the preparation of ethyl aceto(1-adamantyl)acetate.[5] β-Oxohexanoate[6] (35.9 g, 0.227 mol) and 1-adamantol (34.5 g, 0.200 mol) were dissolved in 600 ml of pentane at 5°. BF_3 was passed over the mixture for about 1 hr while maintaining the temperature at 5°. Subsequently the reaction mixture was allowed to reach 15° and then it was cooled down to 5°. After neutralization with KOH the solid was separated by filtration. The filtrate eventually gave an oil which was distilled at 20–40 μm: yield 15.4 g (22%); 92% pure by vpc.

2-Amino-4-hydroxy-5-(1-adamantyl)-6-(1-propyl)pyrimidine (8). Guanidine hydrochloride (1.27 g, 13.3 mmol) was neutralized with a solution of sodium ethoxide (0.615 g, 26.8 mg-atom of Na in 100 ml of absolute EtOH). After cooling, **6** (3.89 g, 13.3 mmol) was added and the reaction mixture refluxed for 5 days. The work-up is the same as that previously described for 2-amino-4-hydroxy-5-(1-octyl)-6-methylpyrimidine.[2] Recrystallization from absolute EtOH–charcoal and washing with Et_2O gave 1.2 g (31%): uv max (absolute EtOH) 293, 229 mμ; uv min 253 mμ; mp 298–299°. *Anal.* ($C_{17}H_{25}N_3O$) C, H, N.

2,4-Diamino-5-(1-adamantyl)-6-(1-propyl)pyrimidine Ethyl Sulfonate (4). The above compound 8 (1.7 g) was converted to its 4-Cl derivative (mp 238–240°) by $POCl_3$–PCl_5 as previously described for the preparation of 2-amino-4-chloro-5-(1-propyl-6-methyl)-pyrimidine.[3] This material was dried in a desiccator for 2 hr and mixed in a bomb with absolute EtOH (150 ml) saturated with NH_3 at 0°. The mixture was heated at 150° for 24 hr and then evaporated to dryness. The residue was stirred with 0.1 *N* NaOH for 2 hr. The solid (1.3 g) was collected, washed with distilled H_2O, and dissolved in the minute amount of hot absolute EtOH which contained ethylsulfonic acid (700 mg). After stirring for a few hours, Et_2O was added to precipitate the product (700 mg). Recrystallization from THF gave 300 mg of pyrimidine: mp 212–214°; uv max (absolute EtOH) 288 mμ; uv min 262 mμ. *Anal.* ($C_{19}H_{32}N_4O_3S$) C, H, N, S.

Ethyl **β-Oxoheptanoate (10).** This compound was prepared according to the method described for preparation of ethyl β-oxohexanoate[6] starting with Mg turnings (12.65 g, 0.52 g-atom), ethyl acetoacetate (67.3 g, 0.52 mol), and valeryl chloride (63.4 g, 0.53 mol). The product was obtained in 59% yield (52.9 g, 95% pure by vpc) by distillation at 128–134° (40 mm) [lit.[7] bp 110–125° (20 mm)]. The identity of this compound was established by ir and nmr spectra.

Ethyl **2-(1-Adamantyl)-3-oxoheptanoate (7).** The above compound **10** (10.6 g, 61.6 mmol) was added to a suspension of 1-adamantol (9.36 g, 61.6 mmol) in 160 ml of pentane at 5°. BF_3 was passed over the reaction mixture for 1.5 hr. The rest of the work-up is the same as that described for **6.** The yield was 6.47 g (34.3%), 96% pure by vpc.

2-Amino-4-hydroxy-5-(1-adamantyl)-6-(1-butyl)pyrimidine (9). Guanidine hydrochloride (2.02 g, 21.2 mmol) was neutralized with NaOEt (975 mg, 42.4 mg-atom in 150 ml of absolute EtOH). 7 (6.47 g, 21.2 mmol) was added to the solution of the guanidine and the reaction mixture refluxed for 93 hr. The volume of the mixture was reduced to one-third and poured into 300 ml of H_2O. Et_2O (150 ml) was added and the mixture stirred until the gum present fully solidified. The solid (3.0 g) was collected and washed with Et_2O, mp 260–262°. Recrystallization twice from 95% EtOH–charcoal and once from ethoxyethanol–charcoal gave 1.60 g: mp 265–270°; uv max (absolute EtOH) 292, 226 mμ; uv min 251 mμ. *Anal.* ($C_8H_{27}N_3O \cdot 0.25C_2H_5OC_2H_4OH$) C, H, N.

2,4-Diamino-5-(1-adamantyl)-6-(1-butyl)pyrimidine (5). The above compound 9 (800 mg) was chlorinated in the usual manner with $POCl_3$–PCl_5. The 4-chloro compound was collected and added immediately to a solution of 100 ml of absolute EtOH saturated with NH_3 at 0°. The mixture was heated at 150° for 24 hr. The work-up procedure was the same as described for **4.** The crude diaminopyrimidine was stirred for 2 days in EtOH containing ethylsulfonic acid and subsequently the product was precipitated with Et_2O. Recrystallization from H_2O yielded 200 mg of product: mp 204–205°; uv max (absolute EtOH) 290, 237 mμ; uv min 263 mμ. *Anal.* ($C_{20}H_{34}N_4O_3S$) C, H, N, S.

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Phenol–Piperazine Adducts Showing Anthelmintic Properties

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It has already been established that complexes formed from *tert*-butylphenols and piperazine are new entities displaying neither the toxicities nor the activities of their constituents,[1] the former being reduced and the latter enhanced to such a degree that complexes containing as little as 15% piperazine in combination with an inactive or barely active phenol can exhibit activity equal or even superior to that of piperazine itself. *This is all the more surprising since, in the case of the salts formed from piperazine and carboxylic acids, activity is generally considered as being directly linked to their piperazine content.*[2] The major advantage of certain of these carboxylates over the hydrate is their reduced toxicity and improved activity due to their solubilization exclusively in the intestinal milieu.[3]

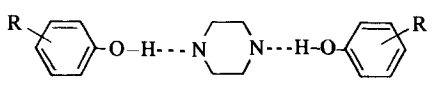
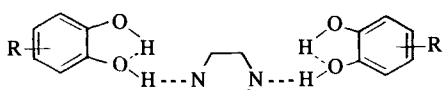
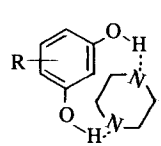
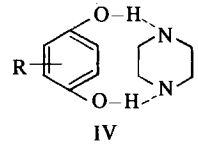
Consideration of the results of work on *tert*-butylphenol–piperazine adducts prompted the following questions. (a) Phenols bearing substituents other than *tert*-butyl have been reported as anthelmintic.[4] What are the activities of their addition compounds with piperazine? Is there, for these complexes, any relation between the nature and site of the substitution on the phenyl group and anthelmintic properties? (b) The activity of salts formed from acids and piperazine is largely dependent on the amount of piperazine present in the adduct, but this rule does not hold for salts formed from phenols. Is then the binding of phenols to piperazine of the salt type, and, if not, what is the nature of this bond? Is there a relationship between the strength of this liaison and anthelmintic activity? The present work is an attempt to elucidate these points.

Physicochemical Study. In view of the small number of phenols already reported as having anthelmintic properties, we conducted a systematic investigation of the influence of Me, *i*-Pr, *tert*-Bu, OMe, Cl, NO_2, and of a second OH as substituents on the phenolic moiety.

With the monophenols, if the binding is not of the ionic (or salt) type it can be by hydrogen bridging or can correspond to a resonance hybrid between the two forms. As seen in Table I (I), the ir spectra of the monophenol adducts show, in place of the phenolic band at 3600 cm^{-1}, a narrow, intense band in the 3300-cm^{-1} region. This shift toward the lower wavelengths, together with the absence of a band in the 2500-2700-cm^{-1} region characteristic of amine salts, indicates a hydrogen bonding.[5] The adduct formed from *o*-*tert*-butylphenol presents a second interesting band at 3260 cm^{-1}. The presence of this, and of another at 3300 cm^{-1}, corresponds most probably to a mixture of isomeric adducts of the forms *Z* and *E*. These bands have already been described for *o*-*tert*-butylphenol.[6]

With the diphenols, both the meta and para derivatives give rise to adducts linking one phenolic hydroxyl to one

Table I

No.	R	Formula	Mp, °C	Crystn solvent[a]	Yield, %	ν_{OH}	Shift[b]	Assays on *Syphacia obvelata* in mice: 200 mg/kg pd × 4 days α[c]	β	γ	200 mg/kg single dose α	β	γ
	 I				 II			 III			 IV		
					I. Adducts Prepared from Monophenols								
1[d]	2-Me	$C_{18}H_{26}N_2O_2$	56[e]	A	62	3260 (20)	354	28/31	90.3	9/40	30/36	83.3	4/40
2[d]	3-Me	$C_{18}H_{26}N_2O_2$	51	B	70.5	3280 (5)	331	27/30	90	0/30	14/20	70	0/20
3[d]	4-Me	$C_{18}H_{26}N_2O_2$	93	C	90.5	3260 (10)	352	17/17	100	3/20	17/19	89.4	1/20
4	2-Me, 3-Me	$C_{20}H_{30}N_2O_2$	98	B	80	3300 (6)	315	12/20	60	0/20	9/20	45	0/20
5	2-Me, 4-Me	$C_{20}H_{30}N_2O_2$	80	B	80	3300 (7)	314	17/20	85	0/20	14/20	70	0/20
6	2-Me, 5-Me	$C_{20}H_{30}N_2O_2$	107	D	82	3250 (20)	364	16/20	84.2	1/20	14/19	73.6	1/20
7	3-Me, 4-Me	$C_{20}H_{30}N_2O_2$	112	B	93	3270 (18)	344	18/20	90	0/20	14/20	70	0/20
8	2-Me, 4-Me, 6-Me	$C_{22}H_{34}N_2O_2$	54	B	68	3300 (12)	320	17/20	85	0/20	0/20	0	0/20
9	4-*i*-Pr	$C_{22}H_{34}N_2O_2$	78	B	73	3300 (25)	316	14/14	100	6/20	12/20	60	0/20
10	5-*i*-Pr, 2-Me	$C_{24}H_{38}N_2O_2$	80	B	70	3280 (16)	335	13/16	81.2	4/20	10/20	50	0/20
11	2-*i*-Pr, 3-Me	$C_{24}H_{38}N_2O_2$	82	B	80	3310 (10)	306	16/20	80	0/20	16/20	80	0/20
12	3-Me, 4-*i*-Pr	$C_{24}H_{38}N_2O_2$	70	B	62	3290 (12)	326	16/18	88.8	2/20	11/16	68.7	4/20
13	3-Me, 5-*i*-Pr	$C_{24}H_{38}N_2O_2$	64	B	67.5	3280 (40)	335	25/37	67.5	3/40	25/30	83.3	0/30
14[d]	3-Me, 6-*i*-Pr	$C_{24}H_{38}N_2O_2$	90	E	82	3280 (10)	335	8/19	42.1	1/20	2/18	11.1	2/20
15	3-Me, 6-*tert*-Bu	$C_{26}H_{42}N_2O_2$	145	C	87	3260 (10)	350	7/11	63.6	9/20	2/11	18.1	9/20
16	4-Me, 6-*tert*-Bu	$C_{26}H_{42}N_2O_2$	112	D	50	3260 (10)	349	15/19	78.9	1/20	14/19	73.6	1/20
17	2-OMe	$C_{18}H_{26}N_2O_4$	98	D	89	3280 (10)	276.5	6/20	30	0/20	6/20	30	0/20
18	3-OMe	$C_{18}H_{26}N_2O_4$	61	F	55	3280 (8)	330	16/20	80	0/20	18/19	94.7	1/20
19	4-OMe	$C_{18}H_{26}N_2O_4$	84	B	54	3280 (6)	335.5	16/20	80	0/20	5/20	25	0/20
20	3-OMe, 5-OMe	$C_{20}H_{30}N_2O_6$	112	G	66	3260 (14)	350	13/18	72.2	2/20	6/18	33.3	2/20
21	2-OMe, 4-allyl	$C_{24}H_{34}N_2O_4$	82	B	78	3270 (20)	290	17/20	85	0/20	11/20	55	0/20
22	2-Cl	$C_{16}H_{20}N_2O_2Cl_2$	71	A	58	3250 (22)	250	17/19	89.4	1/20	13/19	68.4	1/20
23	3-Cl	$C_{16}H_{20}N_2O_2Cl_2$	46	A	37	3280 (10)	324	30/32	93.7	8/40	29/33	87.8	7/40
24[d]	4-Cl	$C_{16}H_{20}N_2O_2Cl_2$	90	A	85	3300 (6)	310	23/30	76.6	10/40	18/29	62	1/30
25	2-Cl, 5-Cl	$C_{16}H_{18}N_2O_2Cl_4$	139	C	78.5	3400 (br)	150	22/26	84.6	4/30	7/20	35	0/20
26	2-Me, 4-Cl	$C_{18}H_{24}N_2O_2Cl_2$	72.5	A	59	3300 (10)	315	23/26	88.4	4/30	14/20	70	0/20
27[d]	2-NO_2	$C_{10}H_{17}N_3O_4$[f,g]	81[h]	H	52	3150 (br)	90	21/26	80.7	4/30	12/20	60	0/20
28[d]	3-NO_2	$C_{16}H_{20}N_4O_6$[f]	100	G	71.5	3270 (20)	329	22/28	78.5	2/30	10/20	50	0/20
29[d]	4-NO_2	$C_{16}H_{22}N_4O_7$[f]	142[i]	1	90.5	3280 (20)	314	16/19	84.2	1/20	10/19	52.6	1/20
30	2-NO_2, 5-NO_2	$C_{16}H_{20}N_6O_{11}$[g]	205	J	63.5	3600 (20)	−35	4/20	20	0/20	3/20	15	0/20
31	2-Me, 5-NO_2	$C_{18}H_{24}N_4O_6$	111	K	64.5	3280 (20)	340	26/30	86.6	0/30	16/20	80	0/20
32	3-Me, 6-NO_2	$C_{11}H_{17}N_3O_3$[g]	110	G	57.5	3260 (5)	−30	28/29	96.5	1/30	18/20	90	0/20
33	4-Me, 6-NO_2	$C_{18}H_{26}N_4O_7$[f]	112	B	81	3210 (br)	40	19/20	95	0/20	9/20	45	0/20

34[d]		$C_{10}H_{16}N_2O_2$[g]	144[i]	L	72	3250 (30)	319	20/27	74	3/30	13/20	65	0/20
35	4-Me	$C_{18}H_{26}N_2O_4$	132	J	61	3240 (br)	310	12/20	60	0/20	8/20	40	0/20
36	4-NO_2	$C_{16}H_{20}N_4O_8$	210	J	75	3150 (br)	150	5/19	26.3	1/20	5/20	25	0/20
37	3-*tert*-Bu, 5-*tert*-Bu	$C_{32}H_{54}N_2O_2$	166	G	56.5	3280 (10)	340	9/16	56.2	4/20	14/16	87.5	4/20
						3460 (26)							
					III. Adducts Prepared from *m*-Diphenols								
38[d,k]		$C_{10}H_{16}N_2O_2$	182[l]	J	61	3260 (20)	349	18/20	90	0/20	17/20	85	0/20
39	2-Me	$C_{11}H_{18}N_2O_2$	160	M	58	3310 (5)	305	18/19	94.7	1/20	19/20	95	0/20
40	2-Cl	$C_{10}H_{15}N_2O_2Cl$	149	G	55.5	3240	302	16/20	80	0/20	7/20	35	0/20
41	4-*tert*-Bu, 6-*tert*-Bu	$C_{18}H_{32}N_2O_2$	172	J	54	3300 (15)	310	18/18	100	2/20	19/19	100	1/20
42	4-Cl, 6-Cl	$C_{10}H_4N_2O_2Cl_2$	184	J	20	3150 (br)	390	15/18	83.3	2/20	9/12	75	8/20
					IV. Adducts Prepared from *p*-Diphenols								
43[d]		$C_{10}H_{16}N_2O_2$	176[m]	J	78	3260 (30)	357	19/20	95	0/20	17/20	85	0/20
44	2-*tert*-Bu, 5-*tert*-Bu	$C_{18}H_{32}N_2O_2$	190	B	70	3330 (16)	385	20/20	100	0/20	18/20	90	0/20

[a] A = cyclohexane; B = pentane; C = heptane; D = hexane; E = petroleum ether; F = BzH + cyclohexane (3:7); G = BzH; H = H_2O; I = BzH + EtOH (8:2); J = EtOH; K = AcOEt; L = Me_2CO + MeOH (7:3); M = Me_2CO. [b] ν_{OH} phenol − ν_{OH} adduct. [c] In the last six columns, α = number of deparasitized mice/number of surviving mice; β = percentage of deparasitation; γ = number of mice that died during test/number of mice tested. [d] Already described.[7] [e] Lit. mp 53–54°. [f] Crystallized with 1 mol of water. [g] Corresponds to only 1 mol of phenol per piperazine. [h] Lit. mp 68–71°. [i] Lit. mp 107–110°. [j] Lit. mp 101–104°. [k] Already described.[8] [l] Lit.[8] mp 187–189°; lit.[7] mp 190–193°. [m] Lit. mp 198–201°.

piperazine nitrogen, *i.e.*, mole:mole, while the new disubstituted *o*-diphenols, like the monophenols, require two hydroxylated molecules for one piperazine mole. The ir spectra of adducts formed from *o*-diphenols show a broad band at 3200 cm^{-1} in place of the narrow band at 3300 cm^{-1}. This broad band corresponds to complex liaisons, and it is more than likely therefore that intra- and intermolecular bindings exist as figured in the formula in Table I (II).

The ir spectra were all recorded in the solid state; in solution the adducts might dissociate, especially when the phenol-piperazine bond is weak or if it corresponds to a resonance hybrid described earlier or to ions. The reference phenols, however, were in solution in CCl_4 ($10^{-4}M$/l.).

Results and Discussion

The effect of a single dose (200 mg/kg *per os*) and of the same dose repeated during 4 days was determined for each compound or *Syphacia obvelata* in mice according to a known method.[1]

Multiple Doses. Monophenols [Table I (I)]. The ortho-, meta-, and para-monomethylated compounds (**1**, **2**, and **3**) all show a high degree of activity† (more than 85% deparasitation‡), which is more or less paralleled in the dimethylated products **4–8** with the exception of 2,3-dimethylphenol which is considerably less active. The methoxy compounds **17–21** show potency when meta and para substituted, to a lesser degree when substituted in the 3,5 position, and are practically inactive when ortho substituted. The chloro compounds **22**, **23**, and **26** lie in the active region, and **25** approaches our 85% limit, but **24** is less active (76.6%). The nitro derivatives are active when they bear an additional methyl group (**31**, **32**, and **33**), approach our limit when the nitro is in the para position (**29**), but are practically devoid of activity when there are two nitro groups in the 2,5 position (**30**). It is interesting to note that this last dinitro derivative has a negative ir shift, which might perhaps have accounted for its nonactivity had not **32** (active) shown a similar negative shift. Isomers of thymol **10–14** are less active than the simple methyl derivatives; thus, addition of an isopropyl is valueless, as is that of a *tert*-butyl (**15** and **16**), and both may at times even have an adverse effect (**14** and **15**). Neither does the presence of a chloro or of a nitro group in addition to a methyl one present any obvious benefit as of now; all these second substitutions would be justifiable only if a reduction in dose of the disubstituted compounds maintained the activity in its entirety and considerably lessened the toxicity, in comparison with the monosubstituted derivatives.

Diphenols. None of the complexes formed with substituted *o*-phenols [Table I (II)], whether bearing a methyl, nitro, or *tert*-butyl group, proved of interest. In contrast, the adducts formed with *m*- [Table I (III)] and *p*-diphenols [Table I (IV)] were all within or close to the active region, whatever the substituents.

To summarize, compounds **1–3**, **5**, **7–9**, **12**, **21–23**, **26**, **31–33**, **38**, **39**, **41**, **43**, and **44** all show an activity superior

†D. K. Chae[7] prepared 24 salts of piperazine with phenols or with acids but described the activity, measured by an *in vitro* method, of only seven of them. It is strange that in this case, as in that of Short and Elslager,[8] highly active compounds were synthesized but no mention was made of their activity nor, to our knowledge, were patents taken out for them.[9] Some of the compounds described by these two groups of authors are investigated in the present work.

‡The choice of 85% is clearly arbitrary, there being no real difference between the activity of compound 5 (selected) and compound 6 (rejected).

or equal to an 85% deparasitation, while piperazine under the same conditions displays only 60–70% activity.

Single Dose. As with the multiple doses, only substances showing activity equal to or higher than 85% were retained. These comprised the adducts prepared from 4-methyl-, 3-methoxy-, 3-chloro-, and 3-methyl-6-nitrophenol, di-*tert*-butyl-3,5-pyrocatechol, resorcine, 2-methylresorcine and di-*tert*-4,6-resorcine, and hydroquinone and di-*tert*-2,5-hydroquinone.

A study is currently underway in regard to the active dose limits and possible side effects. Preliminary results suggest that the di-*tert*-butylphenols **41** and **44** will show promise in this respect, despite the fact that they contain less than 30% piperazine.

Structure–Activity Relationships. Although at the start of this investigation we were attracted by the possibility of a relationship between biological activity and the strength of the hydrogen bond linking the phenol to piperazine, no clear correlation seems to emerge from the results reported here.

Experimental Section

Melting points were determined on a Reichert microscope and are uncorrected. The method used for activity determinations was described in an earlier paper.[1] Ir spectroscopic measurements were performed on a Perkin-Elmer 457 instrument for potassium bromide disks (0.5 mm). Wavelengths are given within ±3 cm^{-1} after calibration of the band at 3027.1 of polystyrene.

Method of Synthesis. To 1 mol of phenol dissolved in toluene, a corresponding quantity of piperazine was added. Either a spontaneous crystallization occurred immediately or the mixture was heated to the boiling point and left to cool, whereupon crystallization took place. In the rare cases where crystallization did not then occur, the solvent was evaporated and the residue crystallized from the appropriate solvent.

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A Note on Molecular Orbital Calculations of Furfuryltrimethylammonium

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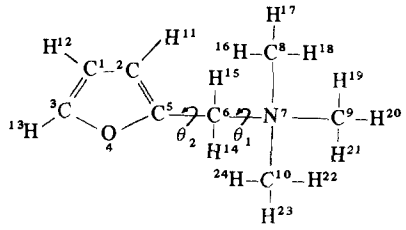
Furfuryltrimethylammonium (I, FTA), a potent muscarinic, exhibits, in general, the pharmacological characteristics of methacholine but has been especially effective in the treatment of urinary retention due to its direct action on the bladder.[1]

If a muscarinic agonist is to produce its activity *via* direct interaction with the muscarine receptor, it is reasonable that the stereochemistry of its active centers approximates that of other muscarine-like agonists.[2-4] Kier,[3] using EHT-MO, has described the preferred conformation of ACh,



I

muscarone, and muscarine. Three active centers were predicted for any muscarine-like compound—a quaternary N, -O-, and C=O or COH. It is interesting to note the presence of two of these centers in FTA (quaternary N and the -O-) but an apparent lack of Kier's third site. To clarify this matter we completed a molecular orbital study on FTA using Hoffmann's extended Hückel theory.[5]

Methods. Hoffmann's extended Hückel theory[5] (EHT) was employed in this study. The two required programs were supplied by the University of Indiana's Quantum Chemistry Program Exchange. Bond angles and bond lengths are of standard magnitude. The planarity of the furan ring, however, produces slightly modified molecular parameters.[6]

Other EHT parameters, which include a choice of K, Slater exponents, and 2 s and 2 p Coulomb integrals, are chosen consistent with Kier.[3] The FTA system shows two torsion angles: θ_1 = C(8)-N(7)-C(6)-C(5) and θ_2 = N(7)-C(6)-C(5)-C(2). As in previous studies,[2-4] the 3-methyl groups attached to the quaternary N are held in a staggered conformation. N(7)-C(6)-C(5)-C(2) is varied from 0 to 180° in increments of 30°. Due to the molecular symmetry the second 180° rotation would yield duplicate results.

The computations were made on the IBM 370 Model 165. All calculations were performed in double precision and PL/I and FORTRAN IV were the programming languages used.

Results

One conformation was determined to be the minimum energy state, N(7)-C(6)-C(5)-C(2) = 90°, with a 1.3 eV energy barrier (Figure 1). It should be stated that the potential well is overestimated in EHT but the energy barrier

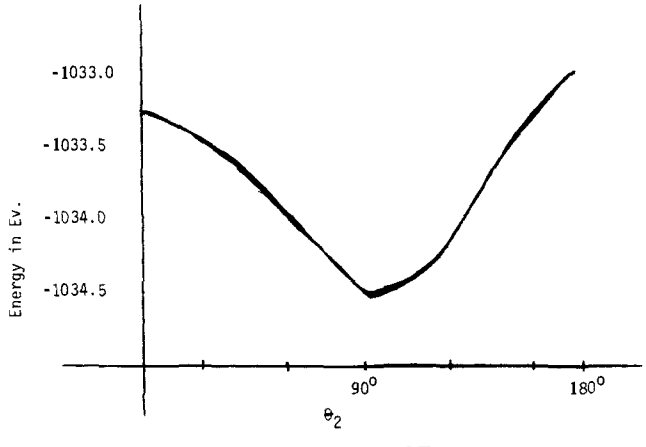


Figure 1. Total energy *vs.* conformation of FTA.

Table I. Interatomic Distances in the FTA System Determined from EHT Calculations

d (1,4)	2.2 Å
d (1,7)	4.5 Å
d (4,7)	3.2 Å
d (4,2)	2.2 Å
d (7,2)	2.4 Å