1,4-naphthoquinones were prepd by treating 2-methoxy-1,4-naphthoquinone in EtOH with the appropriate alkylamine at room temp in a manner similar to that previously described[5] (Table I). After stirring at room temp, the reaction mixt was dild with Et_2O or hexane or both and placed in the freezer. Generally, a dark red or orange ppt was collected and recrystd repeatedly from a suitable solvent(s), usually EtOH (charcoal) or EtOH–Et_2O (charcoal).

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Stereochemical Studies of Antimuscarinic Agents. Diastereoisomeric Esters of 3-Tropanol, 1,3-Dimethyl-4-piperidinol, and Related Compounds

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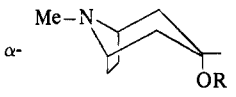
The anticholinergic properties of a series of isomeric 3-tropanol and 1,3-dimethyl-4-piperidinol esters (diphenylacetates and/or benzilates) and related compounds have been determined by measuring their ability to antagonize ACh-induced contractions of guinea pig ileum (pA_2 values) and cause mydriasis in mice eyes. In the pA_2 experiments, isomers with the smaller $^+N\cdots OCOR$ separation (acyloxy function axial in preferred piperidine chair conformation) were the more potent by factors of 2 to 3 in most cases, while differences in the mydriatic ED_{50} values of isomeric pairs were insignificant. A Me substituent α to the acyloxy group substantially reduced the cholinolytic potencies of 4-piperidyl esters but addition of a β group was advantageous in this respect. Potency differences between hydrohalide–methiodide pairs were small except in the case of 1-methyl-3-piperidyl benzilate where N-methylation reduced potency by over a half in the ileum test. The relevance of the structure–activity variations observed to the characteristics of receptors for cholinergic agonists and antagonists in the guinea pig ileum and circular muscles of the mouse eye are discussed.

This paper is concerned with the possible relationship between preferred geometry and antimuscarinic activity in atropine and related basic esters, attention being focussed upon the conformation of the amino alcohol moiety of cholinolytic esters. In atropine and other solanaceous alkaloids, the acyloxy function at C-3 is cis to the 2,6-bimethylene bridge of the tropane skeleton (**1b**). There have been



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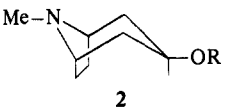

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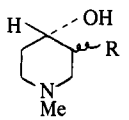
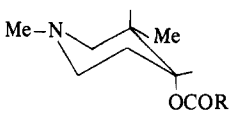
a, R = H
b, R = COR'
c, R = $C(OH)Ph_2$

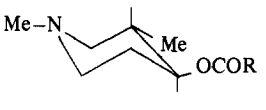
only a few studies of the pharmacology of analogs in which the acyloxy group is trans in the above sense, *e.g.*, reports on benzoate and tropate esters of pseudotropine **2a**,[1,2] and the chief object of the present work was to compare the anticholinergic activities of pairs of isomers which differed in the orientation of the OCOR function. One tropine–pseudotropine pair of esters has been examined but most esters tested are derivatives of 1-methyl-4-piperidinol. The piperidinol **3a** is a simplified version of the 3-tropanols in that it lacks the 2,6-bimethylene bridge, and it forms esters with diphenylacetic and benzilic acids which have high antimuscarinic activities: corresponding esters of 1-methyl-3-piperidinol **6** have similar pharmacological properties.[3-5]



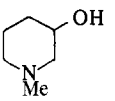
3a, R = H, **b**, R = Me



cis
4



trans
5



6

Introduction of a 3-Me substituent into **3** leads to cis and trans isomers which have the preferred conformation **4** and **5**, respectively.[6] The esters **4** are therefore steric analogs of tropyl esters (axial OCOR function) while those of **5** are related to pseudotropyl derivatives (equatorial OCOR).

Experimental Section

When analyses are indicated, analytical results obtd for those elements were within ±0.4% of the theoretical values. All benzilates were prepd by ester exchange between basic alcohols and methyl benzilate according to Cannon's procedure.[7] Salts were crystd from EtOH–Et_2O unless otherwise stated. Pmr spectra were recorded on a Varian A-60 spectrometer with $CDCl_3$ or DMSO-d_6 as solvents and TMS as standard.

Tropane Derivatives. Benzilate esters of tropine and pseudotropine·HCl were obtd by a reported method;[6] the former base gave a **methiodide**, mp 278° [*Anal.* ($C_{23}H_{28}INO_3$) C, H], and the latter a **methiodide**, mp 246–247° from acetone (*Anal.* C, H). Ester

Table I. Anticholinergic Activities of Some Diphenylacetates and Benzilates of 3-Tropanol, 3-, and 4-Piperidinols, and Related Compounds

No.	Structure	Isomer	Form	pA_2 (ACh)	Relative[a] potency	pA_2 (histamine)	Relative[a] potency	Mydriatic activity, ED_{50}, m*M*/kg × 10^4
1	1c	3-α	HCl	8.81	794			5
2	1c	3-α	MeI	8.93	1047			4
3	2c	3-β	HCl	8.51	398			5
4	2c	3-β	MeI	8.50	389			4
5	*b*	2-β, 3-β	HCl	8.19	190			Inactive at 140
6	3a DPA[c]		HBr	8.27	229			9
7	3a DPA		MeI	8.22	204			7
8	3a B[d]		HCl	8.96	1122			3
9	3a B		MeI	8.92	1023			4
10	3b DPA	Trans	HCl	7.34	27			86
11	3b DPA	Trans	MeI	7.62	52			62
12	3b DPA	Cis	HCl	7.68	59			75
13	3b DPA	Cis	MeI	7.62	51			55
14	3b B	Trans	HCl	8.01	126	<5.6	<489	16
15	3b B	Trans	MeI	7.49	97	<5.7	<616	14
16	3b B	Cis	HCl	8.45	347	<5.6	<489	11
17	3b B	Cis	MeI	8.38	295	<5.7	<616	4
18	6 DPA		HCl	8.19	190	5.33	722	10
19	6 DPA		MeI	8.22	204	5.47	561	10
20	6 B		HCl	9.10[e]	1549	5.51	398	3
21	6 B		MeI	8.71	630	5.60	489	2
22	*f*	*trans*-2Me/5Me, 5Me/OCOR[g]	HCl	8.62	512			Inactive at 250
23	*f*		MeI	8.70	616			Inactive at 160
24	Atropine	3-α	HSO_4	8.91[h]	1000	5.91[i]	1000	1
25	Hyoscine	3-α	HBr	8.75[j]	691	5.57	417	1
26	Ethopropazine		HCl	7.64	54	6.43	3310	>20
27	Orphenadrine		HCl	7.24	21	6.71	6310	>20

[a] Atropine sulfate = 1000. [b] Dibenzilate of 2-β-hydroxymethyl-3-β-tropanol. [c] DPA = diphenylacetate. [d] B = benzilate. [e] Lit.[14] 8.45; these authors also report a lower value for atropine (see footnote *h*). [f] Benzilate of 1,2,5-trimethyl-4-piperidinol. [g] Probable stereochemistry. [h] Lit. 8.77[12] and 8.4.[14] [i] Lit.[12] 5.64. [j] Lit.[15] 7.29 for (+) and 9.12 for (−) isomeric salts; **25** is the racemic mixture.

exchange between methyl benzilate and 2-β-hydroxymethyl-3-β-tropanol[8] gave the dibenzilate of the amino alcohol, isolated as a hydrochloride: mp 127°. *Anal.* ($C_{37}H_{38}ClNO_6$) C, H, N.

1-Methyl-4-piperidinol Derivatives. The diphenylacetate of **3a**[9] gave a hydrobromide, mp 165–166° from acetone [*Anal.* ($C_{20}H_{24}BrNO_2$) C, H, N], and a methiodide, mp 209–211° from EtOH [*Anal.* ($C_{21}H_{26}INO_2$) C, H]. **3a** benzilate formed a hydrochloride, mp 214–215° (lit.[10] 213–214°), and a methiodide, mp 198–200° from EtOH (lit.[9] 199–200°). **3a** acetate formed a methiodide, mp 163–165° from EtOH. *Anal.* ($C_9H_{18}INO_2$) C, H, N. Details of esters of cis- and trans-**3b** are given elsewhere.[6]

1-Methyl-3-piperidinol Derivatives. The acetate formed a methiodide, mp 165–166° (lit.[10] 171–172°), the benzilate a hydrochloride,[6] mp 217–218°, and a methiodide, mp 221–223° from EtOH [*Anal.* ($C_{21}H_{26}INO_3$) C, H], and the diphenylacetate a hydrochloride, mp 192–193° (lit.[4] 193–194°), and a methiodide, mp 95–97° [*Anal.* ($C_{21}H_{26}INO_2$) C, H].

Benzilate of 1,2,5-Trimethyl-4-piperidinol. 1,2,5-Trimethyl-4-piperidone[11] was reduced with LAH[6] to give an isomeric mixt of 1,2,5-trimethyl-4-piperidinols. The total base was esterified with methyl benzilate as usual to give an oily product which solidified on storage; repeated crystn yielded a single isomer of 1,2,5-trimethyl-4-piperidyl benzilate: mp 137–138° from EtOH–H_2O; pmr (δ) in DMSO-d_6 6.51 (singlet, OH), 4.51 (multiplet, base width 31 Hz, C4-H), 2.18 (singlet, *N*-Me), 1.31 and 0.6 (doublets $J \sim 7$ Hz, 2- and 5-Me). *Anal.* ($C_{22}H_{27}NO_3$) C, H. It formed a hydrochloride, mp 118–119° [*Anal.* ($C_{22}H_{28}ClNO_3$) C, H, N], and a methiodide, mp 236–238° [*Anal.* ($C_{23}H_{30}INO_3$) C, H, N].

Pharmacological Methods. (1) pA_2 values were detd on guinea pig ileum by Schild's method.[12] The guinea pigs were killed by breaking their necks. Segments of ileum 2–3 cm in length were removed from points adjacent to the ileocecal junction and suspended in Krebs soln at 37° gassed with 95% O_2–5% CO_2 in the conventional manner. Contractions were recorded using an isotonic ink-writing lever, at least 3 concns of antagonist being used to determine each pA_2 value. The relative potencies were calcd in the following manner: the pA_2 value for atropine was subtracted from the pA_2 value of the drug, and the antilog of this difference gave the relative potency. pA_2 values were also detd against histamine in the cases of esters of **3b** and **6**.

(2) Mydriasis. Male or female albino mice (15–20 g) were used. Drugs were dissolved in distd H_2O and injected sc, and the procedure of Karlen[13] was used to determine mydriatic activity. Eight mice were used at each of 3 dose levels and pupil diameters were measured at 30 min and 24 hr after each dosing. The per cent increase in eye pupil diameter compared with the control value was plotted *vs.* the log dose: from this the ED_{50} (that dose of drug which increases the eye pupil diameter 1.5 times over control) was calcd.

(3) Effects on Rat Blood Pressure (Cholinergic Activity). Male rats (150–300 g) were anesthetized with urethane (1.875 g/kg) injected ip. The trachea was cannulated and arterial blood pressure was recorded using an E & M pressure transducer, type p-1000A connected to an E & M physiograph type DMP-4A. Drugs were dissolved in 0.9% saline and injected through a polythene cannula inserted into a femoral vein. Results are given in item 7 of the Discussion. Drugs used are: (commercial sources) atropine sulfate, orphenadrine·HCl, ethopropazine·HCl, ACh·Cl^-, hyoscine·HBr, and urethane. Solns used are: Krebs–NaCl, 6.9 g; KCl, 0.35 g; $CaCl_2 \cdot 6H_2O$, 0.55 g; KH_2PO_4, 0.16 g; $MgSO_4 \cdot 7H_2O$, 0.29 g; dextrose, 1.0 g; $NaHCO_3$, 2.1 g; distd H_2O to 1 l.

Results and Discussion

Anticholinergic properties of the amino alcohol esters reported here were determined by 2 procedures, namely, inhibition of contractions of the guinea pig ileum induced by ACh and mydriatic action on the mouse pupil. Details of the pharmacological data are given in Table I, and results are summarized as follows.

1. Tropane Derivatives (1–5). The tropyl benzilates were 2–3 times more potent than the pseudotropyl epimers (guinea pig ileum test), the methiodide of **1c** slightly exceeding the potency of atropine. All compounds were potent mydriatics (*cf.* atropine, ED_{50} 1×10^{-4} m*M*/kg in this test) with a duration of action of less than 24 hr (that of atropine persisted for 36 hr). Isomeric pairs differed little in activity in the mydriasis test. The spasmolytic activity of the pseudotropyl derivative **2c** was reduced by a half when a β-benzilyloxymethyl group was introduced into the molecule (**3**, **5**).

2. 4-Piperidyl Benzilates. The unsubstituted esters (**8**, **9**) exceeded atropine in potency as spasmolytics. Analogs with

3-Me substituents were decidedly less potent in the same test but cis isomers (**16**, **17**) were about 3 times as potent as trans analogs (**14**, **15**). The same substituent also reduced the mydriatic activity of **3a** benzilate. The duration of mydriasis was less than 24 hr for all piperidyl benzilates including 3-piperidyl derivatives.

3. 4-Piperidyl Diphenylacetates. The unsubstituted esters (**6**, **7**) were only 0.2 as active as the benzilates (**8**, **9**) in the guinea pig ileum test, and potency was further reduced when a 3-Me group was present (**10–13**). The cis hydrochloride (**12**) was twice as active as the trans salt (**10**) but isomeric methiodides (**11**, **13**) were equipotent. 1-Methyl-4-piperidyl diphenylacetate (**6**, **7**) was reasonably active as a mydriatic.

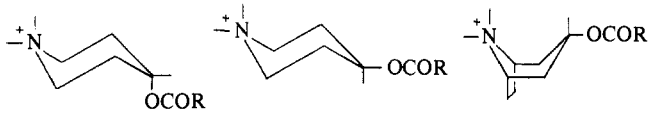
4. 3-Piperidyl Derivatives. In the guinea pig ileum test the benzilate·6HCl (**20**) was superior to the 4-piperidyl analog (**8**), but the potency order of corresponding methiodide salts (**21**, **9**) was reversed to a remarkable degree. Compd **20** (1.5 times as active as atropine sulfate) was the most potent member of the entire series in this test, and (like the methiodide, **21**) was a potent mydriatic. Diphenylacetates of 1-methyl-3-piperidinol had similar potencies to the 4-piperidyl analogs in both tests.

5. The high potency of the 2,5-dimethylpiperidyl benzilates (**22**, **23**) in the guinea pig ileum test (4–6 times that of the trans 3-Me analogs, **14**, **15**) was unexpected. It appears that the detrimental influence of a Me substituent α to the acyloxy function is outweighed by the advantageous influence of the same substituent α to the basic center. The 2,5-Me_2 derivatives were inactive as mydriatics.

6. Specificity. None of the compounds examined for antihistaminic activity was more active against this agonist than atropine and some, notably **20** and **21**, were more specific than atropine.

7. The acetates of all piperidinol methiodides were feeble cholinergic agents, the relative molar potencies (ACh = 1) being: **3a**, 300; **6**, 660; *trans*-**3b**, 2000; *cis*-**3b**, inactive (all acetate methiodides of designated piperidinols). The decreases in blood pressure observed were blocked by hyoscine·HBr, therefore the effects of piperidyl acetates were due to their muscarinic actions.

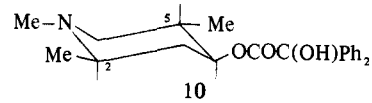
Results upon the isomeric tropanol and 1,3-dimethyl-4-piperidinol derivatives clearly show a preference for the arrangement **7** rather than **8** for the blockade of muscarinic



7 **8** **9**

receptors in the guinea pig ileum. It is unlikely that 3α-tropanol (tropyl) esters adopt boat conformations with the bulky acyloxy substituent pseudoequatorial (see **9**), as pmr data upon atropine sulfate (in D_2O) and other tropyl esters have established.[6] This preference may be a functional group-separation factor, the distance between charged nitrogen and the ether oxygen of the OCOR group being less in **7** by about 0.7 Å.[16]

Substituents α to the acyloxy group, whether axial (*e.g.*, **3**, **5**) or equatorial (*e.g.*, **8**, **14** and **9**, **15**) lead to pronounced falls in the cholinolytic potency of esters of 3β-tropanol and 1-methyl-4-piperidinol at guinea pig ileum sites. Benzilates and diphenylacetates of *trans*-**3b** were about 0.1 as potent as 3-desmethyl analogs. The activity loss was less for benzilates of *cis*-**3b** probably due to the compensating factor of an axially orientated ester function in these isomers. The potencies of **3a** benzilates at mydriatic sites were less depressed by a 3-Me substituent while the same ester of *cis*-**3b**·methiodide was equipotent with that of **3a**·methiodide in these tests. The geometry of the 2,5-dimethylpiperidyl benzilates (**22**, **23**) is not conclusively established but the acyloxy group is clearly equatorial (the 4-H pmr signal is broad and typical of an axial proton, see Experimental Section)[6] and the C-Me substituents are probably also equatorial (**10**) since the parent alcohol is the most abun-



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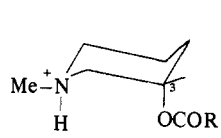
dant isomer formed from the precursor 4-piperidone and LAH. Binding of 4-piperidyl esters to guinea pig ileum sites must therefore be assisted by an equatorial Me group α to charged N since **22** and **23** retain half or more of the activity of **3a** benzilates (**8**, **9**) in spite of their 5-Me (≡ 3-Me in 3a) substituents, and are 4–6 times more potent than corresponding esters of *trans*-1,3-dimethyl-4-piperidinol (**14**, **15**).

Benzilates were more potent than diphenylacetates mostly by factors of 5–6 in the guinea pig ileum test and 3–6 in mydriasis experiments. The presence or absence of an OH function in the acyl moiety (COR) of the piperidyl esters thus had a greater influence upon antimuscarinic properties than the geometrical configuration of the amino alcohol. These findings concur with the observation (in appropriate asymmetric examples) of acyl absolute configuration having a major, and that of amino alcohol a minor, influence upon the ability of cholinolytic esters to block muscarinic receptors.[17]

In most cases, potency differences between hydrohalide-methiodide pairs were small; quaternary salts were less effective in the guinea pig ileum test and slightly more so in the mydriasis experiments. One marked exception was the pair **20** and **21** in which the spasmolytic potency of the hydrochloride (1.5 X atropine) fell sharply after quaternization. If the high potency of **20** is due to its adoption of the conformation **11** in which the acyl substituent (axial) is



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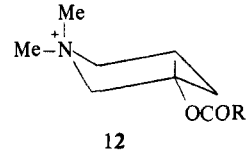

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even closer to charged nitrogen than is the case in α-tropyl esters such as atropine, then methiodide formation would force the 3 substituent into the pharmacologically less favorable (?) equatorial orientation **12** in order to avoid destabilizing 1,3 nonbonded interactions. There is pmr evidence for significant populations (~50%) of the axial 3-acyloxy conformer in solutions of 1-methyl-3-piperidyl ester hydrochlorides.[6]

While the stereochemical specificity of guinea pig ileum receptors was well defined as judged by the pA_2 values of diastereoisomeric pairs, that of muscarinic receptors involved in mydriasis was insignificant. Similarly, although the methiodide of **6** benzilate had less than half the spasmolytic activity of the corresponding hydrochloride, both salts were potent mydriatic agents; further, a 2-Me substituent in the piperidine ring (advantageous in respect of spasmolysis) abolished mydriatic activity (*cf.* **22**, **23**). These results, allowing for variations in the sensitivities of the two tests, are evidence that muscarinic receptors in the guinea pig ileum

differ from those in circular muscles of the eye.

The geometry of the amino alcohol portion of cholinergic antagonists based on tropane and piperidine has been shown to influence the antimuscarinic potencies of these esters—at least at sites in the guinea pig ileum—but the order of the effect is smaller than that caused by variations in the acyloxy moiety, and much smaller than that of absolute configuration in the case of amino alcohols esterified with chiral alcohols (*e.g.*, *l*-tropyl α-methyltropate is 50 times more active than the dextro isomer on rat gut).[18] In sharp contrast, the potencies of cholinergic *agonists* are greatly dependent upon the configuration and structure of the amino alcohol portion of the molecule as witnessed by the relative activities of (*R*)- and (*S*)-β-methylacetylcholine[19] and *cis*- and *trans*-2-acetoxycyclopropyltrimethylammonium iodide.[20] Hence the results presented here support the view that cholinergic agonists and their antagonists occupy different receptors[17,21] although evidence of competitive interactions between agonist-antagonist pairs points to their sharing a common anionic site.

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Compounds Affecting the Central Nervous System. 2.[1] Aromatic Acetals of Tropanediols

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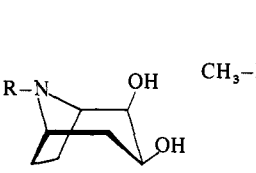
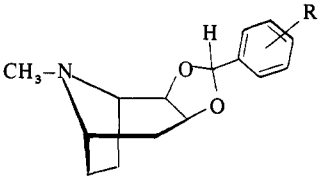
A series of acetals prepared from tropane-2β,3β-diol and variously substituted benzaldehydes was found to produce CNS stimulation and to reverse reserpine-induced eyelid ptosis. These acetals formed as pairs which were isomeric about the benzylic C. Configurational assignments were made on the basis of their nmr spectra. The acetals of ecgoninol and pseudoecgoninol were included in this study.

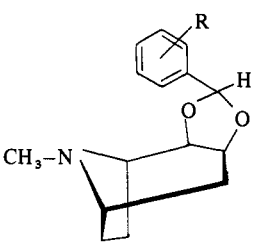
It is always a considerable pleasure to find that a chemical intermediate or a simple derivative of a compound under study has interesting biological activity. 1α*H*,5α*H*-Tropane-2β,3β-diol (**1**) was reported recently[1] as an intermediate in the preparation of a "reverse ester" of cocaine. Benzylidene acetals (**3** and **4**) of this diol, the subject of this paper, are central nervous system stimulants. They were prepared by the reaction of a variety of benzaldehydes with diol **2** followed by reduction of the *N*-ethoxycarbonyl group to Me.



1, R = CH_3
2, R = EtO_2C



3
R as in Table II



4
R as in Table II

Table I lists the 8-ethoxycarbonyl acetals which were prepared. In each case acetal formation gave essentially equal quantities of 2 products which were isomeric about the benzylic C. The configuration of the Ph group is designated β when it lies on the same side of the molecule as the N and α when the converse is true. The basis for configurational assignment is discussed later. Generally, the isomers with the aromatic ring in the α configuration crystallized spontaneously from the reaction mixtures. Purification of the β isomers was then accomplished by plate or column chromatography.