were washed repeatedly with hot THF to ext entrained product. The washings and the filtrate were combined and concd, and the resultant org solid was recrystd from MeOH. Yields and properties are reported in Table III.

Lactonization of the 3-Hydroxybenzodiazepinone.—A soln of 0.25 g (1.0 mmole) of **17** was prepd in 30 ml of anhyd MeOH contg 0.05 g of NaOMe. The reaction mixt was refluxed for 1.5 hr, chilled to 0°, and the pptd pale yellow crystals isolated by filtration. Addl product was obtd by concg the mother liquors. The crystals (0.17 g or 85%) were recrystd from DMSO–H_2O and exhaustively dried *in vacuo*, mp 264–266°. *Anal.* C, H, N.

Antispasmodic Agents. 2.[1] Syntheses and Pharmacological Activity of Ethyl 2-(ω-Aminoalkyl)-2-(3-methoxyphenyl)phenylacetates

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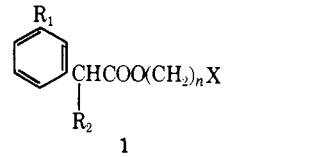
We have recently reported a series of aminoalkyl 3-substituted phenylacetates (**1**)[1] and now wish to describe the synthesis, and the antispasmodic and analgetic activity of ethyl 2-(aminoalkyl)-2-(3-methoxyphenyl)-phenylacetates and related compounds. Some 2-(aminoalkyl)-2,2-diphenylacetates have been reported by other investigators.[2-6]

2-(3-Methoxyphenyl)phenylacetic acid (**3**) was prepared by alkaline hydrolysis of 2-(3-methoxyphenyl)-phenylacetonitrile (**2**), which was obtained in good yield by benzyne reaction between 2-chloroanisole and phenylacetonitrile.[7,8] Ethyl 2-(aminoalkyl)-2-(3-methoxyphenyl)phenylacetates (**7a–7l**) were synthesized as follows; (A) condensation of the ester **4**, prepared from **1**, with aminoalkyl chlorides with the use of NaH;[9] and (B) condensation of ethyl 2-(4-bromobutyl)-2-(3-methoxyphenyl)phenylacetate (**5b**), prepared from **4**, with amines. In the latter method, condensation of ethyl 2-bromomethyl-2-(3-methoxyphenyl)phenylacetate (**5a**) with secondary amines gave only the starting material. The similar reaction of 2-chloromethyl-2-(3-methoxyphenyl)phenylacetonitrile (**6a**) with amines also resulted in failure.

Finally, the nitriles **8a–8c** and the alcohols **9a–9c** were synthesized in order to compare their pharmacological activities with those of ester analogs **7**. Condensation of **2** with aminoalkyl chloride afforded **9a,b**. The treatment of **6b** with dimethylamine gave **8c**. Reduction of **7** with LAH gave the corresponding alcohol **9**.

SCHEME I



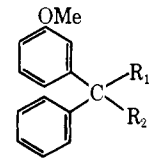
1

R_1 = OMe, OH, OAc

R_2 = H, Me, Et, CHMeEt, Ph

X = $N(Me)_2$, $N(Et)_2$, N□, N⬡, N⬡O

n = 2~3



2, R_1 = CN; R_2 = H

3, R_1 = COOH; R_2 = H

4, R_1 = COOEt; R_2 = H

5a, R_1 = COOEt; R_2 = CH_2Br

5b, R_1 = COOEt; R_2 = $(CH_2)_4Br$

6a, R_1 = CH_2Cl; R_2 = Cl

6b, R_1 = $(CH_2)_4Br$; R_2 = CN

Pharmacology.—Table I gave the results of screening for antispasmodic, anticholinergic, and analgetic activities. The compounds were tested by the Magnus[10] guinea pig ileum screen. The screening for analgetic activity was carried out by the hot plate method in mice. Although all the compounds were inferior to atropine sulfate in anticholinergic activity, the 3 compounds (**7b, 7c,** and **7k**) showed an antispasmodic effect similar to papaverine·HCl. Among them, 6 compounds (**7b,c,f,k,l,** and **9b**) showed analgetic activity; especially, in case of **7k,** the minimum effective dose was 25 mg/kg as shown in Table I.

Experimental Section[11]

Ethyl 2-(3-Methoxyphenyl)phenylacetate (4).—A mixt of 15 g of **3**, 100 ml of EtOH, and 2 ml of 98% H_2SO_4 was refluxed for 5 hr and evapd. The resulting residue was dild (H_2O) and extd (PhH). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The remaining residue was distd *in vacuo* to give 14.3 g (85%) of **4** as a pale yellowish oil: bp 162–164° (1.0 mm); ir (liq) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 1.12 (t, 3 H, CH_2CH_3), 3.53 (s, 3 H, OCH_3) 4.02 (q, 2 H, CH_2CH_3), 4.80 (s, 1 H, CH-COOEt), 6.42–7.16 (m, 9 H, ArH). *Anal.* ($C_{17}H_{18}O_3$) C, H.

Ethyl 2-Bromomethyl-2-(3-methoxyphenyl)phenylacetate (5a).—To a stirred soln of 14.4 g of CH_2Br_2 in 50 ml of dry DMF was added a soln of Na salt of **4** [prepd from 15 g of **4** and 2.9 g of NaH (50% suspension in mineral oil) in 50 ml of DMF]. After stirring for 3 hr at 70–80°, the mixt was poured into H_2O and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The remaining residue was distd *in vacuo* to give 13.5 g (67.5%) of **5a** as a pale yellowish oil:[12] bp 188–189° (0.3 mm); ir (liq) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.17 (t, 3 H, CH_2CH_3), 3.68 (s, 3 H, OCH_3), 4.15 (s, 2 H, CH_2Br), 4.15 (q, CH_2CH_3), 6.60–7.40 (m, 9 H, ArH).

Ethyl 2-(4-Bromobutyl)-2-(3-methoxyphenyl)phenylacetate (5b).—To a stirred soln of 18 g of 1,4-dibromobutane in 50 ml of DMF was added in portions a soln of the Na salt of **4** [prepd

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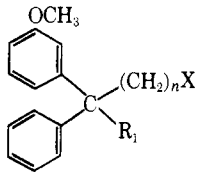
(11) Melting points are uncorrected. Ir spectra were determined on a Shimazu spectrometer and nmr data on a JNM-MH-60 instrument (TMS).

(12) These samples were difficult to microanalyze because of comparatively low boiling points, but unambiguous structures rest on those of the following reaction products which were confirmed.

TABLE I

SYNTHESES AND CHARACTERISTICS OF ETHYL 2-(AMINOALKYL)-2-(3-METHOXYPHENYL)PHENYLACETATE AND ITS ANALOGS



Compd	R_1	n	X	Mp, °C	Method	Yield, %	Formula[k]	Relative activity[a] *in vitro* Act. rel to papaverine·HCl = 1	Relative activity[a] *in vitro* Anticholinergic act. rel to atropine·H_2SO_4 = 1	Analgetic act.[b]
7a	$COOC_2H_5$	2	$N(CH_3)_2$	131.5–133	A	52	$C_{21}H_{27}NO_3 \cdot C_2H_2O_4$[c]	0.525	0.011	–
7b	$COOC_2H_5$	2	$N(C_2H_5)_2$	92–94	A	63	$C_{23}H_{31}NO_3 \cdot C_2H_2O_4$[c]	1.032	0.019	++
7c	$COOC_2H_5$	2	$C_5H_{10}N$[d]	144–145	A	59	$C_{24}H_{31}NO_3 \cdot C_2H_2O_4$[c]	1.001	0.009	++
7d	$COOC_2H_5$	2	C_4H_8NO[e]	113–115	A	64	$C_{23}H_{29}NO_4 \cdot C_2H_2O_4$[c]	0.132	0.005	–
7e	$COOC_2H_5$	3	$N(CH_3)_2$	99–101	A	83	$C_{22}H_{29}NO_3 \cdot C_2H_2O_4$[c]	0.493	0.032	–
7f	$COOC_2H_5$	3	$N(C_2H_5)_2$	89–91	A	79	$C_{24}H_{33}NO_3 \cdot C_2H_2O_4$[c]	0.471	0.010	++
7g	$COOC_2H_5$	3	$C_5H_{10}N$[d]	139–141	A	76	$C_{25}H_{33}NO_3 \cdot C_2H_2O_4$[c]	0.273	0.002	–
7h	$COOC_2H_5$	3	C_4H_8NO[e]	103–105	A	69	$C_{24}H_{31}NO_4 \cdot C_2H_2O_4$[c]	0.224	0.003	–
7i	$COOC_2H_5$	4	$N(CH_3)_2$	134–135.5	B	72	$C_{23}H_{31}NO_3 \cdot C_2H_2O_4$[c]	0.801	0.009	–
7j	$COOC_2H_5$	4	$N(C_2H_5)_2$	77–80	B	81	$C_{25}H_{35}NO_3 \cdot C_2H_2O_4$[c]	0.415	0.011	–
7k	$COOC_2H_5$	4	$C_5H_{10}N$[d]	145–146	B	76	$C_{26}H_{35}NO_3 \cdot C_2H_2O_4$[c]	1.007	0.023	+++
7l	$COOC_2H_5$	4	C_4H_8NO[e]	115–117	B	59	$C_{25}H_{33}NO_4 \cdot C_2H_2O_4$[c]	0.396	0.016	+
8a	CN	2	$N(CH_3)_2$	156–157		78[f]	$C_{19}H_{22}N_2O \cdot HCl$	*j*	*j*	*j*
8b	CN	3	$N(CH_3)_2$	180–181		73[f]	$C_{20}H_{24}N_2O \cdot HCl$	0.598	0.009	–
8c	CN	4	$N(CH_3)_2$	149–151		69[f]	$C_{21}H_{26}N_2O \cdot HCl$	*j*	*j*	*j*
9a	CH_2OH	2	$N(CH_3)_2$	159–161		51[g]	$C_{19}H_{25}NO_2 \cdot HCl$	*j*	*j*	*j*
9b	CH_2OH	3	$N(CH_3)_2$	161–162		65[h]	$C_{20}H_{27}NO_2 \cdot HCl$	0.075	0.002	++
9c	CH_2OH	4	$N(CH_3)_2$	138–140		80[i]	$C_{21}H_{29}NO_2 \cdot C_2H_2O_4$[c]	*j*	*j*	*j*

[a] Papaverine·HCl depressed the contraction (50%) at 4×10^{-4} *M* $BaCl_2$ = 1. Ratio papaverine·HCl/vol of test sample showing the same effect is its antispasmodic activity. For anticholinergic activity, atropine sulfate which depressed the contraction at 1×10^{-6} *M* of ACh to the extent of 50% = 1 is taken as the standard; the ratio between the test samples and the standard was measured as above. [b] Analgetic activity was examined by the hot plate method in mice: +++ for the MED 25 mg/kg; ++ for 25–50 mg/kg; + for 50–100 mg/kg; and – for >100 mg/kg. [c] $C_2H_2O_4$; oxalic acid. [d] $C_5H_{10}N$; piperidino. [e] C_4H_8NO; morpholino. [f] Yield from **6b**. [g] Yield from **7a**. [h] Yield from **7e**. [i] Yield from **7i**. [j] Unexamined. [k] All compds (except **8b** recrystd from EtOH) were recrystd from EtOH–Et_2O and analyzed for C, H, N.

from 15 g of **4** and 3 g of NaH (50% suspension in mineral oil) in 50 ml of DMF] at 110–120°. After stirring for 2 hr at the same temp, the mixt was poured into H_2O and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The residual oil was distd *in vacuo* to give 9 g (40.2%) of **5b** as a pale yellowish oil: bp 200–203° (0.3 mm); ir (liq) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 1.12 (t, 3 H, CH_2CH_3), 1.50–1.95 (m, 4 H, $CH_2CH_2CH_2Br$), 1.95–2.52 (m, 2 H, $CH_2(CH_2)Br$), 3.25 (t, 2 H, CH_2Br), 3.70 (s, 3 H, OCH_3), 4.11 (q, 2 H, CH_2CH_3), 6.58–7.40 (m, 9 H, ArH). *Anal.* ($C_{21}H_{25}BrO_3$) C, H.

Ethyl 2-(ω-Aminoalkyl)-2-(3-methoxyphenyl)phenylacetate (7). General Procedure. A.—A mixt of **4** (1 mole), NaH (1 mole), and DMF was stirred for 1 hr at 40°, and then to this soln was added aminoalkyl chloride (1.1 mole). After stirring at 60–70°, the mixt was poured into H_2O and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The residual oil was characterized in the form of the oxalate.

B.—A mixt of **5b** (1 mole), secondary amine (2–4 moles), and EtOH was refluxed. After completion of the reaction, solvent and excess of amine were evapd, and the resulting residue was made basic (K_2CO_3) and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The residual oil was characterized as the oxalate.

2-Chloromethyl-2-(3-methoxyphenyl)phenylacetonitrile (6a).—A suspension of 10.5 g of $NaNH_2$, 50 g of 2-(3-methoxyphenyl)-phenylacetonitrile (**2**), and 400 ml of dry Et_2O was refluxed for 1 hr; to this soln was added dropwise 58.2 g of CH_2BrCl. After refluxing for 3 hr, the mixt was dild with H_2O and extd (PhH). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The resulting residue was distd *in vacuo* to give 51 g (84%) of **6a** as a yellowish oil: bp 180–184° (0.2 mm); ir (liq) 2220 cm^{-1} (C≡N); nmr (CCl_4) δ 3.65 (s, 3 H, OCH_3), 4.09 (s, 2 H, CH_2Cl), 6.62–7.52 (m, 9 H, ArH). *Anal.* ($C_{16}H_{14}ClNO$) C, H, N.

2-(4-Bromobutyl)-2-(3-methoxyphenyl)phenylacetonitrile (6b).—To a soln of 6.5 g of 1,4-dibromobutane in 30 ml of dry PhH was added a soln of the Na salt of **2** (prepared from 4.4 g of **2** and 0.85 g of $NaNH_2$ in a mixt of 30 ml of dry Et_2O and 30 ml of dry PhH) with refluxing. The mixt was refluxed for 3 hr with stirring, and the solvent layer was washed (H_2O), dried (Na_2SO_4), and evapd. The residual oil was distd *in vacuo* to give 1.3 g (18.4%) of **6b** as a yellow oil: bp 215–220° (0.9 mm);[12] ir (liq) 2230 cm^{-1} (C≡N); nmr (CCl_4) δ 1.22–2.01 (m, 4 H, $CH_2CH_2CH_2Br$), 2.17 (t, 2 H, $CH_2(CH_2)_3Br$), 3.12 (t, 2 H, CH_2Br), 3.55 (s, 3 H, OCH_3), 6.40–7.35 (m, 9 H, ArH).

2-(ω-Aminoalkyl)-2-(3-methoxyphenyl)phenylacetonitrile (8a,b). General Procedure.—A mixt of **2** (1 mole), $NaNH_2$ (1.1 mole), and dry PhH was refluxed for 0.5 hr with stirring, and aminoalkyl chloride (1.1 mole) was added. After stirring under reflux, the mixt was poured into H_2O and extd (PhH). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The resulting oil was characterized as the hydrochloride.

2-(*N*,*N*-Dimethylaminobutyl)-2-(3-methoxyphenyl)phenylacetonitrile (8c).—A mixt of 2 g of **6b**, excess Me_2NH, and EtOH was refluxed for 4 hr. Solvent and excess amine were evapd. The remaining residue was made basic (K_2CO_3) and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The resulting oil was characterized as the hydrochloride.

2-(ω-Aminoalkyl)-2-(3-methoxyphenyl)phenylethyl Alcohol (9a–9c).—To a suspension of LAH (4 moles) in dry THF was added a soln of ethyl 2-(ω-aminoalkyl)-2-(3-methoxyphenyl)-phenylacetate (**7**) (1 mole) in THF with stirring. Stirring was contd for 4 hr under reflux, and then the excess reagent was decompd with 30% NaOH. An inorg ppt was removed by filtration and the filtrate was dried (K_2CO_3). Removal of the solvent afforded an oil which was characterized as the hydrochloride or oxalate.

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Studies on the Cholinergic Receptor. 6.[1] Synthesis and Muscarinic Activity of 2-Methyl-4-(2-dimethylaminoethyl)-1,3-dioxolane Methiodide[2]

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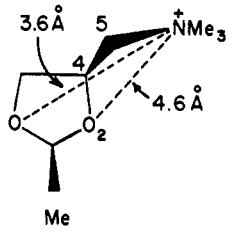
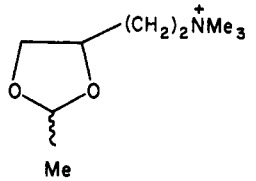
Previous studies[3a-c] utilizing conformationally restricted 1,3-dioxolane analogs of the highly potent muscarinic agent I have suggested that the "active" conformation of I is that in which the N^+Me_3 group is maximally extended from O_1 and O_3. Some further confirmation of this is offered by the finding that II (approximately 80% cis, 20% trans) in which the N^+Me_3 group can sweep an area significantly greater than in I but cannot attain conformation I is very significantly less active than I (ED_{50}, I, 3×10^{-8} *M*; II, 1.9×10^{-5} *M*; *inter alia*, I and II = 1).



I



II

It is of interest that the conformation I deduced by us on the basis of conformationally restricted analogs is in reasonable agreement with that obtained for *cis*-2(*S*)-methyl-4(*R*)-dimethylaminomethyl-1,3-dioxolane methiodide by Pauling and Petcher through X-ray analysis[4] (torsion angle, $O_2C_4C_5N^+$, +94°, $N^+ \rightarrow O_1$, 3.2 Å, $N^+ \rightarrow O_2$ 4.79 Å). However, a number of arguments can be advanced[1,5,6] to suggest quite strongly that there is not a single unique binding conformation for muscarinic agonists: hence, the conformation shown in I may be quite irrelevant to the binding conformations of other agents, particularly if they are structurally unrelated.

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(6) D. J. Triggle in "Neurotransmitter-Receptor Interactions," Academic Press, London and New York, 1971, pp 257–276.

Experimental Section

Chemistry.—Melting points were determined on a Thomas-Kofler hot stage and are corrected. Nmr spectra were recorded with a Varian A-60; glpc analyses were carried out with a 10% Carbowax column using an F and M Research Chromatograph (Model 5750). Elemental analyses were by Dr. A. E. Bernhardt and, where indicated only by symbols of the elements, are within ±0.4% of the theoretical values.

2,2-Dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane was prepd in 46% yield from acetone (6.4 g, 0.11 mole), 1,2,4-trihydroxybutane (10.6 g, 0.1 mole), and *p*-TsOH (0.05 g) in refluxing PhH (50 ml) with azeotropic removal of H_2O and had bp 52–55° (0.2 mm); nmr (neat, Me_4Si), 2-CH_3, τ 8.66, 8.74 (singlets, cis and trans, respectively, to the 4 substituent), CH_2CH_2OH, 8.21 (asymmetric quartet), multiplets at 6.36, and 5.91. *Anal.* ($C_7H_{14}O_3$) C, H.

2-Methyl-4-(2-dimethylaminoethyl)-1,3-dioxolane Methiodide (II).—2,2-Dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane (0.1 mole) was converted to the chloro compound by treatment in $CHCl_3$ (50 ml) with an equimolar amt of $SOCl_2$ at 0°. The mixt was stirred at 35° for 120 min, and then refluxed with an equal vol of MeOH for 15 min and stripped *in vacuo*. The residue was taken up in $CHCl_3$, washed (aq K_2CO_3), dried, and stripped to give crude 4-chloro-1,2-dihydroxybutane which was converted to 2-methyl-4-(2-chloroethyl)-1,3-dioxolane by reaction with paraldehyde in refluxing PhH with azeotropic removal of H_2O; this had bp 56° (15 mm); nmr (neat, Me_4Si), 2-CH_3, τ 8.71 (major doublet, cis), 8.75 (minor doublet, trans), 2-H, 5.0 (unsymmetrical quartet). *Anal.* ($C_6H_{11}ClO_2$) C, H, Cl. 2-Methyl-4-(2-chloroethyl)-1,3-dioxolane was treated with Me_2NH in PhH at 100° for 24 hr and subsequently quaternized with MeI in Et_2O to give II (65%) as colorless prisms with mp 148–151°; nmr (CD_3CN, Me_4Si), 2-CH_3, τ, 8.65 (major doublet, cis), 8.70 (minor doublet, trans). 2-H, 5.0 (overlapping quartets), $N^+(CH_3)_3$, 6.80. *Anal.* ($C_9H_{20}INO_2$), C, H, I, N.

Biology.—Muscarinic activities were determined using the rat jejunum as previously described.[3a-c]

Potential Folic Acid Antagonists. 5. Synthesis and Dihydrofolate Reductase Inhibitory Activities of 2-Amino-4,6-substituted-5-arylazopyrimidines

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Our previous studies of the structural requirements of 5-arylazopyrimidines[1] for inhibitory activity toward dihydrofolate reductase have been largely concerned with 2,4,6-triamino-5-arylazopyrimidines. Optimum activity was found with 2,4,6-triamino-5-(2 ethylphenyl)azopyrimidine.[2] We now report the effect of additional substitution in the pyrimidine ring.

The data in Table I show, in accord with much previous work,[3,4] that significant activity is associated with the 2,4-diaminopyrimidine nucleus. However, optimum activity is found with the 2,4-diamino-6-hydroxypyrimidine nucleus (**4** and **5**) an observation contrasting

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