This material is reported to melt at 133–134.5°,[18] 131–132°,[19] and at 134.5–136°.[25]

Ethyl *N*-Phenylacetimidate.—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate and 9.3 g. (0.10 mole) of aniline was heated under reflux for 1.5 hr. by means of an oil bath maintained at 130–140°. The bath temperature was then raised to 160° and volatile material distilled. Distillation of the residue at 1.75 mm. gave a single fraction, b.p. 71.5–73.5°; yield, 14.3 g. (88%). The boiling point at atmospheric pressure was 213–215°; ethyl *N*-phenylacetimidate is reported to boil at 207–208°.[19]

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.7; H, 8.2; N, 8.7.

The residue from the vacuum distillation above was recrystallized from petroleum ether (60–70°) to give 0.55 g. (5.2%) of a white solid, m.p. 133.5–135.5°, which was identical with an authentic sample of *N,N'*-diphenylacetamidine.

***N,N'*-Bis(*o*-methoxyphenyl)acetamidine.**—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate, 24.6 g. (0.20 mole) of *o*-anisidine, and 6.0 g. (0.10 mole) of glacial acetic acid was heated under reflux by means of an oil bath maintained at 130–140°. After 1.3 hr., the temperature was raised to 155° and volatile material was removed under vacuum. A 10.0-g. sample of the residual sirup (34.7 g.) was shaken in a separatory funnel with a mixture of 100 ml. of ether, 100 ml. of water and 3.8 g. of sodium carbonate. The ether layer was separated, the aqueous layer washed several times with ether, and the combined ether extracts dried over sodium sulfate and evaporated to a small volume under reduced pressure. Recrystallization of the solid residue from petroleum ether (b.p. 60–70°) gave 5.6 g. (72%) of white crystals; m.p. 96–97°. This compound is reported to melt at 99°.[35]

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.1; H, 6.8; N, 10.4.

***N,N'*-Di-*o*-tolylacetamidine.**—A mixture of 8.1 g. (0.05 mole) of ethyl orthoacetate, 10.7 g. (0.10 mole) of *o*-toluidine, and 3.0 g. (0.05 mole) of glacial acetic acid was treated as described in the experiment above. Recrystallization of the crude product, obtained in 57% yield, from petroleum ether (b.p. 60–70°) gave colorless crystals; m.p. 69–70.5°. This material is reported to melt at 69,[36] 65,[37] 136,[38] and 140.5°.[39]

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.6; H, 7.6; N, 11.8. Found: C, 80.9; H, 7.8; N, 11.8.

***N,N'*-Bis(*o*-chlorophenyl)acetamidine.**—A mixture of 8.1 g. (0.05 mole) of ethyl orthoacetate, 12.75 g. (0.10 mole) of *o*-chloroaniline, and 2.0 g. (0.03 mole) of glacial acetic acid was heated under reflux by means of an oil bath maintained at 130–140° for 2 hr., the bath temperature was raised to 160°, and the volatile material was distilled under vacuum (0.75 mm). Recrystallization of the residue from petroleum ether (b.p. 60–70°) gave 4.0 g. (30%) of glittering, fluffy white needles; m.p. 94.5–95.5°.

Anal. Calcd. for $C_{14}H_{12}N_2Cl_2$: C, 60.2; H, 4.3; N, 10.0; Cl, 25.4. Found: C, 60.1; H, 4.5; N, 10.0; Cl, 25.3.

***N,N'*-Bis(*p*-nitrophenyl)acetamidine.**—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate, 7.9 g. (0.10 mole) of pyridine,[40] 27.6 g. (0.20 mole) of *p*-nitroaniline, and 6.0 g. (0.10 mole) of glacial acetic acid was treated as described in the experiment above. Unchanged *p*-nitroaniline was removed from the crude product by trituration with a small amount of hot ethanol. The residue was then recrystallized from a large volume of ethanol to give the desired product, m.p. 262–264°, in 25% yield. This compound is reported to melt at 261–262°.[41]

Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.0; H, 4.0. Found: C, 55.6; H, 4.2.

(35) E. Täuber in Friedländer's "Fortschritte der Theerfarbenfabrikation," Vol. 4, 1894, p. 1179.

(36) O. Wallach, *Ann.*, **214**, 193 (1882).

(37) Weiler-ter Meer in Friedländer's "Fortschritte der Theerfarbenfabrikation," Vol. 14, 1921, p. 409.

(38) O. Wallach and M. Wüsten, *Ber.*, **16**, 144 (1883).

(39) A. Ladenburg, *ibid.*, **10**, 1260 (1877).

(40) Pyridine aids in the dissolution of the otherwise poorly soluble *p*-nitroaniline.

(41) W. Bradley and I. Wright, *J. Chem. Soc.*, 640 (1956).

t-Carbinamines Derived from Partially Hydrogenated Fluorenes and Dibenzofuranes

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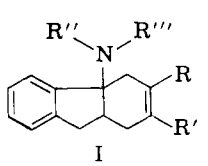
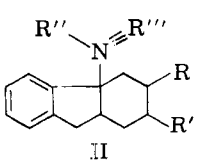
Synthetic pathways leading to the preparation of 1,4,4a,9a-tetrahydro-4a-fluorenamines (type I) and 1,2,3,4,-4a,9a-hexahydro-4a-fluorenamines (type II) have been investigated. One method which has been elaborated features the Diels–Alder reaction of indene-3-carboxylic acid or its ester with various dienes to yield VIII or IX. The corresponding carboxamides (X), upon Hofmann degradation, have afforded tetrahydrofluorenamines of type I, which upon reduction provide hexahydrofluorenamines II. The latter have also been obtained by intramolecular cyclizations of lithio-imines (XXVII). The 1,2,3,4,4a,9a-hexahydro-4a-N-methylfluorenamine obtained by cyclizing XXVII (R = CH_3) has been found to be identical with the one obtained *via* the Diels–Alder sequence, indicating that ring-closures of lithio-imines proceed with the formation of *cis*-fused ring systems. Extension of this method has led to the preparation of a number of 5a,6,7,8,9,9a-hexahydro-9a-dibenzofuranamines (type III). Compounds of types I, II, and III have exhibited potent central nervous system depressant activities.

During the course of investigations leading to the synthesis of biologically active amines it was of interest to prepare a number of partially hydrogenated polycyclic systems bearing angular amino functions.

In this paper we wish to report the preparation of 1,4,4a,9a-tetrahydro-4a-fluorenamines (I), 1,2,3,4,4a,-9a-hexahydro-4a-fluorenamines (II), and 5a,6,7,8,9,9a-hexahydro-9a-dibenzofuranamines (III).



I



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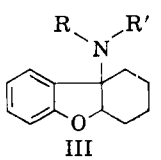
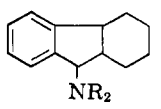
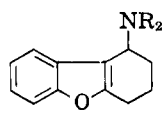


III

Examination of the literature indicated that of all the possible tetrahydro- and hexahydrofluorenamines only the 9-amino isomers (IV) have been reported.[1b]



IV



V

(1)(a) Research Laboratorium, Dr. Janssen Beerse, Belgium; (b) S. Fujise, *Rept. Japan. Assoc. Advan. Sci.*, **17**, 44 (1942) [*Chem. Abstr.*, **44**, 3927b (1950)]; Y. Nakamura, *J. Chem. Soc. Japan*, **61**, 1051 (1949); S. Husiza, *Ber.*, **71**, 2461 (1938).

Recent French work has described the synthesis of partially reduced dibenzofuranamines (V).[2]

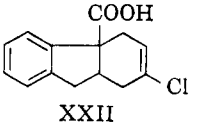
A possible approach towards the synthesis of types I and II was one in which the salient feature consisted of the Diels–Alder reaction of indene-3-carboxylic acid with several dienes to afford the appropriate tricyclic carbon skeleton of known stereochemical configuration, bearing a carboxylate function in the desired angular position. The prerequisite indene-3-carboxylic acid (VI) was prepared in 80% yield by the successive lithiation and carbonation of indene.[3] The resulting acid was then esterified to give VII.

The ambiguity of the position of the carboxylate function introduced in this or in similar fashions on the indene nucleus[3,4] (*i.e.*, 1- *vs.* 3-substitution) has been resolved by Yates and Robb[5] and Cope and co-workers,[6] who inferred that, on the basis of infrared data, acid VI was in fact indene-3-carboxylic acid and not indene-1-carboxylic acid as had been postulated before.[4]

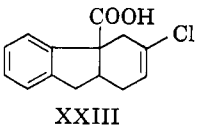
The reaction of indene with butadiene,[7] isoprene,[8] and muconic and sorbic acids,[9] and of spiro[1,3-dioxolane-2,1′-indene] with a variety of dienes[10] was extended by us to include the reaction of VII with butadiene, 2-chlorobutadiene and 2,3-dimethylbutadiene. Saponification of these esters (VIIIA,B,C) by means of potassium hydroxide in diethylene glycol then led to the acids (IXA,B,C).

It was also found that indene-3-carboxylic acid reacted with the dienes at 100–120° in benzene in a sealed vessel to give IX directly and in excellent yields. In those cases where the boiling point of the diene permitted, the additions were sometimes carried out in an open system using xylene as the solvent; the progress of the reaction was then followed by the rise in temperature of the boiling solution.

In the reaction of 2-chlorobutadiene with VI or VII, no definitive proof of the position of the chloro group in the adduct was obtained, although precedent would tend to favor structure XXII over XXIII. For example the only products isolated and characterized in



XXII



XXIII

the reaction of chloroprene with acrylic acid or its derivatives were *p*-chlorotetrahydrobenzoic acid derivatives.[11] Similarly, chloroprene and propiolic acid gave 4-chloro-2,5-dihydrobenzoic acid in good yield.[12] In our hands the reaction of chloroprene and VI produced a pure adduct in yields up to 34%, although the melting point of the crude product would not preclude the initial presence of a mixture.

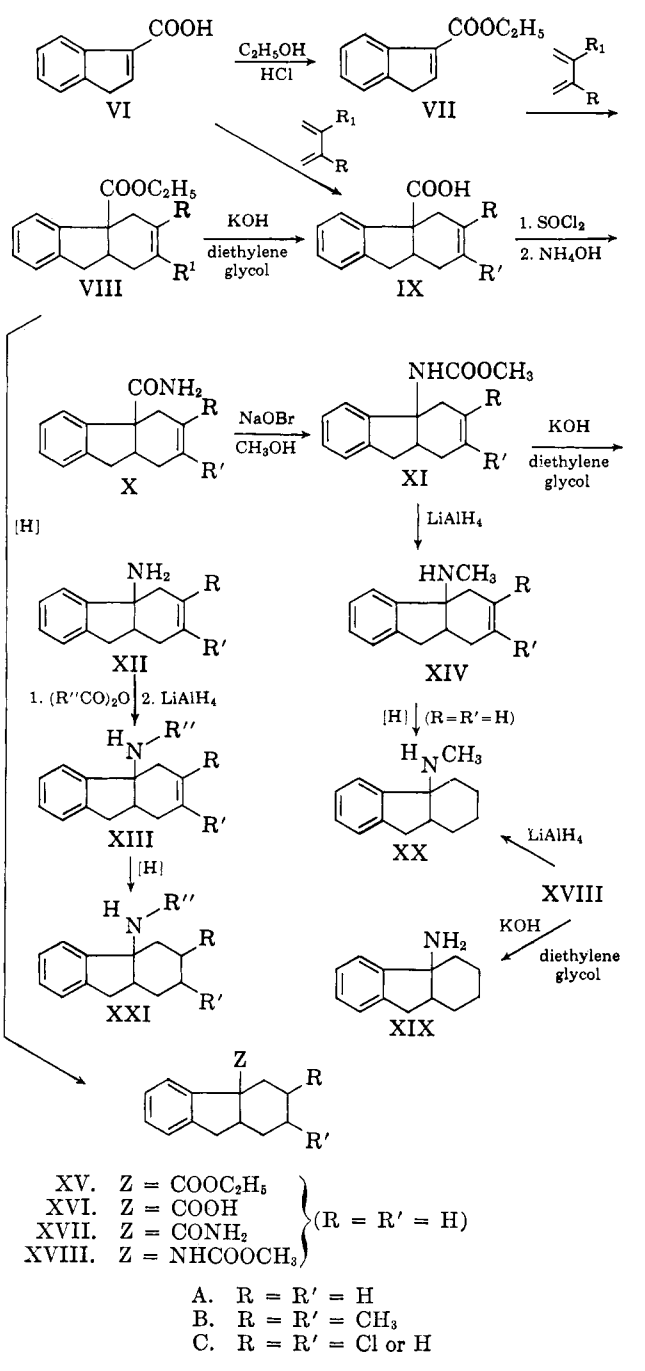
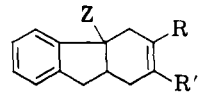


CHART I

The products of VI with butadiene, chloroprene, and 2,3-dimethylbutadiene were then converted to the carboxamides (X) by means of thionyl chloride in benzene followed by ammonolysis. Treatment of the amides XA and XB with sodium hypobromite in methyl alcohol gave carbamates XIA and B. These were hydrolyzed by means of potassium hydroxide in diethylene glycol to yield amines XIIA and B. Acylation followed by lithium aluminum hydride (LAH) reduction, or Clarke–Eschweiler methylation procedures subsequently converted XIIA and B to various N-substituted and N,N-disubstituted derivatives. The tetrahydrofluorenamines thus obtained are presented in Table III.

(2) F. Winternitz, N. J. Antia, and M. Tumlirova, *Bull. soc. chim. France*, 1817 (1956).
(3) N. H. Cromwell and D. B. Capps, *J. Am. Chem. Soc.*, **74**, 4448 (1952).
(4) R. Meier, *Ber.*, **86**, 1483 (1953); W. Wunderlich, *Arch. Pharm.* **286**, 512 (1953); W. S. Knowles, J. A. Kuck, and R. C. Elderfield, *J. Org. Chem.*, **7**, 374 (1942).
(5) P. Yates and E. W. Robb, *J. Am. Chem. Soc.*, **79**, 5760 (1957).
(6) A. C. Cope, J. E. Meili, and D. W. Ll. MacDowell, *ibid.*, **78**, 2551 (1956).
(7) K. Alder and H. F. Rickert, *Ber.*, **71**, 379 (1938).
(8) E. D. Bergmann, *Bull. Res. Council Israel*, **5A**, 150 (1956); [*Chem. Abstr.*, **50**, 15493(1956).]
(9) N. C. Deno, *J. Am. Chem. Soc.*, **72**, 4057 (1950).
(10) H. O. House and V. Paragamian, *ibid.*, **82**, 1457, 1463 (1960).
(11) J. S. Meek and W. B. Trapp, *ibid.*, **74**, 2686 (1952).
(12) A. A. Petrov and K. B. Ball, *Zh. Obshch. Khim.*, **26**, 1588 (1956).

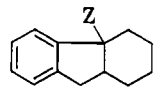
TABLE I



Compound	Z	R	R′	Method[a]	B.p. or m.p., °C.	Yield, %	Empirical formula	Anal. Calcd. C	Anal. Calcd. H	Anal. Found C	Anal. Found H
VIIIA	$COOC_2H_5$	H	H	A	89–92 (0.10 mm.)	49–60	$C_{16}H_{18}O_2$	79.31	7.49	79.13	7.61
VIIIB	$COOC_2H_5$	CH_3	CH_3	A	116–119 (0.17 mm.)	63–77	$C_{18}H_{22}O_2$	79.96	8.20	79.80	8.34
VIIIC	$COOC_2H_5$	H	Cl[b] (?)	A	115–118 (0.15 mm.)	29	$C_{16}H_{17}ClO_2$	69.42	6.19	69.51	6.45
IXA	COOH	H	H	B	119–119.5	96	$C_{14}H_{14}O_2$	78.46	6.58	78.16	6.67
				C	118–119	81					
IXB	COOH	CH_3	CH_3	B	115–116	96	$C_{16}H_{18}O_2$	79.31	7.49	79.22	7.28
IXC	COOH	H	Cl[b] (?)	B	105–108	*ca.* 50	$C_{14}H_{13}ClO_2$	67.61	5.27	67.87	5.45
				C	108–109	34					
XA	$CONH_2$	H	H	D	79.5–81	64	$C_{14}H_{15}NO$	78.83	7.09	79.15	7.25
XB	$CONH_2$	CH_3	CH_3	D	114–115	68	$C_{16}H_{19}NO$	79.85	7.94	79.63	7.69
XC	$CONH_2$	H	Cl[b] (?)	D	146–147	62	$C_{14}H_{14}ClNO$	67.96	5.70	67.92	5.82
XIA	$NHCOOCH_3$	H	H	E	160–165/0.40 mm.	81	$C_{15}H_{17}NO_2$	74.04	7.05	73.94	7.05
XIB	$NHCOOCH_3$	CH_3	CH_3	E	132–138/0.11 mm.	57–71	$C_{17}H_{21}NO_2$	75.23	7.80	75.61	7.40

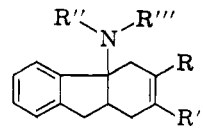
[a] (A) indene-3-carboxylic acid ethyl ester and diene at 180° for 24 hr., with trace of hydroquinone; (B) hydrolysis of VIIIA,B,C; (C) Indene-3-carboxylic acid with diene at 120° for 24 hr. with trace of hydroquinone; (D) treatment of acids IXA,B,C with thionyl chloride and ammonium hydroxide, respectively; (E) Hofmann degradation of amides XA,B. [b] Relative positions of H and Cl not determined.

TABLE II



Compound	X	M.p., °C.	Yield, %	Empirical formula	Anal. Calcd. C	Anal. Calcd. H	Anal. Found C	Anal. Found H
XVI	COOH	117–118	63	$C_{14}H_{16}O_2$	77.73	7.46	77.49	7.73
XVII	$CONH_2$	113–114	77–84	$C_{14}H_{17}NO$	78.32	7.97	78.23	7.81
XVIII	$NHCOOCH_3$	B.p. 132–138 (0.11 mm.) 61–62 (m.p.)	71	$C_{15}H_{19}NO_2$	73.44	7.83	73.38	8.07

TABLE III



R	R′	R″	R‴	Method[a]	M.p., °C., HCl salt	Empirical formula	Anal. Calcd. C	Anal. Calcd. H	Anal. Found C	Anal. Found H
H	H	H	H	A	227–229	$C_{13}H_{15}N \cdot HCl$	70.42	7.28	70.36	7.36
H	H	H	CH_3	B	201–202	$C_{14}H_{17}N \cdot HCl$	71.31	7.69	71.36	7.56
H	H	CH_3	CH_3	C	176–177	$C_{15}H_{19}N \cdot HCl$	72.12	8.07	72.08	8.16
H	H	H	C_2H_5	D	204–206	$C_{15}H_{19}N \cdot HCl$	72.12	8.07	72.43	8.34
H	H	H	$C_3H_7(n)$	D	237–238	$C_{16}H_{21}N \cdot HCl$	72.84	8.41	72.77	8.30
CH_3	CH_3	H	H	A	254–255	$C_{15}H_{19}N \cdot HCl$	72.12	8.07	72.23	8.37
CH_3	CH_3	H	CH_3	B	207–208	$C_{16}H_{21}N \cdot HCl$	72.84	8.41	72.90	8.47
CH_3	CH_3	CH_3	CH_3	C	204–205	$C_{17}H_{23}N \cdot HCl$	73.49	8.71	73.75	8.83
CH_3	CH_3	H	C_2H_5	D	250–251	$C_{17}H_{23}N \cdot HCl$	73.49	8.71	73.50	8.69
CH_3	CH_3	H	$C_3H_7(n)$	D	251–252	$C_{18}H_{25}N \cdot HCl$	74.08	8.98	73.96	9.10

[a] (A) Hydrolysis of methyl carbamates XIA,B; (B) LAH reduction of XIA,B; (C) Clarke–Eschweiler methylation of primary amines XIIA,B; (D) respective acylation and LAH reduction of XIIA,B.

In order to obtain hexahydrofluorenamines XIX and XX, the unsaturated adduct VIIIA was reduced catalytically to ester XV. This ester was converted to the primary amine (XIX) by the same route described above for the unsaturated analog XIIA. Reduction of urethan XVIII with lithium aluminum hydride produced XX. XX was also obtained directly from tetrahydrofluorenamine XIVA by means of catalytic reduction.

The use of the Diels–Alder reaction as a synthetic tool leading to tetrahydro- and hexahydro-4a-fluorenamines has the merit of enabling one to obtain compounds in which the ring fusion of the alicyclic rings is almost certainly in the *cis*-configuration in view of the known stereospecific course of the Diels–Alder reaction.[13]

(13) M. C. Kloetzel, *Org. Reactions*, **4**, 1 (1948); H. L. Holmes *ibid.*, **4**, 60 (1948); L. W. Butz and A. W. Rytina, *ibid.*, **5**, 136 (1949).

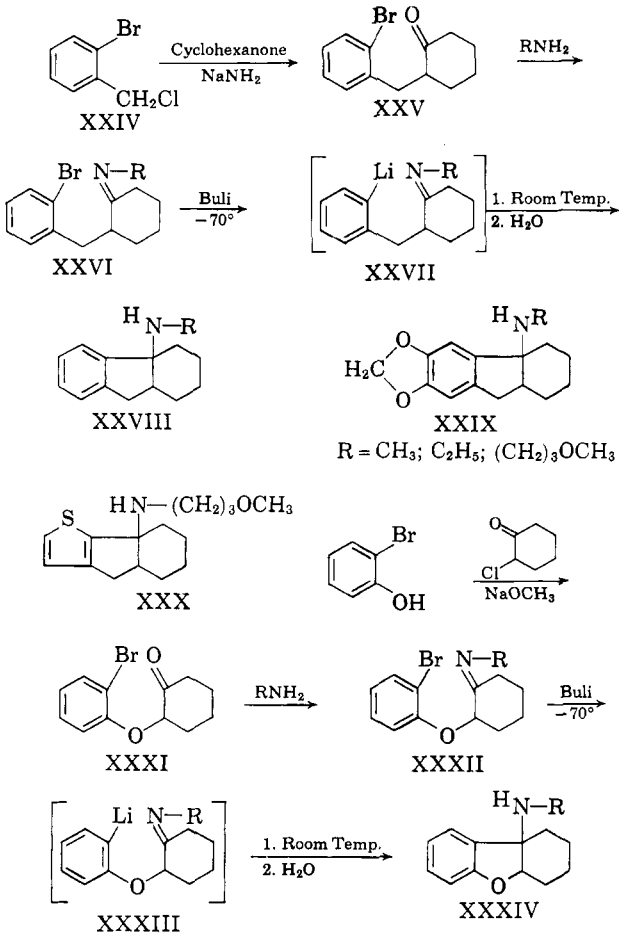


CHART II

None of the subsequent manipulations on the carboxylate functions of adducts VIII or IX could affect the stereochemistry since Hofmann reactions leading to XI and XVIII are known to proceed with retention of configuration.[14]

Hexahydrofluorenamines (II) were alternately prepared by the intramolecular cyclization of lithio-imines (XXVII). The addition of organometallics to anils has been reported in the literature[15,16] but to the best of our knowledge this reaction has never been applied to the production of angularly aminated polycyclic systems.

Cyclohexanone was alkylated with *o*-bromobenzyl chloride in benzene in the presence of sodium amide to give 2-(*o*-bromobenzyl)cyclohexanone (XXV). Considerably lower yields of XXV were obtained using *o*-bromobenzyl bromide. Treatment of XXV with various primary amines, usually in refluxing benzene or toluene with removal of the water, afforded a number of bromo-imines of type XXVI, characterized by infrared absorption studies. When low boiling amines were employed formation was accomplished at room temperature over several days, using an excess of amine, or in sealed vessels at 100° for twelve hours. Treatment of the bromo-imines with butyllithium at −70° gave, presumably, lithio-imines (XXVII), although the formation of benzyne-type intermediates may not be precluded. By allowing the solution to warm to room temperature and stand for several hours, the desired ring-closures were effected yielding hexahydrofluorenamines XXVIII.

It is interesting to note the 1,2,3,4,4a,9a-hexahydro-N-methyl-4a-fluorenamine (XXVIII. R = CH_3) was in all respects identical (mixture melting point; infrared and ultraviolet spectra) to the hexahydro-N-methylfluorenamine XX gained from the Diels–Alder sequence, indicating that ring closures of the type XXVII→XXVIII proceed to give the *cis* fused ring systems.

Application of this ring-closure was explored further in preparing XXIX and XXX. For example α,2-dibromo-4,5-methylenedioxytoluene[17] reacted with cyclohexanone in the presence of sodamide, yielding 2-(6-bromopiperonyl)cyclohexanone. Treatment of this bromo ketone with methyl-, ethyl, and 3-methoxypropylamines, respectively, followed by low-temperature treatment with butyllithium gave the N-substituted derivatives of XXIX.

Similar cyclizations were also found to be applicable towards the preparation of XXX. 2-Bromo-3-bromomethylthiophene obtained by the bromination of 3-methylthiophene[18] followed by side-chain bromination of the resulting 2-bromo-3-methylthiophene with N-bromosuccinimide,[19] reacted with cyclohexanone to give 2-(2-bromo-3-thenyl)cyclohexanone. The action of 3-methoxypropylamine on this bromo ketone resulted in formation of the corresponding bromo-imine, which was then cyclized to XXX.

A list of 1,2,3,4,4a,9a-hexahydro-N-substituted 4a-fluorenamines, prepared either via the Diels–Alder sequence (method A) or by the ring-closure of lithio-imines (method B), has been presented in Table IV.

Intramolecular ring closures of lithio-imines were also found to be applicable to the synthesis of 5a,6,7,8,9,9a-hexahydro-9a-N-substituted dibenzofuranamines (III). 2(*o*-Bromophenoxy)cyclohexanone (XXXI) was prepared by treating the sodium salt of *o*-bromophenol with 2-chlorocyclohexanone in ether. The condensation of this product with primary amines in refluxing benzene proceeded smoothly and considerably faster than the corresponding reactions of XXV. The N-methylimine XXXII (R = CH_3) was prepared most advantageously by treating XXXI with methylamine in benzene in the presence of calcium hydride. The evolved hydrogen was measured by wet testmeter and afforded a quantitative measure of the progress of imine formation. Subsequent treatment of these bromo-imines (XXVI) with butyllithium at −70° and allowing the solution to warm to room temperature gave the 5a,6,7,8,9a-dibenzo-9a-furanamines.

A compilation of the compounds prepared in this fashion is presented in Table V.

Pharmacology.—Pharmacological studies carried out in these laboratories by Drs. G. Chen and D. A. McCarthy have pointed to the fact that compounds of types I, II, and III exert pronounced depressant effects upon the central nervous system.

Experimental

Indene-3-carboxylic Acid (VI).—This compound, m.p. 160–161°, was prepared in 80% yield according to directions of Cromwell and Capps.[3]

(14) E. S. Wallis and J. F. Lane, *Org. Reactions* **3**, 267 (1946).
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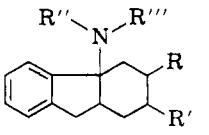
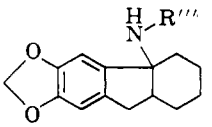
TABLE IV



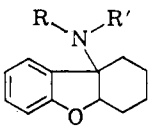
R	R′	R″	R‴	Method[a]	M.p., °C., HCl salt	Yield, %	Empirical formula	Anal. Calcd. C	Calcd. H	Found C	Found H
H	H	H	H	A	256–257	73	$C_{13}H_{17}N\cdot HCl$	69.79	8.11	69.71	8.26
H	H	H	CH_3	E	202–203	96	$C_{14}H_{19}N\cdot HCl$	70.72	8.48	70.49	8.66
				B	201–203	46		70.72	8.48	70.48	8.37
				C	202–203	91		...	...	...	...
H	H	H	C_2H_5	B	198–199	63	$C_{15}H_{21}N\cdot HCl$	71.55	8.81	71.86	8.72
H	H	H	$C_3H_7(n)$	B	229–230		$C_{16}H_{23}N\cdot HCl$	72.29	9.10	72.20	9.13
H	H	H	$(CH_2)_3OCH_3$	B	203–204	56	$C_{17}H_{25}NO\cdot HCl$	69.01	8.86	69.19	8.87
H	H	H	$(CH_2)_2N(C_2H_5)_2$	B	109–114 (0.07 mm.)[b]	23	$C_{19}H_{30}N_2$	79.66	10.50	79.55	10.44
H	H	H	$CH_2C_6H_5$	B	186–187	..	$C_{26}H_{23}N\cdot HCl$	76.53	7.71	76.45	7.78
CH_3	CH_3	H	$C_3H_7(n)$	C	217–218	..	$C_{18}H_{27}N\cdot HCl$	73.56	9.60	73.47	9.73
CH_3	CH_3	H	CH_3	C	231–232	28	$C_{16}H_{23}N\cdot HCl$	72.30	9.10	71.87	9.19
H	H	H	$C_5H_{11}(n)$	B	203–205°	48	$C_{18}H_{27}N\cdot HCl$	73.56	9.60	73.71	9.95
H	H	CH_3	CH_3	D	158–160°	..	$C_{15}H_{21}N\cdot HCl$	...	...	...	...
					90–96/0.15 mm.[c]	..	$C_{15}H_{21}N$	83.66	9.83	83.66	9.78



R‴	Method	M.p., °C., HCl salt	Empirical formula	Anal. Calcd. C	Calcd. H	Found C	Found H
CH_3	B	174–176	$C_{15}H_{19}NO_2\cdot HCl$	63.93	7.15	63.88	7.19
C_2H_5	B	168–169	$C_{16}H_{21}NO_2\cdot HCl$	64.96	7.50	65.06	7.63
$(CH_2)_3OCH_3$	B	161–163	$C_{18}H_{25}NO_3\cdot HCl$	63.59	7.71	63.35	7.78

[a] (A) Hydrolysis of methyl carbamate XVIII; (B) intramolecular ring closure of lithio-imines of type XXVII; (C) catalytic reduction of tetrahydrofurenamines XIII and XIV; (D) Clarke–Eschweiler methylation of XIX; (E) lithium aluminum hydride reduction of methyl carbamate XVIII. [b] B.p. of free base.

TABLE V



R	R′	M.p., °C., HCl salt	Yield, %	Empirical formula	Anal. Calcd. C	Calcd. H	Found C	Found H
H	CH_3	199–200	58	$C_{13}H_{17}NO\cdot HCl$	64.85	7.53	64.95	7.78
H	C_2H_5	184–186	15	$C_{14}H_{19}NO\cdot HCl$	66.26	7.94	66.52	7.92
CH_3	C_2H_5	138–139	..	$C_{15}H_{21}NO\cdot HCl$[b]	67.26	8.28	67.22	8.22
H	$C_3H_7(n)$	181–182	20	$C_{15}H_{21}NO\cdot HCl$	67.26	8.28	67.56	8.09
H	$(CH_2)_3OCH_3$	156–157	42	$C_{16}H_{23}NO_2\cdot HCl$	64.52	8.12	64.84	8.30
H	$(CH_2)_2N(C_2H_5)_2$	127–130 (0.14 mm.)[a]	40	$C_{18}H_{28}N_2O$	74.95	9.78	74.51	10.00
H	$CH_2CH(OC_2H_5)_2$	132–135 (0.17 mm.)[a]	30	$C_{18}H_{27}NO_3$	70.55	9.21	70.28	9.07

[a] B.p. of free base. [b] Obtained from XXXIV (R = CH_3) by acetylation and lithium aluminum hydride reduction, respectively.

Indene-3-carboxylic Acid, Ethyl Ester (VII).—This material, b.p. 100–106° (0.40 mm.) was prepared in 76% yield by refluxing overnight a solution of one part of indene-3-carboxylic acid in eight volumes of ethyl alcohol saturated with anhydrous hydrogen chloride.

Preparation of the 1,4,4a,9a-Tetrahydro-4a-fluorenecarboxylic Acids and/or Their Ethyl Esters. Types VIII and IX, Table I.—Several representative examples of the preparations of types VIII and IX are given below.

(A) 1,4,4a,9a-Tetrahydro-4a-fluorenecarboxylic Acid Ethyl Ester (VIIIA).—A mixture of 450 g. (2.4 moles) of VII, 225 g. (4.2 moles) of butadiene and a trace of *t*-butylcatechol was heated for 15 hr. in a sealed vessel at 180°. Upon cooling, the low boiling material was removed by distillation under aspirator vacuum, after which the main fraction was flash-distilled in order to remove it from polymeric by-products. Redistillation through a Vigreux column yielded 347 g. of adduct, boiling at 102–105° (0.10 mm.). This represents a 60% yield.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.13; H, 7.62.

Saponification of the ester adduct by means of potassium hydroxide in refluxing diethylene glycol for 1 hr., followed by acidification of the diluted reaction mixture with hydrochloric acid gave 1,4,4a,9a-tetrahydro-4a-fluorenecarboxylic acid (IXA) in 96% yield. After recrystallization from isoöctane it melted at 118.5–119.5°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.46; H, 6.58. Found: C, 78.16; H, 6.67.

(B) **The Adduct of Indene-3-carboxylic Acid Ethyl Ester and 2-Chlorobutadiene (VIIIC).**—A solution of 38 g. (0.20 mole) of VII, 200 ml. of xylene, 40 g. of a 50% solution of 2-chlorobutadiene in xylene (containing 20 g. of diene), and a trace of hydroquinone was heated in a three-necked flask equipped with a thermometer, stirrer, and Vigreux column topped with a condenser and thermometer. The reaction mixture was heated, at such a rate that a minimum reflux rate was sustained. This resulted in an initial vapor and pot temperature of 75° and 110° respectively. After a reaction time of 15 hr. the temperatures of the liquid and vapor had essentially reached those of xylene. Removal of the solvent *in vacuo* left a residue which was distilled to give, after a forerun boiling below 101°(0.2 mm.), 16 g. of adduct (a yellow oil); b.p. 115–118°(0.15 mm.); yield, 29%.

Anal. Calcd. for $C_{16}H_{17}ClO_2$: C, 69.42; H, 6.19. Found: C, 69.51; H, 6.45.

Hydrolysis of this adduct ester with potassium hydroxide in diethylene glycol gave the corresponding acid (IXC) which was purified by distillation [b.p. 155°(0.1 mm.)] and subsequent recrystallization from isoöctane, to melt at 108–109°.

Anal. Calcd. for $C_{14}H_{13}ClO_2$: C, 67.61; H, 5.27. Found: C, 67.87; H, 5.45.

(C) **1,4,4a,9a-Tetrahydro-4a-fluorenecarboxylic Acid (IXA). The Reaction of VI and Butadiene.**—Fifty-two grams (0.325 mole of VI, 34 ml. of butadiene and 50 ml. of toluene containing a trace of *t*-butylcatechol was heated to 120° for 24 hr. in a steel bomb. Cooling of the vessel caused part of the product to crystallize out of the reaction mixture. This fraction was removed by filtration and was freed of adhering polymeric material by three extractions with boiling isoöctane. Refrigeration of this solution deposited 19 g. of adduct, m.p. 117–118°. The original mother liquor was then stripped of toluene and the residue was recrystallized from isoöctane containing 5% benzene. The product so obtained weighed 47 g. and melted at 115–117°. The combined fractions (66 g. 95% yield) upon two recrystallizations from benzene–isoöctane (10–90) yielded 56 g. of pure adduct acid, m.p. 118–119°. This represents an 81% yield.

The material was in all respects identical with the acid obtained upon saponification of VIIIA.

The Preparation of 1,4,4a,9a-Tetrahydro-4a-Fluoreneamines. Types XII, XIII, and XIV, Tables I and III.—Experimental details for the conversion of IX, *via* X and XI, to XII, XIII, and XIV are exemplified by the preparation of the series where R = R′ = H.

1,4,4a,9a-Tetrahydro-4a-fluorenecarboxylic Acid Amide (Xa).—A solution of 55 g. (0.26 mole) of IXA in 250 ml. of benzene containing 21.8 ml. (0.30 mole) or reagent grade thionyl chloride was refluxed for 1–2 hr. The cooled mixture was then added slowly and with vigorous stirring to 500 ml. of concentrated ammonium hydroxide at 0–5°, after which it was stirred for another hour with cooling. Separation of the phases (troublesome emulsions were broken by the use of solid sodium sulfate and small amounts of alcohol) and washing of the organic phase with 1 *N* sodium hydroxide followed by drying and stripping of solvent gave the crude solid amide. The material was recrystallized from isoöctane to deposit 35 g. (64% yield) of product melting at 79.5–81°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.83; H, 7.09. Found: C, 79.15; H, 7.25.

1,4,4a,9a-Tetrahydro-4a-fluorenecarbamic Acid Methyl Ester (XIA).—To a sodium methoxide solution freshly prepared from 37 g. (1.60 moles) of sodium in 1250 ml. of reagent grade methyl alcohol was added at room temperature 68 g. (0.32 mole) of amide XA. The mixture was then cooled to −20°, at which stage 17.4 ml. (0.34 mole) of bromine was introduced slowly while keeping the temperature at −20°; upon completion the solution was allowed to reach room temperature and was finally brought to reflux for 1.5 hr. Acetic acid (58.3 ml., 1.02 moles) was added to the cooled solution and solvent was chased off *in vacuo*. The residue, suspended in 500 ml. of ether was washed with water and was dried. Removal of the solvent yielded 63 g. of the essentially pure urethan, which did not exhibit any amide absorption upon infrared examination. The material was purified by distillation and boiled at 160–165°(0.4 mm.) An analytical sample was collected at 162°(0.40 mm.)

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.05. Found: C, 73.94; H, 7.05.

1,4,4a,9a-Tetrahydro-4a-fluorenamine Hydrochloride (XIIA).—A solution of 5.5 g. (0.226 mole) of carbamate XIA in 50 ml. of diethylene glycol containing 6.2 g. of potassium hydroxide was refluxed for 16 hr. It was then poured into 200 ml. of ice-water and was extracted with ether. The addition of isopropanolic hydrogen chloride to the combined, dried organic extracts gave 3.6 g. of amine hydrochloride, which was recrystallized from methyl alcohol ether to melt at 227–229°. The crude yield amounted to 85%.

Anal. Calcd. for $C_{13}H_{15}N \cdot HCl$: C, 70.42; H, 7.28. Found: C, 70.36; H, 7.36.

1,4,4a,9a-Tetrahydro-N-methyl-4a-fluorenamine Hydrochloride (XIVA).—Five grams (0.206 mole) of urethan XIA in 25 ml. of anhydrous ether was added slowly to a stirred slurry of 5 g. of lithium aluminum hydride in 400 ml. of ether. The mixture was stirred for 15 hr. and was subsequently decomposed by the successive additions of 5 ml. of water, 3.75 ml. of 5 *N* sodium hydroxide solution, and 17.5 ml. of water. Removal of the inorganic material by filtration and the addition of isopropanolic hydrogen chloride to the ethereal filtrate yielded 3.5 g. (73% yield) of amine hydrochloride, m.p. 201–202°. An analytical sample from methyl alcohol–ether melted at 201–202°.

Anal. Calcd. for $C_{14}H_{17}N \cdot HCl$: C, 71.31; H, 7.69. Found: C, 71.36; H, 7.56.

1,4,4a,9a-Tetrahydro-N-ethyl-4a-fluorenamine Hydrochloride (XIIIA. R″ = $-C_2H_5$).—To an ice cold solution of 8.0 g. (0.043 mole) of the free base of XII (R = R′ = H) in 50 ml. of methylene chloride was added slowly 5.3 g. (0.056 mole) of acetic anhydride. The mixture was kept at room temperature for 5 hr. and was then washed through with dilute hydrochloric acid and sodium bicarbonate solution, respectively. After drying of the organic phase and removal of the solvent, the crude amide was obtained as a solid material. A small sample recrystallized from benzene melted at 144–145°. The N-acetyl derivative was subsequently extracted into a slurry of 8 g. of lithium aluminum hydride in 500 ml. of ether. Decomposition of the resulting complex with 8 ml. of water, 6 ml. of 5 *N* sodium hydroxide and 28 ml. of water, respectively, and the addition of isopropanolic hydrogen chloride to the ethereal filtrate gave 7.0 g. (65% yield, based on the primary amine) of the hydrochloride salt of the product. A sample recrystallized from methyl alcohol–ether melted at 204–206°.

Anal. Calcd. for $C_{15}H_{19}N \cdot HCl$: C, 72.12; H, 8.07. Found: C, 72.43; H, 8.34.

1,2,3,4,4a,9a-Hexahydro-4a-fluorene Carboxylic Acid (XVI).—Unsaturated ester adduct VIIIA, 39 g. (0.16 mole) in 250 ml. of 95% alcohol was hydrogenated at 50 lb. in the presence of 1 g. of 20% palladium on carbon. The theoretical amount of hydrogen was absorbed after 0.5 hr., and the reaction was terminated. Removal of the catalyst by filtration and stripping of the solvent left the crude hexahydro ester (XV) as a colorless oil, which was saponified without further purification by refluxing for 1 hr. in a solution of 36 g. of potassium hydroxide in 175 ml. of diethylene glycol. The mixture was subsequently poured onto 500 ml. of ice–water, which was then acidified to yield the crude carboxylic acid as an oil. The material was dissolved in benzene and was combined with a benzene extract of the aqueous phase. Drying of the organic phase and evaporation of the solvent gave an anhydrous oil, which was converted to crystalline acid by recrystallization from isoöctane. Twenty-two grams of product was isolated after one further recrystallization from benzene–petroleum ether. The material melted at 117–118°; yield: 63%. An analytical sample from benzene-petroleum ether melted at 117–118°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.73; H, 7.46. Found: C, 77.49; H, 7.73.

The Preparation of 1,2,3,4,4a,9a-Hexahydro-4a-fluorenamines (XIX and XX).—The conversion of acid XVI to **1,2,3,4,4a,9a-hexahydro-4a-fluorenecarboxylic acid amide (XVII)** was carried out in analogous fashion to the one described above for XA. The procedure employed to prepare XIA was found to be applicable towards the preparation of **1,2,3,4,4a,9a-hexahydro-4a-fluorenecarbamic acid methyl ester (XVIII).** The physical properties of

these compounds are described in Table II. The hydrolysis of XVIII to **1,2,3,4,4a,9a-hexahydro-4a-fluorenamide (XIX)** and the lithium aluminum hydride reduction of XVIII to **1,2,3,4,4a,9a-hexahydro-N-methyl-4a-fluorenamine (XX)** were carried out in fashions similar to those given for the preparation of XIIA and XIVA. The results have been included in Table IV.

The reduction of **4,4,4a,9a-tetrahydro-4a-fluorenamines** to the **1,2,3,4,4a,9a-hexahydro-4a-fluorenamines** is best exemplified by the conversion of XIVA to XX:

1,2,3,4,4a,9a-Hexahydro-N-methyl-4a-fluorenamine Hydrochloride (XX).—A X solution of 10.0 g. (0.0423 mole) of XIVA hydrochloride in 300 ml. of methyl alcohol containing 0.2 g. of platinum oxide was hydrogenated at an initial pressure of 48 lb. After 9 min. the theoretical amount of hydrogen had been taken up. The catalyst was then removed by filtration. Removal of the solvent left a solid hydrochloride salt. This material was dissolved in 70 ml. of warm water. A white, flocculent impurity was filtered off. The solution was then rendered basic and the free base was extracted by means of ether. Drying of the organic phase, and the addition of a slight excess of isopropanolic hydrogen chloride yielded 9.1 g. of pure amine hydrochloride, melting at 202–203°. The material was in all respects (infrared spectrum, mixture melting point) identical with amine hydrochloride XX.

2-(*o*-Bromobenzyl)cyclohexanone (XXV).—A suspension of 75 g. (containing 37.5 g., (0.95 mole) of 50% sodium amide dispersion in xylene and 1500 ml. of reagent grade benzene was brought to reflux in a 5-l. flask equipped with stirrer and condenser. To this was introduced dropwise a mixture of 154 g. (0.75 mole) of *o*-bromobenzyl chloride and 98 g. (1.0 mole) of cyclohexanone at such a rate as to maintain a gentle rate of reflux. Upon completion of the addition the reaction mixture was heated for an additional 6 hr. The cautious addition of 1000 ml. of water to the cooled suspension gave a clear, two-phase system. The organic phase was washed two more times with water and was dried over magnesium sulfate. Removal of the solvent and flash distillation of the residue gave 155 g. of crude product boiling at 100–200° (0.3–1.0 mm.). The material was refractionated, giving 140 g. of product, b.p. 146–150° (0.65 mm.) or 108–112° (0.07 mm.). This represents a 70% yield. At times significantly lower yields (45%) were obtained.

Anal. Calcd. for $C_{13}H_{15}BrO$: C, 58.44; H, 5.70. Found: C, 58.44; H, 5.69.

2-(6-Bromopiperonyl)cyclohexanone.—The reaction of 217 g. (0.70 mole) of α,2-dibromo-4,5-methylenedioxytoluene[17] with 98 g. (1.0 mole) of cyclohexanone in 1000 ml. of benzene containing 47.5 g. (1.22 moles) of sodium amide dispersion according to directions presented for the preparation of XXV gave an oil, b.p. *ca.* 165° (0.15 mm.). Trituration of this distillate with isooctane afforded 141 g. (65% yield) of crystalline product, melting at 80–82°. An analytical sample from alcohol melted at 84–85°.

Anal. Calcd. for $C_{14}H_{15}BrO_3$: C, 54.02; H, 4.80. Found: C, 54.17; H, 5.13.

2-(2-Bromo-3-thenyl)cyclohexanone.—This compound was prepared by the reaction of crude 2-bromo-3-bromomethylthiophene with cyclohexanone in benzene using sodium amide as the base to give a crude product, b.p. 150–180° (0.5–1.0 mm.), in 21% yield. Upon refractionation most of this material was found to boil at 138–145° (0.15 mm.). Progressive decomposition during distillations could be retarded by the addition of anhydrous potassium carbonate.

Anal. Calcd. for $C_{11}H_{13}BrOS$: C, 48.35; H, 4.79. Found: C, 48.15; H, 4.98.

The Reaction of the Bromo Ketones with Amines Followed by Cyclization to Give XXVIII, XXIX, and XXX.—This type of reaction is best illustrated by the preparation of **1,2,3,4,4a,9a,-hexahydro-N-(3-methoxypropyl)-4a-fluorenamine hydrochloride** (XXVIII. R = 3-methoxypropyl)—A solution of 26.7 g. (0.10 mole) of XXV, 11.0 g. (0.123 mole) of 3-methoxypropylamine and 200 ml. of benzene containing a few drops of benzenesulfonic acid was refluxed in an apparatus equipped with a water trap. After 2–3 hr. the theoretical amount of water had evolved and the solvent was removed *in vacuo*. Infrared examination of the residue indicated the persistance of some carbonyl residue and the reaction was subsequently carried to completion by the addition of another 5 ml. of methoxypropylamine in 100 ml. of refluxing benzene. About 0.4 ml. of water was again collected. The crude mixture was then freed of solvent and excess amine and was characterized spectrally by a strong imine-band at 6.07 μ and the absence of carbonyl absorption. The bromo-imine (XXVI. R = 3-methoxypropyl) was used without further purification; it was found to be distillable and boiled at 140–150° (0.15m m.).

The crude Schiff's base, assumed to be pure imine (0.10 mole), dissolved in 25 ml. of ether was added rapidly to a solution of 0.20 mole of freshly prepared butyllithium in 175 ml. of ether at −70°. The mixture was cooled by means of a Dry Ice bath during this operation, but the internal temperature rose to −20° during this operation. The mixture was stirred until the temperature had fallen again to −70° and was kept there for another 30 min. The cooling bath was then removed and to it was added 200 ml. of ether. The solution was subsequently allowed to reach room temperature and was stirred for 1–2 hr. Gentle, spontaneous refluxing occurred at this stage, necessitating the use of a condenser. The complex was decomposed by the cautious addition of 200 ml. of water and was washed with two fresh portions of water. Isolation of the stable basic components from the organic layer was carried out by extractions of the ether layer with dilute hydrochloric acid and treatment with base of the aqueous phase. This operation also served to destroy any residual imines present in the reaction mixture. The addition phase was extracted three times with ether and the ether phase was dried. The addition of isopropanolic hydrogen chloride to the ether solution yielded 16 g. (56% yield) of the hexahydrofluorenamine hydrochloride, melting *ca.* 200°. Recrystallization from methyl alcohol-ether gave analytically pure material, m.p. 203–204°.

Anal. Calcd. for $C_{17}H_{25}NO\cdot HCl$: C, 69.01; H, 8.86; N, 4.74. Found: C, 69.19; H, 8.87; N, 4.59.

Other, 1,2,3,4,4a,9a-hexahydro-N-alkyl-4a-fluorenamines prepared by this method have been listed in Table IV under method B.

2-(*o*-Bromophenoxy)cyclohexanone (XXXI).—To a mixture of 80 g. (1.48 moles) of commercial sodium methoxide in 300 ml. of absolute methyl alcohol in a 5-l. three-necked flask was added 211 g. (1.22 moles) of *o*-bromophenol. The solvent was removed *in vacuo* and the solid residue was stripped of residual alcohol by prolonged evacuation by means of an oil pump. Anhydrous ether, 1500 ml., was added to the mixture after which 160 g. (1.22 moles) of fresh 2-chlorocyclohexanone (Aldrich Chemical Co.) was introduced dropwise and with stirring. Upon completion of the addition the mixture was stirred for another hour. The inorganic salts were dissolved by the addition of 500 ml. of water and the ethereal phase was subsequently washed with dilute sodium hydroxide solution, 10% acetic acid and water. It was dried over magnesium sulfate. The solvent was partially stripped *in vacuo* until the volume was 500–700 ml. At that point most of the product had crystallized and the mixture was cooled on ice. Filtration of the product gave 135 g. of product, melting at 103–105°. This represents a 41% yield. An analytical sample of this material, prepared from methyl alcohol, melted at 105–106°.

Anal. Calcd. for $C_{12}H_{13}BrO$: C, 53.54; H, 4.87. Found: C, 53.62; H, 5.61.

The Preparation of the 5a,6,7,8,9,9a-Hexahydro-N-alkyl-9a-dibenzofuranamines (XXXIV).—The reaction of XXXI with various primary amines was carried out analogously to the method described for XXV with amines. The ring closures of bromoimines XXXII *via* lithio-imines XXXIII to the dibenzofuranamines were similar to those discussed for the preparations of XXVIII. Noteworthy is the reaction of XXXV with methylamine in the presence of calcium hydride, followed by ring closure to XXXIV (R = CH_3).

5α,6,7,8,9,9a-Hexahydro-N-methyl-9a-dibenzofuranamine (XXXIV. R = H, R′ = CH_3).—To a stirred mixture of 26.5 g. (0.10 mole) of XXXI in 200 ml. of benzene, cooled on ice, and in apparatus attached to a "wet test meter" was added 6 g. (0.143 mole) of calcium hydride. To this, in turn, was added a solution of 4.65 g. (0.15 mole) of methylamine in 50 ml. of benzene. After 1 hr. *ca.* 0.025 mole of hydrogen had evolved and the reaction was allowed to proceed for 15 hr. by which time the theoretical amount of hydrogen had been collected. The solids were removed by filtration through a Celite pad. Stripping of the solvent from the filtrate left a residue free of ketonic starting material.

The bromo-imine, dissolved in 25 ml. of ether was added to 0.20 mole of butyllithium in 200 ml. of ether at −70°. After 30 min. at −70° the reaction mixture was diluted with 200 ml. of ether and permitted to come to room temperature for 2 hr. This was accompanied by gentle refluxing. Decomposition of

the complex and acid extraction and treatment with base of the acidic aqueous fraction gave the product as a free base, which was isolated by ether extraction. The ether solution was dried and stripped of solvent. Fractionation of this residue gave 11 g. (58% yield) of product, boiling at 87–93° (0.15 mm.).

The hydrochloride salt of the amine prepared by the addition of isopropanolic hydrogen chloride to an ethereal solution of the base melted at 199–200°.

Anal. Calcd. for $C_{13}H_{17}NO \cdot HCl$: C, 64.85; H, 7.53. Found: C, 64.95; H, 7.78.

The hexahydro - 9a - dibenzofuranamines prepared by this method have been listed in Table V.

4a,5,6,7,8,8a-Hexahydro-N-(3-methoxypropyl)-4H-indeno-[1,2 - *b*]thiophen - 8a - amine Hydrochloride (XXX).—This compound was prepared by the reaction of 12 g. (0.0435 mole) of 2-(2-bromo-3-thenyl)cyclohexanone (*vide infra*) with 8 g. of 3-methoxypropylamine in benzene (benzenesulfonic acid as catalyst), followed by treatment of the bromo-imine with butyllithium at −70°, as described for the preparation of XXVIII. There was obtained 7 g. (54%) of product, m.p. 145–146° (methanol/ether).

Anal. Calcd. for $C_{15}H_{23}NOS \cdot HCl$: C, 59.70; H, 8.01. Found: C, 59.73; H, 8.25.

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Synthetic Approaches to Quinoxaline Antibiotics. Synthesis of Bisquinoxaloyl Derivatives[1a]

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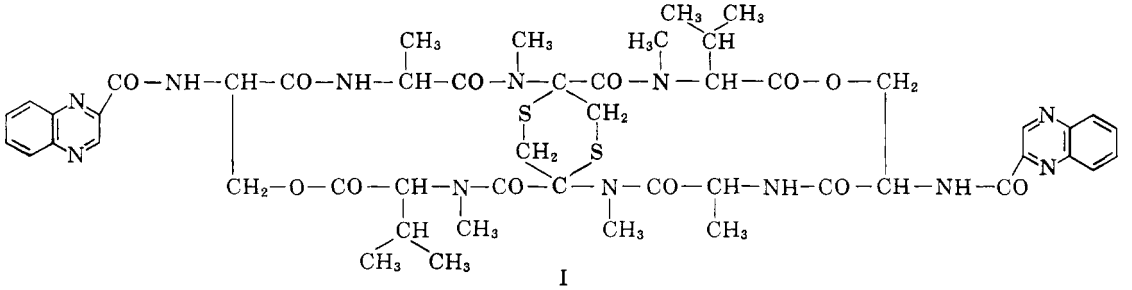
The synthetic approach to the preparation of some antibiotics composed of two quinoxaline rings connected through polypeptide linkages has been studied. Model compounds of the types R—CO—NH$(CH_2)_x$—NH—CO—R and R—CO—NH—CH_2—CO—NH$(CH_2)_x$—NH—CO—CH_2—NH—CO—R, where R = quinoxalinyl group, have been synthesized.

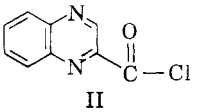
A number of polypeptide antibiotics such as levomycin,[2] actinoleukin,[3] echinomycin,[4] quinomycin,[5] etc., containing the quinoxaline moiety have recently been reported. The structure of echinomycin (I), which was found to be identical with quinomycin A,[6] is composed of two quinoxaline rings linked by peptide chains containing the amino acids D-serine, L-alanine, L-N-methylcysteine, and L-N-methylvaline.



I

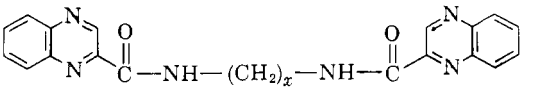
These antibiotics have not yet been synthesized. In order to understand the importance of the peptide link and the requirement for the amino acid sequence in this type of compound,[7] the synthesis of hitherto unreported bisquinoxaloyl (bisquinoxalinecarbonyl) derivatives was investigated.

2-Quinoxalinecarboxylic acid, prepared by the oxidation of 2-methylquinoxaline,[8] was chlorinated in thionyl chloride to yield 2-quinoxaloyl chloride (II). Interaction of two equivalents of II with one equivalent



II

of the appropriate diamine in an inert solvent, in the presence of triethylamine, readily yielded the N,N′-polymethylenebis-2-quinoxalinecarboxamides (III).



III

(1) (a) This investigation was supported by the Cancer Chemotherapy National Service Center (contract SA-43-ph-3025), National Cancer Institute, National Institutes of Health, U. S. Public Health Service. (b) To whom all inquiries should be directed.

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