxide solution (3 ml.), and more water (2 ml.). The reaction mixture was filtered by suction, the filter cake was washed with ether, and the combined filtrates were dried over anhydrous magnesium sulfate. Filtration and treatment of the filtrate with excess ethereal hydrogen chloride, precipitated 9.5 g. (99%) of the hydrochloride of VI (R = $C_6H_5CH_2$), m.p. 141–145°, of a purity sufficient for further use. Recrystallization from ethanol raised the melting point to 145–147°.

By reduction of other bridged amides according to the foregoing procedure, the corresponding bridged amines of type VI were obtained. These are listed in Table IB.

When equimolar amounts of reactants were employed in the reduction of V (R = homoveratryl), yields of the amine VI decreased to 45% due to formation of the by-product, *cis-2-homoveratrylaminomethyl-4-hydroxymethyl-4-phenylchroman* (**VIII**), m.p. 108–109° (from ethanol), also obtained in 45% yield; $\lambda_{max}^{CHCl_3}(\mu)$ 1.43 (OH), 1.55 (NH).

Anal. Calcd. for $C_{27}H_{31}NO_4$: C, 74.81; H, 7.21; N, 3.24. Found: C, 74.72; H, 7.09; N, 3.18.

(**VIII**) **Hydrochloride,** m.p. 233–235° dec. (from ethanol–ether).

Anal. Calcd. for $C_{27}H_{32}ClNO_4$: C, 69.00; H, 6.86; N, 2.98. Found: C, 69.04; H, 7.38; N, 2.59.

The by-product VIII was readily separable from the desired product by utilization of its appreciably more basic character, quantitatively apparent from comparative potentiometric titrations with perchloric acid in dioxane. It easily formed a salt with formic acid which the cyclic amine VI (R = homoveratryl) did not.

(**VIII**) **Formate,** m.p. 156–157° (from ethanol).

Anal. Calcd. for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.93; N, 2.92; O, 20.02. Found: C, 70.32; H, 6.78; N, 3.11; O, 19.98.

Proof of Structure VIII by Independent Synthesis.—A solution of the *cis*-bromoester IIa (10 g., 0.0277 mole) in excess homoveratrylamine (30 ml.) was allowed to stand at room temperature overnight. The semi-solid reaction mixture was taken up in dry ether, filtered from insoluble salt, washed to neutrality with water, and extracted with 3 *N* hydrochloric acid. The combined aqueous extract and insoluble oil was made alkaline with 25% sodium hydroxide solution and extracted with chloroform. Removal of the chloroform by distillation gave a residual glassy substance (4 g.) which was taken up in dry ether and treated with ethereal hydrogen chloride. Filtration of the precipitated salt followed by two recrystallizations from ethanol-ether gave 3.7 g. (27%) of the hydrochloride of *methyl cis-2-homoveratrylaminomethyl-4-phenyl-4-chromancarboxylate* (VIIa, R = homoveratryl), m.p. 183–184°. $\lambda_{max}^{CHCl_3}$ 5.74 μ (C=O).

Anal. Calcd. for $C_{28}H_{32}ClNO_5$: C, 67.53; H, 6.48; N, 2.81. Found: C, 67.55; H, 6.66; N, 2.69.

This salt was converted to the corresponding free base and reduced with lithium aluminum hydride (0.5 g.) in dry ether. Work-up of the reaction mixture in the usual way (Procedure 3) gave 2.0 g. (60%) of VIII, m.p. 108–109°, with infrared spectrum and mixture melting point identical to that of the by-product obtained from the reduction of V (R = homoveratryl).

3-Aza-6,7-benzo-8-oxa-5-phenylbicyclo[3.3.1]nonane (VI, R = H). Procedure 4.—The hydrochloride of VI (R = $C_6H_5CH_2$) (6.7 g., 0.0177 mole) was dissolved in 50% aqueous ethanol (200 ml.) and catalytically hydrogenated (8 g. of 5% Pd on charcoal) at 40° and with an initial hydrogen pressure of 40 pounds per square inch (2.8 kg./cm.^{2}). Hydrogen uptake was complete in 2 hr. after which the catalyst was removed by filtration and the filtrate was concentrated to dryness. Recrystallization of the residue from ethanol gave 4.4 g., of VI (R = H) hydrochloride, m.p. 305–307° dec.

Anal. Calcd. for $C_{17}H_{18}ClNO$: C, 70.97; H, 6.31; N, 4.87. Found: C, 70.69; H, 6.49; N, 4.88.

The free base was obtained from the salt by treatment with alkali (see Table IB).

3-Aza-6,7-benzo-3-methyl-8-oxa-5-phenylbicyclo[3.3.1]nonane (VI, R = CH_3). Procedure 5.—A mixture of VI (R = H) base (5 g., 0.02 mole), formic acid (20 ml., 90%) and formaldehyde (15 ml., 40%) was refluxed overnight. After concentration of the mixture to dryness *in vacuo*, the residue was taken up in dil. hydrochloric acid and made alkaline by the addition of 25% sodium hydroxide solution. The precipitated base was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a glass (5.7 g.) which crystallized on trituration with ethanol. Two recrystallizations from ethanol gave 3.4 g. of pure VI (R = CH_3) (Table IB).

3-Aza-6,7-benzo-3-cinnamyl-8-oxa-5-phenylbicyclo[3.3.1]nonane (VI, R = $C_6H_5CH{=}CHCH_2$). Procedure 6.—A solution of VI (R = H) (5.5 g., 0.022 mole) cinnamyl chloride (3.35 g., 0.022 mole), and triethylamine (2.22 g., 0.022 mole) in dry benzene (200 ml.) was refluxed overnight. The cooled reaction mixture containing precipitated triethylamine hydrochloride was washed with water and the benzene was removed from the organic layer by distillation. The residual glass (6.5 g.) was taken up in dry ether, filtered from insoluble material (1.1 g., m.p. 300–305° dec.) and treated with excess ethereal hydrogen chloride. The crude salt (7.1 g., m.p. 140–150°) which precipitated was collected on the filter, and recrystallized from isopropyl alcohol to give 6 g. of VI (R = $C_6H_5CH{=}CHCH_2$) hydrochloride (see Table IB).

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