Triptycene Derivatives as Medicinal Agents

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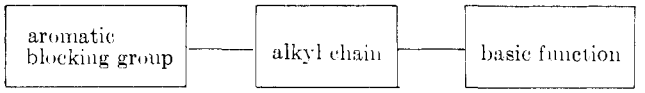
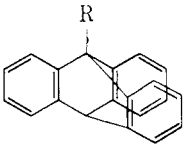
The reaction of benzyne with 9-substituted anthracenes yielded a series of triptycene derivatives, which were converted to a variety of drug-related structures containing triptycene as the aromatic blocking group. Several of the new compounds are active as antiinflammatory agents.

During the recent development of medicinal chemistry, drugs with widely varied clinical application have emerged, and a large number of these may be portrayed by the gross structural arrangement I.



I

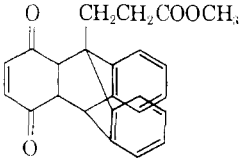
For some time evidence has accumulated[1] supporting the idea that maximum biological activity results only when the blocking group is planar. However, the recent advent of clinically useful drugs with bent or skewed aromatic moieties, *i.e.*, imipramine[2] and amitriptyline,[3] etc., has refocussed attention on the steric requirements of the blocking group. With this in mind it was of interest to examine drugs containing the highly symmetrical, aromatic, but nonplanar triptycene blocking function (II). The present paper describes the preparation and pharmacological evaluation



II

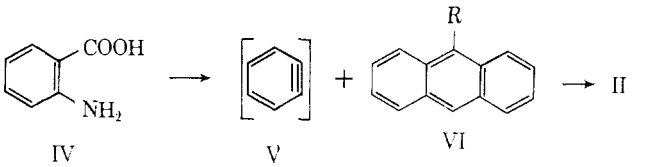
of a series of triptycene derivatives containing typical drug-related side chains at the bridgehead position.

Chemistry.—Synthesis of the derivatives was initiated using the method developed originally by Bartlett[4] for triptycene itself (II, R = H). Condensation of quinone with anthracene propionic ester afforded the adduct III in good yield. It was our plan to use the Bartlett[4,5] or Theilacker[6] procedures to convert this



III

adduct to methyl 9-triptycenepropionate (II, R = $CH_2CH_2COOCH_3$), which could be further transformed to basic side chain derivatives. This approach was abandoned, however, when Wittig[7] reported that benzyne (V) would add to anthracene (VI, R = H) to form triptycene directly. The subsequent development of a very facile generation of benzyne (V) from anthranilic acid (IV) by Stiles and Miller[8] and by Friedman and Logullo[9] made triptycenes readily available. In our hands the formation of triptycenes by the Friedman and Logullo procedure from 9-substituted anthracenes was satisfactory when the substituent was electron donating. However, with electron-attracting groups at the 9-position, the yields were disappointing (Table I). Of key importance for further transformations were triptycenealdehyde ethylene acetal (**7**) and methyl 9-triptycenepropionate (**32**). Of interest was the large difference in yield of acetals **6** and **7** where electronic factors are similar. Steric influences, which are minimized in the cyclic acetal **7**, seem to be of dominant importance.



IV V VI

TABLE I

TRIPTYCENES FROM 9-SUBSTITUTED ANTHRACENES

No.	R	Yield, %
1	NO_2	15
4	CH_2Cl	70
5	CH_2OH	6
6	$CH(OCH_3)_2$	4
7	$HC<^{OCH_2}_{OCH_2}$	53
8	CHO	Nil
10	CN	Nil
23	CH_2CH_2Cl	19
32	$CH_2CH_2COOCH_3$	50

Methyl 9-triptycenepropionate was the starting material for elaboration of the 2-, 3-, and 4-carbon side chain series as outlined in Chart I (T = 9-triptycyl). The ethylene acetal of triptycenealdehyde provided a very convenient entry into the single-carbon side-chain group as summarized in Chart II. Triptycenealdehyde (**8**) was readily available by hydrolysis of the acetal **7**, and oxidation of the aldehyde to triptycene-

(1) (a) A. Burger, R. T. Standridge, N. E. Stjernström, and P. Marchini, *J. Med. Pharm. Chem.*, **4**, 517 (1961); (b) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958).

(2) Tofranil®; W. Schindler and F. Haefliger, *Helv. Chim. Acta*, **37**, 472 (1954).

(3) Elavil®; H. Freed, *Am. J. Psychiat.*, **117**, 455 (1960).

(4) P. D. Bartlett, M. J. Ryan, and S. G. Cohen, *J. Am. Chem. Soc.*, **64**, 2649 (1942).

(5) P. D. Bartlett, S. G. Cohen, J. D. Colman, Jr., N. Kornblum, J. R. Landry, and E. S. Lewis, *ibid.*, **72**, 1003 (1950); P. D. Bartlett and E. S. Lewis, *ibid.*, **72**, 1005 (1950); P. D. Bartlett and F. D. Greene, *ibid.*, **76**, 1088 (1954).

(6) W. Theilacker, U. B. Brose, and K. H. Beyer, *Ber.*, **93**, 1658 (1960); W. Theilacker and K. H. Beyer, *ibid.*, **94**, 2968 (1961).

(7) G. Wittig and R. Ludwig, *Angew. Chem.*, **68**, 40 (1956); G. Wittig, *Org. Syn.*, **39**, 75 (1959).

(8) M. Stiles and R. G. Miller, *J. Am. Chem. Soc.*, **82**, 3802 (1960).

(9) L. Friedman and F. Logullo, *ibid.*, **85**, 1549 (1963).

CHART I

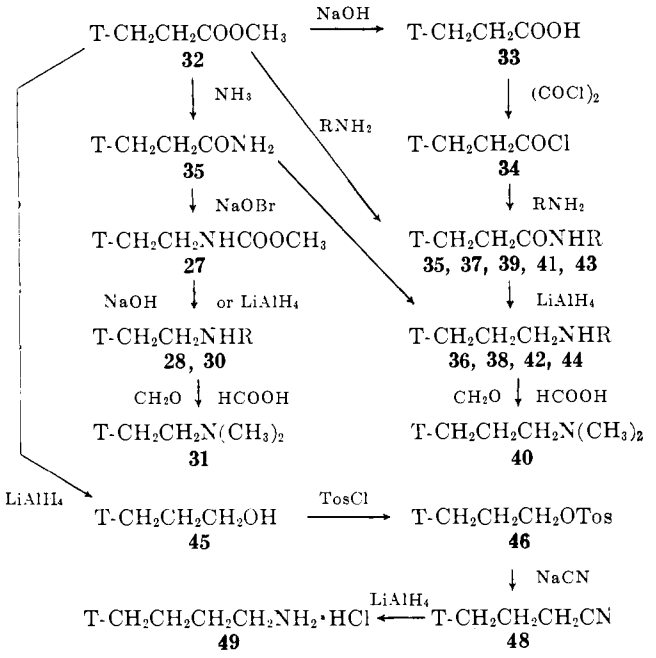
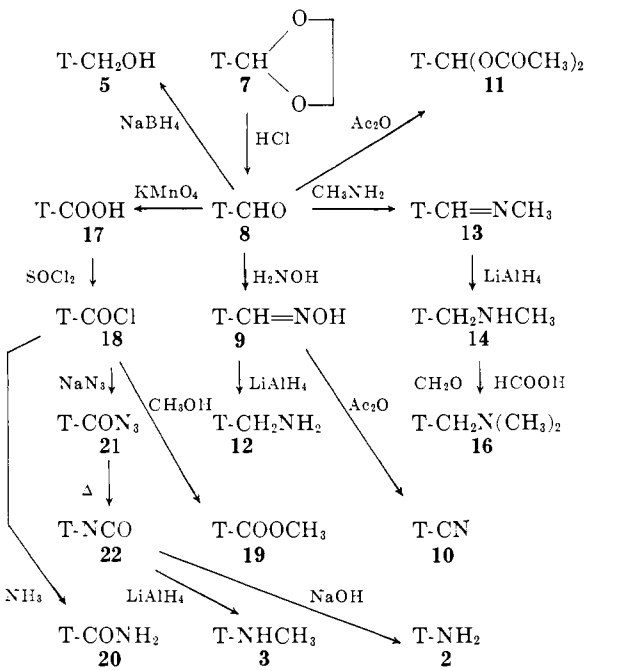


CHART II



carboxylic acid (**17**) was accomplished in excellent yield using potassium permanganate in pyridine. This route to the acid seems more convenient than previous methods.

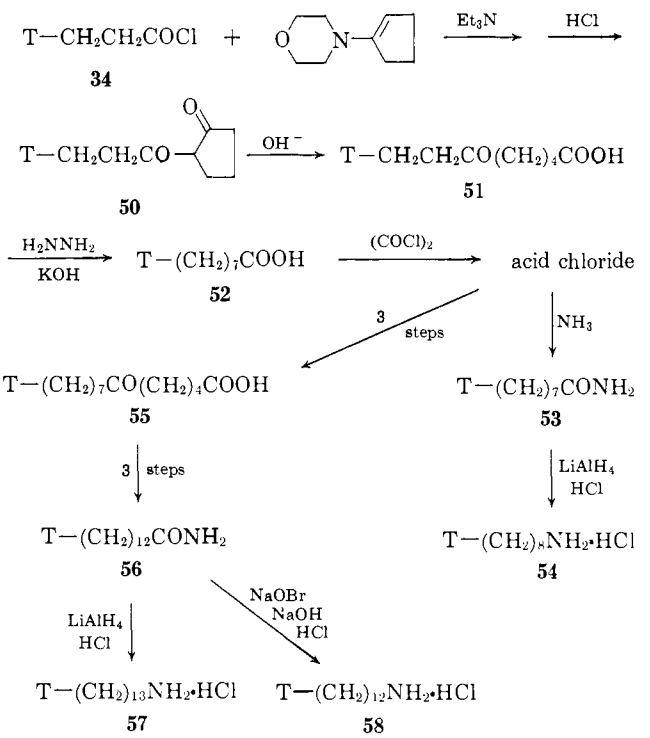
The 8-carbon side-chain series (Chart III) was made available by acylation of the morpholine enamine of cyclopentanone with the acid chloride of triptycenepropionic acid (**34**).[10] Repetition of the enamine procedure on the octanoic acid **52** lengthened the side chain to 13 carbons (Chart III). The amide **56** so formed was transformed to the tridecylamine **57** and by Hofmann degradation to the dodecylamine. **58**.

Properties of the triptycene derivatives prepared in the present work are summarized in Table II.

Pharmacological Evaluation.—The triptycene derivatives were screened in normal mice. Groups of

(10) S. Hünig and W. Lendle, *Ber.*, **93**, 918 (1960).

CHART III



mice were given graded i.p. doses of the various compounds; gross behavioral effects were observed, and comparison was made with known drugs. The bridgehead amines **2** and **3** were CNS depressants, while the 1-carbon side-chain amines **12**, **13**, and **14** showed a mixed CNS stimulant and depressant activity. The longer chain amines were characterized mainly as weak CNS depressants. On the whole the series was lacking in CNS activity of an interesting magnitude. From these results we would conclude that triptycene does *not* function as a very effective aromatic blocking group in CNS-type drugs. The evidence from this series seems to support the idea that gross planarity of the blocking group is important.

With these results as background, the new compounds were then screened in the carragenin-inflamed rat paw antiinflammatory test.[11] At a dose of 50 mg./kg. given subcutaneously, the extent of inhibition of inflammation as recorded in Table II was observed. It may be noted that: (1) triptycenes lacking a basic side chain are devoid of significant activity, (2) bridgehead amines **2** and **3** are also inactive, and (3) best activity is observed with side chains containing two or more carbon atoms. Further testing has indicated rather low oral activity for the series.

Experimental[12]

9-Substituted Anthracenes.—The 9-nitroanthracene and anthracene-9-carboxaldehyde were commercial samples. The aldehyde was converted to the dimethyl acetal using methanol[13] and to the ethylene acetal by means of ethylene glycol.[14] The 9-cyanoanthracene was made from the aldehyde.[15] 9-β-Chloro-

(11) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(12) All melting points are corrected. Infrared, ultraviolet, and n.m.r. spectra were obtained on most of the compounds reported and were consistent with the structures indicated.

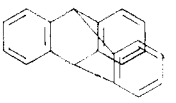
(13) J. S. Meek and J. R. Dann, *J. Org. Chem.*, **21**, 968 (1956).

(14) G. Rio and B. Sillion, *Compt. rend.*, **244**, 625 (1957).

(15) L. F. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.*, **60**, 2555 (1938); J. S. Meek and J. W. Rowe, *ibid.*, **77**, 6677 (1953).

TABLE II

9-SUBSTITUTED TRIPTYCENES



No.	R	M.p., °C.	Solvent[a]	Formula	C, % Calcd.	C, % Found	O, % Calcd.	O, % Found	N, % Calcd.	N, % Found	Yield,[b] %
1	NO_2	246–248.5[c]	P	$C_{20}H_{13}NO_2$	...	...	...	...	...	...	...
2	$NH_2 \cdot HCl$	354–380[c]	...	$C_{20}H_{15}N \cdot HCl$	...	...	...	...	4.58	4.53	0
3	$NHCH_3 \cdot HCl$	330–334	...	$C_{21}H_{17}N \cdot HCl$	...	...	...	...	4.38	4.25	0
4	CH_2Cl	229.5–236.5	L	$C_{21}H_{15}Cl$	83.29	83.26	4.99	5.19	11.71	11.68	...
5	CH_2OH	238–240	M	$C_{21}H_{16}O$	88.70	88.87	5.67	5.81	...	...	...
6	$CH(OCH_3)_2$	259.5–261	M	$C_{23}H_{20}O_2$	84.12	83.88	6.14	6.28	...	...	...
7	$HC<^{OCH_2}_{OCH_2}$	284–285	DM	$C_{24}H_{18}O_2$	84.64	84.42	5.56	5.58	...	...	0
8	CHO	235–238	AW	$C_{21}H_{14}O$	89.33	88.82	5.00	4.99	...	...	0
9	$CH{=}NOH$	227–229	TP	$C_{21}H_{15}NO$	...	...	...	...	4.71	4.70	0
10	CN	297–299	EP	$C_{21}H_{13}N$	90.29	90.24	4.69	4.83	5.02	4.74	...
11	$CH(OCOCH_3)_2$	280.5–281	DM	$C_{25}H_{20}O_4$	78.11	78.00	5.24	5.46	...	...	...
12	$CH_2NH_2 \cdot HCl$	326.5–332	...	$C_{21}H_{17}N \cdot HCl$	78.86	78.85	5.67	5.67	4.38	4.25	24
13	$CH{=}NCH_3$	260–262	DMW	$C_{22}H_{17}N$	89.46	88.80	5.80	6.12	4.74	4.61	...
14	CH_2NHCH_3	207–210	DM	$C_{22}H_{19}N$	88.85	88.97	6.44	6.56	4.71	4.43	...
15	$CH_2NHCH_3 \cdot HCl$	325–328	ME	$C_{22}H_{19}N \cdot HCl$	79.14	79.04	6.03	6.09	4.20	3.97	0
16	$CH_2N(CH_3)_2 \cdot HCl$	295–300	ME	$C_{23}H_{21}N \cdot HCl$	79.40	79.61	6.37	6.60	4.03	3.82	19
17	COOH	353–357[c]	DM	$C_{21}H_{14}O_2$	84.54	84.30	4.73	4.96	...	...	...
18	COCl	192–194[c]	BP	$C_{21}H_{13}ClO$	11.11[e]	11.11	...	...	...	...	...
19	$COOCH_3$	195[c]	M	$C_{22}H_{16}O_2$	...	...	...	...	...	...	...
20	$CONH_2$	294–298[c]	...	$C_{21}H_{15}NO$	84.82	84.56	5.09	4.97	4.71	4.65	...
21	CON_3	248.5–249[c]	...	$C_{21}H_{13}N_3O$	...	...	...	...	...	...	...
22	NCO	248–249[c]	CW	$C_{22}H_{13}NO$	...	...	...	...	...	...	...
23	CH_2CH_2Cl	168–170.5	DM	$C_{23}H_{17}Cl$	83.40	82.63	5.40	5.38	11.19	11.42	...
24	CH_2CH_2N⟨⟩$\cdot HCl$	293–296	M	$C_{28}H_{25}N \cdot HCl$	80.49	80.32	6.75	6.76	3.61	3.55	...
25	CHOHCN	224–227	TP	$C_{22}H_{15}NO$	85.41	85.37	4.89	5.01	4.53	4.46	...
26	$CHOHCH_2NH_2 \cdot HCl$	325–327	NE	$C_{22}H_{19}NO \cdot HCl \cdot 0.5H_2O$	73.59	73.57	5.89	5.96	3.90	3.75	60
27	$CH_2CH_2NHCOOCH_3$	243–248.5	SW	$C_{24}H_{21}NO_2$	81.10	81.01	5.96	5.91	3.94	3.98	0
28	$CH_2CH_2NH_2$	193–194.5	DM	$C_{22}H_{19}N$	88.85	88.61	6.44	6.51	4.71	4.52	33
29	$CH_2CH_2NH_2 \cdot HCl$	342–349	SE	$C_{22}H_{19}N \cdot HCl$	79.14	78.03	6.03	6.68	...	...	55/30
30	$CH_2CH_2NHCH_3 \cdot HCl$	>350	SE	$C_{23}H_{21}N \cdot HCl$	79.40	79.50	6.37	6.51	4.03	3.84	50
31	$CH_2CH_2N(CH_3)_2 \cdot HCl$	345–349	ME	$C_{24}H_{23}N \cdot HCl$	79.64	79.39	6.68	6.90	3.87	3.82	38
32	$CH_2CH_2COOCH_3$	156–158	M	$C_{24}H_{20}O_2$	84.68	84.60	5.92	5.94	...	...	20
33	CH_2CH_2COOH	204.5–208	BP	$C_{23}H_{18}O_2$	84.05	84.32	5.77	5.71	...	...	...
34	CH_2CH_2COCl	168–172	BP	$C_{23}H_{17}ClO$	10.28[e]	10.14	...	...	...	...	...
35	$CH_2CH_2CONH_2$	265–267	MW	$C_{23}H_{19}NO$	84.89	85.02	5.89	5.95	4.30	4.27	...
36	$(CH_2)_3NH_2 \cdot HCl$	295–300	SE	$C_{24}H_{21}N \cdot HCl$	79.40	79.47	6.37	6.88	4.03	3.88	68
37	$CH_2CH_2CONHCH_3$	247.5–249	M	$C_{24}H_{21}NO$	84.92	84.60	6.24	6.18	4.13	4.12	0
38	$(CH_2)_3NHCH_3 \cdot HCl$	334–336	SE	$C_{24}H_{23}N \cdot HCl$	79.64	79.43	6.68	6.75	3.87	3.84	63
39	$CH_2CH_2CON(CH_3)_2$	219–221	BP	$C_{25}H_{23}NO$	84.95	84.99	6.56	6.75	3.96	3.78	8
40	$(CH_2)_3N(CH_3)_2 \cdot HCl$	285–314	SE	$C_{25}H_{25}N \cdot HCl$	79.87	79.97	6.97	7.08	3.73	3.49	37
41	$CH_2CH_2CONHAd$[d]	235–237	OP	$C_{33}H_{33}NO$	...	...	...	...	3.05	2.94	...
42	$(CH_2)_3NHAd \cdot HCl$[d]	>380	...	$C_{33}H_{35}N \cdot HCl$	82.21	82.03	7.52	7.60	2.91	2.87	0
43	CH_2CH_2CONHV[e]	191.5–194	DMW	$C_{33}H_{31}NO_3$	80.95	80.71	6.38	6.51	2.86	2.83	...
44	$(CH_2)_3NHV \cdot HCl$[e]	265.5–266.5	DE	$C_{33}H_{33}NO_2 \cdot HCl$	6.92[e]	6.92	...	...	2.74	2.94	34
45	$CH_2CH_2CH_2OH$	196–199	BP	$C_{23}H_{20}O$	88.42	88.26	6.45	6.46	...	...	...
46	$(CH_2)_3OSO_2C_6H_4CH_3$	220–222	FE	$C_{30}H_{26}O_3S$	6.87[f]	6.99	...	...	...	...	...
47	$(CH_2)_3OCOCH_3$	179–181	GM	$C_{25}H_{22}O_2$	84.71	84.59	6.26	6.35	...	...	...
48	$CH_2CH_2CH_2CN$	218–221	DMW	$C_{24}H_{19}N$	89.68	89.68	5.96	6.01	4.36	4.23	...
49	$(CH_2)_4NH_2 \cdot HCl$	290	MB	$C_{24}H_{23}N \cdot HCl$	9.80[e]	9.99	...	...	3.87	3.59	61
50	CH_2CH_2CO⟨⟩=O	206–209	FEP	$C_{28}H_{24}O_2$	85.68	85.56	6.16	6.31	...	...	...
51	$CH_2CH_2CO(CH_2)_5COOH$	201–203	O	$C_{28}H_{26}O_3$	81.92	82.28	6.38	6.45	...	...	...
52	$(CH_2)_5COOH$	175–178	M	$C_{25}H_{24}O_2$	84.81	84.45	7.12	7.11	...	...	...
53	$(CH_2)_5CONH_2$	167–169	BP	$C_{25}H_{25}NO$	85.02	84.83	7.39	7.38	3.54	3.53	...

TABLE II (*Continued*)

No.	R	M.p., °C.	Solvent[a]	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	%[b] inhibit.
54	$(CH_2)_8NH_2 \cdot HCl$	233–235	NE	$C_{28}H_{31}N \cdot HCl$	80.44	79.66	7.71	7.76	3.35	3.05	60
55	$(CH_2)_7CO(CH_2)_4COOH$	153–154	OE	$C_{33}H_{36}O_3$	82.46	82.20	7.55	7.58	...	...	...
56	$(CH_2)_{12}CONH_2$	117–121	BS	$C_{33}H_{34}NO$	...	...	...	...	3.01	2.82	...
57	$(CH_2)_{13}NH_2 \cdot HCl$	160–162	ME	$C_{33}H_{41}N \cdot HCl$	7.26[c]	7.20	...	...	2.86	2.83	34/20
58	$(CH_2)_{12}NH_2 \cdot HCl$	163–165	NE	$C_{32}H_{39}N \cdot HCl$	7.48[c]	7.38	...	...	2.95	2.91	52/20

[a] A = acetic acid, B = benzene, C = acetone, D = dimethylformamide, E = ether, F = ethylene dichloride, G = methylene chloride, L = ligroin, M = methanol, N = ethanol, O = toluene, P = petroleum ether, S = Methyl Cellosolve, T = ethyl acetate, W = water. [b] Antiinflammatory assay.[11] [c] Cl analysis. [d] Ad = 1-adamantyl. [e] V = homoveratryl. [f] S analysis.

ethylanthracene was made from 9-β-hydroxyethylanthracene[16] using the following procedure described for 1-β-hydroxyethylnaphthalene.[17]

9-β-Chloroethylanthracene.—Thionyl chloride (2.3 ml.) was added slowly to a mixture of 6.6 g. of 9-β-hydroxyethylanthracene, 3.9 ml. of dimethylaniline, and 25 ml. of benzene. The solution was warmed for 30 min. on a steam bath, after which it was diluted with 3 vol. of ether. The mixture was washed first with water, twice with dilute HCl, and once with aqueous $NaHCO_3$. The ether solution was dried and concentrated, and the crude product was crystallized from ether–petroleum ether; yield 4.14 g. (57%), m.p. 87–90°. Recrystallization raised the melting point to 90–91.5°.

Anal. Calcd. for $C_{16}H_{13}Cl$: C, 79.82; H, 5.44; Cl, 14.73. Found: C, 79.39; H, 5.69; Cl, 14.82.

9-Hydroxymethylanthracene.—To a solution of 10.3 g. of 9-anthraldehyde in 100 ml. of warm ethanol was added 3.8 g. of $NaBH_4$ in small portions with stirring. The mixture was allowed to cool to room temperature. Water was added, and the product was filtered, washed with water and ethanol, and dried; yield 10.0 g. (96%), m.p. 158–161°.

9-Chloromethylanthracene.—Dry HCl was passed into a warm solution of 4.0 g. of 9-hydroxymethylanthracene in 80 ml. of ethanol keeping the temperature at 30–40°. The mixture was cooled in ice, and the product was filtered, washed with cold ethanol, and dried; yield 3.01 g., m.p. 132–133°.[18]

9-(β-Carbomethoxyethyl)anthracene.—A solution of 133 g. of 9-(β-carboxyethyl)anthracene[19] in 4.5 l. of methanol was saturated with dry HCl below 25°. The solution was kept at 25° overnight and then concentrated to dryness *in vacuo*. The crude ester was crystallized from methanol; yield 132 g., m.p. 65°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.94; H, 5.99.

9-(β-Carbomethoxyethyl)-5,8,8a,9,10,10a-hexahydro-9,10-*o*-benzenoanthracene-5,8-dione (II, R = $CH_2CH_2COOCH_3$).—A solution of 26 g. of pure quinone and 26 g. of 9-(β-carbomethoxyethyl)anthracene in 350 ml. of ligroin (b.p. 80–100°) was refluxed for 45 min. The solution was cooled, and the product (39 g.) was filtered and recrystallized from a mixture of benzene and ligroin; yield 30 g., m.p. 186–189°.

Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.45; H, 5.41. Found: C, 77.67; H, 5.49.

Preparation of Triptycenes by the Friedman and Logullo Procedure.[9]—The derivatives listed in Table I were made by either of the methods given below for **32** and **7**. No attempt was made to study conditions to maximize the yields.

9-(β-Carbomethoxyethyl)triptycene (32).—A solution of 157.5 g. of 9-(β-carbomethoxyethyl)anthracene and 138 ml. of amyl nitrite in 1500 ml. of methylene chloride was added dropwise during 4 hr. to a stirred and refluxing solution of 118.5 g. of anthranilic acid in 600 ml. of acetone. Refluxing was continued for 15 min., after which time the mixture was cooled and washed twice with dilute HCl and twice with saturated aqueous $NaHCO_3$. The solution was dried, and the solvent was distilled *in vacuo*. The product was crystallized from methanol; yield 108 g.

Triptycene-9-carboxaldehyde Ethylene Acetal (7).—To a stirred and refluxing solution of 122.5 g. of anthracene-9-carboxaldehyde ethylene acetal in 1225 ml. of dioxane was added simultaneously during 6 hr. from separate dropping funnels solutions of 73.5 g. of anthranilic acid in 2450 ml. of dioxane and 78.3 g. of amyl nitrite in 2450 ml. of dioxane. The mixture was refluxed for another 30 min., after which time the solvent was distilled *in vacuo*. The product was crystallized from methanol; yield (two crops) 85.5 g.

9-(β-Carboxyethyl)triptycene (33).—The methyl ester (5 g.) in 85 ml. of methanol was hydrolyzed using 2.2 g. of NaOH and 17 ml. of water during a reflux period of 2 hr. The methanol was distilled *in vacuo*, and the residue was dissolved in water. The product was precipitated by acidification with HCl. The acid was filtered and washed thoroughly with water; yield 4.8 g.

Acid Chloride of 9-(β-Carboxyethyl)triptycene (34).—A solution of the acid (21.2 g.) in 300 ml. of dry benzene and 16.75 ml. of oxalyl chloride was refluxed and stirred for 1 hr. The mixture was concentrated *in vacuo*, and the crude acid chloride was recrystallized from a mixture of toluene and petroleum ether (b.p. 60–68°)[20]; yield 16.3 g. (73%).

Amides of Triptycenepropionic Acid.—These were made either from the methyl ester (**32**) or from the acid chloride (**34**). The following two procedures are illustrative.

Triptycene-9-propionamide (35).—A solution of 9-(β-carbomethoxyethyl)triptycene (5.0 g.) in 50 ml. of methanol and 100 ml. of liquid ammonia was heated for 18 hr. at 100° in a sealed vessel. The mixture was evaporated to dryness, and the crude product was crystallized from aqueous methanol; yield 3.92 g. (82%). The methylamide (**37**) and the dimethylamide (**39**) were also prepared by this procedure; yields 86 and 60%, respectively.

9-(β-Homoveratrylcarbamoylethyl)triptycene (43).—A solution of 4.56 g. of homoveratrylamine in 25 ml. of dry benzene was added to a solution of 3.4 g. of the acid chloride of 9-(β-carboxyethyl)triptycene in 25 ml. of benzene. The mixture was refluxed for 1 hr. Homoveratrylamine hydrochloride (1.91 g.) was filtered, and the filtrate was washed twice with dilute HCl and dried ($MgSO_4$). The benzene was distilled, and the amide was crystallized from methanol; yield 4.3 g. (90%).

Preparation of Amines by Reduction with Lithium Aluminum Hydride.—The amines **3, 12, 14, 26, 30, 36, 38, 40, 42, 44, 49,** and **54** were prepared by reduction of the corresponding isocyanates, amides, nitriles, oximes, carbamates, etc. (see charts) using an equal weight of $LiAlH_4$ in either tetrahydrofuran or benzene–ether mixtures. The following will illustrate the general procedure.

9-(γ-Methylaminopropyl)triptycene Hydrochloride (38).—To a solution of 2.0 g. of $LiAlH_4$ in 35 ml. of dry tetrahydrofuran was added dropwise with stirring during 30 min. a solution of 2.0 g. of the amide **37** in 50 ml. of tetrahydrofuran. Stirring was continued at room temperature for 1 hr., after which time the mixture was refluxed for 45 min. The solution was cooled and

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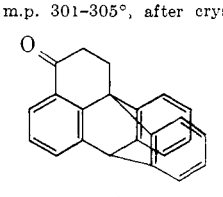
(20) When excess thionyl chloride at reflux temperature was used in this preparation, the acid chloride lost HCl and cyclized to form the α-tetralone derivative i, m.p. 301–305°, after crystallization from Methyl Cellosolve–methanol. Anhydrous HF also effected the same cyclodehydration of the acid. *Anal.* Calcd. for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.33; H, 5.45.



i

treated dropwise with a mixture of 13.5 ml. of water and 20 ml. of tetrahydrofuran. The organic layer was decanted, and the sludge was extracted with benzene. The combined solution was evaporated to dryness *in vacuo*. The crude product was dissolved in benzene, and the hydrochloride salt was precipitated using dry HCl; yield 2.08 g. (97%).

Methyl 2-(9-Triptycyl)ethyl Carbamate (27).—Triptycenepropionamide (**35**) (4.0 g.) was dissolved in a mixture of 40 ml. of methanol and 40 ml. of tetrahydrofuran, and this solution was added to 57 ml. of 0.435 *M* sodium methoxide in methanol. To the resulting solution was added dropwise with stirring 20 ml. of a 0.625 *M* solution of bromine in methanol, and the reaction mixture was heated under reflux for 1.75 hr. The mixture was evaporated to dryness, and the residue was taken up in water. The product was filtered, washed with methanol, and recrystallized from toluene; yield 67%.

9-(β-Aminoethyl)triptycene Hydrochloride (29).—A mixture of 2.5 g. of the urethan **27** and 1.23 g. of KOH in 75 ml. of ethylene glycol and 5 ml. of water was refluxed gently for 2 hr. Part of the solvent was distilled *in vacuo*, and the mixture was diluted with water. The aminoethyltriptycene (**28**) was filtered and washed with water. The hydrochloride salt was prepared in ether and was crystallized from a mixture of Methyl Cellosolve and ether; yield 54%.

9-(β-Dimethylaminoethyl)triptycene Hydrochloride (31).—9-(β-Methylaminoethyl)triptycene hydrochloride (**30**) (1.7 g.) was converted with aqueous NaOH to the free base, which was recrystallized from aqueous methanol; yield 1.09 g., m.p. 161–168°.

Anal. Calcd. for $C_{23}H_{21}N$: C, 88.70; H, 6.80; N, 4.50. Found: C, 88.07; H, 7.00; N, 4.27.

The free base (1.0 g.) was dissolved in 10 ml. of toluene, and 0.3 ml. of 37% aqueous formaldehyde was added. The solution was thoroughly mixed, warmed, and treated with 0.15 ml. of 98% formic acid. The resulting mixture was refluxed for 1 hr. and evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml. of ether, and the resulting solution was washed with aqueous $NaHCO_3$. The solution was dried, and the hydrochloride was precipitated with dry HCl and recrystallized from methanol–ether; yield 0.98 g. (92%).

9-(γ-Hydroxypropyl)triptycene (45).—A solution of 15 g. of the propionate ester **32** in 150 ml. of benzene was added with stirring in 10 min. to a solution of 10 g. of $LiAlH_4$ in 450 ml. of dry ether. The mixture was stirred and refluxed for 1 hr., after which time the excess hydride was decomposed with 60 ml. of ethyl acetate, and 300 ml. of 10% HCl was added slowly. The organic layer was separated, washed with dilute acid and with aqueous $NaHCO_3$, and dried ($MgSO_4$). The solvent was distilled, and the product was triturated under petroleum ether and filtered; yield 13.1 g. (95%).

9-(γ-Acetoxypropyl)triptycene (47).—A mixture of 2.0 g. of the propanol **45** in 25 ml. of a 30% solution of HBr in acetic acid was kept at 25° for 2 hr. The solution was evaporated to dryness under reduced pressure, and the product was crystallized from ether–petroleum ether; yield 1.71 g. (75%).

9-(γ-Tosyloxypropyl)triptycene (46).—A solution of 7.8 g. of the propanol **45** in 20 ml. of dry pyridine was cooled to about 5°, and 5.25 g. of *p*-toluenesulfonyl chloride was added with stirring. The cooling bath was removed, and the mixture was stirred for 3 hr. at room temperature. The solution was then poured into excess ice containing 50 ml. of concentrated HCl. The product was filtered, washed with water, dried, and recrystallized from a mixture of ethylene dichloride and ether; yield 7.05 g.

9-(γ-Cyanopropyl)triptycene (48).—A mixture of 7.0 g. of the tosylate **46** and 2.0 g. of dry NaCN powder in 30 ml. of dimethyl sulfoxide was stirred and heated to 140° in 3 min. and was kept at that temperature for 10 min. It was cooled and poured into ice-water. The product was filtered, washed with water, and dried; yield 4.72 g.

Triptycene-9-carboxaldehyde (8).—A solution of 77.5 g. of the ethylene acetal (**7**) in 3880 ml. of glacial acetic acid, 1000 ml. of water, and 775 ml. of concentrated HCl was refluxed for 2 hr. The solution was cooled to −5°, and the product was filtered and washed with 50% acetic acid, water, and methanol; yield 62.5 g. (93%).

Triptycene-9-carboxaldoxime (9).—A solution of the aldehyde **8** (3.0 g.) and 3.0 g. of hydroxylamine hydrochloride in 100 ml. of pyridine was refluxed for 2 hr. after which the pyridine was distilled *in vacuo*. The residue was dissolved in methylene chloride, and the solution was washed with dilute HCl and aqueous $NaHCO_3$. The solvent was distilled, and the oxime was crystallized from ethyl acetate–petroleum ether; yield 80%.

9-Cyanotriptycene (10).—A solution of 0.4 g. of the oxime **9** in 20 ml. of acetic anhydride was refluxed for 2 hr. The solvent was distilled *in vacuo*, and the product was crystallized from ether–petroleum ether; yield 0.29 g. (77%).

9-Hydroxymethyltriptycene (5) from Triptycene-9-carboxaldehyde (8).—A mixture of 1.0 g. of the aldehyde **8** and 50 ml. of methanol was warmed until homogeneous. It was cooled to room temperature and then treated with 1.0 g. of $NaBH_4$. The solution was stirred for 1 hr. and then diluted gradually with 15 ml. of water. Some of the methanol was evaporated *in vacuo*, and the product was filtered and washed with water and methanol; yield 0.8 g. This route to the alcohol **5** is superior to that based on addition of benzyne to 9-hydroxymethylanthracene.

9-Diacetoxymethyltriptycene (11).—In an attempt to condense triptycene-9-carboxaldehyde with γ-picoline, only the ahlehyde diacetate **11** was isolated. A solution of 1.0 g. of triptycene-9-carboxaldehyde (**8**) in 30 ml. of acetic anhydride and 1 ml. of γ-picoline was refluxed for 18 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was crystallized from methanol; yield 0.25 g.

9-Methyliminomethyltriptycene (13).—Triptycenealdehyde **8** (2.0 g.) was dissolved in 100 ml. of dioxane and 25 ml. of liquid methylamine, and the solution was heated for 7 hr. at 120° under 105.45 kg./cm.² hydrogen pressure using about 5 g. of Raney nickel catalyst. No hydrogen was absorbed, so the catalyst was filtered, and the filtrate was evaporated to dryness *in vacuo*. The Schiff base was crystallized from a mixture of dimethylformamide, methanol, and a little water; yield 1.64 g. (78%). Acid hydrolysis of this Schiff base regenerated triptycene-9-carboxaldehyde. Although catalytic reduction failed under the above conditions, the Schiff base was converted in good yield to corresponding methylaminomethyl compound **14** by means of $LiAlH_4$.

9-Dimethylaminomethyltriptycene Hydrochloride (16).—This was prepared in 95% yield from 9-monomethylaminomethyltriptycene (**14**) by the method given above for **31**.

Attempts to prepare this compound by alkylation of dimethylamine with 9-chloromethyltriptycene (**4**) were fruitless. Attempted reaction even at 180° resulted in 70% recovery of starting material. This was not unexpected in view of the neopentyl nature of the chloride (**4**).

Triptycene-9-carboxaldehyde Cyanohydrin (25).—A solution of the aldehyde **8** (4.0 g.) in 250 ml. of liquid HCN was cooled in ice, and 16 g. of dry, powdered NaCN was added. The mixture was stirred at 0° for 30 min., after which time it was evaporated quickly to dryness *in vacuo* below 25°. The residue was taken up in ethyl acetate and ice-water, and the organic layer was washed well with cold water, with dilute HCl, and again with water. The extract was dried and then concentrated to about 25 ml. under reduced pressure. Petroleum ether (75 ml.) was added, and the product was filtered; yield 3.7 g. (84%).

Triptycene-9-carboxylic Acid (17).—To a solution of 3.0 g. of triptycene-9-carboxaldehyde (**8**) in 40 ml. of pyridine was added with stirring a solution of 1.68 g. of $KMnO_4$ in 50 ml. of water during 90 min. The reaction mixture was maintained at about 45–55° during the addition and for an additional 90 min. The mixture was evaporated to dryness *in vacuo*, and the residue was taken up in water and 2 ml. of 50% NaOH. The manganese dioxide was filtered, and the filtrate was acidified with HCl. The product was filtered and washed with water; yield 2.94 g. (93%). Compounds **2** and **18–22** were prepared from this acid by the methods given by Barlett.[21]

9-(β-Pyrrolidinoethyl)triptycene Hydrochloride (24).—A solution of 0.65 g. of the chloroethyltriptycene (**23**) in about 25 ml. of pyrrolidine was heated for 18 hr. at 125° in a sealed vessel. The mixture was evaporated to dryness under reduced pressure. The residue was taken up in ether and excess aqueous $NaHCO_3$. The ether layer was dried, and the hydrochloride was precipitated with dry HCl; yield 50%.

2-(β-9-Triptycylpropionyl)cyclopentanone (50).—To a solution of 7.5 g. of the morpholine enamine of cyclopentanone[22] and 5.1 g. of triethylamine in 50 ml. of dry chloroform was added with stirring a solution of 16.3 g. of the acid chloride (**34**) in 50 ml. of dry chloroform. The temperature rose to 35–40°, and stirring

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(22) S. Hünig and W. Lendle, *Ber.*, **93**, 909 (1960).

at 35–38° was continued for 30 min. The reaction mixture was kept overnight at room temperature, after which 25 ml. of 6 *N* HCl was added. The mixture was stirred at 35–42° for 30 min. The chloroform layer was separated and washed with water, and the solvent was distilled *in vacuo*. The residue was crystallized from ether–petroleum ether; yield 8.5 g., m.p. 193–203°. A sample was recrystallized from ethylene dichloride–ether–petroleum ether.

5-(β-9-Triptycylpropionyl)valeric Acid (51).—A solution of the diketone **50** (7.85 g.) and 0.95 g. of NaOH in 100 ml. of 50% ethanol was refluxed for 4 hr. Concentrated HCl (2.5 ml.) was added, and most of the ethanol was distilled *in vacuo*. The product was filtered and washed with water; yield 7.5 g., m.p. 193–197°. A sample was recrystallized from toluene for analysis.

8-(9-Triptycyl)octanoic Acid (52).—A mixture of 7.3 g. of the keto acid **51**, 1.05 g. of KOH, 7.5 ml. of 85% hydrazine hydrate, and 20 ml. of diethylene glycol was stirred and refluxed for 6 hr. Diethylene glycol (20 ml.) and 5.5 g. of KOH were added, and the mixture was heated for 17 hr. in an open flask in an oil bath kept at 195°. The reaction mixture was poured into several volumes of water. Then 12 *N* HCl (20 ml.) was added, and the mixture was heated, then cooled, and the product was filtered and washed well with water; yield 6.7 g., m.p. 160–168°. It was recrystallized from methanol–ether. The acid chloride was prepared using oxalyl chloride according to the procedure given above for the acid chloride **34**. This was converted to the amide **53** using excess dry NH_3 in ether solution, and the amide was reduced with $LiAlH_4$ by the general procedure above to yield the amine hydrochloride **54**.

13-(9-Triptycyl)-6-ketotridecanoic Acid (55).—The acid chloride of 8-(9-triptycyl)octanoic acid (**52**) was used to acylate the morpholine enamine of cyclopentanone by the procedure used above. The crude β-diketone on alkaline hydrolysis afforded the keto acid **55**.

13-(9-Triptycyl)tridecanoic Acid Amide (56).—Wolff-Kischner reduction of the keto acid **55** by the procedure used for **52** gave the tridecanoic acid, which was converted to the amide **56** in the usual way. Reduction of the amide afforded the amine hydrochloride **57**.

12-(9-Triptycyl)dodecylamine Hydrochloride (58).—Hofmann degradation of the amide **56** was carried out using the procedure employed with **35**. The crude carbamate so formed was hydrolyzed by the method used for conversion **27** → **29** above.

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Derivatives of Fluorene. XIX.[1,2] 9-*o*-Chlorocinnamylidenefluorene and Related Compounds

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In screening sponsored by the National Service Center of the National Cancer Institute, activity against an animal tumor was discovered with a compound presumed (and first reported in 1919) to be 9-*o*-chlorobenzylidenefluorene. Upon examination, the compound has been found to be 9-*o*-chlorocinnamylidenefluorene which was produced in small yield as the only recognizable product in an attempted sodium ethoxide–ethanol condensation of *o*-chlorobenzaldehyde and fluorene, presumably after formation of acetaldehyde and then *o*-chlorocinnamaldehyde or 9-ethylidenefluorene or both. A number of analogs have been made for antitumor screening, particularly by the phosphonium–ylide route which, in general, is much superior to the alkaline condensation method. Spectral properties were recorded and some new triphenylphosphonium fluorenylides were made as intermediates.

Included in the preparation of a number of derivatives of fluorene and aminofluorenes, with extended conjugation from the 9-position, we repeated the reaction reported by Sieglitz between fluorene and *o*-chlorobenzaldehyde in the presence of sodium ethoxide. We, too, obtained a small yield of the yellow product (m.p. 177–178°, lit. 176°) which had been named *o*-chlorobenzalfluorene,[3] and observed the same distressing facts that analyses were not good, and that further attempted purification did not result in better analyses. About this time we were notified that the compound was showing slight antitumor activity against S180 in tests sponsored by the Cancer Chemotherapy National Service Center, and that a relatively large amount was wanted for further testing. In view of the poor analyses and low yields of this substance (which also seemed to be a deeper yellow than expected from comparison with similar 9-benzylidenefluorenes), it appeared necessary both to prepare the *o*-chlorobenzylidenefluorene by an alternate route and to examine more critically the structure of the compound melting at 178°. It was then observed that analyses were consistent with an empirical formula C_2H_2 greater than that for the alleged compound. Thus we were led to feel that the compound wanted in further amounts by the CCNSC was probably 9-*o*-chlorocinnamylidenefluorene.

Badger and Spotswood described and confirmed the synthesis of 9-*o*-chlorobenzylidenefluorene[4] (m.p. 69–70°), essentially by Sieglitz's method, with no reference to Sieglitz's data or to the fact that there was a difference of over 100° in the melting points of the reported compounds. Reaction of *o*-chlorobenzaldehyde and 9-triphenylphosphine fluorenylide gives authentic 9-*o*-chlorobenzylidenefluorene. The melting point, al-

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