water, followed by 150 ml. of a saturated solution of potassium sodium tartarate. The slurry was filtered and the filtrate concentrated to an oil which was dried by azeotropic distillation with benzene. The crude product weighed 51.4 g. (100%) and was used without further purification in the following step.

1-[2-N-(3-Benzyloxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol.—A solution of crude 1-[2-(3-benzyloxyphenylamino)-ethyl]-4-phenyl-4-piperidinol (51.4 g., 0.128 mole) in 100 ml. of chloroform was treated with propionyl chloride (11.9 g., 0.128 mole). After standing for 3 hr., the solution was concentrated to an oil (56.2 g., 95.7%) which could not be obtained crystalline, either as the free base or as a salt. It was used directly in the next step.

1-[2-N-(3-Hydroxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol Hydrochloride.—A solution of crude 1-[2-N-(3-benzyloxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol (56.2 g., 0.123 mole) in 700 ml. of absolute ethanol was hydrogenated at 111 kg./cm.^{2} and 27°, using 6 g. of 10% palladium–charcoal. After 6.75 hr., 80% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated to about 100 ml. The solution was made strongly basic with 35% sodium hydroxide and extracted with ether to remove non-phenolic material. The aqueous solution was brought to about pH 8 by the slow addition of acetic acid and the precipitated oil was extracted with ether. The ether extracts deposited a crystalline solid after standing for 1 hr. The solid was converted to the hydrochloride by stirring with ethereal hydrogen chloride. Recrystallization from methanol–ethyl acetate gave 12.4 g. (24.9%) of product, m.p. 215.8–217.8°.

4-Phenyl-1-[2-(N-phenylpropionamidoethyl)]-1,2,3,6-tetrahydropyridine Hydrochloride.—A mixture of 4-phenyl-1,2,3,6-tetrahydropyridine[4] (63.6 g., 0.4 mole), 2-anilinoethyl bromide hydrobromide (112 g., 0.4 mole), 500 ml. of chloroform, and 60 ml. of triethylamine was refluxed for 24 hr. Propionic anhydride (150 ml.) was added and the mixture allowed to stand overnight. Methanol (150 ml.) was added and the solution concentrated to an oil which was made basic with 35% sodium hydroxide. The oil was extracted with benzene, washed with water, and concentrated. The oil was dissolved in ether, filtered to remove some insoluble material, and concentrated again to an oil which was distilled through a short path column. The fraction boiling at 190–200° (0.3 mm.) was collected, dissolved in ether, and treated with ethereal hydrogen chloride. The resulting gum yielded a solid on trituration with ether. The solid was recrystallized from methanol–ethyl acetate to give 27 g. of product. The methochloride of this compound was prepared as described for the methochloride of the analogous piperidinol.

4-Phenyl-1-[2-(N-phenylpropionamidoethyl)]piperidine Hydrochloride.—A solution of 4-phenyl-1-[2-(N-phenylpropionamidoethyl)]-1,2,3,6-tetrahydropyridine hydrochloride (4.7 g., 0.0126 mole) in 100 ml. of ethanol was hydrogenated at 3.5 kg./cm.^{2} in a Parr apparatus using 150 mg. of platinum oxide as catalyst. The theoretical amount of hydrogen was absorbed in 15 min. The catalyst was removed by filtration and the filtrate concentrated to about 25 ml. Crystals were deposited on standing for a short time. After recrystallization from ethanol–ether, 2.9 g. of product was obtained.

Acknowledgments.—We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer, and staff for the chemical analyses, to Dr. F. C. Nachod and staff for spectral data, and to Mrs. A. Pierson and Mrs. H. Lawyer for technical assistance in the pharmacological evaluations.

Investigations in Heterocycles. XIII. Structure-Activity Relationships of Heterocyclic Compounds with Potent Analgetic Effects

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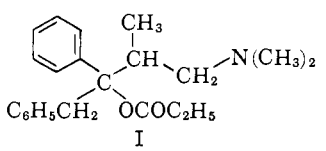
A variety of tetralin, chromane, and thiachromane compounds structurally related to propoxyphene have been prepared, and the structure–activity relationship has been discussed. It has been observed that the 2-picolyl moiety markedly enhances the analgetic activity in this group of compounds. Some stereochemical considerations have been deduced by means of chemical and spectral data.

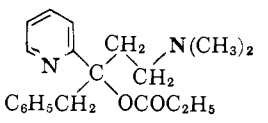
As part of a continuing program directed toward the preparation of clinically effective analgetic agents, we wish to outline a phase of work carried out in our Laboratories which has led to some highly active compounds.

Since *d*-propoxyphene[1] (I) was reported to be a clinically useful analgetic without possessing appreciable addiction liability, it was of interest to prepare some heterocyclic analogs of I, as well as cyclic analogs containing hetero atoms. This could be done in two ways; namely, replacing at least one of the phenyl groups with a heterocycle (*e.g.*, pyridyl) or preparing cyclic analogs of I in the chromane and thiachromane series. It is also conceivable that a compound incorporating a combination of these ideas could also be prepared.

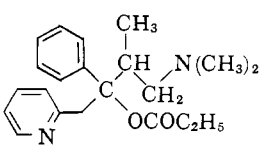


I

The initial phase of the study involved the preparation of a pyridyl analog (II) of I. Thus, 3-dimethylamino-1-(2-pyridyl)-1-propanone was allowed to react with benzylmagnesium chloride to form a tertiary alcohol which was esterified with propionic anhydride



II

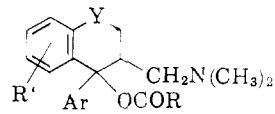


III

(1) A. Pohland, H. R. Sullivan, and R. E. McMahon, *J. Am. Chem. Soc.*, **79**, 1442 (1957).

TABLE I

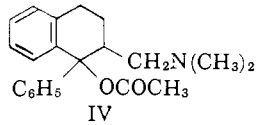
TERTIARY ESTERS OF TETRALINS, CHROMANES, AND THIACHROMANES



Compound no.	Ar	R	R'	Y	M.p., °C.	Empirical formula	Calcd. C	Calcd. H	Found C	Found H
V	C_6H_5	C_2H_5	H	CH_2	166	$C_{22}H_{27}NO_2 \cdot HCl$	70.67	7.56	70.35	7.77
VIa	$CH_2C_6H_5$	C_2H_5	H	CH_2	58–62	$C_{23}H_{29}NO_2$	78.59	8.32	78.87	8.21
VIb	$CH_2C_6H_5$	C_2H_5	H	CH_2	62–63	$C_{23}H_{29}NO_2$	78.59	8.32	78.89	8.28
VII	$CH_2C_5H_4N$	C_2H_5	H	CH_2	146–150	$C_{22}N_{28}N_2O_2 \cdot C_4H_4O_4$	66.65	6.88	66.56	6.87
VIII	C_6H_5	C_2H_5	H	O	158	$C_{21}H_{25}NO_3 \cdot HCl$	67.10	6.97	66.89	7.01
IX	$CH_2C_6H_4$	C_2H_5	H	O	166	$C_{22}H_{27}NO_2 \cdot HCl$	67.77	7.24	67.71	7.23
X	$CH_2C_6H_4N$	C_2H_5	H	O	118–120	$C_{21}H_{26}NO_3 \cdot C_4H_4O_4$	63.81	6.42	63.55	6.42
XI	C_6H_5	C_2H_5	6-OCH_3	O	155–156	$C_{22}H_{27}NO_4 \cdot HCl$	65.09	6.95	64.78	7.21
XII	C_6H_5	C_2H_5	6-CH_3	O	174–175	$C_{22}H_{27}NO_3 \cdot HCl$	67.77	7.24	67.60	7.16
XIII	C_6H_5	C_2H_5	6-Cl	O	178–180	$C_{21}H_{24}ClNO_3 \cdot HCl$	61.46	6.14	61.13	6.11
XIV	C_6H_5	C_2H_5	8-CH_3	O	146	$C_{22}H_{27}NO_3 \cdot HCl$	67.77	7.24	67.64	7.30
XV	p-$CH_3C_6H_4$	C_2H_5	H	O	158–160	$C_{22}H_{27}NO_3 \cdot HCl$	67.77	7.24	67.53	7.14
XVI	C_6H_5	C_2H_5	H	S	170–172	$C_{21}H_{25}NO_2S \cdot HCl$	64.35	6.69	64.37	6.93
XVIIa	C_6H_5	CH_3	H	S	215–217	$C_{20}H_{23}NO_2S \cdot HCl$	63.57	6.41	63.70	6.74
XVIIb	C_6H_5	CH_3	H	S	172–173	$C_{20}H_{23}NO_2S \cdot HCl$	63.57	6.41	63.66	6.55

to yield II. This compound was completely devoid of analgetic activity. Consequently, a similar compound (III) was prepared by treating 3-dimethylamino-2-methyl-1-propiophenone[1] with 2-picolyl lithium. The resulting tertiary alcohol was in turn esterified to the propionate (III) which was found to be twice as potent as *d*-propoxyphene when tested in experimental animals according to a modification of the tail flick method in mice.[2]

An extension to this work would be the preparation of cyclized derivatives in the chromane, thiachromane and tetralin class. The starting materials in this synthesis were the Mannich bases of 4-chromanone, substituted 4-chromanones, 4-thiachromanones, and α-tetralone. These ketone intermediates were allowed to react with Grignard reagents or aryl lithium compounds to afford the diastereoisomeric alcohols. Repeated attempts to separate these racemates by fractional crystallization or column chromatography were unsuccessful. Consequently, the diastereoisomeric mixture of tertiary alcohols was used directly in the subsequent esterification with propionyl chloride in toluene to afford the desired esters. It should be emphasized that at the time work was begun in our laboratories, it had already been noted that compound IV had been prepared in 1949 by Morrison and Rinderknecht[3] and was found to have some analgetic effect.



IV

The corresponding propionate ester (V; see Table I) was therefore prepared and found to exhibit analgetic effects.

In our hands, it was possible to separate VI into its two racemates (VIa and VIb). Compound VIa had only weak analgetic activity, whereas VIb was a good analgetic with a potency 0.1 that of morphine.[4] Consequently, the 2-picolyl compound VII, corresponding to the open chain analog III, was prepared and tested for its analgetic effects in experimental animals. Compound VII was found to be 5 times more potent than morphine. This corresponds to a 15-fold increase over the benzyl derivative VIb. Only one diaster of VII could be isolated

The chromanes also gave rise to analgetically active compounds. Compounds VIII and IX had comparable analgetic activity (0.5 that of codeine), whereas the 2-picolyl derivative X was approximately 0.2 as potent as morphine (or twice as active as codeine). Other structural modifications in the chromane series involved substitutions on the chromane benzene ring (compounds XI through XIV). In all cases there was observed a diminution in activity. Substitution on the benzene ring attached to the quaternary carbon (XV) also was of no advantage. Finally, the thiachromane analog of compound VIII was synthesized according to the described sequence and was found to be weakly analgetic. Although the yield of acetylated product was poor, it was possible to separate the diastereoisomers XVIIa and XVIIb. Neither of these substances possesses significant analgetic effects.

Consequently, the structure–activity relationship in this series of compounds is somewhat specific. As observed by Patchett and Giarruso, the imposition of restricted rotation on *d*-propoxyphene certainly leads to an increased analgetic effect. However, we have also observed that the replacement of the benzyl group at the quaternary carbon with a 2-picolyl group in *d*-propoxyphene and in the tetralin and chromane series gives rise to decidedly more potent compounds. As far as we know, this has not been observed previously in structure–activity relationship studies of analgetics.

Since these compounds possess two centers of asymmetry, it was also of interest to determine their stereo-

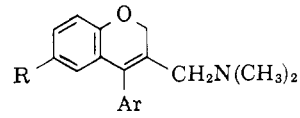
(2) L. Witkin, C. F. Huebner, F. Galdi, E. O'Keefe, P. Spitaletta, and A. Plummer, *J. Pharmacol. Exptl. Therap.*, **133**, 400 (1961).

(3) A. J. Morrison and H. Rinderknecht, British Patent 615,136 (January 3, 1949).

(4) While this work was in progress, A. Patchett and P. Giarruso [*J. Med. Pharm. Chem.*, **4**, 403 (1961)] reported on the synthesis of VIb, but were not able to isolate the other diastereoisomer VIa. These investigators also indicated that in their test, VIb was approximately 1/3 as potent as morphine.

TABLE II

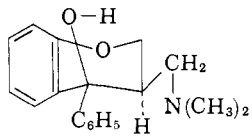
3-DIMETHYLAMINOMETHYL-4-PHENYL-$\Delta^{3,4}$ CHROMANES



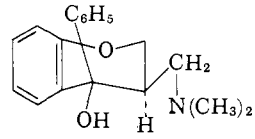
Compound no.	Ar	R	M.p., °C.	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIX	C_6H_5	H	214–215	$C_{18}H_{19}NO \cdot HCl$	71.62	6.68	4.64	71.69	6.96	4.71
XX	C_6H_5	6-OCH_3	207–208	$C_{19}H_{22}NO_2 \cdot HCl$	68.43	7.25	4.20	68.69	7.40	4.15
XXI	C_6H_5	6-CH_3	208	$C_{19}H_{21}NO \cdot HCl$	72.25	7.03		71.93	7.00	
XXII	C_6H_5	6-Cl	181–183	$C_{18}H_{18}ClNO \cdot HCl \cdot H_2O$	61.15	5.98		61.41	6.13	
XXIII	p-$CH_3C_6H_4$	H	246–247	$C_{19}H_{21}NO \cdot HCl$	72.26	7.04	4.43	71.46	7.13	4.40

chemistry. Chemical evidence supported by spectral data served to establish the stereochemistry of the chromanes. The tertiary alcohol, 3-dimethylaminomethyl-4-hydroxy-4-phenyl chromane (XVIII), was found to be an equal mixture of the two diastereoisomeric alcohols by paper chromatography. This mixture gave a 40% yield of the propionate ester (VIII) and an equal amount of 3-dimethylaminomethyl-4-phenyl-$\Delta^{3,4}$-chromane (XIX, Table II), on treatment with propionyl chloride in toluene. The remaining material isolated from the mother liquors was unreacted tertiary alcohol.[5] Moreover, paper chromatographic analysis of VIII indicated that only one racemate was present.

Since the esterification reaction yields an equal amount of ester and dehydrated substance, it is possible to make the following stereochemical assignment to the two alcohol racemates of XVIII.



XVIIIa



XVIIIb

The conformational arrangement in XVIIIa is suitable for a facile *trans* di-axial elimination of water, whereas this is not the case with XVIIIb. To establish whether or not XVIIIb could be transformed to olefin under the same esterification conditions previously described, VIII was allowed to react with lithium aluminum hydride to afford one racemic alcohol. The homogeneity of this substance was supported by paper chromatographic analysis. Esterification of this alcohol with propionyl chloride gave a 65% yield of VIII. Chromatographic analysis of the mother liquors revealed approximately another 10% of VIII, and the remaining substance was shown to be *only* starting material. No trace of the unsaturated compound XIX could be isolated or detected by chromatography. This then clearly demonstrates that the active compound has the configuration assigned to the ester of XVIIIb.

This conclusion was supported by n.m.r. measurements. In ester VIII the protons at position 2 exhibit a quartet centered at 4.3 τ. The splitting constants are 2.3 c.p.s. indicative of an axial–equatorial interaction and at 6.0 c.p.s. which is due to the axial–axial relation. These data establish the equatorial conformation of the dimethylaminomethyl group. In compound VIII the aromatic proton at position 5 is shielded by the phenyl group only when this group is in the axial conformation, a doublet occurring at 3.46 τ (J = 7.5 c.p.s.).

A number of chemical methods were applied in order to elucidate the stereochemistry of the tetralin analgetics IV–VII. However, none of these has given, as yet, unequivocal results in spite of the fact that both racemates, active and inactive, VIa and VIb, respectively, were available to us. The n.m.r. data on these substances also do not facilitate a single stereochemical assignment. However, since it has been possible to separate the active isomer VIb from the inactive one VIa, it is reasonable to consider VIb to be stereochemically related to VIII.

(5) Similar results were obtained in the preparation of all esters in the chromane series with a phenyl group substituted at the quaternary carbon. Compound XIX was also prepared by treating the diastereoisomeric mixture (XVIII) with 10% hydrochloric acid under mild reflux.

Experimental

The Mannich bases used as intermediates in this study have been previously described. Harradence, *et al.*,[6] have outlined the preparation of 3-dimethylaminomethyl-6-methoxy-4-chromanone and 3-dimethylaminomethyl-8-methyl-4-chromanone. Wiley[7] also has outlined the remaining chromane aminoketones. 2-Dimethylaminomethyl-1-tetralone was described by Mannich[8] and co-workers and 3-dimethylaminomethyl-4-thiachromanone was prepared by Chem[9] and co-workers.

1-Benzyl-4-dimethylamino-3-propionyloxy-1-(2-pyridyl)-butane Hydrochloride (II).—In a 3-necked flask connected with a stirrer, reflux condenser and dropping funnel, benzylmagnesium chloride was prepared from 8.85 g. (0.07 mole) of benzyl chloride and 1.7 g. (0.07 mole) of magnesium in 200 ml. of dry ether. The solution was then treated with 12.0 g. (0.68 mole) of 3-dimethylamino-1-(2-pyridyl)-1-propanone dissolved in 100 ml. of ether. The resulting mixture was refluxed for 5 hr. and then allowed to stand at room temperature overnight. The mixture was then decomposed with 100 ml. of ice cold aqueous 20% hydrochloric acid. The acid layer was separated, extracted with ether, and then made basic with sodium hydroxide solution and again extracted with ether. The ether extract was dried over magnesium sulfate. After filtering off the drying agent, the ether filtrate was evaporated to dryness to give a yellow oil. The residue on distillation yielded 1-benzyl-4-dimethylamino-1-(2-pyridyl)-2-butanol, b.p. 160–167° (0.5 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.24; H, 8.20; N, 10.37. Found: C, 75.81; H, 7.54; N, 9.50.

(6) R. H. Harradence, G. K. Hughes, and J. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1939).

(7) P. F. Wiley, *J. Am. Chem. Soc.*, **73**, 4205 (1951).

(8) C. Mannich, F. Borkowsky, and W. A. Lin, *Arch. Pharm.*, **275**, 54 (1937).

(9) T. C. Chem, C. S. Sum, H. C. Soong, and C. C. Chyan, *Chem. Abstr.*, **52**, 11,029 (1958); S. H. Chu, W. W. Chyan, and C. C. Chang, *ibid.*, **52** 11,044 (1958).

Repeated attempts to purify this further were not successful. Infrared spectroscopic analyses indicated some 2-acetyl pyridine impurity and possibly some dehydration product. Consequently, the substance was used directly for the preparation of the propionate.

Two grams of the above tertiary alcohol was allowed to react with 2 ml. of propionic anhydride in 3 ml. of pyridine at room temperature for 48 hr., after which time the pyridine was removed *in vacuo*. The residue was diluted with water and the resulting solution made basic with ammonium hydroxide. After extracting this basic solution with ether, the extract was concentrated to give an oil which became semicrystalline on standing. This material was recrystallized from ethyl ether to give 0.15 g. of II, m.p. 63–66°. The substance crystallizes quite slowly from ether.

Anal. Calcd. for $C_{21}H_{25}N_2O_2$: C, 74.08; H, 8.29. Found: C, 74.26; H, 8.05.

The infrared spectrum showed a strong absorption band at 1742 cm.$^{-1}$ for the ester band.

4-Dimethylamino-3-methyl-1-(2-picolyl)-1-phenyl-5-propionyloxybutane Hydrochloride (III).—To a solution of phenyl lithium prepared from 9.1 g. of lithium and 67.5 g. of bromobenzene in 400 ml. of ether in a nitrogen atmosphere, 49 ml. of α-picoline was added dropwise with stirring. After standing 3 hr. at room temperature, a solution of 31.9 g. of 3-dimethylamino-2-methyl-1-phenyl-1-propanone in 100 ml. of ether was added dropwise with stirring. After standing overnight at room temperature, the small amount of unreacted lithium was filtered and the filtrate poured onto ice water. The ether was separated, washed with water, dried, and evaporated. The residue on distillation gave 69 g. of a crude mixture of the two diastereomeric 4-dimethylamino-3-methyl-2-phenyl-1-(2-pyridyl)-2-butanols, b.p. 150–160° (0.6 mm.).

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 8.23. Found: C, 76.89; H, 8.05; N, 9.70.

A mixture of 3 g. of the above alcohol, 3 ml. of propionic anhydride, and 3 ml. of pyridine was allowed to stand at room temperature for 2 weeks. After evaporation of the pyridine *in vacuo* and dilution with water, the mixture was made basic with ammonium hydroxide, and then extracted with ether. Removal of most of the ether gave a mixture which partly crystallized after standing for several days. After recrystallization from ethyl ether, III melted at 90–91°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.78; H, 8.22; N, 8.00.

1-Benzyl-2-dimethylaminomethyl-1-propionyloxy-1,2,3,4-tetrahydronaphthalene Hydrochloride.—This procedure is outlined in detail to show the sequence of steps which led to the isolation of racemates VIa and VIb.

A solution of 17 g. of 2-dimethylaminomethyl-1-tetralone in 50 ml. of dry ether was added dropwise, with cooling to about room temperature, to the Grignard reagent prepared from 9 g. of magnesium and 40 ml. of benzyl chloride in 150 ml. of ether. After standing overnight, the mixture was refluxed for 2 hr. The mixture was again cooled to room temperature and 18.5 ml. of propionyl chloride in 50 ml. of ether added dropwise with stirring. After refluxing for 30 min., the mixture was cooled in ice water and dilute ammonium hydroxide added until the mixture was basic. The ether was separated, extracted with dilute hydrochloric acid, and the acid extract, after being made basic with ammonia, was extracted with ether. The ether was then dried over sodium sulfate and concentrated to dryness *in vacuo*. Some unesterified alcohol was shown to be present from the infrared spectrum. Upon the addition of one equiv. of maleic acid to this base in coned. ethanol solution, the crude maleate separated, m.p. 151–155°.

Anal. Calcd. for $C_{25}H_{29}NO_2 \cdot C_4H_4O_4 \cdot \frac{1}{2}H_2O$: C, 68.05; H, 7.12; N, 2.94. Found: C, 68.01; H, 7.30; N, 2.87.

The base generated from the maleate by extraction with ether of an aqueous suspension made basic with ammonia no longer showed alcohol absorption. However, paper chromatography [immobile phase: formamide (pH 5.6 with benzoic acid)–methanol (1:1); mobile phase: benzene–cyclohexane (1:1)] showed an approximately 1:1 mixture of diastereomeric esters with R_f values of 0.40 and 0.65. This mixture on standing in the icebox for several days as a very coned. methanol solution deposited large prisms. Upon filtration and two recrystallizations from methanol–water, one of the pure diastereomeric 1-benzyl-2-dimethylaminomethyl-1-propionyloxy-1,2,3,4-tetrahydronaphthalenes (VIb) was obtained, m.p. 62–63°.

Some of the crude maleate described above was recrystallized 4 times from ethanol which raised the melting point to 173–175°. The base obtained from this salt crystallized upon removal of the ether from its extract. After two recrystallizations from ethanol–water, the second pure diastereomer (VIa) was obtained (R_f 0.65), m.p. 58–62°. The melting point of a mixture of VIa and VIb was 50–52°. VIa and VIb have different infrared spectra, especially in the fingerprint region.

VIa and VIb were made into aqueous solutions with one molar equivalent of hydrochloric acid just prior to testing.

2-Dimethylaminomethyl-1-(2-picolyl)-1-propionyloxy-1,2,3,4-tetrahydronaphthalene Maleate.—To a solution of α-picolyl lithium in 200 ml. of ether prepared as described above from 1.75 g. of lithium, 14 ml. of bromobenzene, and 12.5 ml. of α-picoline was added dropwise with stirring a solution of 17 g. of 2-dimethylaminomethyl-1-tetralone in 50 ml. of ether. After standing for 30 min., the mixture was treated while stirring at room temperature with 14 ml. of propionic anhydride in 50 ml. of ether. After stirring for 6 hr., the voluminous cream-colored precipitate was filtered, washed several times with ether, and suspended in 100 ml. of water. The aqueous solution was made basic with ammonia and the resulting oil extracted with ether. Upon removal of the ether, the residue partly crystallized. The crystalline material was collected, carefully washed with a small amount of ether, and recrystallized from ethanol, m.p. 110°.

Anal. Calcd. for $C_{29}H_{32}N_2O_6$: C, 71.96; H, 8.01; N, 7.75. Found: C, 75.10; H, 8.01; N, 8.01.

The maleate salt was prepared in acetone solution and recrystallized from ethanol–ether, m.p. 146–150°.

3-Dimethylaminomethyl-4-(2-picolyl)-4-propionyloxychromane maleate, m.p. 118–120°, was prepared in a similar manner.

3-Dimethylaminomethyl-4-phenyl-4-propionyloxychromane Hydrochloride (VIII).—A description of the synthesis of this substance will serve to illustrate the procedure whereby all the chromane esters described in Table I were prepared. Phenyl magnesium bromide was prepared in 200 ml. of ether in a 1-l. flask from 12.0 g. (0.77 mole) of bromobenzene and 1.81 g. of magnesium ribbon. An ether solution (100 ml.) of 2-dimethylaminomethyl-1-chromanone (14.0 g.; 0.07 mole) was then added dropwise at 5–10° with stirring over a 1 hr. period. After the addition was complete, the mixture was refluxed gently for 5 hr. and then allowed to stand at room temperature overnight. The mixture was treated dropwise with 100 ml. of saturated ammonium chloride solution and the aqueous solution was separated from the ethereal layer. The ether extract was washed with water and then dried over magnesium sulfate. The dried ether extract was filtered and the filtrate was concentrated to an oily residue which solidified on standing, thus yielding 7.5 g. of product. Paper chromatographic analysis indicated 2 main fractions (2 racemates). However, all attempts to separate these racemates were unsuccessful. Consequently, the following acylation reaction was carried out on the diastereoisomeric mixture.

Propionyl chloride (2.9 g.) dissolved in 15 ml. of toluene was treated dropwise while stirring at 25–28° with 3.5 g. of the above tertiary alcohol dissolved in 15 ml. of toluene. After a short time, a white solid separated from solution. The reaction mixture was stirred at 60° for 2 hr. after addition of the tertiary alcohol was complete. The precipitate was then collected on a filter and washed with a small amount of toluene. This material, which contained some starting material as impurity, was recrystallized from acetone–ether (2:1) to afford one crystalline racemate. Work-up of the toluene mother liquors yielded an equivalent amount of unsaturated compound XIX.

The free base (350 mg.) of compound VIII was dissolved in dry ether and added with stirring to 150 mg. of lithium aluminum hydride in dry ether. The mixture was heated on the steam bath for 2 hr. The solution was chilled and the lithium salt decomposed with sodium potassium tartrate solution. The mixture was filtered and the ether filtrate dried over magnesium sulfate. Removal of the ether after drying resulted in a white solid which was recrystallized from ethanol to give 140 mg. of crystalline substance, m.p. 122°. The crude and purified substance both contained only one isomer according to paper chromatographic analysis.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 76.28; H, 7.47. Found: C, 76.11; H, 7.32.

The above racemic alcohol (140 mg.) was esterified with 180 mg. of propionyl chloride as described. Propionate ester (75 mg.) was obtained. Chromatographic analysis of the mother liquors revealed an additional amount of the same ester, some

starting material, and no dehydrated compound XIX. No other substance could be detected.

Acknowledgment.—The authors extend their gratitude to Dr. E. Schlittler for his interest in this project. We also wish to thank the members of our Microanalytical and Spectral Sections for their coöperation, and Dr. A. J. Plummer and Dr. L. Witkin for the biological data.

An Empirical Relationship between Anthelmintic Activity and Chemical Structure

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The anthelmintic activity against the mouse pinworm *Syphacia obvelata* is reported for several different types of compound, including N,N-dialkylnaphthamidine salts, some highly substituted dihydropyridines with quaternary salt groupings, and some stilbazole and other quaternary salts. Based on these results it was postulated that an association of a ring moiety with a center which is cationic at physiological pH values might confer anthelmintic properties on molecules. Random selection of four groups of compounds with such structures gave three groups which had active members.

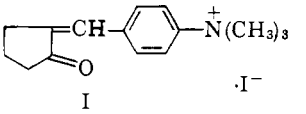
In previous publications[1,2] we have mentioned that one structural feature found in a high proportion of our compounds with anthelmintic activity against the mouse pinworm *Syphacia obvelata* was the existence of a center of positive charge near or in a cyclic system. Some of the compounds tested, which were not previously reported, and the results which led to this empirical observation are given below. This is followed by the results of arbitrary selection of some compounds fitting the same criterion of structure, which previously had been prepared for other purposes, and a description of their activity against *S. obvelata* in the mouse.

Methods

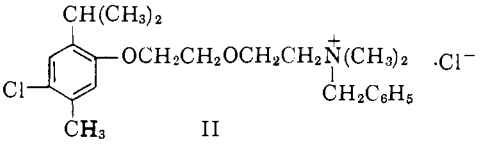
The compounds were prepared by methods reported in the literature unless otherwise annotated. All alkyl groups are normal unless stated otherwise. Those compounds tested initially were selected as representative substances with a high numerical ratio of oral to intraperitoneal LD_{50} in the mouse as determined by Mr. R. V. Fanelli of these Laboratories. Testing for pinworm activity was done essentially as described in a previous publication[3] using mice infected by exposure to infected "source mice" for 8 days, and dosed by gavage once a day for 2 days thereafter, unless otherwise stated. Results are reported as per cent clearance of worms by autopsy in comparison to the worm count in simultaneously infected but untreated "control" mice. Each result and each "control" result are averages of 3 mice.

Experimental Data

Anthelmintic activities are given in Table I for representative examples of the 2 types of compounds, 4-methoxynaphthamidines[4] and quaternary salts of highly substituted 4-(aminophenyl)-1,4-dihydropyridines,[5] of which several members were found to be reasonably active against *S. obvelata* in the mouse, under our test conditions. In addition to these, a few miscellaneous quaternary salts either of substituted anilines (*e.g.*, I) or benzylamines (*e.g.*, II) had appreciable activity.



I

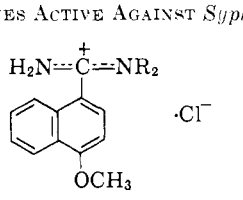


II

A number of other mono- and bis-quaternary salts were prepared or purchased. Those with purely aliphatic substituents were inactive or had only slight activity at a readily attainable dosage. One alicyclic candidate, methyldodecylpiperidinium bromide, had slight activity. As had been reported previously, however, various quaternary piperazinium salts had substantial activity.[1-3]

TABLE I

NAPHTHAMIDINES ACTIVE AGAINST *Syphacia obvelata*



R	Approx. oral LD_{50}	Dose, mg./kg./day	% worm count reduction
i-C_5H_{11}	170	50	51
C_6H_{13}	240	80	93
C_7H_{15}	2000	200	98
C_8H_{17}	3000	200	95

A small group of cinnamamidine salts[6] (III) were found to contain one member, 2-chloro-N,N-dibutylcinnamamidine, R = Cl, R′ = C_4H_9, which cleared an

(1) M. Harfenist, *J. Am. Chem. Soc.*, **79**, 2211 (1957).

(2) H. W. Brown, K. L. Hussey, K. F. Chan, M. Harfenist, R. V. Fanelli, and E. Magnien, *Toxicol. Appl. Pharmacol.*, **1**, 350 (1959).

(3) (a) K. F. Chan, *Am. J. Hygiene*, **56**, 22 (1952); (b) M. Harfenist, R. V. Fanelli, R. Baltzly, H. W. Brown, K. L. Hussey, and K. F. Chan, *J. Pharmacol. Exptl. Therap.*, **121**, 347 (1957). Unless otherwise stated the tests reported here were done by Drs. Brown, Hussey, and Chan.

(4) Prepared originally by Mr. E. Lorz as potential local anesthetics. See E. Lorz and R. Baltzly, *J. Am. Chem. Soc.*, **70**, 1904 (1948). These are shown in their symmetrical protonated form, as is reasonable in view of the pK_a values reported by E. Lorz and R. Baltzly, *ibid.*, **71**, 3992 (1949), for related compounds.

(5) Prepared originally as potential curareform substances by Dr. A. P. Phillips. See A. P. Phillips, *ibid.*, **71**, 4003 (1949).

(6) M. Harfenist and A. P. Phillips, *ibid.*, **80**, 6261 (1958).