once. The temp rose rapidly to 40°. The mixt was then heated during 1 hr to 80°, cooled, and poured onto aq KOH (200 ml, 1%) cooled in ice. The resulting solid was filtered and crystd from EtOH; mp 101-102°; ir (KBr) 1675 (C=O), 1130 and 1140 cm^{-1} (C=S); nmr ($CDCl_3$) 8.78 (t, 3, CH_3, J = 7 cps), 7.00 (q, 2, CH_2, J = 7 cps), 6.64 (s, 3, NCH_3), 6.54 (s, 3, NCH_3). *Anal.* ($C_{12}H_{15}NO_2S$) C, H, N.

S-p-Propionylphenyl Dimethylthiocarbamate (73). Compd 72 was heated at 240-245° for 40 min, the conversion was checked on tlc and the product crystd (EtOH); mp 85-87°; ir (KBr), 1686 cm^{-1} (C=O); nmr ($CDCl_3$) 6.94 (s, 6, N=$(CH_3)_2$). *Anal.* ($C_{12}H_{15}NO_2S$) C, H, N.

p-Propionylthiophenol (74). A soln of 73 (0.95 g) in MeOH (10 ml) contg aq NaOH (1.5 ml, 10%) was refluxed for 4 hr under N_2. The soln was concd to dryness, the residue was suspended in H_2O, and extd with Et_2O. The aq layer was acidified with dil HCl and extd with Et_2O, which on concn gave 0.6 g (90%) of the thiophenol; mp 47-49°; nmr ($CDCl_3$) 8.76 (t, 3, CH_3, J = 7 cps), 7.04 (q, 2, CH_2, J = 7 cps), 2.48 (d each splitting into t, 2, ArH ortho to SH), 2.08 (d each splitting into t, ArH, ortho to C=O) for ArH J = 7, 1.5-2.0 and 0.5 cps. *Anal.* ($C_9H_{10}OS$) C, H.

p-Mesyloxyphenyl Ethyl Sulfide (75). MsCl (12.5 ml, 160 mmoles) was added to a soln of *p*-hydroxyphenyl ethyl sulfide[16] (12.3 g 80 mmoles) in 160 ml of dry pyridine below 5°, the mixt was kept for 16 hr at 0-5° and poured onto ice-concd HCl (200 ml) with stirring. The ppt which sepd was filtered and crystd (aq MeOH); yield 16 g; mp 63-65°; nmr ($CDCl_3$) 8.71 (t, 3, CCH_3, J = 7 cps), 7.09 (q, 2, CH_2, J = 7 cps), 6.89 (s, 3, OSO_2CH_3), 2.55-2.82 (m, 4, ArH).

p-Ethylsulfonylphenyl Methanesulfonate (76). A mixt of 75 (6.9 g, 30 mmoles), H_2O_2 (30 ml of 30%, 270 mmoles), and glacial AcOH (40 ml) was heated for 30 min under reflux. The mixt was poured onto ice, the ppt which sepd was filtered and washed with H_2O; yield 6.2 g; mp 90-92°; nmr ($CDCl_3$) 8.72 (t, 3, CH_3, J = 7 cps), 6.83 (q, 2, SO_2CH_2, J = 7 cps), 6.7 (s, 3, OSO_2CH_3). *Anal.* ($C_9H_{12}S_2O_5$) C, H.

p-Ethylsulfinylphenyl Methanesulfonate (77). Fuming HNO_3 (1.01 g, 16 mmoles) in Ac_2O (8 ml) was added slowly under stirring to a soln of 75 (6.9 g, 30 mmoles) in Ac_2O (8 ml) below −10°. The mixt was kept at 0-5° for another 20 hr, poured onto ice-H_2O and neutralized with $NaHCO_3$. It was then extd with $CHCl_3$, washed with satd NaCl, and dried (Na_2SO_4). Removal of solvent gave oil which was purified by passing its C_6H_6 soln through an alumina column to yield 6.0 g of colorless oil, crystd (C_6H_6-hexane); mp 68-70°. *Anal.* ($C_9H_{12}S_2O_4$) C, H.

Cyclopropyl *p*-Hydroxyphenyl Ketone (78). *p*-Hydroxy-γ-chlorobutyrophenone[17] (9.9 g, 50 mmoles) was added, in portions during 20 min, to a refluxing soln of aq NaOH (8 ml, 50%). After addn of half of the compd, aq NaOH (35 ml, 25%) was added followed by addn of the remaining chloro ketone. The mixt was heated to 140° and an addnl 8 g of NaOH was added. A yellow ppt sepd out which remained undissolved by heating and stirring. After 1 hr, 10 ml of H_2O was added to dissolve the solid and stirred with heating at 140° for another 1 hr. The reaction mixt was cooled, dild with H_2O, and neutralized with AcOH. The ppt was filtered, air-dried, and extd with $CHCl_3$. The ext concd and crystd ($CHCl_3$-hexane); yield 5.6 g (70%); mp 95-99°; nmr ($CDCl_3$) 8.6-9.1 (complex multiplet, 4, cyclopropyl CH_2 7.1-7.5 (complex multiplet, 1, $COCH\langle\rangle$), 3.8 (d, 2, ArH, ortho to OH, J = 9 cps), 2.79 (d, 1, ArH, ortho to CO, J = 9 cps), 2.3-3.2 (broad hump, 1, D_2O exchangeable, OH); mass fragmentation, M^+ 162 and other prominent fragments at *m/e* 136 ($M^+ - C_2H_2$), 121 ($M^+ - C_3H_5$), 93 ($M^+ - C_4H_5O$), 65 and 39 (cyclopropenyl).

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Local Anesthetic Activity of 2-Piperazinecarboxanilides

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The synthesis and local anesthetic activity of a series of 2-piperazinecarboxanilides, -toluidides, -xylidides, and -mesidides are described. This series may be described as relatively active local anesthetics exhibiting acceptable irritation liabilities and toxicities. Structure-activity studies revealed the following relationships: increased duration of activity and toxicity with increased alkyl function of the piperazine rings; decreased pK_1 and increased distribution coefficient with increased alkyl function of the piperazine rings. Increased duration of activity with decreased pK_1 and with increased distribution coefficient, which should follow, was not statistically significant. It appears that the dialkylpiperazine function plays a greater role in altering physicochemical and biological properties than does the anilide function.

N-Substituted piperazinoacyl anilides have been prepared as analogs of procainamide[1] and lidocaine,[2-6] but no C-substituted piperazines have been synthesized as potential local anesthetics. Furthermore, no 2-piperazinecarbox- or -acylanilides have appeared in the literature. In view of the local anesthetic activity reported for 2-piperidine analogs,[7] the synthesis of a series of 2-piperazinecarboxanilide analogs of lidocaine (comprising anilides, toluidides, xylidides,

and mesidides), both unalkylated and N,N′-dialkylated on the piperazine ring, was attempted. Open-chain derivatives of 2-piperazine analogs of lidocaine have, however, been prepared.[8-10]

Synthesis. Formation of the desired anilides from 2-piperazinecarboxylic acid was unsuccessful. This acid proved to be quite unreactive either toward acid chloride formation or amide formation using either the free acid, the dihydrochloride, or the sodium salt. Since the desired anilides (1) of 2-pyrazinecarboxylic acid were readily obtainable, various attempts were made to reduce them to the corresponding 2-piperazinecarboxanilides (3). A satisfactory procedure was found in a 2-step reduction procedure utilizing first 10% Pd/C followed by Adams' PtO_2 catalyst. Use of Adams' catalyst alone gave the desired piperazines (3), but the 2-step procedure proved to be more convenient.

Dialkylation of the 2-piperazinecarboxanilides was achieved by means of the alkyl halides and corresponding alcohol in the presence of Na_2CO_3. The dialkylpiperazine derivatives (4) were isolated as the dinitrate salts since the hydrochlorides gave unstable syrups which crystallized only with great difficulty.

Reduction of the 2-pyrazinecarboxanilides (1) using 10% Pd/C and abs EtOH as solvent led to consumption of only 2 moles of H_2 rather than the required 3. In the case of the anilide and toluidide derivatives, the tetrahydropyrazine derivatives (2) were isolated as the hydrochlorides. The xylidide and mesidide derivatives yielded ethylenediamine dihydrochloride under the same conditions. In the presence of a stoichiometric amount of HCl, no reduction took place. With glac AcOH as solvent, however, the reduction rate was increased 12-fold, but only the anilide could be obtained. With the toluidide, xylidide, and mesidide derivatives, only ethylenediamine dihydrochloride was obtained.

The tetrahydropyrazines obtained were considered to be the 3,4,5,6-tetrahydro derivatives (2) on the basis of the following evidence. First, only monohydrochlorides could be obtained, indicating the remaining double bond to be attached to N. Furthermore, isolation of ethylenediamine on acid cleavage indicates the double bond to be 1,2, which also gives a preferred conjugated structure. An uv hypsochromic shift, noted on reduction of the pyrazine ring, also would be expected for a conjugated system. Finally, on allowing the tetrahydropyrazinecarboxanilide to remain in H_2O for 2 hr at room temp, an hypsochromic shift (290 to 240 mμ) occurred, giving a uv spectrum identical with that of the corresponding piperazine derivative. A similar effect noted previously with a tetramethyltetrahydropyrazine[11] was attributed to hydration of the double bond. It is probable that hydration also took place with the tetrahydropyrazine reported here to give the 2-hydroxypiperazine derivative. Attempted isolation of this compound led only to ethylenediamine. This hydration was inhibited but not reversed by alkali.

Local Anesthetic Evaluation. Tests for local anesthetic activity were done by the guinea pig intradermal wheal method[12] and the rat sciatic nerve block method[13,14] using lidocaine and bupivacaine as standards. The former method was used to determine duration and onset of activity. The latter method was used to determine frequency of block as well as side effects. Results of these tests are shown in Tables I and II. In general, the 14 2-piperazinecarboxanilides tested represent a relatively active series of compounds, although the dialkylpiperazines (tertiary amines) were superior to the nonalkylated derivatives (secondary amines).

The overall toxicity of this series of compounds, as determined from the rat sciatic block procedure and LD_{50} (iv in mice) values, was low in comparison to that of amide anesthetics presently in use. Toxicity data are included in Table III.

Table I. Local Anesthetic Activity. Rat Sciatic Nerve Block Method

Compound[a]	% as base	pH	Onset, min	Frequency	Duration, min	Norm duration[b]
Lidocaine	2.0	6.4	1	10/10	169	1.0
Bupivacaine	0.5	5.9	2	10/10	212	1.25
2-CP 000	2.0	5.1	18	5/10	99	0.6
2-CP 100	2.0	5.4	12	9/10	194	1.2
2-CP 200	1.0	5.5	21	7/10	226	1.5
2-CP 300	1.0	5.2	18	9/10	133	1.0
2-CP 022	2.0	5.7	2	10/10	161	0.8
2-CP 122	2.0	5.8	2	10/10	258	1.7
2-CP 222	2.0	6.5	2	10/10	166	1.0
2-CP 322	2.0	5.5	2	10/10	153	0.8
2-CP 111	2.0	5.4	6	10/10	168	0.9
2-CP 133	1.0	5.2	2	10/10	231	1.25
2-CP 144	1.0	4.2	4	9/10	145	0.9
2-CP 211	2.0	4.8	3	10/10	251	1.7
2-CP 233	1.0	5.8	2	10/10	146	1.3
2-CP 244	1.0	4.2	4	10/10	183	1.2

[a] 2CP = 2-piperazinecarboxanilide, the first number indicates the number of anilide Me groups, and the second two numbers indicate the length of the piperazine alkyl groups. [b] Normalized duration in comparison to duration of activity of lidocaine, which varied somewhat on different runs.

Table II. Local Anesthetic Activity. Guinea Pig Intradermal Wheal Method

Compound[a]	% as base	pH	Onset, min	Frequency	Duration, min	Norm duration[b]
Lidocaine	2.0	6.9	1	8/8	98	1.0
Bupivacaine	1.0	5.5	1	8/8	349	4.0
2-CP 000	2.0	5.9	1	8/8	80	0.8
2-CP 100	2.0	5.1	12	7/8	47	0.4
2-CP 200	2.0	5.0	3	8/8	90	0.9
2-CP 300	2.0	5.9	7	8/8	41	0.4
2-CP 022	2.0	5.8	1	8/8	124	0.9
2-CP 122	2.0	5.9	5	8/8	65	0.8
2-CP 222	2.0	6.9	1	8/8	147	1.1
2-CP 322	2.0	5.5	1	8/8	98	0.7
2-CP 111	2.0	5.4	1	8/8	77	0.5
2-CP 133	2.0	6.1	1	8/8	154	1.1
2-CP 144	1.0	4.7	1	8/8	82	0.8
2-CP 211	2.0	4.7	1	8/8	91	0.6
2-CP 233	2.0	5.0	1	8/8	102	0.8
2-CP 244	2.0	4.7	1	8/8	139	1.0

[a] See note *a*, Table I. [b] Normalized duration in comparison to duration of activity of lidocaine, which varied somewhat on different runs.

Determination of irritation liability was done by a modified rabbit intradermal wheal method of Truant.[14] Results are shown in Table III, and it may be concluded that the 2-piperazinecarboxanilides possess low irritation liabilities.

Structure-Activity Relationships. In regard to activity determined by the guinea pig wheal method, with both the nonalkylated and the diethylpiperazines longest duration of activity was shown by the xylidides. Also, the diethyl derivatives showed longer durations in general than did the nonalkylated piperazines. Considering only the dialkyl piperazines of the toluidide series, the greatest duration was obtained with the dipropyl derivative. In the xylidide series, activity in general was greater than in the toluidide series. The entire series of compounds exhibited a significant increase in duration of activity going from the nonalkylated to the more highly alkylated piperazines.

Correlation of anilide structure with acute toxicity for both the nonalkylated and diethylpiperazines showed an

Table III. Irritation and Toxicity

Compound[a]	% as base	pH	Irritation norm index[b]	LD_{50} (iv) in mice, mg/kg	Norm toxicity[c]	Status[d]
Lidocaine	2.0	7.0	1.0	20	1.0	Stand.
Bupivacaine	2.0	5.6	8.0	5	4.0	Stand.
2-CP 000	2.0	7.1	2.5	174	0.11	–
2-CP 100	2.0	6.0	2.0	188	0.10	–
2-CP 200	2.0	5.3	0.2	159	0.125	–
2-CP 300	2.0	6.4	5.0	113	0.18	–
2-CP 022	2.0	5.9	1.3	79	0.25	+
2-CP 122	2.0	5.3	2.0	58	0.33	–
2-CP 222	2.0	5.9	1.0	22	0.9	+
2-CP 322	2.0	5.5	1.0	33	0.6	+
2-CP 111	2.0	5.6	0.0	104	0.2	–
2-CP 133	2.0	2.1	5.0	24	0.8	+
2-CP 144	2.0	4.6	8.0	25	0.8	–
2-CP 211	2.0	3.9	1.0	107	0.2	+
2-CP 233	2.0	5.8	1.5	9	2.2	+
2-CP 244	2.0	4.4	2.0	14	1.4	+

[a] See note *a*, Table I. [b] Normalized index in comparison to irritation index of lidocaine. [c] Normalized toxicity in comparison to toxicity of lidocaine. [d] + = Acceptable, – = unacceptable.

Table IV. Ionization Constants and Distribution Coefficients

Compound	pK_1	pK_2	Dist coeff C_{org}/C_{aq}	Norm duration[d]
Lidocaine	7.89[a]		44.6[c]	1.0
Piperazine	9.83[b]	5.56[b]		
2-CP 000	8.00	3.55	0.6	0.8
2-CP 100	8.12	3.60	0.3	0.4
2-CP 200	7.98	3.58	0.5	0.9
2-CP 300	7.95	3.56	2.4	0.4
2-CP 022	7.21	3.08	4.6	0.9
2-CP 122	7.24	3.09	4.2	0.8
2-CP 222	7.00	3.11	13.4	1.1
2-CP 322	6.70	2.96	9.9	0.7
2-CP 111	6.85	2.98	1.7	0.5
2-CP 133	7.06	3.03	8.2	1.1
2-CP 144	6.81	3.00	9.2	0.8
2-CP 211	7.00	3.24	7.5	0.6
2-CP 233	6.95	3.09	16.3	0.8
2-CP 244	6.89	3.05	16.1	1.0

[a] Lit.[16] value 7.86. [b] Lit.[19] values 9.81 and 5.57. [c] Lit.[16] value 46.8. [d] Guinea pig intradermal wheal method.

increase in toxicity proceeding from the anilide to the mesidide. Also, the dialkyl compounds were more toxic than the nonalkylated piperazines. A similar increase in toxicity was observed with both the toluidide and xylidide series proceeding from the nonalkyl to the dibutyl structures. The xylidides were also more toxic than the toluidides, and in general, increase in alkyl function resulted in increased toxicity.

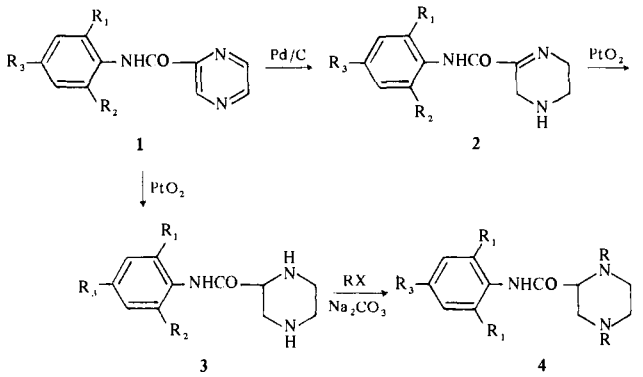
In the case of rabbit wheal irritation, no difference was observed between the nonalkylated and the diethylpiperazines. The toluidides, however, were more irritating than the other anilides. With both toluidides and xylidides, irritation increased with increasing alkyl function on the piperazine ring.

Correlation of Activity with Physical Constants. No relation between ir stretching frequency of the amide I band and local anesthetic activity was evident. Also, no relation between pK_1 and activity was apparent for the entire series. However, in regard to structure, the nonalkylated piperazines generally gave higher pK_1 values than the diethyl derivatives, which exhibited a decrease in pK_1 going from the anilide to the mesidide. Also, a decrease in pK_1 was observed as the piperazine alkyl groups became larger. Dialkyl toluidides and xylidides gave comparable pK_1 values, as expected. Ionization constants are listed in Table IV.

Distribution coefficients were determined using aqueous phosphate buffer and *n*-OctOH. Generally, an increase in duration of activity was accompanied by an increase in distribution coefficient, but the relationship proved not to be statistically significant at the 0.05 level. In regard to structure, the coefficients of the diethyl derivatives were consistently higher than those of the nonalkylated piperazines. Also, the xylidides possessed significantly higher coefficients than did the other anilides. In regard to correlation with dialkylpiperazine structure, the coefficients exhibited a leveling with *n*-Pr_2 and *n*-Bu_2 derivatives. Distribution coefficients are found in Table IV.

In summary, the 1,4-dialkyl-2-piperazinecarboxanilides constitute a relatively active series of local anesthetics having acceptable toxicities and irritation liabilities. No particular structure appeared to be most suitable among the acceptable compounds. Several significant structure-activity relationships were observed. Both duration of activity and toxicity increased with increasing alkyl function on the piperazine rings. An increase in alkyl function of the piperazine rings was also accompanied by an increase in distribution coefficient and a decrease in pK_1. Although there appeared to be a general increase in duration of activity with increase in distribution coefficient and decrease in pK_1, these relationships were not statistically significant at the 0.05 level. No such correlations were apparent in relation to alkyl structure of the anilide rings.

It may be concluded that the piperazine moiety of these compounds plays a more effective role in altering their physical-chemical and therefore biological properties, although both anilide and alkylamino functions are necessary for satisfactory local anesthetic activity.



1 2 3 4

Experimental Section

Melting points were taken with a Mel-Temp apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer 137B spectrometer, and uv spectra on a Perkin-Elmer 202 spectrometer. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or by Alfred Bernhardt Microanalytical Laboratory, Germany. Where analyses are indicated only by symbols of the elements, analytical results obtd were within ±0.4% of the theoretical values. All recrystns were done with charcoal. Physical properties are listed in Table V.

3,4,5,6-Tetrahydro-2-pyrazinecarboxanilides. The appropriate pyrazinecarboxanilide[15] (0.1 mole) in 200 ml of abs EtOH was heated to boiling with 3 g of activated C, filtered into a Parr hydrogenation vessel, and cooled to room temp. The filtrate was flushed with N_2 and treated with 2.5 g of 10% Pd/C, and the hydrogenation was carried out at 3.15–4.2 kg/cm^2 at room temp. After uptake of 0.2 mole of H_2, the reaction mixt was filtered, and the filtrate was treated with 10 ml of concd HCl. Evaporation to approximately 100 ml pptd the hydrochloride. Ice-water cooling and filtering gave the product which was recrystallized from 95% EtOH. Further evaporation to a syrup, and crystallization by addition of

Table V. Physical Properties of Ar–NHC(=O)–(R,N,N,R)

Ar	R	Salt	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
C_6H_5	H	2HCl	57	221 dec	EtOH	$C_{11}H_{15}N_3O \cdot 2HCl$
C_6H_5	H			143–145	$CHCl_3$–CCl_4	$C_{11}H_{15}N_3O$ ·
C_6H_4-2-Me	H	2HCl	55	262 dec	$CHCl_3$–CCl_4 (2:1)	$C_{12}H_{17}N_3O \cdot 2HCl$
C_6H_4-2-Me	H			94–95	$CHCl_3$–CCl_4 (5:1)	$C_{12}H_{17}N_3O$ ·
C_6H_3-2,6-Me_2	H	2HCl	64	272 dec	EtOH	$C_{13}H_{19}N_3O \cdot 2HCl$
C_6H_3-2,6-Me_2	H			171–172	$CHCl_3$–CCl_4 (5:1)	$C_{13}H_{19}N_3O$ ·
C_6H_2-2,4,6-Me_3	H	2HCl	45	266 dec	EtOH	$C_{14}H_{21}N_3O \cdot 2HCl$
C_6H_2-2,4,6-Me_3	H			168–171	$CHCl_3$–CCl_4	$C_{14}H_{21}N_3O$ ·
C_6H_5	Et	$2HNO_3$[b]	46	118 dec	EtOH	$C_{15}H_{23}N_3O \cdot 2HNO_3$
C_6H_4-2-Me	Et	$2HNO_3$	52	124 dec	EtOH	$C_{16}H_{25}N_3O \cdot 2HNO_3$
C_6H_3-2,6-Me_2	Et	$2HNO_3$[c]	35	120 dec	EtOH	$C_{17}H_{27}N_3O \cdot 2HNO_3$
C_6H_2-2,4,6-Me_3	Et	$2HNO_3$[d]	47	113 dec	EtOH	$C_{18}H_{29}N_3O \cdot 2HNO_3$
C_6H_4-2-Me	Me	$2HNO_3$	31	160 dec	EtOH	$C_{14}H_{21}N_3O \cdot 2HNO_3$
C_6H_4-2-Me	Pr	$2HNO_3$	45	133 dec	EtOH	$C_{18}H_{29}N_3O \cdot 2HNO_3$
C_6H_4-2-Me	Bu	$2HNO_3$	42	137 dec	EtOH	$C_{20}H_{33}N_3O \cdot 2HNO_3$
C_6H_3-2,6-Me_2	Me	$2HNO_3$[e]	27	128 dec	EtOH	$C_{15}H_{23}N_3O \cdot 2HNO_3$
C_6H_3-2,6-Me_2	Pr	$2HNO_3$[f]	45	129 dec	EtOH	$C_{19}H_{31}N_3O \cdot 2HNO_3$
C_6H_3-2,6-Me_2	Bu	$2HNO_3$[g]	45	120 dec	EtOH	$C_{21}H_{35}N_3O \cdot 2HNO_3$

[a] *Anal.* for C, H, N. [b] Free base, mp 69–71°. [c] Free base, mp 72–74°. [d] Free base, mp 104–106°. [e] Free base, mp 160–162°. [f] Free base, mp 68–70°. [g] Free base, mp 62–64°.

95% EtOH gave only ethylenediamine dihydrochloride. Attempts to prepare the tetrahydropyrazine xylidide and mesidide derivatives using abs EtOH as solvent gave ethylenediamine dihydrochloride. The free bases of the tetrahydropyrazine anilide and toluidide derivatives were unstable on ambient storage.

3,4,5,6-Tetrahydro-2-pyrazinecarboxanilide Hydrochloride. The reduction required 7 hr, and a yield of 13 g (56%) was obtd: mp 242° dec; ν_{max}^{KBr} 3350, 3000–2800, 1650, 1600 (doublet), 1550, 750 cm^{-1}; $\lambda_{max}^{H_2O}$ 250 mμ. *Anal.* ($C_{11}H_{13}N_3O \cdot HCl$) C, H, N.

3,4,5,6-Tetrahydro-2-pyrazinecarbox-2'-toluidide Hydrochloride. The reduction required 9 hr, giving a yield of 12 g (47%): mp 213° dec; ν_{max}^{KBr} 3300, 3000–2800, 1650, 1600, 1575, 1540, 760 cm^{-1}. *Anal.* ($C_{12}H_{15}N_3O \cdot HCl$) C, H, N.

2-Piperazinecarboxanilides. The reduction procedure described above was carried out with 5.0 g of 10% Pd/C and glacial AcOH. When the rate of H_2 uptake was less than 70 g/cm^2 hr, the reaction mixt was filtered, and to the filtrate, previously flushed with N_2, was added 0.5 g of PtO_2. Hydrogenation was continued under the same conditions until a total of 0.3 mole of H_2 was absorbed. The reaction mixt was filtered and the filtrate was treated with 20 ml of concd HCl. Precipitation of the dihydrochloride occurred after spontaneous evaporation to approximately 100 ml. Filtration and washing with 2-PrOH gave the desired product. Additional product was obtained by evaporating to 50 ml, adding an equal vol of 2-PrOH, storing at 5°, and filtering. Total yields were 46–64%. The dihydrochlorides obtained were generally greater than 3% sol in H_2O at room temp. The free bases were obtained by treatment with NaOH and extn with $CHCl_3$, but were not analyzed.

1,4-Dialkylation of the 2-Piperazinecarboxanilides. To 0.05 mole of the appropriate 2-piperazinecarboxanilide dihydrochloride were added 21.2 g (0.2 mole) of anhyd Na_2CO_3, 0.1 mole of the alkyl halide, and 100 ml of the corresponding alcohol. The alkyl halides used were Me and Et iodides and *n*-Pr and *n*-Bu bromides. The reaction mixt was refluxed with stirring for 6 hr, and was cooled and filtered. The filtrate was evapd to a syrup which was suspended in 50 ml of H_2O and extracted with $CHCl_3$. The ext was dried (Na_2SO_4) and evaporated over steam to an oily liquid or solid. This residue was dissolved in 100 ml of MeOH, treated with charcoal, cooled to 5°, and treated with 7.0 ml of concd HNO_3. Storage at 5° for several hours caused separation of the oily dihydronitrates; second crops were obtained on further chilling. Crystallization was achieved by triturating with Et_2O. The dihydronitrates were greater than 3% soluble in H_2O at room temp. Hydrochlorides of these compounds were crystallized with great difficulty. Free bases were obtained by treatment with NaOH and extraction with $CHCl_3$, but they were not analyzed.

Ionization Constants. Purified amine salts, 0.4, 0.6, 0.8, and 1.0 mequiv, were treated with 0.02 *N* NaOH soln using CO_2-free H_2O. The pH of three portions of the amine salt solution was determined with a Coleman Model 7 pH-meter and a combination electrode after addition of 0.75 (pK_1) and 0.25 equiv (pK_2) of alkali at 24–27°.

Distribution Coefficients. The methods of Löfgren[16] and Hansch, *et al.*,[17] were modified. Amine salts (3.5×10^{-2} mmole) were distributed between phosphate buffer, pH 7.4 (USP XVIII), and *n*-OctOH, each saturated with the other phase, by means of shaking for 2 hr. Concentration of amine in the aqueous phase was determined by its uv spectrum. All values are the average of 3 determinations.

Local Anesthetic Evaluation. Primary local anesthetic testing was done with 1:100,000 epinephrine added to the test solutions, using lidocaine as standard. The guinea pig intradermal wheal method[12] was utilized for duration of activity; each compound was tested at a minimum of 3 concentrations with 3 animals used at each concn. Rat sciatic nerve blocks[13,14] were used to determine frequency of block. The rabbit intradermal wheal method[14] was used to determine irritation indices. Acute toxicity was determined by the method of Truant.[14] Values for LD_{50}, 95% Fieller confidence limits, and 95% approximate limits were calcd by the minimum logit square method of Berkson.[18] A compd was classified as acceptable if it gave a frequency of block of 80% or greater, the absence of severe side effects at the concentration giving ≥80% frequency of block, an onset time of ≤3 min at the 1–2% level in either activity test, a normalized (lidocaine) irritation index of ≤5 at the 2% level, and a normalized (lidocaine) acute toxicity of ≤3.

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Triphenylpropylpiperazine Derivatives as New Potent Analgetic Substances

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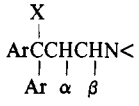
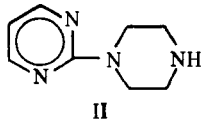
Sixty-four 1,4-disubstituted piperazines have been synthesized in which the 1 substituents are chiefly triphenylpropyl or *i*-Pr groups and the 4 substituents are pyrimidyl and its substituted derivatives, as well as closely related isosteric heterocycles, such as pyridazinyl, pyrazinyl, triazinyl, thiazolyl, and quinazolinyl. These compounds have a methadone-like structure and the most interesting one (**25**) shows good analgetic properties and seems to have a low dependence liability.

Many synthetic organic compounds with pronounced morphine-like activity have been described and among them, the diphenylpropylamines related to methadone. Up to now, several hundred of these compounds have been synthesized[1a] but no significant separation of analgesia and dependence liability has been demonstrated in that field. Nevertheless certain quantitative and time-effect differences have helped to make methadone the drug of choice, generally as a substitute for another opiate to minimize withdrawal symptoms. Thus we undertook a search for compounds structurally related to methadone with the structural requirements



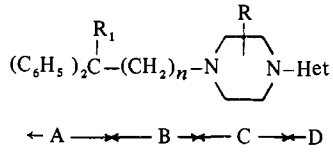
I

hoping to obtain compounds useful in the relief of pain, and, as far as possible, devoid of addicting properties and other undesirable effects. Generally, it is considered[1b] that the most active products are those in which X is an electronegative substituent taken from the following group listed in decreasing order of potency: CON<, COR, >CHOCOR, OCOR, CN, etc.... associated with the presence of a Me group in the α or β position. The N substituent is a basic dialkylamino or cycloalkylamino group. The greatest activity is usually confined to the levo form of the β-branched compounds, the α-branched one being nearly inactive. Our approach was influenced by 2 observations: (1) when we began an extensive research on vasodilatory piperazine derivatives[2] 10 years ago, we discovered a clear but not pronounced analgetic activity in one of them, the pyrimidylpiperazine II.



II

We therefore took this as a structural basis for the basic dialkylamino group in I, despite the fact that some authors[3,4] have pointed out a weak activity and high toxicity for piperazine derivatives structurally related to methadone; (2) a search of the literature revealed that the electronegative Ph group had rarely been employed as a third substituent X. Nevertheless, the triphenylpropylamine structure was included in the structure of spasmolytic substances studied by Swedish workers.[5] These findings prompted us to synthesize some compounds of the following formula:



III

To study the effect of appropriate changes on the activity of this class of compounds, structure III was divided into 4 portions and each one was varied selectively (See Tables II, III, and IV).

(a) In portion A, R_1 is more generally Ph optionally substituted by an alkoxy group. In 3 compounds (**9**, **11**, **12**) R_1 is H and in one R_1 is CN (**10**).

(b) In portion B, which is usually an unbranched $(CH_2)_n$ chain ($n = 2$), we studied the influence of lengthening the chain as well as its α branching. Unfortunately we did not succeed in preparing the β-branched compound.†

(c) For the modification of portion C, we altered piperazine to 2-methylpiperazine, homopiperazine, and decahydroquinoxaline.

(d) In portion D, the pyrimidine group optionally substituted by various groups (See Table III), was replaced en-

†The reaction of the 1-methyl-3,3,3-triphenylpropyl *p*-toluenesulfonate with a monosubstituted piperazine failed and 4,4,4-triphenyl-2-butene was exclusively found as the Swedish workers have described it in the case of its condensation with morpholine.