melted at 150°. After the product was dried at 100° *in vacuo*, it melted at 140–153°.

Method C. Halogenation with N-Bromosuccinimide. 2-{*p*-(2-Bromo-2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy}triethylamine Dihydrogen Citrate (8).—To a solution of 46.1 g (0.095 mole) of 2-[*p*-(2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy]triethylamine hydrochloride in 200 ml of dry $CHCl_3$ at 0° was added a suspension of 19.6 g (0.11 mole) of N-bromosuccinimide in 300 ml of dry chloroform. The mixture was stirred at 0° for 8 hr then was allowed to stand for 24 hr at 0°. The reaction mixture was kept at 0° while an excess of 10% NaOH was added. The organic layer was removed and dried ($MgSO_4$). The residue that remained upon removal of the chloroform was converted to the dihydrogen citrate salt, using 18.3 g (0.095 mole) of citric acid in butanone. The crystalline product obtained was recrystallized seven times from butanone and once from 2-propanol to give 4.0 g (6.2%) of product, melting at 128–130°.

Method D. Bromine in Glacial Acetic Acid. N-[2-{*p*-(2-Bromo-2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy}ethyl]dimethylamine Dihydrogen Citrate (6).—To a solution of 10.0 g (0.025 mole) of 1-[*p*-(β-dimethylaminoethoxy)phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol in 50 ml of glacial acetic acid was added a solution of 8.0 g (0.05 mole) of bromine in 50 ml of glacial acetic acid at 15°. The reaction mixture was stirred for 1 hr after the addition was completed at 15°, then cooled to 0° and made basic with an excess of NaOH. The free amine was extracted with ether and dried ($MgSO_4$). The residue that remained after removal of the ether was converted to the dihydrogen citrate salt, using 4.8 g (0.025 mole) of citric acid in butanone. The product was recrystallized six times from butanone to give 1.5 g (9.3%) of product melting at 114–116°.

Method E. Fractional Recrystallization. Isomers of 2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine Hydrochloride.

The dihydrogen citrate salt of **1** was converted to the base with aqueous NaOH solution. The base was extracted with ether, dried ($MgSO_4$), filtered, and treated with alcoholic HCl. The oil which separated was taken up in hot butanone, and upon cooling, a solid fraction was obtained. Further fractions were obtained by condensing the mother liquor of the previous fraction and cooling. Repetition of this process yielded isomer **a** hydrochloride (**1a**) which melted at 156.5–158.0° [$\lambda_{max}^{CH_3OH}$ 230 mμ (ε 20,500), 291 mμ (ε 12,700)], and isomer **b** hydrochloride (**1b**) which melted at 149.0–150.5° [$\lambda_{max}^{CH_3OH}$ 239 mμ (ε 22,100), 297 mμ (ε 11,600)].

The longest wavelength maximum in each of the ultraviolet spectra has been attributed to a stilbene-type chromophore. These data suggest that **1b** is the *cis*[8] isomer and therefore **1a** is the *trans*[8] isomer.

Synthesis and Pharmacological Properties of New 9,10-Dihydro-9,10-ethanoanthracene Derivatives

JACQUES R. BOISSIER,

Institut de Pharmacologie, Faculté de Médecine, 75-Paris 6ème, France

ROGER RATOUIS, CLAUDE DUMONT, LAURENT TALIANI, AND JEANNINE FOREST

Centre de Recherches, S.I.F.A.-Diamant, 93-La Plaine Saint Denis, France

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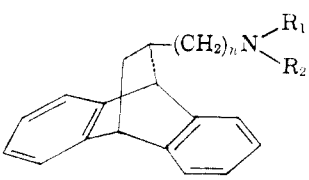
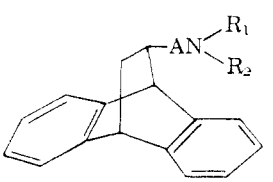
A number of substituted 9,10-dihydro-9,10-ethanoanthracenes have been synthesized and evaluated for their pharmacological activity. Some of these compounds show marked anticholinergic, hypotensive, antihistaminic, and local anesthetic activities.

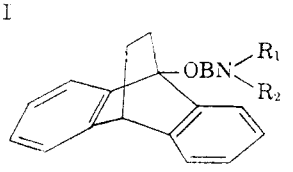
The ability of anthracene to act as a conjugated diene in a Diels–Alder reaction was first reported in 1931.[1] The resulting 9,10-dihydro-9,10-ethanoanthracenes represent a fairly simple polycyclic system which has remained unexplored in the field of medicinal chemistry. Recently, a series of 9-aminoalkyl-9,10-dihydro-9,10-ethanoanthracenes was patented[2] and, while our work was in progress, two patents[3,4] reporting the preparation of 11-aminoalkyl-9,10-dihydro-9,10-ethanoanthracenes were published. Some of these compounds were studied especially for their psychotropic activity.[2,3,5] The present paper describes two series (I and II) of derivatives of 9,10-dihydro-9,10-ethanoanthracene substituted in the 11 position by an aminoalkyl or an aminoalkylamino group (I), or by an aminoalkoxy or an aminoalkoxyalkyl group (II), and one series of 9,10-dihydro-9,10-ethanoanthracene derivatives substituted in the 9 position by an aminoalkoxy group (III). In



I



II



III

each series, NR_1R_2 represents alkylamino or dialkylamino groups or a saturated heterocyclic moiety. In I, NR_1R_2 can represent a 2-dimethylaminoethyl group.

The most convenient route to 11-aminomethyl compounds (I, $n = 1$) was the reductive amination of the readily available 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde[6] by the Leuckart method (method A). Alternatively, the compounds were obtained in two steps from the above aldehyde [or from 9,10-dihydro-9,10-ethanoanthracen-11-one[7] (I, $n = 0$)] and

(1) O. Diels, K. Ahler, and S. Beckmann, *Ann. Chem.*, **486**, 191 (1931).

(2) (a) Ciba S. A., French Patent 1,332,530 (1963); (b) Ciba S. A., French Patent 1,744 M (1963); (c) Ciba Ltd., South African Patent 64/4818 (1965); (d) P. Schmidt, M. Wilhem, and K. Eichenberger (to Ciba Ltd.), Swiss Patent 398,570 (1966); (e) Ciba Ltd., South African Patent 65/6631 (1966).

(3) Geigy A. G., Dutch Patent 6,412,215 (1965).

(4) K. Kitahonoki and R. Kuhl (to Shionogi and Co., Ltd.), French Patent 1,421,996 (1965).

(5) K. A. Flügel, R. Soerger, and Th. Veil, *Arzneimittel-Forsch.*, **12**, 1302 (1965).

(6) (a) B. A. Arbuzov and E. K. Iskakova, *Uch. Zap. Kazansk. Gos. Univ.*, **116**, 113 (1956); (b) Bataafsche Petroleum Maatschappij, British Patent 749,723 (1956).

(7) S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, **18**, 288 (1953).

Table I

11-Aminoalkyl-9,10-dihydro-9,10-ethanoanthracenes (I)

No.	n	R_1, R_2	Method	Crystn solvent[a]	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	IC_{50}, μg/ml Acetylcholine	IC_{50}, μg/ml Histamine	Estd[b] LD_{50}
1	1	CH_3, CH_3	A	E	70	78[c]	$C_{19}H_{21}N$	86.6	8.0	5.3	86.8	8.3	5.2	0.3	0.04	75
2	1	C_2H_5, C_2H_5	A	E-Pr	82	78	$C_{21}H_{25}N$	86.6	8.7	4.8	86.8	8.6	4.8	0.1	0.02	50
3	1	H, $CH(CH_3)CH_2C_6H_5$	B	H	57	67	$C_{31}H_{27}N$	88.3	7.7	4.0	88.4	7.7	3.9	0.2	0.06	300
4	1	$(CH_2)_5$	A	Pr	35	145	$C_{22}H_{25}N$	87.1	8.3	4.6	86.8	8.2	4.6	0.1	0.02	300
5	1	$(CH_2)_5$	A	Pr	..	215	$C_{22}H_{25}N \cdot HCl$	77.7	7.7	4.1	78.0	7.7	4.0	...	...	...
6	2	CH_3, CH_3	C	Pr	84	254[d]	$C_{20}H_{23}N \cdot HCl$	76.5	7.7	4.5	76.4	7.4	4.3	1	1	150
7	2	CH_3, CH_3	..	A-Et	..	245	$C_{20}H_{23}N \cdot CH_3I$	60.1	6.3	3.3	59.8	6.1	3.2	0.1	0.14	75
8	2	C_2H_5, C_2H_5	C	Pr	85	228[e]	$C_{22}H_{27}N \cdot HCl$	77.3	8.3	4.1	77.0	8.0	4.0	0.3	0.13	150
9	3	CH_3, CH_3	C	A	84	195[f]	$C_{21}H_{25}N \cdot HCl$	76.9	8.0	4.3	76.7	8.0	4.2	0.05	0.1	150
10	3	CH_3, CH_3	..	E	..	211	$C_{21}H_{25}N \cdot CH_3I$	61.0	6.5	3.2	60.7	6.4	3.3	0.05	0.22	25
11	3	C_2H_5, C_2H_5	C	Pr	70	163	$C_{23}H_{29}N \cdot HCl$	77.6	8.5	3.9	77.4	8.4	3.9	0.17	0.05	75
12	3	$(CH_2)_5$	C	Pr	55	248	$C_{24}H_{29}N \cdot HCl$	78.3	8.2	3.8	78.3	8.2	3.9	0.3	0.14	50
13	0	H, $CH_2CH_2N(CH_3)_2$	B	E	60	225-230	$C_{20}H_{24}N_2 \cdot 2HCl$	65.8	7.2	7.7	65.6	7.3	7.3	0.5	0.5	100
14	0	CH_3, $CH_2CH_2N(CH_3)_2$	D	M-W	58	246-248	$C_{21}H_{26}N_2 \cdot 2HCl$	66.5	7.4	7.4	66.4	7.6	7.4	1	1	150
15	0	CH_3, $CH_2CH_2N(CH_3)_2$	..	An	..	185-190	$C_{21}H_{26}N_2 \cdot 2CH_3I$	46.8	5.5	4.8	47.0	5.5	4.8	50	10	100
16	1	CH_3, $CH_2CH_2N(CH_3)_2$	A	M	40	253	$C_{22}H_{28}N_2 \cdot 2HCl$	67.2	7.7	7.1	67.4	7.7	6.9	0.1	0.5	150
17	1	CH_3, $CH_2CH_2N(CH_3)_2$	..	M-W	..	234	$C_{23}H_{28}N_2 \cdot 2CH_3I$	47.7	5.7	4.6	47.4	5.7	4.6	50	5	75
18	1	$(CH_2CH_2)_2NCH_3$	A	A-W	41	115	$C_{22}H_{26}N_2$	83.0	8.2	8.8	82.9	8.2	8.9	0.5	0.01	50
19	1	$(CH_2CH_2)_2NCH_3$	..	M-W	..	230-240	$C_{22}H_{26}N_2 \cdot 2CH_3I$	47.9	5.4	4.7	47.5	5.5	4.7	5	0.5	150
20	1	$(CH_2CH_2)_2NCH_2CH_2OH$	A	Pe	39	135-137	$C_{23}H_{28}N_2O$	79.3	8.1	8.0	79.3	8.1	8.1	...	...	...
21	1	$(CH_2CH_2)_2NCH_2CH_2OH$	..	M-W	..	222-225	$C_{23}H_{28}N_2O \cdot 2CH_3I$	47.5	5.4	4.4	47.4	5.5	4.4	20	20	25

[a] A, acetone; An, acetonitrile; E, ethanol; Et, ethyl ether; H, heptane; M, methanol; P, pentane; Pe, petroleum ether (bp 50–65°); Pr, 2-propanol; W, water. [b] Acute toxicity determined by intraperitoneal injection of increasing doses (25, 50, 100, 200, 400, and 800 mg/kg) to pairs of mice according to W. G. Smith in "Progress in Medicinal Chemistry," G. P. Ellis and G. B. West, Ed., Butterworth and Co. (Publishers) Ltd., London, 1961, p 1. The LD_{50} is approximately the dose killing one out of two mice or the average of the two successive doses for which mortalities of 0/2 and 2/2 have been observed. [c] Lit.[3] mp 70–78. [d] Lit.[3] mp 259–261°. [e] Lit.[3] mp 221–223°. [f] Lit.[3] mp 191–192°.

the appropriate amine or diamine. In the initial step, the amino derivative was condensed with the carbonyl compound. Reduction of the crude condensation product with hydrogen over platinum oxide furnished the desired 11-substituted ethanoanthracene (method B). The preparation of the 11-aminoethyl (I, $n = 2$) and 11-aminopropyl (I, $n = 3$) compounds proceeded from 9,10-dihydro-9,10-ethanoanthracene-11-acetic and -propionic acids, respectively, *via* the acid chlorides and the amides, which were reduced with lithium aluminum hydride (method C). The acids required as starting materials were made under the conditions of the Diels–Alder reaction from anthracene and vinyl- and allylacetic acids, respectively. Methylation of **13** was accomplished according to Eschweiler–Clarke (method D). The compounds prepared by these procedures are summarized in Table I.

Most of the amino ethers of Tables II and III were obtained by treatment of the corresponding alcohols with the appropriate basically substituted alkyl halide in the presence of an excess of sodium hydroxide (method E). Alternatively the alcohols were converted to their lithium (method F) or sodium (method H) salts and then treated with the halide. The syntheses of two new alcohols are outlined in the Experimental Section.

Treatment of the lithium salt of 9,10-dihydro-9,10-ethanoanthracene-11-methanol[8] with the aminoalkyl halide from 1-dimethylamino-2-propyl chloride hydrochloride, followed by addition of hydrochloric acid gave a mixture of two isomeric hydrochlorides **32** and **33**, and vpc analysis of the bases indicated that the composition was approximately 20 and 80%. These salts were recrystallized to give **33** as a crystalline product which, by vpc of the base, proved to be a single substance. Diels–Alder addition of 1-dimethylamino-2-allyloxypropane to anthracene (method G) provided an unambiguous path to **32**. Structural assignment for these isomers was based on the gas chromatograms. During vpc analysis of the corresponding bases, these Diels–Alder adducts were thermically dissociated into their components (injection port at 450°). Compound **32** yielded anthracene and 1-dimethylamino-2-allyloxypropane, and **33** yielded anthracene and 2-dimethylamino-1-allyloxypropane as shown by comparison with authentic specimens prepared by unequivocal procedures (see Experimental Section). Nmr spectra were in accordance with these structures. N-Demethylation of **40** to **38** was effected by reaction with ethyl chloroformate followed by hydrolysis of the resulting urethan (method I). In the Experimental Section, each of the reactions discussed above is illustrated by one example.

Results

The pharmacological methods are described in the Experimental Section.

The approximate acute intraperitoneal toxicities of compounds **1–37** were determined (Tables I and II); more precise values were attained for compounds **38–64** (Table III). The quaternary ammonium compounds are more toxic than the corresponding bases except for **19** and **57**.

The anticholinergic potency of the substances was systematically evaluated on the guinea pig ileum preparation. The IC_{50} values lie between 0.03 and 50 μg/ml; the value for atropine sulfate used as a standard was 0.005 μg/ml. Compound **33** which was the more active in the last test also exhibited a strong protection against tremorine in mice.[9]

Bisquaternary ethylenediamine compounds (**15**, **17**, **19**, and **21**) were studied further for hypotensive and ganglioplegic properties. Actually, they lower the blood pressure in the anesthetized dog and block the effect of preganglionic excitation of the cervical sym-

(8) K. Alder, *Chem. Ber.*, **71**, 1952 (1938).

(9) J. R. Boissier, C. Dumont, and R. Ratouis, manuscript in preparation.

TABLE II: 11-AMINOALKOXY- AND 11-AMINOALKOXYALKYL-9,10-DIHYDRO-9,10-ETHANOANTHRACENES (II)

No.	A	R_1, R_2	Method	Cryst. solvent[a]	Yield, %	M.p., °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	IC_{50}, μg/ml Acetylcholine	IC_{50}, μg/ml Histamine	Estd[b] LD_{50}
22	$O(CH_2)_2$	CH_3, CH_3	E	A	78	171	$C_{20}H_{23}NO \cdot C_4H_4O_4$[c]	70.4	6.7	3.4	70.6	6.8	3.3	0.3	0.05	150
23	$O(CH_2)_2$	C_2H_5, C_2H_5	E	A–Et	81	95–98	$C_{22}H_{27}NO \cdot C_6H_{13}NO_3S$[d]	67.2	8.1	5.6	67.1	8.1	5.4	0.2	0.3	150
24	$O(CH_2)_2$	$(CH_2)_5$	E	A	64	193–195	$C_{23}H_{27}NO \cdot C_4H_4O_4$[c]	72.1	7.0	3.1	72.0	6.8	3.1	1	0.2	150
25	$O(CH_2)_3$	CH_3, CH_3	E	An–Et	73	148	$C_{21}H_{25}NO \cdot C_4H_4O_4$[c]	70.9	6.9	3.3	70.6	6.7	3.3	0.3	0.6	150
26	$CH_2O(CH_2)_2$	CH_3, CH_3	E	An	70	194	$C_{21}H_{25}NO \cdot HCl$	73.3	7.6	4.1	72.8	7.7	4.1	0.1	0.05	150
27	$CH_2O(CH_2)_2$	C_2H_5, C_2H_5	E	A–E	64	140–142	$C_{23}H_{29}NO \cdot C_6H_{13}NO_3S$[d]	67.7	8.2	5.4	67.6	8.3	5.2	2	0.07	50
28	$CH_2O(CH_2)_2$	$(CH_2)_4$	F	An	65	203–207	$C_{23}H_{27}NO \cdot HCl$	74.7	7.6	3.8	74.8	7.6	3.9	0.7	0.1	75
29	$CH_2O(CH_2)_2$	$(CH_2)_5$	E	W	65.5	207–208	$C_{24}H_{29}NO \cdot HCl$	75.1	7.9	3.7	74.9	7.7	3.7	1	1	75
30	$CH_2O(CH_2)_2$	$(CH_2)_6$	F	An	93	181–184	$C_{25}H_{31}NO \cdot HCl$	75.4	8.1	3.5	75.4	8.2	3.4	0.3	0.2	75
31	$CH_2O(CH_2)_2$	$(CH_2CH_2)_2O$	F	E	47	218–220	$C_{23}H_{27}NO_2 \cdot HCl$	71.6	7.3	3.6	71.4	7.3	3.6	2	3	600
32	$CH_2OCH(CH_3)CH_2$	CH_3, CH_3	G	An–Et	32	195–197	$C_{22}H_{27}NO \cdot HCl$	73.8	7.9	3.9	73.8	7.9	3.8	0.2	0.1	100
33	$CH_2OCH_2CH(CH_3)$	CH_3, CH_3	F	An	30	181–182	$C_{22}H_{27}NO \cdot HCl$	73.8	7.9	3.9	73.8	7.9	4.0	0.03	0.02	75
34	$CH_2OCH_2CH(CH_3)$	CH_3, CH_3	..	...	81	147–150	$C_{22}H_{27}NO \cdot CH_3I$	59.6	6.5	3.0	59.3	6.4	3.2	0.1	0.1	37.5
35	$CH_2O(CH_2)_3$	CH_3, CH_3	E	An	50	165	$C_{23}H_{27}NO \cdot HCl$	73.8	7.9	3.9	73.7	7.7	3.9	0.2	0.4	75
36	$CH(CH_3)O(CH_2)_2$	CH_3, CH_3	E	A–Et	82	149	$C_{23}H_{27}NO \cdot C_4H_4O_4$[c]	71.4	7.1	3.2	71.2	7.2	3.3	1	0.05	150
37	$(CH_2)_2O(CH_2)_2$	CH_3, CH_3	E	A–An	46	168–170	$C_{23}H_{27}NO \cdot HCl$	73.8	7.9	3.9	73.6	8.0	3.8	1.4	0.5	75

[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] $C_4H_4O_4$ = maleic acid. [d] $C_6H_{13}NO_3S$ = cyclohexylsulfamic acid. [e] $C_4H_4O_4$ = fumaric acid.

TABLE III: 9-AMINOALKOXY-9,10-DIHYDRO-9,10-ETHANOANTHRACENES (III)

No.	B	R_3, R_4	Method	Cryst. solvent[a]	Yield, %	M.p., °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	IC_{50}, μg/ml Acetylcholine	IC_{50}, μg/ml Histamine	LD_{50}, mg/kg[b]
38	$(CH_2)_2$	H, CH_3	I	P	75	92–94	$C_{19}H_{21}NO$	81.7	7.6	5.0	81.6	7.5	5.0	...	...	...
39	$(CH_2)_2$	H, CH_3	..	E	...	260–263	$C_{19}H_{21}NO \cdot HCl$	72.3	7.0	4.4	72.2	6.9	4.3	0.15	0.02	134
40	$(CH_2)_2$	CH_3, CH_3	E	P	73	60–61	$C_{20}H_{23}NO$	81.9	7.9	4.8	82.0	8.0	4.8	...	...	...
41	$(CH_2)_2$	CH_3, CH_3	..	E	...	231–232	$C_{20}H_{23}NO \cdot HCl$	72.8	7.3	4.3	72.8	7.5	4.2	0.2	0.005	135
42	$(CH_2)_2$	CH_3, CH_3	..	E	...	187–188	$C_{20}H_{23}NO \cdot HNO_3$	67.4	6.8	7.9	67.3	6.8	7.8	...	...	...
43	$(CH_2)_2$	CH_3, CH_3	..	W	...	195	$C_{20}H_{23}NO \cdot H_2SO_4$	61.4	6.4	3.6	61.4	6.5	3.5	...	...	...
44	$(CH_2)_2$	CH_3, CH_3	..	A	...	147–148	$C_{20}H_{23}NO \cdot HO_3SCH_3$	64.8	7.0	3.6	64.3	7.2	3.5	...	...	...
45	$(CH_2)_2$	CH_3, CH_3	..	E	78	178–179	$C_{20}H_{23}NO \cdot C_7H_7ClN_4O_2$[c]	63.8	6.0	13.8	63.8	6.4	13.6	2	0.005	164
46	$(CH_2)_2$	CH_3, CH_3	..	E	76	172–175	$C_{20}H_{23}NO \cdot C_9H_{10}N_4O_3$[d]	65.5	6.3	13.2	65.5	6.4	13.2	0.25	0.01	293
47	$(CH_2)_2$	CH_3, CH_3	..	An	...	250	$C_{20}H_{23}NO \cdot CH_3I$	57.9	6.0	3.2	58.1	6.0	3.1	0.1	0.02	57
48	$(CH_2)_2$	CH_3, CH_3	..	M	...	209	$C_{20}H_{23}NO \cdot HOCH_2CH_2I$	56.8	6.1	3.0	56.8	5.9	2.9	0.5	0.01	84
49	$(CH_2)_2$	C_2H_5, C_2H_5	E	A–Pr	70	174–176	$C_{22}H_{27}NO \cdot HCl$	73.8	7.9	3.9	73.9	7.8	4.0	0.2	0.01	141
50	$(CH_2)_2$	$(CH_2)_4$	E	Pe	60	90–91	$C_{22}H_{25}NO$	82.7	7.9	4.4	82.7	8.0	4.3	...	...	...
51	$(CH_2)_2$	$(CH_2)_4$	..	W	...	205–207	$C_{22}H_{25}NO \cdot HCl$	74.2	7.4	3.9	74.2	7.5	3.8	1	0.005	127
52	$(CH_2)_2$	$(CH_2)_4$	..	Pr	...	221–222	$C_{22}H_{25}NO \cdot HBr$	66.0	6.6	3.5	66.1	6.6	3.4	...	...	...
53	$(CH_2)_2$	$(CH_2)_5$	..	E	...	228–230	$C_{22}H_{25}NO \cdot H_2SO_4$	63.3	6.5	3.4	63.3	6.8	3.3	2	0.005	114
54	$(CH_2)_2$	$(CH_2)_5$	..	An–Et	...	169–170	$C_{22}H_{25}NO \cdot HO_3SCH_3$	66.5	7.0	3.4	66.7	6.9	3.3	1.5	0.005	128
55	$(CH_2)_2$	$(CH_2)_5$	E	H	60	101	$C_{23}H_{27}NO$	82.8	8.2	4.2	82.9	8.2	4.3	...	...	...
56	$(CH_2)_2$	$(CH_2)_5$	..	Pr	...	225	$C_{23}H_{27}NO \cdot HCl$	74.7	7.6	3.8	74.5	7.7	3.7	0.25	<0.005	146
57	$(CH_2)_2$	$(CH_2)_5$	..	An–M	...	264–265	$C_{23}H_{27}NO \cdot CH_3I$	60.6	6.4	3.0	60.7	6.3	3.1	0.7	0.005	205
58	$(CH_2)_2$	$(CH_2CH_2)_2O$	H	An	50	214–217	$C_{22}H_{25}NO_2 \cdot HCl$	71.1	7.1	3.8	71.0	7.1	3.7	10	0.1	120
59	$(CH_2)_2$	$(CH_2CH_2)_2NCH_3$	E	Pe	43	107	$C_{23}H_{28}N_2O$	79.3	8.1	8.0	79.1	8.4	8.0	...	...	...
60	$(CH_2)_2$	$(CH_2CH_2)_2NCH_3$	..	E	...	230–235	$C_{23}H_{28}N_2O \cdot 2HCl$	65.6	7.2	6.7	65.6	7.2	6.6	2	0.1	174
61	$CH_2CH(CH_3)$	CH_3, CH_3	H	Pr	35	192–195	$C_{19}H_{23}NO \cdot HCl$	73.3	7.6	4.1	73.3	7.5	4.1	1	0.05	125
62	$(CH_2)_3$	CH_3, CH_3	E	P	42.5	44–45	$C_{21}H_{25}NO$	82.0	8.2	4.6	82.0	8.3	4.5	0.1	0.1	133
63	$(CH_2)_3$	$(CH_2CH_2)_2NCH_3$	H	...	45	233–234	$C_{21}H_{30}N_2O \cdot 2HCl$	66.2	7.4	6.4	66.0	7.6	6.2	5	1	143
64	$CH_2CH(CH_3)CH_2$	$(CH_2CH_2)_2NCH_3$	H	M–W	47	190–195	$C_{25}H_{32}N_2O \cdot 2HCl$	66.8	7.6	6.2	66.7	7.7	6.1	2	1	149

[a] See footnote *a* of Table I. [b] The number of mice used for each determination ranged from 50 to 80. The ratio of any two successive doses was constant at 1.2, and the LD_{50} values were calculated by the method of B. Behrens and G. Kärber, *Arch. Exptl. Pathol. Pharmakol.*, **117**, 379 (1934). [c] $C_7H_7ClN_4O_2$ = 8-chlorotheophylline. [d] $C_9H_{10}N_4O_3$ = 7-theophyllinylacetic acid.

pathetic nerve of the anesthetized cat. The minimal active doses start from 0.1 mg/kg iv as for hexamethonium.

The antihistaminic activity was screened *in vitro* in guinea pig ileum. The most potent compounds were found to be of type III. Their IC_{50} range was between 0.005 and 1 μg/ml (Table III). Under similar experimental conditions, the activities of promethazine and triprolidine were 0.02 and 0.005 μg/ml, respectively. The agents also prevent *in vivo* effects of histamine as reported in Table IV. They show marked protective activity against lethal doses of intravenously injected and of nebulized histamine in guinea pigs. Some of the compounds were more active than the two antihistaminic standard drugs used in this study. From the structure–activity relationships it appears that two carbon atoms between the oxygen and nitrogen atoms of the aminoalkoxy group were needed for good antihistaminic activity. Compound **41**[10] and the demethylamino derivative **39** had similar potencies.

Table IV

	Antihistaminic protection			
No.	No. of $100LD_{99}$ of histamine *vs.* antihistamine[a]	ED_{50}, μg/100 g of antihistamine *vs.* one LD_{99} of histamine[b]	histamine aerosol[b]	Local anesthetic activity Total score[c]
39	8–10	5	5	196
41	10	1.2	5	96
45	10	2.5	10	...
46	10	2.5	5	...
47	8	0.6–1.2	2.5	...
48	4	2.5	10	...
49	<2	>5	>20	479
51	12–14	0.6–1.2	5	927
53	10	1.2–2.5	2.5	1041
54	10	2.5	2.5	1074
56	6–8	2.5–5	10	1287
57	2	>5	>20	46
58	10	2.5	5–10	85
60	10–12	2.5	10	201
61	8–10	2.5	10–20	517
62	<2	>5	>20	322
63	<2	>5	>20	476
64	<2	>5	>20	746
Promethazine	8	2.5	5–10	538
Triprolidine	8–10	<0.6	5	468

[a] The values express how many times $100LD_{99}$ of histamine can be tolerated by the treated animals for a protection of 2/4 (*i.e.*, 50% protection). [b] The values express the doses of antihistamines sufficient to protect 2/4 animals. When the score of 2/4 was not reached, the intermediate value(s) comprised between 0/4 and 4/4 protection. [c] The maximal total score is 1300 for a complete anesthesia. The value for lidocaine used as standard compound was about 300.

Type III compounds were also tested for local anesthetic effects on the rabbit's cornea (Table IV). The pyrrolidino and piperidino derivatives (**51**, **53**, **54**, and **56**) were among the most active members of the series. The aminopropoxy and aminoisobutoxy compounds (**62–64**), which had no antihistaminic effectiveness, induced some local anesthesia.

(10) Other pharmacological data on compound **41** will be published: J. R. Boissier, C. Dumont, R. Ratouis, and D. Moisy, submitted for publication.

Experimental Section[11]

Pharmacology.—Acute intraperitoneal toxicities were determined in mice weighing from 19 to 23 g. All deaths occurring during the following 24 hr after the administration of the drug were recorded for estimation of LD_{50} values.

Comparative spasmolytic activity on isolated guinea pig ileum was determined against acetylcholine and histamine. Isolated strips were put in Tyrode solution at 37° through which air was bubbled. Drugs were allowed to remain in contact with the isolated ileum in the tissue chamber for 30 sec before the addition of the spasmogenic agent. The dose required to produce a 50% inhibition of induced spasm (IC_{50}) was estimated from a semilogarithmic plot of dose against the average per cent inhibitory action.

Protection against toxicity of intravenously injected histamine was evaluated on guinea pigs using two procedures. In the first one, compounds were administered subcutaneously to groups of four guinea pigs at a standard dose of 20 mg/kg. Thirty minutes later a single injection of histamine several times the minimal lethal dose was given intravenously. This minimal lethal dose (LD_{99}) of histamine dihydrochloride was found to be 0.8 mg/kg in control groups. The doses selected for testing were in arithmetical progression from 200 to 1400 times the LD_{99} increasing by 200 intervals. Results were expressed as the numbers of individual lethal doses of histamine which the animals survived. In the second procedure a constant dose of histamine and various doses of antagonist were used. Groups of four guinea pigs were pretreated subcutaneously at different doses of each antihistamine ranging from 0.006 to 0.050 mg/kg, spaced at two fold increments. Thirty minutes later, one LD_{99} of histamine was administered intravenously into a vein of the penis or hind leg. Results are expressed as the dose of drug required to protect 50% of the guinea pigs.

Protection against histamine aerosol induced bronchospasm was investigated by a modified Halpern technique.[12] Guinea pigs were confined individually in a glass chamber and exposed to a nebulized 0.4% histamine dihydrochloride solution in glycerol and water. Control animals suffered asphyxial collapse within 3 min. All the animals were employed only for one test. Compounds were administered subcutaneously 30 min before inhalation of the aerosol. The animals surviving after 10 min were deemed protected. Results are expressed as the protective dose for 50% of treated animals.

Surface anesthetic action was studied on the rabbit cornea according to a modified Regnier method.[13] The surface of the cornea was touched with a hair. Numbers of successive stimulations necessary to produce corneal reflex (not exceeding 100) were recorded at different time intervals after instillation with a 0.1% aqueous solution of the examined compound. The duration of exposure was 2 min, and the cornea was tested for anesthesia the third, sixth, and tenth minute and every 5 min up to 1 hr. The sum of scores determined at the different time intervals express local anesthetic activity.

Hypotensive action was evaluated in dogs anesthetized with chloralose (110 mg/kg iv). A mercury manometer was used to measure blood pressure from the carotid artery. Ganglionic blocking action was determined in cats anesthetized with pentobarbital sodium. The preganglionic nerve trunk of the left superior cervical ganglion was severed and stimulated electrically. The contractions of the nictitating membrane were recorded on a kymograph. Drugs were injected intravenously.

Chemistry.—Only one representative example of each procedure is described. The remainder of the products were made in an analogous way, as indicated in the tables.

9,10-Dihydro-9,10-ethanoanthracene-11-acetic Acid.—A solution of 50 g (0.28 mole) of anthracene, 50 g (0.58 mole) of vinylacetic acid, 0.4 g of hydroquinone, and 300 ml of benzene was stored in a pressure bottle at 200° for 15 hr. After cooling and extraction with dilute NaOH, the aqueous basic layer was acidified with dilute HCl. The solid which separated was collected

(11) Gas chromatographic analyses were carried out on a Perkin-Elmer Model 800 chromatograph. The nmr spectra were obtained with a Varian A-60 spectrophotometer in $CDCl_3$ with Me_4Si as the internal standard, and the ultraviolet spectra were obtained with a Cary 15 spectrophotometer. The melting points were determined on a Kofler hot stage microscope and are uncorrected. The boiling points are uncorrected.

(12) B. N. Halpern, *Arch. Intern. Pharmacodyn.*, **68**, 339 (1942).

(13) J. Regnier, *Compt. Rend.*, **177**, 558 (1923).

and dried to give 54 g (73%) of white product. The analytical sample was recrystallized twice from heptane; mp 188–190° (99% pure by nonaqueous acid–base titration).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.5; H, 6.2.

This compound had been prepared previously by hydrolysis of 9,10-dihydro-9,10-ethanoanthracene-11-acetonitrile;[3] mp 167–172°. The yield and analysis were not given.

9,10-Dihydro-9,10-ethanoanthracene-11-propionic acid was prepared by the same procedure from allylacetic acid; yield 53%, mp 152° after crystallization from benzene–heptane (98.5% pure by nonaqueous acid–base titration).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 81.6; H, 6.5.

This compound had been prepared by the malonic ester synthesis [sodium diethylmalonate and (9,10-dihydro-9,10-ethaneanthracen-11-yl)methyl *p*-toluenesulfonate];[3] mp 149–151°.

α-Methyl-9,10-dihydro-9,10-ethanoanthracene-11-methanol.—To a solution of 0.36 mole of methylmagnesium iodide in 500 ml of anhydrous ether was added, dropwise, 70 g (0.3 mole) of 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde[6] in 300 ml of anhydrous benzene and the mixture was refluxed for 1 hr with stirring. The mixture was poured into cold NH_4Cl solution, and the aqueous phase was extracted with ether. Evaporation of the ether solution gave 71 g (95%) of solid residue. Crystallization from heptane gave white product, mp 168°.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.4; H, 7.3. Found: C, 86.2; H, 7.4.

9,10-Dihydro-9,10-ethanoanthracene-11-ethanol.—Ethyl 9,10-dihydro-9,10-ethanoanthracene-11-acetate was obtained by refluxing overnight a mixture of 9,10-dihydro-9,10-ethanoanthracene-11-acetic acid (39.6 g, 0.15 mole), 1.2 g of *p*-toluenesulfonic acid monohydrate, 50 ml of ethanol, and 500 ml of benzene with removal of the water formed by a Dean–Stark trap. The acid solution was treated with $NaHCO_3$ solution and with water. The dried organic layer (Na_2SO_4) was evaporated and the residue was fractionated to give a colorless product, 77.5% yield, bp 158–160° (0.1 mm). The distillate slowly solidified, mp 90–91°. The product was used without further purification. To a stirred suspension of 3.8 g (0.1 mole) of $LiAlH_4$ in 100 ml of anhydrous ether was added 20 g (0.0685 mole) of the above ester in 100 ml of anhydrous ether. The mixture was refluxed for 15 hr, cooled, and treated dropwise with ethyl acetate (20 ml), water (20 ml), and 20% H_2SO_4 (50 ml). The ether layer was separated, washed with water, and concentrated to dryness. The residue was recrystallized from benzene–heptane to give 12.5 g (73%) of white crystals, mp 118–120°.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.4; H, 7.3. Found: C, 86.4; H, 7.3.

1-Dimethylamino-2-allyloxypropane.—To sodium 1-dimethylamino-2-propoxide from 9.2 g (0.4 g-atom) of sodium and 41.2 g (0.4 mole) of 1-dimethylamino-2-propanol in 50 ml of anhydrous toluene was added 48.4 g (0.4 mole) of allyl bromide. The mixture was refluxed for 2 hr. After cooling, the NaBr precipitate was removed by filtration. The filtrate was extracted with dilute HCl. The water layer was made alkaline and extracted with ether. Removal of the solvent and distillation of the residue gave 34.3 g (60%) of colorless product: bp 155°; $n^{24}D$ 1.4250; nmr, doublet centered at τ 7.64 (methylene protons of CH_2N), multiplet centered at 6.48 (methine protons of CH_2-CHO).

Anal. Calcd for $C_8H_{17}NO$: N, 9.8. Found: N, 9.5 (nonaqueous titration).

2-Dimethylamino-1-allyloxypropane was synthesized by the above procedure from 2-dimethylamino-1-propanol; yield 30%; bp 166°; $n^{24}D$ 1.4318; nmr, multiplet centered at τ 6.59 (methylene protons of CH_2O), multiplet centered at 7.21 (methine protons of CH_3CHN).

Anal. Calcd for $C_8H_{17}NO$: N, 9.8. Found: N, 9.7 (nonaqueous titration).

11-Diethylaminomethyl-9,10-dihydro-9,10-ethanoanthracene (2). Method A.—A solution of 23.4 g (0.1 mole) of 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde, 7.3 g (0.1 mole) of diethylamine, and 9.2 g (0.2 mole) of formic acid in 200 ml of benzene was refluxed for 12 hr. The cooled solution was added to 200 ml of 0.5 *N* HCl. The aqueous phase was treated with 20 ml of 5 *N* NaOH, and the mixture was extracted three times with 200-ml portions of benzene. After drying (Na_2SO_4), the benzene was evaporated to give 24 g of colorless crystals. Diamines **16**, **18**, and **20** were obtained by the same procedure, but using 4 moles of formic acid for 1 mole of diamine.

***d*-11-(1-Methylphenethylaminomethyl)-9,10-dihydro-9,10-ethanoanthracene (3). Method B.**—A solution of 2.34 g (0.01 mole) of 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde, 1.35 g (0.01 mole) of *d*-1-phenyl-2-aminopropane in 100 ml of methanol was stored overnight at room temperature. Platinum oxide catalyst (100 mg) was added and the suspension was shaken in an atmosphere of hydrogen under atmospheric pressure and at room temperature until the theoretical amount of hydrogen was absorbed. The mixture was filtered and the filtrate was concentrated to dryness. The residue was recrystallized from heptane to give 2.2 g of the desired product.

11-(N-2-Dimethylaminoethyl)amino-9,10-dihydro-9,10-ethanoanthracene dihydrochloride (13) was prepared as above from 22 g (0.1 mole) of 9,10-dihydro-9,10-ethanoanthracen-11-one[7] and 10 g (0.115 mole) of N,N-dimethylethylenediamine, but reduction was carried out at an initial pressure of 50 kg/cm² and at room temperature over 0.5 g of PtO_2 to give the desired amine as an oily product. The **dihydrochloride** was recrystallized from ethanol; yield 22 g.

11-(3-Piperidinopropyl)-9,10-dihydro-9,10-ethanoanthracene Hydrochloride (12). Method C.—To a solution of 27.8 g (0.1 mole) of 9,10-dihydro-9,10-ethanoanthracene-11-propionic acid, 7.9 g (0.1 mole) of pyridine, and 100 ml of anhydrous benzene was added dropwise 11.9 g (0.1 mole) of $SOCl_2$. The solution was refluxed for 1.5 hr. After cooling, the pyridine hydrochloride precipitate was removed by filtration and washed with benzene. The filtrate and washings were evaporated under reduced pressure to give an oily residue of acid chloride (82% pure by chloride titration). To a solution of 4.25 g (0.05 mole) of piperidine in 80 ml of anhydrous benzene was added slowly 9.05 g of the crude acid chloride. After standing overnight, the precipitate of piperidine hydrochloride was removed by filtration and washed with benzene. The benzene solutions were washed successively with dilute HCl, dilute NaOH, and with water and dried (Na_2SO_4). On the removal of the solvent, 9 g of an oily product was obtained which was treated with a suspension of 1.9 g (0.05 mole) of $LiAlH_4$ in 100 ml of anhydrous ether. The mixture was refluxed for 15 hr, the excess hydride and complex were destroyed with 5 ml of water, and the product was extracted with ether. The combined ether extract was treated with an equivalent quantity of HCl in ether to give 5.05 g of **12**.

11-(N-2-Dimethylaminoethyl-N-methylamino)-9,10-dihydro-9,10-ethanoanthracene Dihydrochloride (14). Method D.—A solution of 8.7 g (0.03 mole) of 11-(N-2-dimethylaminoethyl)-amino-9,10-dihydro-9,10-ethanoanthracene (from dihydrochloride **13**), 6 ml (0.06 mole) of 30% formaldehyde, and 4.15 g (0.09 mole) of formic acid was refluxed for 15 hr. After cooling, the solution was made alkaline with NaOH and extracted with ether. The ethereal solution was dried (K_2CO_3) and the solvent was evaporated to give the free base. A solution of this material in 25 ml of ethanol was treated with an equivalent quantity of HCl in 25 ml of ethanol to give a solution from which the **dihydrochloride** salt rapidly crystallized (after recrystallization from aqueous methanol the material weighed 6.6 g).

9-(2-Dimethylaminoethoxy)-9,10-dihydro-9,10-ethanoanthracene (40). Method E.—A suspension of 250 g (1.13 moles) of 9,10-dihydro-9,10-ethano-9-anthrol,[11] 163 g (1.13 moles) of 2-dimethylaminoethyl chloride hydrochloride, and 181 g (4.5 moles) of powdered NaOH in 1.5 l. of benzene was refluxed with stirring for 8 hr. After being cooled to 40–50°, it was treated again with 163 g (1.13 moles) of 2-dimethylaminoethyl chloride hydrochloride. Stirring and refluxing were continued for 12 hr longer. The inorganic salts were filtered off and washed with benzene. The combined benzene solution was concentrated to dryness *in vacuo* and the oily residue was triturated with 80 ml of petroleum ether (bp 35–50°) to give 240 g of product, mp 58°. After crystallization from pentane, the material weighed 180 g; mp 60–61°; $\lambda_{max}^{95\%\ C_2H_5OH}$ 264 mμ (ε 1145), 271 mμ (ε 1425).

11-(2-Dimethylamino-2-methylethoxymethyl)-9,10-dihydro-9,10-ethanoanthracene Hydrochloride (33). Method F.—To a solution of phenyllithium prepared from 4.6 g (0.66 g-atom) of lithium ribbon, 51.8 (0.33 mole) of bromobenzene, and 300 ml of anhydrous ether was added 70.8 g (0.3 mole) of 9,10-dihydro-9,10-ethanoanthracene-11-methanol[8] under an atmosphere of dry nitrogen. Anhydrous toluene (300 ml) was added, and ether

(6) A. S. Meek, W. B. Evans, V. Godefroi, W. R. Benson, M. C. Wilcox, W. G. Clark, and T. Tieluman, *J. Org. Chem.*, **26**, 1281 (1961).

was removed by distillation. To the cooled mixture was added dropwise 44 g (0.36 mole) of 1-dimethylamino-2-propyl chloride (prepared by treatment of a slurry of the hydrochloride in ether containing 1% of water with powdered NaOH, decantation, extraction by three portions of ether, drying, and distillation, bp 118–120°). The mixture was refluxed with stirring for 15 hr, cooled, and treated with 100 ml of water. The organic phase was washed with water and then added to dilute HCl. The aqueous phase was treated with dilute NaOH, and the mixture was extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue was distilled under reduced pressure [47.4 g, bp 160–170° (0.1 mm)]. This material was dissolved in 250 ml of ether and treated with an equivalent quantity of HCl in ethanol. The solvent was evaporated to give 46.5 g of colorless solid, mp 168° (mixture of **33** and **32**, 80:20 by vpc analysis). The solid was dissolved in 100 ml of hot acetonitrile and cooled to give 32 g of pure **33**. An ethereal extract of the corresponding base was chromatographed (injection port at 450°) on a 2-m alkaline Carbowax 20M column at 120°; a single peak was observed whose retention time was identical with 2-dimethylamino-1-allyloxypropane; on a 2-m SE 30 gum silicone column at 200° a peak, developed as anthracene, was observed.

11-(2-Dimethylamino-1-methylethoxymethyl)-9,10-dihydro-9,10-ethanoanthracene Hydrochloride (32). Method G.—A mixture of 21.5 g (0.15 mole) of 1-dimethylamino-2-allyloxypropane, 26.7 g (0.15 mole) of anthracene, and 0.4 g of hydroquinone in 50 ml of toluene was stored in a pressure bottle at 210° for 15 hr. After cooling and extraction with dilute HCl, the aqueous acid layer was made basic with NaOH solution and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residual oil was converted to the **hydrochloride** by dissolving in dry ether and treating with HCl. Recrystallization from acetonitrile–ether gave 17.2 g of analytically pure **32**. An ethereal extract of the corresponding base was chromatographed as above to give on Carbowax 20M a single peak the retention time of which was identical with 1-dimethylamino-2-allyloxypropane and, on SE 30 gum silicone, a peak of anthracene.

9-[2-Methyl-3-(4-methyl-1-piperazinyl)propoxy]-9,10-dihydro-9,10-ethanoanthracene Dihydrochloride (64). Method H.—A solution of 22.2 g (0.1 mole) of 9,10-dihydro-9,10-ethano-9-anthrol in 250 ml of anhydrous toluene was treated with 5.3 g (0.11 mole) of a 50% dispersion of NaH in mineral oil. The mixture was refluxed with stirring under an atmosphere of dry nitrogen until the evolution of hydrogen ceased and the sodium salt precipitated (*ca.* 3 hr). To this suspension was then added 20.4 g (0.11 mole) of 1-chloro-2-methyl-3-(4-methyl-1-piperazinyl)propyl chloride[15] and the resulting mixture was stirred and refluxed under nitrogen for 24 hr. The mixture was filtered and the filtrate was evaporated to yield an oily residue. A solution of this material in 50 ml of ether was treated with an equivalent quantity of HCl in 100 ml of ethanol to give 21 g of white crystals: $\lambda_{max}^{95\%\ C_2H_5OH}$ 264 mμ (ε 1145), 271 mμ (ε 1410).

9-(2-Methylaminoethoxy)-9,10-dihydro-9,10-ethanoanthracene (38). Method I.—A solution of 10.85 g (0.1 mole) of ethyl chloroformate in 50 ml of benzene was added dropwise to a solution of 14.65 g (0.05 mole) of **40** in 50 ml of benzene, and the mixture was refluxed for 6 hr. After cooling, the solution was treated with 200 ml of 2 *N* HCl and with water. The solvent was removed under reduced pressure. The residual oily liquid (15.6 g, 86.5%) of crude 9-(N-carbethoxy-N-methyl-2-aminoethoxy)-9,10-dihydro-9,10-ethanoanthracene was added to a stirred solution of KOH (14 g) in 100 ml of diethylene glycol. The mixture was then refluxed for 8 hr and added to 200 ml of water. The solution was extracted with ether. Evaporation of the ether solution gave 10.5 g of product. For analysis the latter was crystallized from 200 ml of pentane to give 6 g of colorless solid.

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(15) J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1072 (1958).

Notes

Nitrofuryl Heterocycles. V.[1] 4-Acyl-5,5-dialkyl-2-(5-nitro-2-furyl)-Δ^2-1,3,4-oxadiazolines

HOMER A. BURCH

Chemistry Division, The Norwich Pharmacal Company, Norwich, New York

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A continuing search for nitrofuryl heterocyclic chemotherapeutic agents led to an investigation of 2-(5-nitro-2-furyl)-1,3,4-oxadiazole analogs (III). It was reported by Sherman[2] that 2-(5-nitro-2-furyl)-Δ^2-1,3,4-oxadiazolin-5-one possessed excellent antibacterial properties both *in vitro* and *in vivo*. Furthermore, antifungal and trichomonacidal activities have been reported recently for a series of 2-(5-nitro-2-furyl)-5-alkyl-1,3,4-oxadiazoles.[3] Thus, further work in this area appeared promising.

A survey of the literature revealed that very few analogs of 4-acyl-5,5-disubstituted Δ^2-1,3,4-oxadiazoline had been reported. Such compounds have been synthesized by four methods. Stolle[4] and later Fahr, *et al.*,[5] treated the silver salt of an acylhydrazone with an acid chloride. Yale, *et al.*,[6] and Sagitullin and Kost[7] improved this method by treating an acylhydrazone with an acid anhydride. A novel rearrangement of 5-benzyltetrazole to 2-benzylidene-3-aroyl-5-aryl-Δ^2-1,3,4-oxadiazoline on treatment with an aroyl chloride in pyridine was reported by Huisgen, *et al.*[8] Finally, Breslow[9] obtained 4-acyl-Δ^2-1,3,4-oxadiazolines from the reaction of azodicarbonyl compounds with aliphatic diazo compounds.

The method of Yale, *et al.*[6] (Scheme I), was chosen for this project because of the availability of starting

(1) For the previous paper in this series see H. A. Burch, *J. Med. Chem.*, **9**, 408 (1966).

(2) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(3) Y. Haraoka, A. Sugihara, and M. Ito, Japanese Patents 19,451 (1964) and 20,164 (1964); *Chem. Abstr.*, **62**, 10444*e*, 11821*d* (1965).

(4) R. Stolle, *J. Prakt. Chem.*, [2] **68**, 413, 418, 421 (1903); **70**, 412, 419 (1904); R. Stolle and G. Muench, *ibid.*, **70**, 408, 410 (1904).

(5) E. Fahr, K. Doeppert, and F. Scheckenbach, *Angew. Chem.*, **75**, 670 (1963).

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