J. C. Wilker, and W. J. Novick, *Pharmacologist*, **17**, 226 (1975); M. Messer, D. Farge, J. C. Guyonnet, C. Jeanmart, and L. Julou, *Arzneim.-Forsch.*, **19**, 1193 (1969); A. W. Pircio, M. E. Bierwagen, W. E. Strofe, and W. D. Nicolosi, *Arch. Int. Pharmacodyn. Ther.*, **199**, 151 (1972); E. T. Steller, P. A. Diassi, D. Gerschutz, D. Meikle, J. Moetz, P. A. Principe, and S. D. Levine, *J. Med. Chem.*, **15**, 1029 (1972).

(4) Bristol Myers Co., Netherlands Patent Application 66-09235 [*Chem. Abstr.*, **67**, 82215u (1967)].

(5) J. K. Harrington, J. E. Robertson, D. C. Kvam, R. R. Hamilton, K. T. McGurran, R. J. Trancik, K. F. Swingle, G. G. Moore, and J. F. Gerster, *J. Med. Chem.*, **13**, 137 (1970).

(6) G. Lambelin, N. P. Buu-Hoi, H. Brouilhet, M. Gautier, C. Gillet, J. Roba, and J. Thiriaux, *Arzneim.-Forsch.*, **18**, 1404 (1968).

(7) T. Y. Shen in "Non-Steroidal Antiinflammatory Drugs", S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1965, p 13.

(8) (a) L. Julou, G. Guyonnet, R. Ducrot, C. Garret, M. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.*, **2**, 259 (1971); (b) A. Allais, G. Rousseau, J. Meier, R. Deraedt, J. Benzoni, and L. Chifflot, *Eur. J. Med. Chem.-Chim. Ther.*, **9**, 381 (1974).

(9) W. Tochtermann, G. Schnabel, and A. Mannschreck, *Justus Liebigs Ann. Chem.*, **705**, 169 (1967); W. Tochtermann, U. Walter, and A. Mannschreck, *Tetrahedron Lett.*, 2981 (1964).

(10) See H. L. Slates and N. L. Wendler, *J. Med. Chem.*, **8**, 886 (1965), for an alternative formulation of the dibenztropylium compound obtained by reacting dibenzsuberone with phosphorus pentachloride.

(11) G. Thompson and J. Collins, Syntex Institute of Pharmaceutical Sciences, unpublished results.

(12) (a) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962), modified as described in ref 12b; (b) A. P. Roszkowski, W. H. Rooks II, A. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114 (1971).

(13) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1959), modified as described in ref 12b.

(14) D. G. Kaiser, G. J. Vangeissen, R. J. Reischer, and W. J. Wechter, *J. Pharm. Sci.*, **65**, 269 (1976).

(15) G. Nannini, P. N. Giraldi, G. Molgora, G. Biasoli, F. Spinelli, W. Logemann, E. Dradi, G. Zanni, A. Buttinoni, and R. Tomassini, *Arzneim.-Forsch.*, **23**, 1090 (1973); H. Miyamatsu, S. Ueno, M. Shimizu, J. Hosono, M. Tomari, K. Seida, T. Suzuki, and J. Wada, *J. Med. Chem.*, **17**, 491 (1974).

(16) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).

(17) C. M. Pearson, *Proc. Soc. Exp. Biol. Med.*, **91**, 95 (1956).

(18) J. G. Lombardino, I. G. Otterness, and E. H. Wiseman, *Arzneim.-Forsch.*, **25**, 1629 (1975).

(19) See, for example, K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Tsubokawa, H. Kojima, and A. Kasahara, *J. Med. Chem.*, **19**, 941 (1976).

(20) All animals were obtained from Simonsen Laboratories, Inc., Gilroy, Calif. Rats were designated as "Sprague–Dawley derived". Mice were designated as "Swiss–Webster".

(21) D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, N.Y., 1964.

Pyrazolodiazepines. 2. 4-Aryl-1,3-dialkyl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones as Antianxiety and Anticonvulsant Agents

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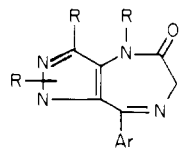
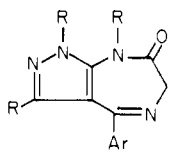
A series of 4-aryl-1,3-dialkyl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones was synthesized and screened for psychotropic activity. In animals, a number of these pyrazolodiazepinones had strong CNS effects similar to diazepam. One compound, 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (**54**), is being studied in the clinic as a component of a new animal anesthetic, Tilazol.

A number of years ago, we became interested in preparing 1,4-diazepines fused to a heterocylic system instead of a benzene system, a type of compound that was relatively unexplored at that time. An earlier paper[1] described the initial results of that work, a series of 8-arylpyrazolo[4,3-*e*][1,4]diazepin-5(1*H*)-ones (I) which were active CNS agents. An isomeric series, the 4-aryl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones (II), was developed concurrently and is the subject of this paper.[2] 1,4-Diazepines fused to thiophenes,[3a] imidazoles,[3b] pyrazines,[3c] pyrroles,[3d] and isoxazoles[3e] have been discussed. However, of all these systems, the pyrazolodiazepines appear to be most accessible and amenable to the transformations that have been performed on the 1,4-benzodiazepines.



I

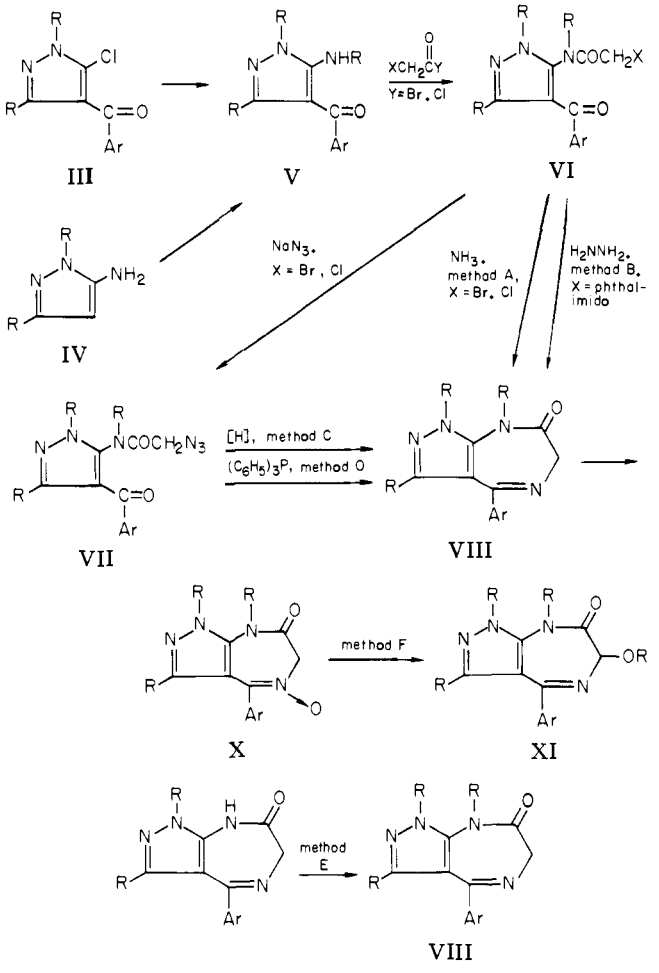


II

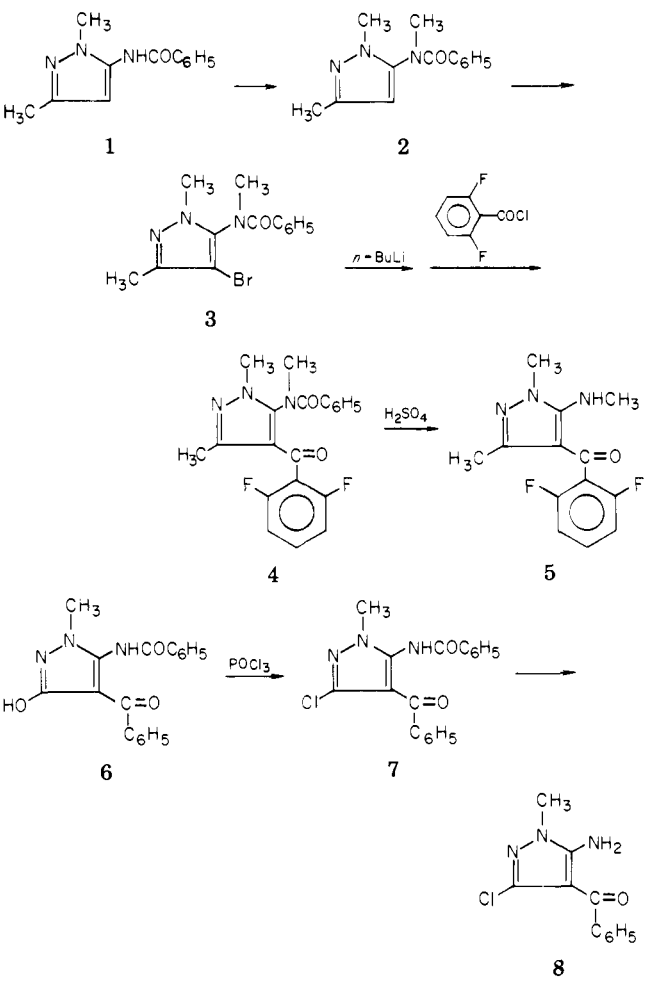
Key intermediates to II were the amino ketones V which were generally prepared by treatment of (1,3-dialkyl-5-chloro-1*H*-pyrazol-4-yl)arylmethanones[4] (III) with amines or by a Friedel–Crafts aroylation of 1,3-dialkyl-1*H*-pyrazol-5-amines IV (Scheme I). The preparation and physical properties of many of the amino ketones V used as intermediates were described in the patent literature[5] and are the subject of a manuscript in preparation. The detailed procedures for several amino ketones not described[5] have been included in the Experimental Section to illustrate approaches used for the synthesis of special compounds in this series. Two of these procedures are shown in Scheme II to prepare amino ketones **5** and **8**.

Elaboration of the pyrazolodiazepinones from the amino ketones V was accomplished by acylation with a potential glycyl radical and conversion to the uncharacterized aminoacetamide by processes of aminolysis, hydrazinolysis, or hydrogenation. The uncharacterized 2-aminoacetamides cyclized under the conditions of the reaction. These methods have been used previously for benzodiazepines. Acylation of the weakly nucleophilic 1*H*-pyrazol-5-amine system was accomplished only with the use of stable acid chlorides, haloacetyl halides, phthalimidoacetyl chloride, and azidoacetyl chloride. Acylation with esters, anhydrides, or activated glycyl intermediates useful in peptide synthesis failed. Alkylation of the amide nitrogen (method

Scheme I



Scheme II



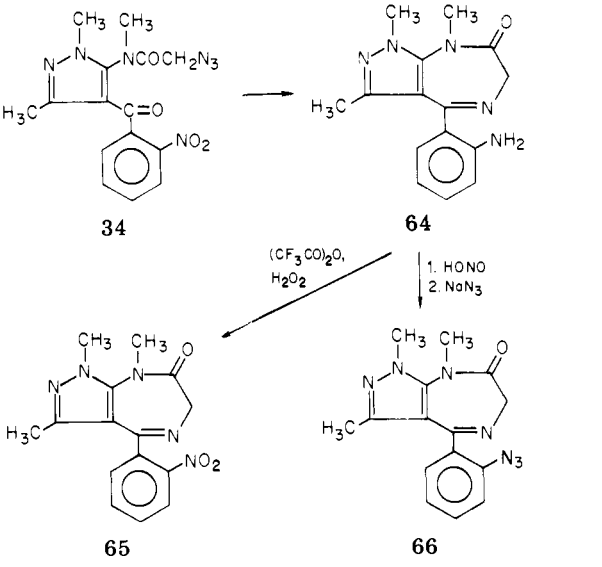
E) was achieved very often in poor to moderate yields. If the alkylated product was the primary goal, the most efficient process was to incorporate the alkyl group at an early stage, for example, compound **2**, Scheme II. The most dependable overall procedure for pyrazolodiazepinone synthesis was via acylation of the amino ketone by bromoacetyl bromide (or chloroacetyl chloride), conversion to the azidoacetamide, and catalytic hydrogenation of the azide in glacial acetic acid with cyclization to the diazepinones (method C).

Hydrogenation [a nonreductive cyclization procedure using triphenylphosphine presumably would have given the nitro compound **65** directly, but this method was not applied to this particular compound (see experimental method E)] of the azidoacetamide **34** resulted in reduction of the nitro group. The amine **64** was reoxidized[6] to the desired nitro compound **65**, and a sample of **64** was converted to the azido compound **66** by diazotization in the presence of sodium azide (Scheme III).

Several of these pyrazolodiazepinones (e.g., **46** and **54**) were converted to 6-hydroxy derivatives XI (**94** and **97**) by rearrangement of the corresponding *N*-oxides X in acetic anhydride (method F).

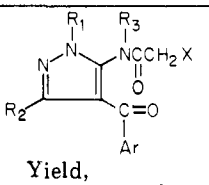
Biological Activity. The compounds were tested in mice and rats for potential tranquilizer and anticonvulsant activity according to previously described procedures. These included antagonism to pentylenetetrazole (PM)[7] and by the drug's effectiveness in abolishing the inhibited behavior of rats placed in an anxiety-producing environment as measured by consumption of a milk preparation (AX).[8] Selected compounds were evaluated further by determining their effect on conditional conflict in

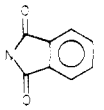
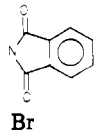
Scheme III



Skinner boxes and their effect upon intracranial self-stimulation.[9] A number of compounds in this series, including **46**, **49**, **51**, **54**, **56**, **57**, **78**, **80**, **97**, and **99**, have antianxiety and anticonvulsant activity comparable to diazepam according to these two animal screens. Comparison of these compounds with those of lesser activity shows that methyl and ethyl are the optimal groups attached to the pyrazole nucleus. The substitution pattern of the 4-phenyl substituent is the same as that observed for the "hanging" phenyl of the 1,4-benzodiazepines; i.e.,

Table I. *N*-(1,3-Dialkyl-4-aryl-1*H*-pyrazol-5-yl)acetamides



Compd no.	R_1	R_2	R_3	Ar	X	Yield, %	Mp, °C	Purifn solvent	Formula	Analyses[a]
9	CH_3	H	H	C_6H_5	Br	80	173-175	EtOAc	$C_{13}H_{12}BrN_3O_2 \cdot HBr$	C, H, N
10	CH_3	CH_3	H	C_6H_5	Br	92	175 dec	EtOH-ether	$C_{14}H_{14}Br_2N_3O$	H, N; C[b]
12	CH_3	CH_3	CH_3	C_6H_5	N_3	85	105-107	EtOAc-petr ether	$C_{15}H_{16}N_6O_2$	C, H, N
11	CH_3	CH_3	CH_3	C_6H_5	Br	82	122-124	2-PrOH	$C_{15}H_{16}BrN_3O_2$	C, H, N
13	CH_3	CH_3	CH_3	C_6H_5		55	178-180	EtOAc	$C_{23}H_{20}N_4O_4$	C, H
14	CH_3	C_2H_5	H	C_6H_5	Br	93	188-189	2-PrOH-ether	$C_{15}H_{16}BrN_3O_2 \cdot HBr$	C, H, N
15	CH_3	C_2H_5	CH_3	C_6H_5	N_3	50	119-121	EtOAc-petr ether	$C_{16}H_{18}N_6O_2$	C, H; N[c]
16	CH_3	CH_3	H	$2\text{-}ClC_6H_4$	Br	83	153-155	$CHCl_3$	$C_{14}H_{13}BrClN_3O_2$	C, H, N
17	CH_3	CH_3	CH_3	$2\text{-}ClC_6H_4$	N_3	72	99-101	Ether	$C_{15}H_{15}ClN_6O_2$	C, H, N
18	CH_3	CH_3	CH_3	$2\text{-}ClC_6H_4$	Cl	74	86-88	Ether-petr ether	$C_{15}H_{15}Cl_2N_3O_2$	C, H, N
19	CH_3	CH_3	H	$3\text{-}ClC_6H_4$	Br	67	155-157	Ether	$C_{14}H_{12}BrClN_3O_2$	H, N; C[d]
20	CH_3	CH_3	H	$3\text{-}ClC_6H_4$	N_3	75	138-140	Ether	$C_{14}H_{13}ClN_6O_2$	C, H, N
21	CH_3	CH_3	H	$2\text{-}FC_6H_4$	Br	90	190-192	2-PrOH	$C_{14}H_{13}BrFN_3O_2$	C, H, N
22	CH_3	CH_3	CH_3	$2\text{-}FC_6H_4$	Br	89	112-114	Ether	$C_{15}H_{15}BrFN_3O_2$	C, H, N
23	CH_3	CH_3	CH_3	$2\text{-}FC_6H_4$	N_3	93	124-125	EtOAc-petr ether	$C_{15}H_{15}FN_6O_2$	C, H, N
24	CH_3	CH_3	CH_3	$2\text{-}FC_6H_4$	Cl	92	132-133	EtOAc-petr ether	$C_{15}H_{15}FClN_3O_2$	C, H, N
25	CH_3	C_2H_5	H	$2\text{-}FC_6H_4$	Br	95	178-181	2-PrOH	$C_{15}H_{15}BrFN_3O_2$	C, H, N
26	CH_3	C_2H_5	H	$2\text{-}FC_6H_4$	N_3	67	143-145	EtOAc-petr ether	$C_{15}H_{15}FN_6O_2$	C, H, N
27	CH_3	C_2H_5	H	$3\text{-}FC_6H_4$	Br	97	196-198	2-PrOH-ether	$C_{15}H_{15}BrFN_3O_2 \cdot HBr$	C, H, N
28	CH_3	C_2H_5	H	$4\text{-}FC_6H_4$	Br	96	160	2-PrOH-ether	$C_{15}H_{15}BrFN_3O_2 \cdot 0.5HBr$	C, H
29	CH_3	CH_3	CH_3	$2\text{-}BrC_6H_4$	Br	91	123-125	Ether	$C_{15}H_{15}Br_2N_3O_2$	C, H, N
30	CH_3	CH_3	CH_3	$2\text{-}BrC_6H_4$	N_3	90	92-94	Ether-petr ether	$C_{15}H_{15}BrN_6O_2$	C, H, N
31	CH_3	CH_3	CH_3	$2,6\text{-}F_2C_6H_3$	Br	76	115-117	Ether	$C_{15}H_{19}F_2BrN_3O_2$	C, H, N
32	CH_3	CH_3	CH_3	$2,6\text{-}F_2C_6H_3$	N_3	86	90-93	Ether	$C_{15}H_{14}F_2N_6O_2$	C, H, N
33	CH_3	CH_3	CH_3	$2\text{-}NO_2C_6H_4$	Cl	62	120-122	Ether	$C_{15}H_{15}ClN_4O_4$	C, H, N
34	CH_3	CH_3	CH_3	$2\text{-}NO_2C_6H_4$	N_3	92	118-120	Ether	$C_{15}H_{15}N_7O_4$	C, H, N
35	CH_3	Cl	H	C_6H_5	Br	50	155-158	Ether	$C_{13}H_{11}BrClN_3O_2$	C, H, N
36	CH_3	CH_3O	CH_3	$2\text{-}FC_6H_4$	Br	95	113-115	Ether	$C_{15}H_{15}FBrN_3O_3$	C, H, N
37	CH_3	CH_3O	CH_3	$2\text{-}FC_6H_4$	N_3	80	128-130	EtOAc-petr ether	$C_{15}H_{15}FN_6O_3$	C, H, N
38	CH_3	C_2H_5	H	$2\text{-}ClC_6H_5$		71	173-175	Ether	$C_{23}H_{19}ClN_4O_4$	H; C[e]
39	CH_3	$n\text{-}C_3H_7$	H	$2\text{-}ClC_6H_4$	Br	80	164-166	EtOH-ether	$C_{16}H_{18}BrN_3O_2 \cdot HBr$	C, H
40	CH_3	$n\text{-}C_4H_9$	H	$2\text{-}ClC_6H_4$	Br	90	183-185	EtOAc	$C_{17}H_{19}BrN_3O_2 \cdot HBr$	C, H
41	$n\text{-}C_4H_9$	CH_3	H	$3\text{-}ClC_6H_4$	Br	72	132-140	EtOAc	$C_{17}H_{20}BrClN_3O_2 \cdot HBr$	C, H
42	$c\text{-}C_6H_{11}$	CH_3	H	$2\text{-}ClC_6H_4$	Br	90	226-228	EtOAc	$C_{19}H_{21}BrClN_3O_2 \cdot HBr$	C, H
43	C_6H_5	CH_3	H	$2\text{-}ClC_6H_4$	Br	90	188-190	2-PrOH	$C_{19}H_{15}BrClN_3O_2$	C, H, N

[a] Analyses for the elements indicated were within ±0.04% of the theoretical values. [b] C: calcd, 40.31; found, 40.89. [c] N: calcd, 25.75; found, 26.72. [d] C: calcd, 45.60; found, 46.04. [e] C: calcd, 61.26; found, 60.00.

substitution in the 2 position by Cl or F increases potency, and 3- and particularly 4-substitution decreases activity. In contrast to the SAR of the previous pyrazolodiazepinone series,[1] but *like* the benzodiazepines, alkylation of the amide nitrogen with methyl gives compounds with the most activity. Compounds in a higher oxidation state (**94** and **97**) and metabolites[11] of the parent pyrazolodiazepines are active. On the basis of qualitative structure–activity relationships, potency, and possibly stronger depressant character, this series resembles the diazepam series more closely than the 8-arylpyrazolodiazepinones.[1]

The most potent member of this series, 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]-diazepin-7(1*H*)-one (**54**), appears to be 5–10 times as potent as diazepam as an antianxiety agent. Because of its strong anticonvulsant properties and tranquilizing activity, **54** is being studied clinically as a component of a new animal anesthetic, Tilazol.[10] The comparative metabolism of **54** in rat, dog, and monkey has been reported.[11]

Experimental Section

The melting points were determined in a Thomas-Hoover apparatus. IR spectra were determined on a Beckman IR-9 spectrometer. NMR spectra were recorded with a Varian A-60 instrument with Me_4Si as internal standard.

2-Bromo-*N*-[4-(2-fluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-*N*-methylacetamide (22). A solution of 120 g (0.48

mol) of [1,3-dimethyl-5-(methylamino)-1*H*-pyrazol-4-yl](2-fluorophenyl)methanone[5] (V, $R_1 = R_2 = R_3 = CH_3$; Ar = 2-FC_6H_4) in 1 L of 1,3-dichloroethane was cooled to 10 °C and mixed with 280 mL of water and 30 g (0.3 mol) of calcium carbonate. To the stirred mixture was added 100 g (0.485 mol) of bromoacetyl bromide at 10–12 °C. After stirring an additional 2 h, the mixture was filtered, the organic layer was separated and dried over magnesium sulfate, and the solvent was evaporated in vacuo. The semisolid residue was slurried in 500 mL of cyclohexane and the product collected by filtering to yield 158 g (89%) of **22**: mp 112–114 °C; NMR ($CDCl_3$) δ 7.0–7.8 (Ar), 3.75 (CH_3N, CH_2Br), 3.1 (CH_3N), 2.1 (CH_3C).

2-Azido-*N*-[4-(2-fluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-*N*-methylacetamide (23). A solution of 158 g (0.43 mol) of compound **22** in 420 mL of *N,N*-dimethylformamide was treated in portions with 30 g (0.46 mol) of sodium azide, as the temperature rose to 38 °C. The mixture was stirred at 35–40 °C for 3 h and then poured slowly with stirring into 5.5 L of ice water. The precipitated solid was collected by filtration, washed with water, and air-dried to yield 137 g (94%) of **23**: mp 123–125 °C; NMR ($CDCl_3$) δ 7.0–7.8 (m, Ar), 3.7 (s, CH_3N), 3.6–4.0 (q, CH_2N_3), 3.05 (s, CH_3N), 2.0 (s, CH_3C).

4-(2-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (54). Method C. A solution of 164 g (0.5 mol) of **23** in 820 mL of glacial acetic acid was shaken in the presence of 3 g of 5% Pd/C catalyst in an atmosphere of hydrogen (50 psi) for 7 h. The hydrogenation vessel was vented four times during the course of the reaction and recharged with hydrogen. The catalyst was removed by filtering and the solvent was evaporated in vacuo. The residual oil was dissolved in 550 mL of 1 N HCl and extracted with ethyl acetate. The aqueous layer was mixed with 400 mL of dichloromethane and made basic with 50% aqueous sodium hydroxide. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated in vacuo. The semisolid residue was warmed in 250 mL of toluene and filtered to yield 123 g (86%) of **54**: mp 183–185 °C; NMR ($CDCl_3$) δ 7.0–7.8 (m, 4-HAr), 3.8 (s, CH_3N), 3.8–5.05 (q, NCH_2CO), 3.32 (s, CH_3N), 1.8 (s, CH_3C).

Method D. A mixture of **23** (3.3 g, 0.01 mol) and 2.6 g (0.01 mol) of triphenylphosphine in 9 mL of toluene and 1 mL of glacial acetic acid was stirred as vigorous gas evolution occurred, the temperature rose to 50 °C during 10 min, and a clear solution was obtained. The mixture was stirred overnight as a new solid began to precipitate after 0.5 h. The product, **54**, weighed 2.3 g (81%), mp 180–183 °C.

***N*-(4-Benzoyl-3-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-bromoacetamide Hydrobromide (14).** To a solution of **23** g (0.1 mol) of (5-amino-3-ethyl-1-methyl-1*H*-pyrazol-4-yl)phenylmethanone[5] in 200 mL of hot (60 °C) ethyl acetate was added at a fast droprate 20 g (0.1 mol) of bromoacetyl bromide. The mixture was stirred under reflux about 5 min and then another hour at room temperature. The mixture was filtered; the filter cake was washed with ethyl acetate and then ether to yield 40.5 g (93%) of **14**, mp 188–189 °C.

3-Ethyl-6,8-dihydro-1-methyl-4-phenylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (48). Method A. Liquid ammonia (75 mL) was added to a solution of 16 g (0.036 mol) of **14** dissolved in 100 mL of dichloromethane. The mixture was stirred under reflux 5 h and then treated with 75 mL of water. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallized from methanol to give 3.5 g (35%) of **48**: mp 268–270 °C; NMR ($CDCl_3$) δ 8.8 (s, NH), 7.5 (m, 5-HAr), 4.3 (s, NCH_2CO), 3.8 (s, CH_3N), 2.0–2.4 (q, CH_2C), 1.0 (t, CH_3C).

3-Ethyl-6,8-dihydro-1,8-dimethyl-4-phenylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (49). Method E. Sodium hydride (1.5 g, 0.025 mol, of a 50% dispersion in oil) was added to a solution of 6.7 g (0.025 mol) of **48** in 30 mL of *N,N*-dimethylformamide. The mixture was stirred 0.5 h and 5 g of iodomethane was added. After stirring at room temperature for 2 h, the mixture was diluted with 300 mL of ether and washed several times with water. The ether solution was dried over $MgSO_4$ and concentrated to about 70 mL on the steam bath as a colorless solid precipitated, 2.1 g (30%) of **49**, mp 191–193 °C.

***N*-(4-Benzoyl-1,3-dimethyl-1*H*-pyrazol-5-yl)-1,3-dihydro-*N*-methyl-1,3-dioxo-2*H*-isoindole-2-acetamide (13).** A solution of 11 g (0.05 mol) of phthaloylglycyl chloride in 50 mL of warm ethyl acetate was added at a rapid droprate to 11 g (0.05 mol) of [1,3-dimethyl-5-(methylamino)-1*H*-pyrazol-4-yl]-phenylmethanone[5] in hot ethyl acetate. The mixture was stirred under reflux 1 h as a solid separated. The mixture was cooled and filtered to yield 11.5 g (55%) of **13**, mp 178–180 °C.

6,8-Dihydro-1,3,8-trimethyl-4-phenylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (46). Method B. A mixture of 8.2 g (0.02 mol) of **13** and 1.2 g (0.04 mol) of anhydrous hydrazine in 150 mL of dichloromethane was stirred under reflux 5 h and filtered from the insolubles. The filtrate was evaporated in vacuo. The residue was extracted with 75 mL of 1 N HCl. The aqueous extract was made basic with concentrated ammonium hydroxide to precipitate a tan solid. The crude product was crystallized from toluene to give 3.2 g (60%) of **46**, mp 183–185 °C.

2-Chloro-*N*-methyl-*N*-[4-(2-nitrobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]acetamide (33). A solution of 17 g (0.062 mol) of [1,3-dimethyl-5-(methylamino)-1*H*-pyrazol-4-yl](2-nitrophenyl)methanone (V, $R_1 = R_2 = R_3 = CH_3$; Ar = 2-$NO_2C_6H_4$) in 200 mL of 1,2-dichloroethane was acylated with 8.5 g (0.075 mol) of chloroacetyl chloride in the presence of 10 g of calcium carbonate and 40 mL of water as described for the preparation of **22** to give 13.5 g (62%) of **33**, mp 120–122 °C.

[1,3-Dimethyl-5-(methylamino)-1*H*-pyrazol-4-yl](2-nitrophenyl)methanone was prepared in moderate yield (46%) by refluxing a solution of 37 g (0.132 mol) of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-nitrophenyl)methanone in a mixture of 250 mL of methanol and 250 mL of 40% aqueous methylamine overnight. The mixture was evaporated in vacuo and the residue was partitioned in 250 mL of 2 N HCl and 200 mL of ethyl acetate. The aqueous layer was made basic with concentrated ammonium hydroxide and extracted with dichloromethane. Evaporation of the organic solvent gave 17 g of the amino ketone: mp 127–129 °C from ethyl acetate–petroleum ether; IR (KBr) 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.3–7.4 (m, 1 NH, 4 aromatic H), 3.85 (s, CH_3N), 3.3 (d, CH_3NH), 1.52 (s, CH_3C). Anal. ($C_{13}H_{14}N_{14}O_3$) C, H, N.

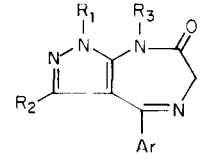
(5-Chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-nitrophenyl)methanone was prepared in 80% yield from the reaction of 2-nitrobenzoyl chloride (55 g, 0.3 mol) with (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)lithium [from 60 g (0.3 mol) of 4-bromo-3-chloro-1,3-dimethyl-1*H*-pyrazole and 220 mL of commercial butyllithium in tetrahydrofuran at −40 °C by a previously published procedure].[4] The ketone melted at 94–96 °C from ethyl acetate–petroleum ether: IR (KBr) 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.3–7.3 (m, 4 aromatic H), 3.75 (s, CH_3N), 2.35 (s, CH_3C). Anal. ($C_{12}H_{10}ClN_3O_3$) C, H, N.

2-Azido-*N*-methyl-*N*-[4-(2-nitrobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]acetamide (34). The reaction of **33** (13.5 g, 0.04 mol) with 4 g (0.06 mol) of sodium azide in 30 mL of *N,N*-dimethylformamide at 40 °C for 3 h gave a 92% yield of **34**: mp 118–120 °C from ether; IR (KBr) 1650 (C=O), 1690 cm^{-1}; NMR ($CDCl_3$) δ 8.4–7.3 (m, 4 aromatic H), 4.1–3.35 (q, N_3CH_2CO), 3.75 (s, CH_3N), 3.15 (s, CH_3N), 1.85 (s, CH_3C).

4-(2-Aminophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (64). Method C. Hydrogenation of 7.2 g (0.02 mol) of **34** in 70 mL of glacial acetic acid in the presence of 0.5 g of 5% Pd/C catalyst by the procedure described for **54** caused reductive cyclization to the diazepinone and concurrent reduction of the nitro group to amino to give **64**, mp 160 °C.

6,8-Dihydro-1,3,8-trimethyl-4-(2-nitrophenyl)pyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (65). To a stirred solution of 34 mL of trifluoroacetic anhydride in 150 mL of dichloromethane was added dropwise at 0–5 °C 5.4 mL of 90% hydrogen peroxide. The mixture was allowed to warm to room temperature and a solution of 10 g (0.03 mol) of **64** in 50 mL of dichloromethane was added dropwise. The mixture was stirred under reflux 5 h, cooled, and stirred with 150 mL of water and then an excess of a saturated aqueous solution of sodium bicarbonate. The organic layer was separated and dried ($MgSO_4$) and the solvent evaporated. The solid obtained by treating the residue with ether was recrystallized from acetonitrile to give 1.3 g (11%) of **65**: mp 184–186 °C; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.5 (m, 4 aromatic

Table II. Anticonvulsant and Antianxiety Results

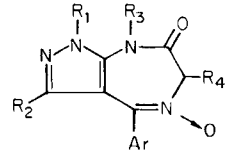


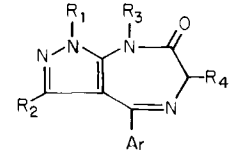
Compd no.	R_1	R_2	R_3	Ar	Mp, °C	Purifn solvent	Method	Yield, %	Formula	Analyses[a]	PM,[b] MED, mg/kg	AX,[c] MED, mg/kg
Diazepam											4–8	1.25
44	CH_3	H	H	C_6H_5	285	2-PrOH–ether	A	20	$C_{13}H_{12}N_4O\cdot HCl\cdot H_2O$	C, H, N	250	>80
45	CH_3	CH_3	H	C_6H_5	265–267	Toluene	A	65	$C_{14}H_{14}N_4O$	C, H, N	16	10
46	CH_3	CH_3	CH_3	C_6H_5	183–185	Toluene	E[d]	34	$C_{15}H_{16}N_4O$	C, H, N	4	2.5
46·HCl	CH_3	CH_3	CH_3	C_6H_5	180 dec	2-PrOH–HCl	C	90	$C_{15}H_{16}N_4\cdot HCl\cdot H_2O$	C, H, N	4	2.5
47	CH_3	CH_3	H	$2\text{-}C_4H_3S$	228–230	Toluene	A	4	$C_{12}H_{12}N_4OS$	C, H		40
48	CH_3	C_2H_5	H	C_6H_5	268–270	MeOH	A	35	$C_{15}H_{16}N_4O$	C, H, N	8	2.5
49	CH_3	C_2H_5	CH_3	C_6H_5	193–195	Ether	C[e]	79	$C_{16}H_{18}N_4O$	C, H, N	4	1.25
50	CH_3	CH_3	H	$2\text{-}ClC_6H_4$	245–248	Toluene	C[f]	84	$C_{14}H_{13}ClN_4O$	C, H, N	16	2.5
51	CH_3	CH_3	CH_3	$2\text{-}ClC_6H_4$	265 dec	2-PrOH	C	90	$C_{15}H_{15}ClN_4O\cdot HCl$	C, H; N[g]	4	2.5
52	CH_3	CH_3	H	$3\text{-}ClC_6H_4$	255–257	Acetone	C	95	$C_{14}H_{13}ClN_4O$	C, H, N	>500	>40
53	CH_3	CH_3	H	$2\text{-}FC_6H_4$	235–237	Toluene	A	40	$C_{14}H_{13}FN_4O$	C, H, N	8	2.5
54	CH_3	CH_3	CH_3	$2\text{-}FC_6H_4$	183–185	MeOH–ether	C[h]	86	$C_{15}H_{15}FN_4O$	C, H, N	2	0.32
54·HCl	CH_3	CH_3	CH_3	$2\text{-}FC_6H_4$	248 dec	2-PrOH			$C_{15}H_{15}FN_4O\cdot HCl$	C, H, N	2	0.32
55	CH_3	CH_3	C_2H_5	$2\text{-}FC_6H_4$	133–135	Ether	E	27	$C_{16}H_{17}FN_4O$	C, H, N	32	5
56	CH_3	C_2H_5	H	$2\text{-}FC_6H_4$	253–255	Acetone	C[i]	81	$C_{15}H_{15}FN_4O$	C, H, N	2	1.25
56·HCl	CH_3	C_2H_5	H	$2\text{-}FC_6H_4$					$C_{15}H_{15}FN_4O\cdot HCl$	C, H, N	2	1.25
57	CH_3	C_2H_5	CH_3	$2\text{-}FC_6H_4$	165–168	Ether	E	50	$C_{16}H_{17}FN_4O$	C, H, N	4	1.25
58	CH_3	C_2H_5	H	$3\text{-}FC_6H_4$	263–265	Acetone	A	19	$C_{15}H_{15}FN_4O$	C, H, N	32	20
59	CH_3	C_2H_5	CH_3	$3\text{-}FC_6H_4$	163–165	Ether	E	50	$C_{16}H_{17}FN_4O$	C, H, N	32	10
60	CH_3	C_2H_5	H	$4\text{-}FC_6H_4$	247–250	Acetone	A	33	$C_{15}H_{15}FN_4O$	C, H, N	>500	>40
61	CH_3	C_2H_5	CH_3	$4\text{-}FC_6H_4$	216–218	Toluene	E	40	$C_{16}H_{17}FN_4O$	C, H, N	>500	>40
62	CH_3	CH_3	CH_3	$2\text{-}BrC_6H_4$	169–171	Ether	C	80	$C_{15}H_{15}BrN_4O$	C, H, N	4–8	5
63	CH_3	CH_3	CH_3	$2,6\text{-}F_2C_6H_3$	247–250	2-PrOH–THF	C	81	$C_{15}H_{14}F_2N_4O\cdot HCl$	C, H, N	2	20
64	CH_3	CH_3	CH_3	$2\text{-}NH_2C_6H_4$	160	Ether	C	90	$C_{15}H_{17}N_5O$	H, N; C[j]		
65	CH_3	CH_3	CH_3	$2\text{-}NO_2C_6H_4$	184–186	CH_3CN		11	$C_{15}H_{15}N_5O_3$	C, H, N	8	
66	CH_3	CH_3	CH_3	$2\text{-}N_3C_6H_4$	137–139	EtOAc–petr ether		40	$C_{15}H_{15}N_7O$	C, H, N	63	>40
67	CH_3	Cl	H	C_6H_5	253–255	CH_3CN	A	44	$C_{13}H_{11}ClN_4O\cdot 0.5H_2O$	C, H, N	63	40
68	CH_3	OCH_3	CH_3	$2\text{-}FC_6H_4$	212–214	$CHCl_3$–ether	C	80	$C_{15}H_{15}FN_4O_2$	C, H, N	8	10
69	CH_3	C_2H_5	H	$2\text{-}ClC_6H_4$	258–260	Toluene	B	18	$C_{15}H_{15}ClN_4O$	C, H	32	2.5–5
70	CH_3	C_2H_5	CH_3	$2\text{-}ClC_6H_4$	115–117	Ether	E	70	$C_{16}H_{17}ClN_4O$	C, H	16	0.63
71	CH_3	$i\text{-}C_3H_7$	H	$2\text{-}ClC_6H_4$	223–224	Toluene	A	29	$C_{16}H_{17}ClN_4O$	C, H	125	>40
72	CH_3	$i\text{-}C_3H_7$	CH_3	$2\text{-}ClC_6H_4$	168–170	Ether	E	56	$C_{17}H_{19}ClN_4O$	C, H	63	>40
73	CH_3	$n\text{-}C_3H_7$	H	$2\text{-}ClC_6H_4$	179–180	Acetone	A	48	$C_{16}H_{17}ClN_4O$	C, H	250	>40
74	CH_3	$n\text{-}C_3H_7$	CH_3	$2\text{-}ClC_6H_4$	120–122	Ether–petr ether	E	20	$C_{17}H_{19}ClN_4O$	C, H	63	>40
75	CH_3	$n\text{-}C_4H_9$	H	$2\text{-}ClC_6H_4$	191–193	Ether	A	41	$C_{17}H_{19}ClN_4O$	H; C[k]	>500	>40
76	CH_3	$n\text{-}C_4H_9$	CH_3	$2\text{-}ClC_6H_4$	96–98	Ether	E	42	$C_{18}H_{21}ClN_4O$	C, H	125	>40

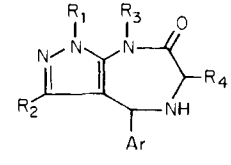
77	C_2H_5	CH_3	H	2-FC_6H_4	250-252	Toluene	A	17	$C_{15}H_{15}FN_4O$	C, H	8-16	2.5
78	C_2H_5	CH_3	CH_3	2-FC_6H_4	74-77	Hexane	E	70	$C_{16}H_{17}FN_4O$	C, H	4	1.25
79	C_2H_5	CH_3	H	2-ClC_6H_4	246-248	Toluene	A	30	$C_{15}H_{16}ClN_4O$	C, H	8-16	5
80	C_2H_5	CH_3	CH_3	2-ClC_6H_4	105-108	Ether	E	20	$C_{16}H_{17}ClN_4O$	C, H	4	0.63
81	C_2H_5	CH_3	CH_2=$CHCH_2$	2-ClC_6H_4	Glass	Ether	E	50	$C_{18}H_{19}ClN_4O$	C, H	63	>40
82	n-C_3H_7	CH_3	H	2-ClC_6H_4	171-173	Ether	A	40	$C_{16}H_{17}ClN_4O$	C, H	63	40
83	n-C_3H_7	CH_3	CH_3	2-ClC_6H_4	Glass	Ether	E	60	$C_{17}H_{19}ClN_4O$	C, H, N	16	2.5
84	i-C_3H_7	CH_3	H	2-ClC_6H_4	253-255	EtOAc	A	20	$C_{16}H_{17}ClN_4O$	H; C[l]	16-32	20
85	n-C_4H_9	CH_3	H	2-ClC_6H_4	183-185	Ether	A	40	$C_{17}H_{19}ClN_4O$	C, H	32-63	40
86	n-C_4H_9	CH_3	CH_3	2-ClC_6H_4	Glass	Ether	E	95	$C_{18}H_{21}ClN_4O$	C, H	16-32	40
87	n-C_4H_9	CH_3	H	3-ClC_6H_4	137-139	Ether	A	65	$C_{17}H_{19}ClN_4O$	C, H	>500	>40
88	c-C_6H_{11}	CH_3	H	2-ClC_6H_4	203-205	MeOH	A	65	$C_{19}H_{21}ClN_4O$	C, H, N	>500	>40
89	c-C_6H_{11}	CH_3	CH_3	2-ClC_6H_4	Glass	Ether	E	60	$C_{20}H_{23}ClN_4O$	C, H	63	>40
90	C_6H_5	CH_3	H	C_6H_5	255-257	Acetone	A	30	$C_{19}H_{16}N_4O\cdot 0.5H_2O$	C, H, N	>500	>40
91	C_6H_5	CH_3	H	2-ClC_6H_4	229-231	Toluene	A	12	$C_{19}H_{15}ClN_4O$	C, H, N	500	20

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values required. [b] Five fasted rats weighing between 100 and 150 g were used for each dose level (500, 250, 125, . . ., mg/kg). MED represents the minimal effective dose required to prevent clonic seizures in four out of five rats. [c] Eight Holtzman male rats weighing 200-230 g are treated at each dose level (40, 20, 10, . . ., mg/kg) and are used only once in the procedure. A control group of eight rats treated with water or 0.2% methanol solution is run at the same time. The volume of milk consumed is averaged for each group and the effective dose recorded is that required to elicit an increase in milk consumption over that of the control average (ca. 5 mL). [d] Method A, yield 20%. Method B, yield 60%. [e] Method E, yield 30%. [f] Method A, yield 27%. [g] N: calcd, 16.51; found, 16.01. [h] Method E, yield 35%. Method D, yield 81%. [i] Method A, yield 36%. [j] C: calcd, 63.59; found, 62.94. [k] C: calcd, 61.71; found, 61.15. [l] C: calcd, 60.66; found, 59.98.

Table III. Oxidation and Reduction Derivatives of 4-Aryl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones.







Compd no.	R_1	R_2	R_3	R_4	Ar	Mp, °C	Purifn solvent	Yield, %	Formula	Analyses[a]	PM,[b] MED, mg/kg	AX,[c] MED, mg/kg
92	CH_3	CH_3	CH_3	H *N*-oxide	C_6H_5	232-235	Acetone	73	$C_{15}H_{16}N_4O_2$	C, H, N	63	>40
93	CH_3	CH_3	CH_3	OAc	C_6H_5	218-220	EtOAc	83	$C_{17}H_{18}N_4O_3$	C, H, N		
94	CH_3	CH_3	CH_3	OH	C_6H_5	243-245	MeOH-H_2O	56	$C_{15}H_{16}N_4O_2$	H, N; C[d]	16	5
95	CH_3	CH_3	CH_3	H *N*-oxide	2-FC_6H_4	182-184	2-PrOH–ether	85	$C_{15}H_{15}FN_4O_2$	C, H, N	8	10
96	CH_3	CH_3	CH_3	OAc	2-FC_6H_4	203-205	Benzene-petr ether	81	$C_{17}H_{17}FN_4O_3$	H, N; C[e]	8	20
97	CH_3	CH_3	CH_3	OH	2-FC_6H_4	250-252	MeOH-H_2O	90	$C_{15}H_{15}FN_4O_2$	C, H, N	4	2.5-5.0
98	CH_3	C_2H_5	CH_3	H 4,5-dihydro	C_6H_5	202-204	2-PrOH	70	$C_{16}H_{20}N_4O\cdot HCl\cdot H_2O$	C, H, N	63	>40
99	CH_3	CH_3	CH_3	H 4,5-dihydro	2-FC_6H_4	218-220	2-PrOH	93	$C_{15}H_{17}FN_4O\cdot HCl$	C, H, N	4	1.2-2.0

[a-c] See Table II, footnotes *a–c*. [d] C: calcd, 63.36; found, 63.99. [e] C: calcd, 59.29; found, 59.80.

H), 5.1–3.9 (unresolved m, NCH_2CO), 3.9 (s, CH_3N), 3.4 (s, CH_3N), 1.65 (s, CH_3C).

4-(2-Azidophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (66). A solution of 6 g (0.02 mol) of **64** in 120 mL of water containing 5 mL of 12 N HCl was cooled to 0 °C and treated portionwise with a solution of 1.6 g of sodium nitrite in 5 mL of water. After stirring for 10 min at 2 °C, a solution of 1.5 g of sodium azide in 5 mL of water was added. The mixture was stirred at 0–2 °C for 1 h, made basic with concentrated sodium hydroxide solution, and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and the solvent evaporated. The residual oil crystallized in ether to give 2.4 g (40%) of **66**: mp 137–139 °C; IR (KBr) 1680 (C=O), 2100 cm^{-1} (N_3).

Preparation of (2,6-Difluorophenyl)[1,3-dimethyl-5-(methylamino)-1*H*-pyrazol-4-yl]methanone (5), Intermediate to 31 and 63. A stirred mixture of 195 g (1.75 mol) of 5-amino-1,3-dimethyl-1*H*-pyrazole[12] and 175 g (2.36 mol) of calcium hydroxide powder in 2 L of tetrahydrofuran was treated at a rapid droprate with 246 g (1.75 mol) of benzoyl chloride as the temperature rose to 55 °C. The mixture was stirred under reflux 2 h, cooled to room temperature, and filtered. The filtrate was evaporated in vacuo and the residue was digested in 800 mL of toluene. The cooled mixture was filtered to yield 325 g (86%), mp 133–136 °C, of *N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**1**). Anal. ($C_{12}H_{13}N_3O$) C, H, N.

Compound **1** (323 g, 1.5 mol) was dissolved in 1.5 L of tetrahydrofuran and cooled to ca. 5 °C with an ice bath; then 284 g (2 mol) of iodomethane was added. The cooled mixture was stirred vigorously under N_2 as 100 g (2 mol) of sodium methoxide (Olin) was added during 1–2 min. The mixture was stirred at 10 °C for 2 h and at room temperature overnight and filtered. The filtrate was evaporated in vacuo and the residue was dissolved in dichloromethane and washed with water. After drying over magnesium sulfate, the solvent was evaporated and the solid residue was slurried in cyclohexane and filtered to give 270 g (78%), mp 96–99 °C, of *N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*-methylbenzamide (**2**): NMR ($CDCl_3$) δ 7.3 (s, 5 aromatic H), 5.8 (s, pyrazole H), 3.5 (s, CH_3N), 3.35 (s, CH_3N), 2.15 (s, CH_3C). Anal. ($C_{13}H_{15}N_3O$) C, H, N.

Compound **2** (23 g, 0.1 mol) was dissolved in 120 mL of glacial acetic acid and 16 g of bromine was added dropwise. After 1 h the solution was evaporated, the residue was dissolved in dichloromethane, washed with bisulfite solution, and dried ($MgSO_4$), and the solvent evaporated to give 28 g (94%), mp 139–141 °C, of **3**: mp 139–141 °C from ether–petroleum ether; NMR ($CDCl_3$) δ 7.5 (s, 5 aromatic H), 3.5 (s, CH_3N), 3.3 (s, CH_3N), 2.1 (s, CH_3C). Anal. ($C_{13}H_{14}BrN_3O$) C, H, N.

Butyllithium (70 mL) was added dropwise to a stirred solution of **3** (28 g, 0.09 mol) in 200 mL of tetrahydrofuran at −50 °C under N_2. The yellow suspension was stirred at −40 to −50 °C for 2 h and then added in portions to a stirred solution of 19 g (0.1 mol) of 2,6-difluorobenzoyl chloride at −50 °C. The mixture was allowed to warm to 20 °C, treated with 25 mL of water, and evaporated in vacuo. The residue was dissolved in 250 mL of benzene, washed with dilute hydrochloric acid, and then stirred 1 h with 100 mL of 1 N sodium hydroxide. The benzene solution was separated and dried ($MgSO_4$) and the solvent evaporated. The residue was crystallized from ether to yield 15 g (41%) of *N*-[4-(2,6-difluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-*N*-methylbenzamide (**4**): mp 113–115 °C; IR (KBr) 1650 (C=O), 1618 cm^{-1}; NMR ($CDCl_3$) δ 7.5–6.9 (m, 8 aromatic H), 3.55 (s, CH_3N), 3.3 (s, CH_3N), 1.9 (s, CH_3C). Anal. ($C_{20}H_{17}F_2N_3O_2$) C, H, N.

Compound **4** (15 g, 0.04 mol) was added to 75% sulfuric acid (75 mL of concentrated H_2SO_4 added to 25 g of ice) at 80 °C and the mixture was stirred at 70–80 °C for 4 h and poured into 200 mL of ice water. The mixture was made basic with ammonium hydroxide and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and the solvent evaporated. The residue was crystallized from ethyl acetate–petroleum ether to give 9 g (80%) of **5**: mp 116–119 °C; IR (KBr) 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.0–6.7 (m, 3 aromatic H and NH), 3.75 (s, CH_3N), 3.1, 3.2 (d, CH_3NH), 1.7 (CH_3C). Anal. ($C_{13}H_{13}F_2N_3O$) C, H, N.

Preparation of (5-Amino-3-chloro-1-methyl-1*H*-pyrazol-4-yl)phenylmethanone (8), Intermediate to 35 and 67. To 75 g (0.5 mol) of phosphorus oxychloride was added 20 g (0.062 mol) of *N*-(4-benzoyl-3-hydroxy-1-methyl-1*H*-pyrazol-5-yl)-benzamide (**6**) and the resulting red solution was heated and stirred at 100–110 °C overnight. The cooled mixture was poured slowly with stirring into 600 mL of ice water. The solid was collected, washed with water, and recrystallized from ethanol to give 18 g (86%) of **7**: mp 193–195 °C; IR (KBr) 1690 (C=O), 1650 cm^{-1}; NMR (CF_3COOH) δ 8.0–7.2 (m, 10 aromatic H), 4 (s, CH_3N). Anal. ($C_{18}H_{14}ClN_3O_2$) C, H, N.

The above compound (**7**) (16.5 g, 0.051 mol) was stirred under reflux 3 h in 100 mL of glacial acetic acid and 50 mL of 48% hydrobromic acid. The mixture was evaporated in vacuo. The residue was dissolved in chloroform and stirred with an excess of sodium bicarbonate solution. The chloroform layer was dried over $MgSO_4$ and evaporated in vacuo to give 7.6 g (63%) of **8**: mp 160–162 °C from $CHCl_3$–petroleum ether; IR (KBr) 1640 cm^{-1} (C=O). Anal. ($C_{11}H_{10}ClN_3O$) C, H, N.

4-(2-Fluorophenyl)-4,5,6,8-tetrahydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one Monohydrochloride (99). A solution of 7 g (0.025 mol) of **54** in 100 mL of methanol was hydrogenated in the presence of 0.5 g of 5% Pt/C at room temperature with an initial pressure of 50 psi. When the theoretical absorption of hydrogen was observed, the mixture was filtered from the catalyst and the filtrate was evaporated. The colorless oil was dissolved in 30 mL of 2-propanol containing an equivalent of anhydrous HCl and diluted with 20 mL of ethyl acetate. After refrigeration, 7.5 g (93%) of **99** was obtained: mp 218–220 °C; IR (KBr) 1686 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 12 (2 H, NH, HCl), 7.7–7.1 (m, 4 aromatic H), 5.8 (s, benzylic H), 4.1–3.5 (q, NCH_2C=O), 3.75 (s, CH_3N), 3.2 (s, CH_3N), 1.8 (s, CH_3C).

4-(2-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-3(1*H*)-one 5-Oxide (95). 3-Chloroperbenzoic acid (10.5 g, 0.06 mol) was added to a solution of 14 g (0.05 mol) of compound **54** in 180 mL of glacial acetic acid. After standing at room temperature overnight, the mixture was evaporated in vacuo. The residue was dissolved in dichloromethane, washed with sodium bicarbonate solution, and dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was crystallized from chloroform–ether to give 12.6 g (85%) of **95**: mp 182–184 °C dec; NMR ($CDCl_3$) δ 7.7–7.1 (m, 4 aromatic H), 4.7 (s, NCH_2C=O), 3.8 (s, CH_3N), 3.4 (s, CH_3N), 1.6 (s, CH_3C).

4-(2-Fluorophenyl)-6,8-dihydro-6-hydroxy-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one Acetate (Ester) (96). A solution of 10 g (0.033 mol) of **95** in 75 mL of acetic anhydride was heated on the steam bath for 1 h and evaporated in vacuo. The residue was dissolved in chloroform and stirred 0.5 h with an aqueous saturated solution of sodium bicarbonate. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallized from benzene–petroleum ether to give **96** in 81% yield: mp 203–205 °C; NMR ($CDCl_3$) δ 7.7–7.1 (m, 4 aromatic H), 6.0 (s, NCHOAc), 3.8, 3.3, and 2.2 (3 s for CH_3N, CH_3N, and CH_3C=O), 1.72 (s, CH_3C).

4-(2-Fluorophenyl)-6,8-dihydro-6-hydroxy-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (97). Compound **96** (15.5 g, 0.045 mol) was suspended in 60 mL of methanol and stirred with 50 mL of 1 N NaOH. A clear solution was obtained within minutes; then a new solid began to separate. After stirring for 2 h, the mixture was neutralized by passing in carbon dioxide and filtered to give 12.3 g (90%) of **97**, mp 251–253 °C.

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References and Notes

(1) H. A. DeWald, I. C. Nordin, Y. J. L'Italien, and R. F. Parcell, *J. Med. Chem.*, **16**, 1346 (1973).
(2) H. A. DeWald and D. E. Butler, U.S. Patent 3558605 (1971).
(3) (a) F. J. Tinney, J. P. Sanchez, and J. A. Nogas, *J. Med. Chem.*, **17**, 624 (1974); (b) A. Edenhofer, *Helv. Chim. Acta*,

58, 2192 (1974); (c) U.S. Patent 3880840 (1975); (d) L. Fontanella, L. Mariani, and G. Tarzia, *Eur. J. Med. Chem.*, 11, 217 (1976); (e) R. Jaunin, *Helv. Chim. Acta*, 57, 1934 (1974).
(4) D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **36**, 2542 (1971).
(5) H. A. DeWald and D. E. Butler, U.S. Patent 3660425 (1972).
(6) M. D. Coburn, *J. Heterocycl. Chem.*, 7, 455 (1970); W. D. Emmons, *J. Am. Chem. Soc.*, 76, 3470 (1954).
(7) G. Chen, C. Ensor, and I. Clark, *AMA Arch. Neurol. Psychiatry*, 66, 329 (1951); 68, 498 (1952); G. Chen, R. Porterman, C. Ensor, and A. Bratton, Jr., *J. Pharmacol. Exp. Ther.*, **103**, 54 (1951).
(8) B. P. H. Poschel, *Psychopharmacologia*, 19, 193 (1971).
(9) B. P. H. Poschel and F. Ninteman, *Life Sci.*, 7, 317 (1968).
(10) M. M. Bree, B. J. Cohens, and S. E. Rowe, *Lab. Anim. Sci.*, 22 (6), 878 (1972); G. H. Conner, R. W. Coppock, and C. C. Beck, *Vet. Med. Small Anim. Clin.*, **69** (4), 479 (1974).
(11) J. Baukema, R. A. Okerholm, and A. J. Glazko, *Res. Commun. Chem. Pathol. Pharmacol.*, **10**, 227 (1975).
(12) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, 81, 2456 (1959).

Antischistosomal Effects of 5-(2,4,5-Trichlorophenyl)hydantoin and Related Compounds

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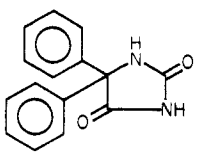
5-(2,4,5-Trichlorophenyl)hydantoin and several analogues effected an 80–90% reduction of live schistosomes in infected mice at doses ranging from 265 to 329 mg/kg per day when administered orally in the diet for 14 days. The sodium salt of 5-(2,4,5-trichlorophenyl)hydantoin, when given by gavage to rhesus monkeys infected with *Schistosoma mansoni* at 200 mg/kg/day for 5 or 10 days, removed all but a few live worms with no evidence of intolerance.

Although the utility of hydantoin derivatives as anticonvulsant and antiarrhythmic drugs is well recognized, little is known about the antiparasite properties of such substances.

In 1954 it was reported that 5,5-diphenylhydantoin (**1**) and 5-(*p*-chlorophenyl)-5-methylhydantoin (**2**) showed activity against *Schistosoma mansoni* infections in mice.[1] The only other reported interest in hydantoins as schis-



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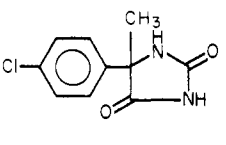

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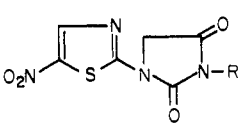
tosomicides has been in the N-substituted derivatives (**3**) related to niridazole.[2]



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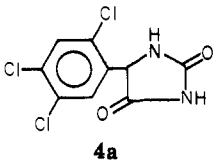
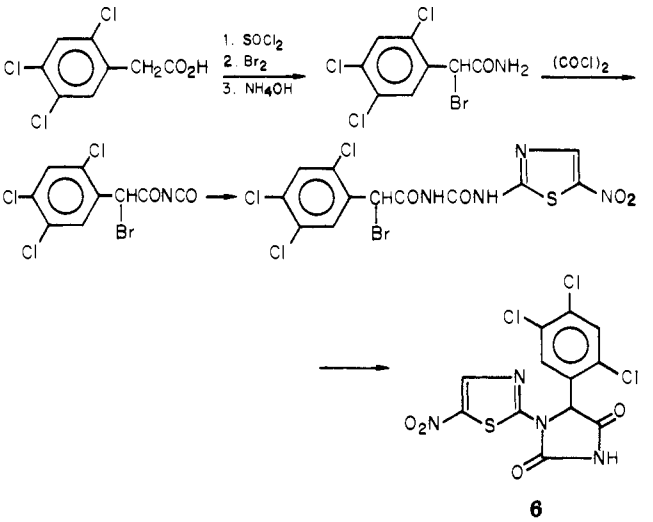


4a

We have examined through the years a wide variety of hydantoins as potential schistosomicides. Our studies confirmed the modest activity at toxic levels of **1**,[3] and we now wish to report the potent activity of 5-(2,4,5-trichlorophenyl)hydantoin (**4a**) and some related substances.[4]

Chemistry. A standard hydantoin synthesis was used for the most part.[5] Thus a suitably substituted aromatic aldehyde heated in aqueous ethanol with potassium cyanide and ammonium carbonate provided the 5-(substituted phenyl)hydantoins (Table I). Suitably substituted acetophenones were used similarly to prepare the 5-methyl-5-phenylhydantoins (**5a–g**, Table II). The 3-methyl and 3-(dimethylaminopropyl) analogues (compounds **4e** and **4i**, Table I) of **4a** were obtained by alkylation of the parent. Compound **4i** was treated with methyl iodide to provide the quaternary salt (compound **4j**, Table I). Hydroxymethylation of **4a** provided the 3-hydroxymethyl derivative (compound **4g**, Table I). 1-Methyl-5-(2,4,5-trichlorophenyl)hydantoin (compound **4f**, Table I) was obtained by treating 2,4,5-trichlorobenzaldehyde with methylamine and sodium cyanide in the presence of $Na_2S_2O_5$ and allowing the intermediate formed to react with potassium cyanate in hydrochloric acid.[6] Alkylation of this material then provided the 1,3-dimethyl derivative (compound **4h**, Table I).

Scheme I



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In an attempt to combine the features of the nitrothiazolylhydantoins (**3**) and 5-(2,4,5-trichlorophenyl)hydantoin (**4a**), 1-(5-nitro-2-thiazolyl)-5-(2,4,5-trichlorophenyl)hydantoin (**6**) was prepared (Scheme I). (2,4,5-Trichlorophenyl)acetic acid was converted to 2-bromo-