Parke, Davis and Company, for providing the estrogen assays. We are grateful to Mrs. Kay W. Berrodin, Miss Teresa H. Dittrich, Mrs. Lorraine Scheinman, Mrs. Joyce Holmes, and Miss Carol J. Stefanac for preparing some of the compounds. Microanalyses were by Mr. C. E. Childs and his associates and spectra were by Dr. J. M. Vandenbelt, Mr. R. B. Scott, and Mr. E. J. Schoeb and their associates. We also wish to thank Mr. Paul D. Uhlendorf and Mr. Claude H. Spencer for their able assistance in the biochemical studies.

Imidazoline Derivatives with Antiarrhythmic Activity[1]

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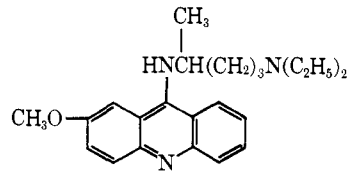
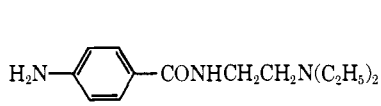
Imidazolinylmethyl derivatives of a number of bicyclic and tricyclic ring systems were prepared and studied for their effect on experimental cardiac arrhythmias. One of the bicyclic compounds, 3-phenyl-2,3,4,5-tetrahydro-1-benzazepine, obtained by means of a Schmidt reaction on 2-phenyl-3,4-dihydro-1-naphthalenone followed by reduction with $LiAlH_4$, yielded imidazoline derivatives of particular interest and was studied in greater detail. Numerous analogs were prepared.

It has been found that many chemical drug groups have the ability to suppress cardiac arrhythmias. In general these drugs belong to the group of local anesthetics, antispasmodics, antihistamines, and β-adrenergic receptor blockers, *e.g.*, quinidine, quinacrin (I), procainamide (II), antazoline[2] (III), and propranolol (IV).[3] All have in common the property of depressing the physiological functions of the cardiac muscle in such a way as to affect favorably the course of an arrhythmia. None, however, are uniformly successful.[4]



I



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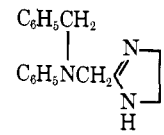
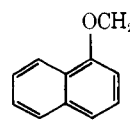
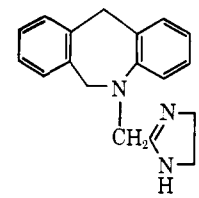


III



IV



V

In a previous paper[5] we had reported that 5-(2-imidazolinylmethyl)-5,6-dihydromorphanthridine (V) had shown interesting antifibrillatory effects on aconitine-induced cardiac arrhythmias. The present report is an extension of our previous work and describes a number of bicyclic and tricyclic ring systems to which a 2-imidazolinylmethyl group has been attached in an attempt to find compounds with improved antifibrillatory activity. Derivatives of 3-phenyl-2,3,4,5-tetrahydro-1-benzazepine were of particular interest and were studied in greater detail. In Tables I and II are shown a variety of tricyclic ring systems attached to a 2-imidazolinylmethyl group. The ring systems employed as starting materials in this part of the study are 10,11-dihydrodibenz[*b*,*f*][1,4]thiazepine,[6] 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine,[7] 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine,[8] 10,11-dihydrodibenz[*b*,*f*]azepine (iminodibenzyl), phenoxazine, phenothiazine, acridan, dihydrophenanthridine, carbazole, tetrahydrocarbazole, 6,7-dihydrobenz[*c*,*e*]azepine,[9] thioxanthene, anthrone, and 10,11-dihydrodibenz[*a*,*d*]cyclohepten-5-one.[10] The resulting imidazoline derivatives and their relative activity are shown in Tables I and II. A number of previously reported compounds have been included in these tables for comparative purposes. Four procedures were used to attach the imidazolinylmethyl group to the above described bicyclic and tricyclic ring systems. As shown in Chart I, the nature of the ring system determined the method employed.

Derivatives of the bicyclic 3-, 4-, and 5-phenyl-2,3,4,5-tetrahydrobenzazepines were included in the second part of this study. It is possible to visualize these compounds as being formed from a tricyclic structure merely by separating one of the benzene rings and attaching it to the remaining bicyclic ring system by a single bond. The 3-, 4-, and 5-phenyl-3,4-dihydrobenzazepinones were obtained by means of a Schmidt reaction on the corresponding 2-, 3-, or 4-phenyl-3,4-dihydro-1-naphthalenone (VIa–d). This reaction can lead to the isomeric benzazepinones VII and VIII,

(1) Presented in part before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) L. D. Dreifus, T. F. McGarry, Y. Watanabe, S. R. Kline, M. Waldman, and W. Likoff, *Am. Heart. J.*, **65**, 607 (1963).

(3) W. M. Ginn, Jr., G. V. Irons, Jr., and E. S. Orgain, *Circulation*, **32**, Supp. II, 97 (1965); J. P. Payne and R. M. Senfield, *Brit. Med. J.*, **1**, 603 (1964). See also Symposium on β-Adrenergic Receptor Blockade, *Am. J. Cardiol.*, **18**, 303 (1966).

(4) J. R. DiPalma in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 624.

(5) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).

(6) R. Jaques, A. Rossi, E. Urech, H. J. Bein, and K. Hoffmann, *Helv Chim. Acta*, **42**, 1265 (1959).

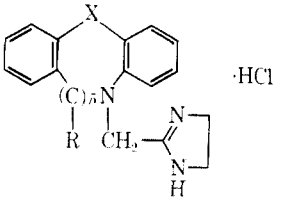
(7) J. O. Jilek, J. Pomikacek, and M. Protiva, Czechoslovakian Patent 111,215 (June 15, 1964); *Chem. Abstr.*, **62**, 14707 (1965).

(8) A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963).

(9) W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951).

(10) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951).

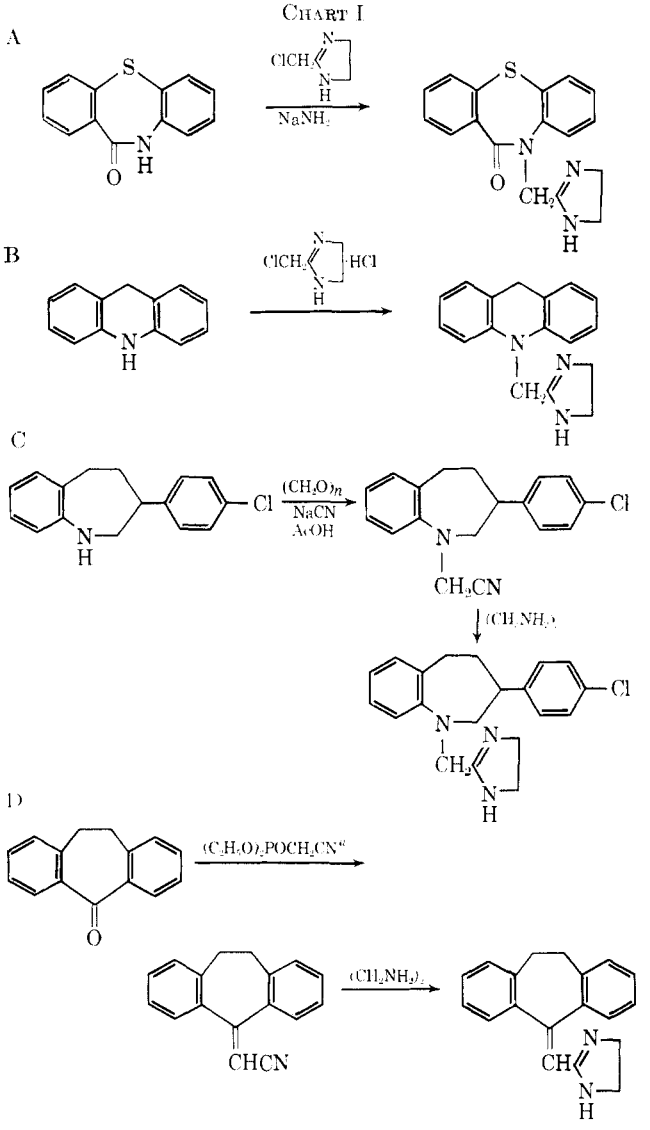
TABLE I: TRICYCLIC DERIVATIVES



No.[a]	X	n	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity
1	S	1	O	282–284	$C_{17}H_{15}N_3OS \cdot HCl$	59.04	4.7	12.1	59.2	4.8	12.0	+1
2	S	1	H_2	236–238	$C_{17}H_{17}N_3S \cdot HCl$	61.5	5.5	12.7	61.8	5.7	12.3	+1
3	O	1	H_2	240–242	$C_{17}H_{17}N_3O \cdot HCl$	64.7	5.7	13.3	64.9	6.0	13.8	+1
4	CH_2CH_2	1	H_2	142–144	$C_{18}H_{21}N_3$	78.3	7.3	14.4	78.3	7.4	14.4	+2
5[b]	CH_2CH_2	0	...	270–272	$C_{18}H_{19}N_3 \cdot HCl$							+3
6[b]	O	0	...	243–246	$C_{16}H_{15}N_3O \cdot HCl$							0
7[b]	S	0	...	239 dec	$C_{16}H_{15}N_3S \cdot HCl$							0
8	CH_2	0	...	268–271	$C_{17}H_{17}N_3 \cdot HCl$	68.1	6.0	14.0	68.1	6.0	14.1	+1
9	...[c]	1	O	284–286	$C_{17}H_{15}N_3O \cdot HCl$	65.1	5.1	13.4	64.5	5.3	13.3	+1
10	...	1	H_2	204–208	$C_{17}H_{17}N_3 \cdot HCl$	68.1	6.0	14.0				−1
11	...	1	H, CH_3	267–269	$C_{18}H_{19}N_3 \cdot HCl$	68.9	6.4	13.4	69.0	6.5	12.9	+1
12[d]	...	0	...	285–286	$C_{16}H_{15}N_3 \cdot HCl$							0

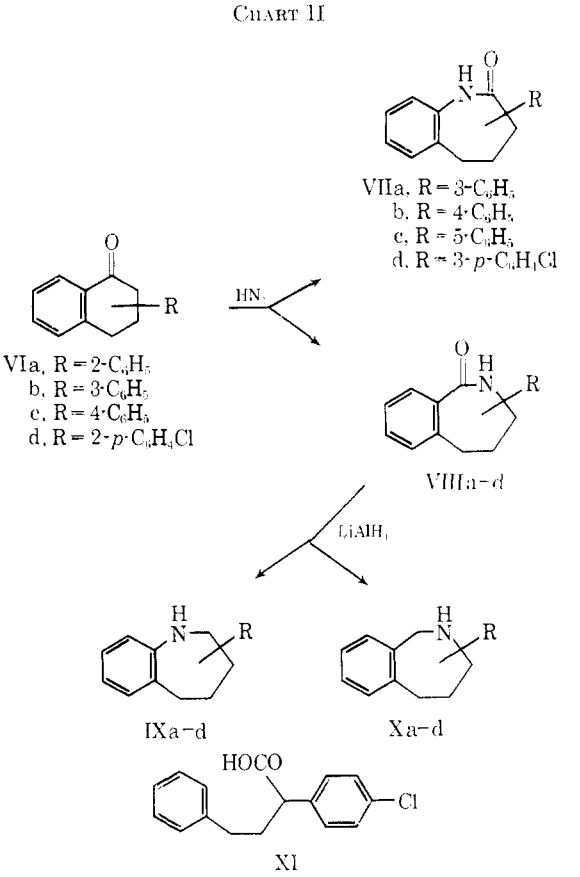
[a] W. Schindler and F. Hafliger, *Helv. Chim. Acta*, **37**, 472 (1954). [b] E. Urech, A. Marxer, and K. Miescher, *ibid.*, **33**, 1386 (1950); (to CIBA Pharmaceutical Co.), U. S. Patent 2,485,212 (Oct 18, 1949). [c] Direct linkage. [d] M. Hartmann and S. Studer (to CIBA Pharmaceutical Co.), U. S. Patent 2,569,415 (Sept 25, 1951). [e] Compounds **1**, **9**, and **12** were prepared by procedure A, **5–8** by procedure B, and **2–4**, **10**, and **11** by procedure C, Chart I.

CHART I



[a] W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

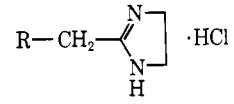
CHART II

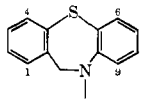
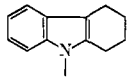
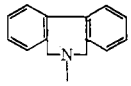
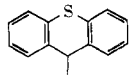
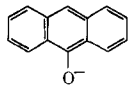
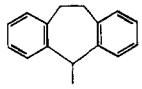
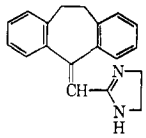


as shown in Chart II. In the case of the 2-phenyl-3,4-dihydro-1-naphthalenones (VIa and VId) only one isomer, VIIa and VIId, respectively, was isolated. The structure of VIId was proven by hydrolytic cleavage of the lactam followed by diazotization and elimination of the diazonium group leading to 2-(*p*-chlorophenyl)-4-phenylbutyric acid (XI) which was identical

TABLE II

TRICYCLIC DERIVATIVES



No.[c]	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity
										
13	8-CH_3	247–249	$C_{18}H_{19}N_3S \cdot HCl$	62.5	5.8	12.1	62.8	5.8	11.6	+2
14	4-CH_3	265 dec					62.7	5.9	12.0	0
15	7-Cl-2-CH_3	270	$C_{18}H_{18}ClN_3S \cdot HCl$	56.8	5.0	11.0	56.6	5.1	11.1	0
16[a]		278	$C_{16}H_{19}N_3 \cdot HCl$							0
17		260 dec	$C_{18}H_{19}N_3 \cdot HCl$	61.7	6.0	12.0	61.7	6.4	11.9	+1
18[b]		229-230	$C_{17}H_{16}N_2S \cdot HCl$							+2
19		223–225	$C_{18}H_{16}N_2O \cdot HCl$	69.1	5.5	8.9	68.7	5.6	8.4	+1 to +2
20		260	$C_{19}H_{20}N_2 \cdot HCl$	72.9	6.8	8.9	72.4	6.8	8.5	+2
21		258–260	$C_{19}H_{18}N_2 \cdot HCl$	73.4	6.2	9.0	73.2	6.4	8.6	+1

[a] See ref *d*, Table I. [b] J. A. Faust and M. Sahyun, U. S. Patent 3,042,674 (July 3, 1962). [c] Compounds **13–15** were prepared by procedure C, **16** and **19** by procedure A, **17** by procedure B, and **18, 20,** and **21** by procedure D, Chart I. In the case of **18** and **20,** the intermediate unsaturated nitrile was hydrogenated using Pd-C in ethanol.

with an authentic sample prepared according to Ansell, *et al.*[11]

Reduction of VII and VIIIa–d with $LiAlH_4$ gave the tetrahydrobenzazepines IX and X. Compounds IXa–d, in which the nitrogen atom is adjacent to the benzene ring showed a typical aniline-type absorption in the ultraviolet which was reduced to a benzene-type absorption on addition of HCl. The other isomer, X, showed only benzene-type absorption as expected. These criteria were used to assign structures to the various tetrahydrobenzazepines obtained *via* the Schmidt reaction. It was also noted that the lactams VII and VIII could be differentiated on the basis of the infrared absorption band of the lactam.

The Schmidt reaction on 3- and 4-phenyl-3,4-dihydro-1-naphthalenone (VIb and VIc) yielded mixtures of the two possible isomeric benzazepinones VIIb and c and VIIIb and c, respectively. In the case of the 4-phenyl derivatives VIIb and VIIIb the isomers could be separated quite readily by crystallization. However, the 5-phenyl derivatives VIIc and VIIIc could be separated only with difficulty, VIIc was obtained by direct crystallization from the mixture of the isomers, and VIIIc was isolated from the mother liquors following acid hydrolysis which resulted in cleavage of the "anilide"-type lactam VIIc but did not affect the "benzamide" lactam VIIIc. In both instances the anilide-type lactam VIIb and c represented the major product.

The 2-phenyl-3,4-dihydro-1-naphthalenones used as starting materials were prepared according to Newman[12] and Ansell, *et al.*;[11] 3-phenyl- and 4-phenyl-3,4-dihydro-1-naphthalenone have been described by Spring[13] and Wawzonek and Kozikowski,[14] respectively. Various substituted 2-phenyl-3,4-dihydro-1-naphthalenones have also been reported by Bencze, *et al.*[15] The intermediate dihydrobenzazepinones and tetrahydrobenzazepines employed are listed in Table III. N-Substituted derivatives of the phenyltetrahydrobenzazepines and phenyldihydrobenzazepinones were prepared using procedures A or C, Chart I, and are shown in Table IV.

(11) M. F. Ansell, G. T. Brooks, and B. A. Knights, *J. Chem. Soc.*, 212 (1961).

(12) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938); **62**, 870 (1940).

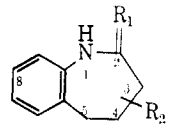
(13) F. S. Spring, *J. Chem. Soc.* 1332 (1934).

(14) S. Wawzonek and J. Kozikowski, *J. Am. Chem. Soc.*, **76**, 1641 (1954).

(15) W. L. Bencze, L. I. Barsky, R. W. J. Carney, A. A. Renzi, and G. deStevens, *J. Med. Chem.*, **10**, 138 (1967).

TABLE III

INTERMEDIATE 3,4-DIHYDROBENZAZEPONONES AND 2,3,4,5-TETRAHYDROBENZAZEPINES



No.	R_1	R_2	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
22	O	3-C_6H_5	197–199	$C_{16}H_{15}NO$	81.0	6.4	5.9	80.5	6.3	5.9
23	O	3-*p*-$C_6H_4CH_3$	193–195	$C_{17}H_{17}NO$	81.2	6.8	5.6	81.3	6.9	5.7
24	O	3-*p*-C_6H_5Cl	193–195	$C_{16}H_{14}ClNO$	70.7	5.2	5.2	70.7	5.2	5.0
25	O	3-*m*-C_6H_4Cl	204–207					70.3	5.2	5.1
26	O	3-*o*-C_6H_4Cl	245–247					70.9	5.3	5.2
27	O	3-C_6H_5, 8-Cl	228–230					70.6	5.1	5.1
28[a]	O	4-C_6H_5	142–144	$C_{16}H_{15}NO$	81.0	6.4	5.9	80.8	6.5	6.1
29[b]	O	5-C_6H_5	180–182					81.2	6.4	6.2
30	H_2	3-C_6H_5	122–124	$C_{16}H_{17}N$	86.0	7.7	6.3	85.8	7.5	6.2
31	H_2	3-*p*-$C_6H_4CH_3$	76–78	$C_{17}H_{19}N$	86.0	8.1		85.9	8.1	
32	H_2	3-*p*-C_6H_4Cl	100–102	$C_{16}H_{16}ClN$	74.6	6.3	5.4	74.3	6.2	5.4
33	H_2	3-*m*-C_6H_4Cl	Oil					74.8	6.5	5.4
34	H_2	3-*o*-C_6H_4Cl	138–139					74.6	6.6	5.4
35	H_2	3-C_6H_5, 8-Cl	73–75					74.5	6.3	5.3
36	H_2	4-C_6H_5	145 (0.05)[c]	$C_{16}H_{17}N$	86.0	7.7	6.3	86.6	7.7	6.2
37	H_2	5-C_6H_5						85.8	7.6	6.3
			240–243	$C_{16}H_{17}N \cdot HCl$	74.0	6.6	5.4	74.3	6.9	5.4

[a] Reference 18. [b] A. Bertho, *Chem. Ber.*, **90**, 29 (1957), prepared this compound by an alternate synthesis, mp 180–180.5°. [c] Boiling point, °C (mm).

To further extend the study of the relationship between chemical structure and antifibrillatory activity, the imidazolinylmethyl group was also attached to a number of other bicyclic structures, *e.g.*, 2-phenyl-[16] and 3-phenyl-1,2,3,4-tetrahydroquinoline,[17] 2-phenyl-2,3,4,5-tetrahydro-1,5-benzthiazepine,[18] 1-phenyl-1,2,-3,4-tetrahydroisoquinoline,[19] 4-phenyl-1,5(1H)-benzodiazepin-2-one,[20] and other structures as shown in Table V. It is worthy of note that alkylation of 2-phenylindole with 2-chloromethylimidazoline did not result in the N-alkylated derivative as indicated by Schindler, *et al.*,[21] but yielded instead 3-(2-imidazolinylmethyl)-2-phenylindole (Table V, **62**), which was confirmed by nmr spectroscopy.

Pharmacological Evaluation.—The compounds described above were tested for antifibrillatory activity by our Division of Macrobiology. The activity was graded from 0 to +4 depending on the dose, therapeutic range, and toxicity of the compound studied. The substance was given orally by capsule to unanesthetized cats. After several hours the hearts were removed and perfused with Ringers solution containing 0.022 μg/ml of aconitine nitrate. In untreated animals this resulted in ventricular fibrillation after 18 min. The effectiveness of the compound was judged by the length of time the onset of fibrillation was delayed after starting perfusion with aconitine nitrate. These results were compared in all cases to untreated animals.

In Table I, compounds incorporating a lactam group (**1** and **9**) were only slightly active and the same result was observed for **10–12** in which the two benzene rings are connected by a direct bond. The dibenzoazocine derivative (**4**) and the iminodibenzyl derivative (**5**) showed moderate and good activity, respectively. The phenoxazine and phenothiazine derivatives, **6** and **7**, were inactive. In Table II it is of interest to note that the dibenzoazepine derivative, **17**, was only slightly active in contrast to the isomeric compounds **5** (Table I) and the morphanthridine derivative V. The imidazolinylmethyl derivatives of 3-phenyltetrahydro-1-benzazepine listed in Table IV were of particular interest. Here again **39** with a lactam grouping was only slightly active. The tetrahydrobenzazepine derivative **42** showed moderate to good activity which was enhanced considerably by substitution with chlorine in the phenyl ring, *e.g.*, **47–49**. This activity was retained when the imidazoline ring was substituted by a methyl group in position 4 (**44**) or enlarged to a tetrahydropyrimidine ring (**45**).

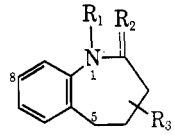
The imidazolinylmethyl derivatives of 4- and 5-phenyltetrahydro-1-benzazepine **52** and **53** were considerably less active than the 3-phenyl derivative **42**. Moderate antiarrhythmic activity was found for the tetrahydroquinoline and isoquinoline analogs (**58–61**).

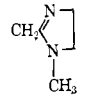
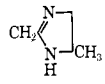
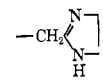
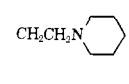
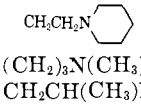
The most interesting substance in this series, due to its high activity and relatively broad therapeutic range, was **47**. In the above described test, **47**, at a dose of 4.5–22 mg/kg, delayed the onset of ventricular fibrillation significantly longer than a maximal effective dose of quinidine or procainamide. Compounds **48** and **49** delayed the onset of ventricular fibrillation to a comparable degree, however, only over a narrower dose range as compared to **47**.

The pharmacology of **47** has been reported by Barrett, *et al.*,[22] and a more detailed paper by the same authors is in preparation.

(16) W. Oldham and I. B. Jones, *J. Am. Chem. Soc.*, **61**, 3289 (1939).
(17) J. v. Braun, *Chem. Ber.*, **55**, 3779 (1922).
(18) J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).
(19) W. Leithe, *Monatsh.*, **53–54**, 956 (1929).
(20) W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 828 (1957).
(21) W. Schindler and F. Hafliger (to I. R. Geigy), U. S. Patent 2,751,393 (Sept 19, 1956); H. L. Kung and W. Schindler, *Experientia*, **15**, 66 (1959).
(22) W. E. Barrett, T. Garces, R. Rutledge, and A. J. Plummer, *Pharmacologist*, **7**, 229 (1965). Compound **47** has also been designated Sn-13197.

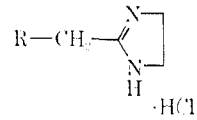
TABLE IV: BICYCLIC DERIVATIVES

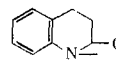
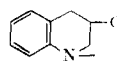
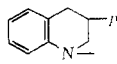
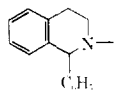
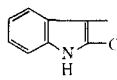
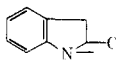
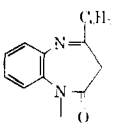
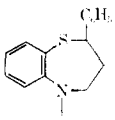
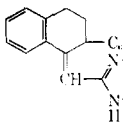


No.[a]	R_1	R_2	R_3	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity
38	$CH_2CH_2N(C_2H_5)_2$	O	3-C_6H_5	60–62	$C_{22}H_{28}N_2O$	78.5	8.4	8.3	78.3	8.4	8.3	...
39		O	3-C_6H_5	>265	$C_{20}H_{21}N_3O \cdot HCl \cdot H_2O$	64.3	6.2	11.2	64.7	6.6	11.5	+1
40	CH_3	O	3-C_6H_5	113–114	$C_{17}H_{17}NO$	81.2	6.8	5.6	81.1	7.1	5.6	...
41	CH_3	H_2	3-C_6H_5	64–66	$C_{17}H_{19}N$	86.0	8.1	5.9	85.3	8.1	5.6	...
42		H_2	3-C_6H_5	280–283	$C_{20}H_{23}N_3 \cdot HCl$	70.3	7.1	12.3	70.7	7.3	11.9	+2 to +3
43		H_2	3-C_6H_5	145 dec	$C_{21}H_{25}N_3 \cdot HI$	56.4	5.9	9.4	56.2	6.1	9.2	+1
44		H_2	3-C_6H_5	218–220	$C_{21}H_{25}N_3 \cdot HCl$	70.9	7.4	11.8	70.8	7.5	11.8	+3
45		H_2	3-C_6H_5	256-259					70.3	7.5		+3
46		H_2	3-*p*-$C_6H_4CH_3$	190 dec	$C_{21}H_{25}N_3 \cdot HCl$	70.9	7.4	11.8	70.3	7.5	11.3	+2
47		H_2	3-*p*-C_6H_4Cl	239–241	$C_{20}H_{22}ClN_3 \cdot HCl$	63.8	6.2	11.2	63.6	6.1	11.5	+4
48		H_2	3-*m*-C_6H_4Cl	241–242					6.40	6.3	11.0	+4
49		H_2	3-*o*-C_6H_4Cl	231–233	$C_{20}H_{22}ClN_3 \cdot HCl$	63.8	6.2	11.2	63.7	6.2	11.1	+4
50		H_2	3-C_6H_5, 8-Cl	238 dec					63.7	6.4	11.0	+1
51		O	4-C_6H_5	100 dec	$C_{20}H_{21}N_3O \cdot HCl \cdot 0.5H_2O$	65.8	6.3	11.5	65.9	6.3	11.3	+2
52		H_2	4-C_6H_5	>270 dec	$C_{20}H_{23}N_3 \cdot HCl$	70.3	7.1	12.3	70.7	7.1	12.6	+1
53		H_2	5-C_6H_5	230–232					70.1	7.2	12.1	+1
54		O	5-C_6H_5	230–231	$C_{23}H_{28}N_2O \cdot HCl$	71.8	7.6	7.3	71.6	7.5	7.6	0
55		H_2	5-C_6H_5	208–209	$C_{23}H_{30}N_2 \cdot HCl$	74.5	8.4	7.6	74.4	8.4	7.6	0
56	$(CH_2)_3N(CH_3)_2$	O	5-C_6H_5	230–231	$C_{21}H_{26}N_2O \cdot HCl$	70.3	7.6	7.8	70.2	7.7	7.6	0
57	$CH_2CH(CH_3)N(CH_3)_2$	O	5-C_6H_5	248–249					70.6	7.8	7.6	0

[a] Compounds **38–40, 51, 54, 56,** and **57** were prepared according to procedure A using the appropriate alkyl halide and sodamide. **41** was obtained by $LiAlH_4$ reduction of the formyl derivative of **30**. **42, 44–50, 52,** and **53** were prepared according to procedure C, Chart I. **43** was obtained by treating the free base of **42** at 25° with excess MeI in ethanol solution. **55** was obtained by $LiAlH_4$ reduction in THF of **54**.

TABLE V
BICYCLIC DERIVATIVES



No.[a]	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity
58		220	$C_{19}H_{21}N_3 \cdot HCl$	69.6	6.8	12.8	69.3	7.0	12.7	+2
59		287–290 dec					70.1	6.8	12.4	+2
60		284–286	$C_{19}H_{20}ClN_3 \cdot HCl$	63.0	5.8	11.6	62.6	6.0	11.6	+1 to +2
61		233–235	$C_{14}H_{21}N_3 \cdot 2HCl$	62.6	6.4	11.5	62.3	6.9	11.2	+2
62[b]		280–284 dec	$C_{15}H_{17}N_3 \cdot HCl$	69.3	5.8	13.5	69.8	5.9	13.8	+2
63[b]		147–148	$C_{18}H_{19}N_3 \cdot HCl$							+2
64		281 dec	$C_{19}H_{18}N_4O \cdot HCl$	64.3	5.4	15.8	64.0	5.5	15.2	0
65		251–252	$C_{19}H_{21}N_3S \cdot HCl$	63.4	6.1	11.7	63.2	6.0	11.5	0
66		230–232	$C_{20}H_{20}N_2 \cdot HCl$	73.9	6.5	8.6	73.7	6.6	8.4	+1

[a] Reference 21. [b] W. Schindler and F. Hafliger (to I. R. Geigy), U. S. Patent 2,808,413 (Oct 1, 1957). [c] **64** was prepared by procedure A, **62** and **63** by procedure B, **58–61** and **65** by procedure C, and **66** by procedure D, Chart I.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer; ultraviolet spectra were determined in methanol solution on a Cary Model 14 spectrometer.

Alkylation Procedures (Chart I). Procedure A. 10-(2-Imidazolin-2-ylmethyl)dibenzo[*b*,*f*][1,4]thiazepin-11-one Hydrochloride (1).—To a suspension of 6.8 g (0.03 mole) of dibenz[*b*,*f*][1,4]thiazepin-11-one in 40 ml of dimethylformamide (DMF), 1.35 g (0.035 mole) of $NaNH_2$ was added gradually. After stirring for 0.5 hr a solution of approximately 0.03 mole of 2-chloromethylimidazoline in 50 ml of benzene (prepared by treating 6.7 g of 2-chloromethylimidazoline hydrochloride with 5 ml of water, 6.7 g of K_2CO_3, and 50 ml of benzene) was added and stirring was continued at room temperature for 16 hr. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and converted to the hydrochloride by addition of anhydrous HCl, and the salt was then filtered off. The crude hydrochloride was dissolved in water; after addition of 2 *N* NaOH the free base was extracted with ethyl acetate, the solvent was removed *in vacuo*, and the residue was recrystallized from a mixture of ethyl acetate and hexane. This yielded 6.0 g of product, mp 156–157°. After conversion to the hydrochloride 6.1 g (60%) of product (1), mp 282–284° recrystallized from ethanol, was obtained.

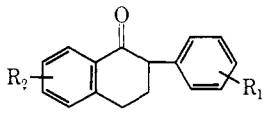
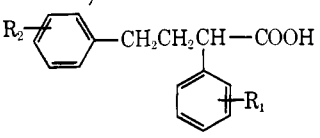
The identical procedure was used to alkylate the other bi- and tricyclic compounds shown in Tables I, II, IV, and V as indicated in the subscript to the tables.

Procedure B. 10-(2-Imidazolinylmethyl)acridan Hydrochloride (8).—A solution of 9.05 g (0.05 mole) of acridan and 3.87 g (0.025 mole) of 2-chloromethylimidazoline hydrochloride in 25 ml of ethanol was refluxed under N_2 for 5 min, after which time the ethanol was allowed to evaporate. The residue was heated in an oil bath for 12 hr at 150°; after cooling, 50 ml of hot water and 25 ml of ethyl acetate were added whereupon two dark brown layers formed. The aqueous phase was separated, filtered, and concentrated *in vacuo*. A crystalline solid remained which was washed with a small amount of water. The crystals were collected on a Büchner funnel, washed with ethanol, and then recrystallized from a mixture of water and ethanol; yield 3.0 g (40%), mp 268–271°.

Procedure C. 3-(*p*-Chlorophenyl)-1-(2-imidazolin-2-ylmethyl)-2,3,4,5-tetrahydro-1-benzazepine Hydrochloride (47).—To a solution of 26.0 g (0.10 mole) of 3-(*p*-chlorophenyl)-2,3,4,5-tetrahydro-1-benzazepine in 52 ml of AcOH 3.03 g (0.10 mole) of paraformaldehyde was added. The reaction mixture was stirred and cooled to 15° while adding a solution of 5.93 g (0.12 mole) of NaCN in 15 ml of water dropwise. The temperature was raised to 45° over a 30-min period and maintained at 45–50° for 3 hr. After cooling to 35°, 4.4 ml of 37% formaldehyde solution was added; after 20 min, 6 ml of water was added and the 3-(*p*-chlorophenyl)-1-cyanomethyl-2,3,4,5-tetrahydrobenzaze-

TABLE VI

INTERMEDIATE COMPOUNDS

R_1	R_2	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
							
2-Cl	H	69-70	$C_{16}H_{13}ClO$	74.9	5.1	74.7	5.0
3-Cl	H	93-94				75.1	5.0
4-Cl[a]	H	108–109					
H[a]	7-Cl	88–89					
							
2-Cl	H	Oil	$C_{16}H_{13}ClO_2$	69.9	5.5	70.1	5.9
3-Cl	H	Oil					
4-Cl[b]	H	81–83				69.9	5.6
H	4-Cl	78–79				70.0	5.5

[a] Reference 15. [b] W. A. Wali, A. K. Khalil, R. L. Bhatia, and S. S. Ahmad, *Proc. Indian Acad. Sci.*, **14A**, 139 (1941); *Chem. Abstr.*, **36**, 1598 (1942), report mp 150° for this compound prepared by reduction of 3-benzoyl-2-*p*-chlorophenylpropionic acid.

pine was filtered off. One recrystallization of this material from ethanol yielded 21.4 g (70%) of product which melted at 101–102°.

Anal. Calcd for $C_{18}H_{17}ClN_2$: C, 72.8; H, 5.8; N, 9.4. Found: C, 73.0; H, 5.8, N, 9.4.

A mixture of 21.3 g (0.07 mole) of the above nitrile, 5.17 g (0.086 mole) of anhydrous ethylenediamine, and 0.16 ml of CS_2 was heated for 6 hr to 120–123°. After cooling, the reaction mixture was triturated with 90 ml of warm water which was decanted. The residue was dissolved in 350 ml of ethyl acetate, and the solution was dried (Na_2SO_4) and concentrated. The residue was redissolved in 250 ml of ethyl acetate and converted to the hydrochloride by adding a solution of anhydrous HCl in ethyl acetate. The hydrochloride salt was filtered off and recrystallized from a mixture of 2-propanol and ethyl acetate to afford 17.8 g (73%) of product **47**, mp 239–241°.

This procedure was used in the preparation of related compounds as shown in Tables I, II, IV, and V. In some instances the intermediate cyanomethyl intermediates were obtained in crystalline form; however, they were converted directly to the imidazolinylmethyl derivatives without further purification.

Procedure D. 2-(10,11-Dihydrodibenzo[*a*,*d*]cycloheptenyliden-5-ylmethyl)-2-imidazoline Hydrochloride (21).—A suspension of $NaOCH_3$, prepared by adding 4.32 g (0.09 mole) of 50% NaH to 22 ml of methanol and 7.5 ml of DMF, was added dropwise with stirring at 50° to a mixture of 15.6 g (0.075 mole) of 10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one,[10] 13.2 g (0.07 mole) of O,O-diethyl cyanomethylphosphonate, and 12 ml of DMF. The reaction was exothermic and required cooling. The temperature was maintained for 5.5 hr at 50°; after cooling to 25°, 4.2 ml of AcOH was added. The reaction mixture was concentrated *in vacuo* and extracted with water and ether. The ether extract was dried (Na_2SO_4) and concentrated, and the residue was distilled *in vacuo*. The fraction boiling between 170–190° (0.1 mm) crystallized on triturating with pentane. Recrystallization from 2-propanol gave 4.5 g (26%) of (10,11 dihydrodibenzo[*a*,*d*]cycloheptyliden-5-yl)acetonitrile, mp 105–106°.

Anal. Calcd for $C_{17}H_{13}N$: C, 88.3; H, 5.7; N, 6.1. Found: C, 88.2; H, 5.8; N, 5.9.

A mixture of 4.5 g (0.0195 mole) of the dihydrodibenzocycloheptylidenylacetonitrile, 3.0 g (0.05 mole) of anhydrous ethylenediamine, and 3 drops of CS_2 was heated for 17 hr in an oil bath (bath temperature 160–165°). The reaction mixture was worked up as described under procedure C. The hydrochloride of the product (**21**) melted at 253–255°, after recrystallization from a mixture of 2-propanol and ether; yield 1.8 g (30%).

3-*p*-Chlorophenyl-4,5-dihydro-1-benzazepin-2-one (VIId). General Procedure.—NaN_3 (22.9 g, 0.35 mole) was gradually added to a solution of 69 g (0.27 mole) of 2-*p*-chlorophenyl-3,4-dihydro-1-naphthalenone (Table VI) in 345 ml of acetic acid. With stirring, 69 ml of concentrated H_2SO_4 was added dropwise over 100 min. The temperature was kept below 38°. Stirring was continued for 2 hr at room temperature and at 50° for 1 hr and again 1 hr at room temperature. The reaction mixture was poured into 1.7 l. of water, and the benzazepinone separated as a solid which slowly crystallized. It was filtered off, washed with water, and recrystallized from ethanol. The yield of 3-*p*-chlorophenyl-4,5-dihydro-1-benzazepin-2-one, mp 193–195°, was 34.8 g (47%) (VIId). The identical procedure was used in the preparation of the other 3-phenyl-dihydrobenzazepin-2-ones in Table III.

3-*p*-Chlorophenyl-2,3,4,5-tetrahydro-1-benzazepine (IXd). General Procedure.—To 500 ml of anhydrous THF, 16.3 g (0.43 mole) of $LiAlH_4$ was added gradually. After stirring for 0.5 hr, 39 g (0.14 mole) of 3-*p*-chlorophenyldihydrobenzazepinone (VIId) was added. The reaction mixture was stirred at room temperature for 1 hr, refluxed for 5 hr and then allowed to stand at room temperature overnight. It was worked up by adding in sequence 49 ml of ethyl acetate, 16.5 ml of water, 33 ml of 15% aqueous NaOH, and 49 ml of water with stirring for 2 hr and filtering. The filtered residue was washed thoroughly with $CHCl_3$ and the washings were combined with the filtrate. The filtrate was concentrated *in vacuo* to afford a crystalline residue which was dissolved in 500 ml of ethyl acetate and filtered through Norit, and the solution was concentrated to a small volume. On addition of 200 ml of hexane, the tetrahydrobenzazepine IXd crystallized; yield 26.7 g (73%), mp 100–102°.

4-Phenyl-4,5-dihydro-1-benzazepin-2-one (VIIb) and 4-Phenyl-4,5-dihydro-2-benzazepin-1-one (VIIIb).—A solution of 6.0 g (0.027 mole) of 3-phenyl-2,3-dihydro-1-naphthalenone and 2.2 g (0.034 mole) of NaN_3 in 33 ml of AcOH was treated with 6.4 ml of concentrated H_2SO_4 as described for the 2-*p*-chlorophenyldihydronaphthalenone. The reaction mixture was quenched with water and the product was extracted with a mixture of ethyl acetate and CH_2Cl_2 (1:1). The extract was washed with water and 10% aqueous Na_2CO_3, dried (Na_2SO_4), and concentrated. The residue crystallized on trituration with hexane. After two recrystallizations from 2-propanol, 2.5 g of VIIb, mp 142–144°, was obtained, ν_{max}^{Nujol} 1667 cm.$^{-1}$

The mother liquors from the recrystallization were concentrated to a small volume which yielded additional crystalline material. Recrystallization of this substance from 2-propanol gave 1.5 g of the isomeric VIIIb: mp 103–105°; ν_{max}^{Nujol} 1631 and a much weaker band at 1667 cm^{-1}, indicating that separation was not complete as was confirmed by thin layer chromatography.

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.0; H, 6.4; N, 5.9. Found: C, 81.2; H, 6.7; N, 6.3.

5-Phenyl-4,5-dihydro-1-benzazepin-2-one (VIIc) and 5-Phenyl-4,5-dihydro-2-benzazepin-1-one (VIIIc).—Reaction of 12.0 g (0.054 mole) of 4-phenyl-2,3-dihydro-1-naphthalenone with 4.4 g (0.068 mole) of NaN_3 in 65 ml of AcOH acid and 13 ml of H_2SO_4 as described for the 2-phenyl-dihydronaphthalenone, gave 8.0 g (63%) of a mixture of the 5-phenyldihydrobenzazepinones VIIc and VIIIc, mp 161–163°. Repeated recrystallization from ethanol gave almost pure VIIc, mp 180–182°, ν_{max}^{Nujol} 1671 cm^{-1}. A much weaker infrared band at 1636 cm^{-1} indicated the presence of a small amount of the isomeric dihydro-2-benzazepin-1-one.

The ethanol mother liquors from the recrystallization of the 5-phenyl-4,5-dihydro-1-benzazepin-2-one were evaporated to dryness; 2.3 g of the residue (mp 165–190°) was refluxed for 2 hr with 57 ml of concentrated HCl and 12.5 ml of AcOH. After the reaction mixture was concentrated *in vacuo*, 50 ml of water and 4.6 g of NaOAc were added to the residue which was then extracted with ethyl acetate. A small amount of material (0.3 g) did not dissolve and was filtered off. The ethyl acetate solution was washed with water and Na_2CO_3 solution, dried (Na_2SO_4), and concentrated. On addition of ether to the concentrate, crystals (0.3 g) were obtained. These were combined with the material previously filtered off and recrystallized from aqueous ethanol, yielding VIIIc, mp 226–228°.

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.0, H, 6.4; N, 5.9. Found: C, 81.0; H, 6.7; N, 5.7.

Spectral Data.—Infrared absorption of the lactam group of 3,4-dihydro-1-benzazepin-2-ones (VII), ν_{max}^{Nujol} 1660–1680 cm^{-1}; 3,4-dihydro-2-benzazepin-1-ones (VIII), ν_{max}^{Nujol} 1630–1646 cm^{-1} (Table III). Ultraviolet absorption of 2,3,4,5-tetrahydro-1-benzazepines: λ_{max} 237–240 mμ (ε 7700–8350) due to anilino

group; absorption in dilute HCl, λ_{max} 250–260 mμ (ε 580–1000) (Table III).

Hydrolysis and Deamination of 3-*p*-Chlorophenyl-4,5-dihydro-1-benzazepin-2-one (VIId).—A mixture of 20 g of benzazepinone VIId, 650 ml of concentrated HCl, and 60 ml of AcOH acid was heated under reflux for 4 hr. The solution then was decanted from a small amount of dark oil, diluted with 250 ml of water, and cooled to +5°. The crystalline hydrolysis product was filtered off and dissolved in 2 *N* NaOH. The alkaline solution was acidified carefully to pH 4.5, whereupon the 4-(*o*-aminophenyl)-2-(*p*-chlorophenyl)butyric acid crystallized. It was filtered off and recrystallized from aqueous ethanol (1:1). The yield of product was 15.6 g (73%), mp 150–152°.

Anal. Calcd for $C_{16}H_{16}ClNO_2$: C, 66.3; H, 5.6; N, 4.8. Found: C, 66.5; H, 5.9; N, 5.0.

To a solution of 7 g (0.024 mole) of the above acid in 175 ml of water containing 1 g of NaOH (0.025 mole), there was added 1.72 g (0.025 mole) of $NaNO_2$. This solution was added dropwise with vigorous stirring to a mixture of 12 ml of water and 12 ml of concentrated HCl, the temperature being maintained at approximately 5°. After this addition was completed, stirring of the solution was continued for an additional 20 min at 5°. The diazonium salt solution was then divided into two equal parts. One half was allowed to react with ethanol and $CuSO_4$, the other half was added dropwise to 25 ml of 50% hypophosphorous acid with stirring at 0°. After stirring the latter portion for 2 hr at +5°, the reaction mixture was allowed to stand in the refrigerator for 24 hr. An oil separated, the supernatant solution was decanted, and the oil was dissolved in ether and washed with dilute HCl and then repeatedly with 1 *N* NaOH. Acidification of the NaOH extracts yielded an oil which was taken up in ether, washed with water, and dried. Removal of the ether left 3.1 g of a brown oil which was extracted with four 50-ml portions of boiling hexane. Removal of the hexane *in vacuo* left 1.2 g of a light brown oil which crystallized on seeding. Repeated recrystallization from hexane followed by sublimation gave 4-phenyl-2-*p*-chlorophenylbutyric acid, mp 79–81°, which was identified by mixture melting point with an authentic sample and by thin layer chromatography.

Decomposition of the diazonium salt with ethanol and $CuSO_4$ gave less favorable results than the above described procedure.

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Cassaine Analogs. II. 7-Deoxy Basic Esters

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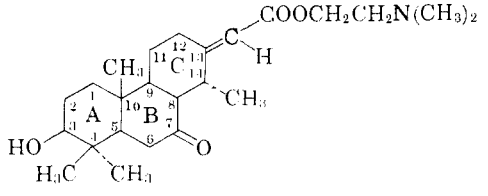
Analogs of the *Erythrophleum* alkaloid cassaine (**1**) have been made in an effort to determine the structural requirements for the cardiotonic effects produced by this alkaloid. None of these has greater cardiotonic activity than that shown by cassaine.

The *Erythrophleum* alkaloid cassaine (**1**) has been recognized for many years as having an intense action on the heart which is quite like that produced by the digitalis glycosides.[1] This rather complex molecule was synthesized recently by Turner, *et al.*[2]



1

With the usual optimism of medicinal chemists, we felt that perhaps the complications of having an oxygen function at C-7 and methyl groups at C-4, -10, and -14 might not be necessary for cardiotonic activity and that a modified cassaine, carrying substituents only at C-3 and C-13, might be a useful cardiac drug. The present paper describes the preparation and biological testing of several such simplified analogs together with compounds in which the C-4, -10, and -14 methyl groups have been in part replaced.

The general synthetic reaction utilized in preparing the requisite α,β-unsaturated basic esters is illustrated in Scheme I. Triethyl phosphonoacetate reacted with tricyclic hydroxy ketone **2** to form a 1:1 mixture of esters **3** and **5** which are isomeric about the double bond.[3] This mixture was not separable in our hands by thin layer chromatography (tlc) but its composition was demonstrable by gas–liquid partition chromatography (glpc). The *trans* structure (present in **3**) is defined as that in which the carboxyl group lies away from the bulge of the B ring.

In the present work the *trans* structure is assigned to that isomer of each pair having the longer glpc retention time. It is perhaps significant that in four of the five cases presently reported where pairs of isomers have been actually separated, the *trans* isomer has a significantly greater ultraviolet extinction coefficient than does its *cis* counterpart. In the sixth case the coefficients were about equal. The cause of such differences

(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley, *Alkaloids*, **5**, 101 (1955), and references therein.

(2) R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riehl, and J. M. Sanders, *J. Am. Chem. Soc.*, **88**, 1766 (1966).

(3) In the large number of Wittig reactions reported here, we found no evidence of any stereospecificity in formation of the *trans vs.* the *cis* unsaturated esters with the exception of the case where an equatorial methyl group was present at C-1 (phenanthrene numbering). Here there appeared to be a preponderance of the *trans* isomer. A. K. Bose and R. T. Dahill, *J. Org. Chem.*, **30**, 505 (1965), report obtaining essentially a single isomer from the reaction of triethyl phosphonoacetate with 3-keto steroids and H. Kaneko and M. Okazaki, *Tetrahedron Letters*, 219 (1966), found that the isomer ratio in this reaction could be varied by choice of reaction conditions. These steroids differ from the presently reported compounds in having an axial methyl group "*para*" to the ketone undergoing reaction which might effect some stereochemical direction in the reaction.