while being stirred at room temperature. The clear solution was allowed to stand overnight. After acidification with HCl (18%), the precipitated acid was filtered off under suction, washed with H_2O, and dried at 100° to yield 23.2 g (99%), mp 254°. A sample recrystallized from acetonitrile melted at 256°.

4-[2-(4,7-Dihydro-3,7-dimethyl-1-ethyl-4-oxo-1*H*-pyrazolo-[3,4-*b*]pyridine-5-formamido)ethyl]benzenesulfonamide (VII). A solution of 4,7-dihydro-3,7-dimethyl-1-ethyl-4-oxo-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylic acid (14 g, 0.06 mol) in 300 ml of $CHCl_3$ and 12 ml of triethylamine was cooled to 0°. At this temperature, isobutyl chloroformate (11.5 g, 0.085 mol) dissolved in 60 ml of $CHCl_3$ was added dropwise and the whole mixture was stirred at 0–5° for 20 min. A solution of *p*-(β-aminoethyl)benzenesulfonamide (12 g, 0.06 mol) in 120 ml of $CHCl_3$ and 12 ml of triethylamine was then added to the mixture. After being stirred at room temperature for 2 hr, the precipitate was filtered off under suction and washed with $CHCl_3$ to give 24.7 g (98.8%), mp 236–238°. A sample recrystallized from glacial AcOH melted at 238–240°.

1-Cyclohexyl-3-[[*p*-[2-[(4,7-dihydro-3,7-dimethyl-1-ethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)formamido]ethyl]phenyl]-sulfonyl]urea (VIII, 36). 4-[2-(4,7-Dihydro-3,7-dimethyl-1-ethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-5-formamido)ethyl]benzenesulfonamide (6.3 g, 0.015 mol) was added to a solution of K (0.65 g, 0.0165 mol) in 50 ml of absolute MeOH, and the mixture was stirred at room temperature for 45 min. The MeOH was evaporated *in vacuo*, and 75 ml of acetone and cyclohexyl isocyanate (2.1 g, 0.0165 mol) were added to the K salt. The whole mixture was stirred for 2 hr at 65–70° (bath temperature) and then the acetone was decanted from the oily residue. The latter was dissolved in 125 ml of H_2O, with stirring, and the aqueous solution was filtered and then acidified with HCl (18%), and the precipitated product was filtered off, washed with H_2O, and dried in the desiccator to yield 6.5 g (80%). Shortly after the crude product was dissolved in acetone, the sulfonylurea crystallized, mp 190–192°; when recrystallized from MeOH, it melted at 195–196°. For the preparation of the Na salt, the sulfonylurea was treated with an equimolar amount of EtONa in EtOH. At room temperature the precipitated Na salt was filtered off under suction and washed with EtOH and Et_2O, mp 246–249° dec.

In Table IV are listed the melting points of those pyrazolo[3,4-*b*]pyridin-5-ylformamidoalkylbenzenesulfonamides (VII) that have not been described in the Experimental Section.

Acknowledgment. We thank Mr. R. Baer, Regensburg, for assistance in the preparation of these compounds and Drs. M. Chasin and D. N. Harris for their kind permission to report some unpublished biological data; the latter two are members of the Squibb Institute for Medical Research, Princeton, N. J.

References

(1) M. Chasin, D. Harris, M. Phillips, and S. M. Hess, *Biochem. Pharmacol.*, **21**, 2443 (1972).
(2) M. Chasin, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 1286 (1971).
(3) W. Montague and J. R. Cook, *Biochem. J.*, **122**, 115 (1971).
(4) W. J. Malaisse, F. Malaisse-Lagae, and D. Mayhew, *J. Clin. Invest.*, **46**, 1724 (1967).
(5) J. R. Turtle and D. M. Kipnis, *Biochem. Biophys. Res. Commun.*, **28**, 797 (1967).
(6) A. E. Renold, *N. Engl. J. Med.*, **282**, 173 (1970).
(7) O. Rosen, A. Hirsch, and E. Goren, *Arch. Biochem. Biophys.*, **146**, 660 (1971).
(8) A. E. Lambert, A. Junod, W. Stauffacher, B. Jeanrenaud, and A. E. Renold, *Biochim. Biophys. Acta*, **184**, 529 (1969).
(9) E. B. Marliss, C. B. Wollheim, B. Blondel, L. Orci, A. E. Lambert, W. Stauffacher, A. A. Like, and A. E. Renold, *Eur. J. Clin. Invest.*, **3**, 16 (1973).
(10) H. Höhn, T. Denzel, and W. Janssen, *J. Heterocycl. Chem.*, **9**, 235 (1972).
(11) G. Brooker, L. J. Thomas, and M. M. Appleman, *Biochemistry*, **7**, 4177 (1968).
(12) W. S. Hoffmann, *J. Biol. Chem.*, **120**, 51 (1937).
(13) H. Weber, W. Aumüller, K. Muth, R. Weyer, R. Heerdt, E. Fauland, A. Bänder, W. Pfaff, F. Schmidt, and H. Stork, *Arzneim.-Forsch.*, **19**, 1334 (1969).
(14) H. Lund, *Chem. Ber.*, **67**, 935 (1934).
(15) H. Höhn, *Z. Chem.*, **10**, 386 (1970).
(16) E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Amer. Chem. Soc.*, **62**, 2099 (1940).

Pyrazolodiazepines. 1,3- (and 2,3-) Dialkyl-4,6-dihydro-8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones as Antianxiety Agents

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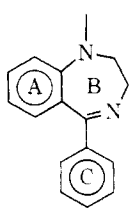
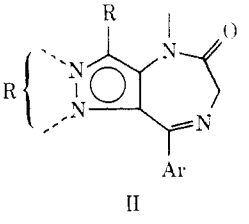
A series of 1,3- (and 2,3-) dialkyl-4,6-dihydro-8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones was synthesized and evaluated for psychotropic activity. Intermediates are new dialkylnitropyrazolyl aryl ketones VIII and IX prepared from dialkylnitropyrazolecarboxylic acids. Many of these pyrazolodiazepines exhibit high CNS activity in animals. One compound, 1-ethyl-4,6-dihydro-3-methyl-8-phenylpyrazolo[4,3-*e*][1,4]diazepin-5(1*H*)-one (98), is about as potent as diazepam as an antianxiety agent with less sedative properties and is being studied in the clinic (CI-683).

In extensive research efforts, thousands of benzodiazepines and related compounds have been synthesized and studied, but the vast majority of these efforts have been directed to changes in ring B and/or C. At the time this work was started in 1967, the only published change from the fused benzo ring A, aside from nuclear substitution, was the synthesis of 5-aryl-1,3-dihydro-2*H*-pyrido-1,4-diazepin-2-ones.[1] These appeared to be electronically analogous to the requirement of an electronegative substituent at position 7 to obtain high drug potency. Our work was directed toward the incorporation of other hetero systems in place of the fused ring A of I. The first compounds to be synthesized were 8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones[2] II and are the subject of this paper. An isomeric pyrazole series, the 4-arylpyrazolo[3,4-*e*][1,4]diazepin-7-ones,[3] was developed simultaneously and is to be the subject of a future communication.†



I



II

Chemistry. Potential intermediates to II have been

†A third series, the thienodiazepinones, was prepared and studied concurrently in these laboratories. A recent paper[4] and also prior reports[5] describe some of these thienodiazepinones.

known for a long time and have been used to prepare heterocyclic systems related to the purines. The 4-nitropyrazole-3- (and 5-) carboxylic acids VI and VII are attractive precursors to the required 4-aminopyrazol-3- (and 5-) yl aryl ketones X and XI. 1,5-Dialkyl-3-pyrazolecarboxylic acid esters IV and the 1,3 isomers V were prepared by alkylation of the pyrazole ester III in alcoholic sodium ethoxide, with separation of the isomers by distillation (Scheme I). This old procedure[6] gave predominantly isomer IV. When it became evident that isomer V (1,3-dialkyl) led to the pyrazolodiazepinones with the more interesting biological activity, it was found that isomer V could be prepared almost exclusively with the Meerwein reagent or more simply by heating III with dialkylsulfonates neat at 150–160°. These results are in agreement with observations made earlier by Auwers and Breyhan[7] on alkylation of pyrazoles. The pyrazolecarboxylic esters were hydrolyzed and nitrated smoothly[8,‡] to afford VI and VII. The nitro acids were converted to aroylnitropyrazoles VIII and IX, a new series of compounds, *via* a Friedel–Crafts reaction of their acid chlorides with the appropriate aromatic compound. Reduction to aminopyrazolyl aryl ketones X and XI was accomplished chemically (Fe) or catalytically (Raney nickel). One nitropyrazolyl aryl ketone (**50**) which was not accessible by this Friedel–Crafts sequence was prepared by the reaction of the appropriate phenyllithium reagent with an acid chloride of VII. A few aminopyrazolyl aryl ketones (**59**, **65**, and **68**) were also prepared directly from the reaction of an organometallic reagent with a 4-amino-5-cyanopyrazole XIII. The conversion of X and XI to pyrazolodiazepinones XVI and XIX was effected by a variety of procedures (Scheme II); all of these methods (H–M) have been described in previous syntheses of 1,4-benzodiazepin-2-ones.[9] Two 8-meta-substituted phenyl analogs XX were prepared by direct nitration and bromination of XVI in sulfuric acid (method N). The nitration of 7-substituted 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones has been reported to give exclusively the 5-*m*-nitrophenyl derivatives.[10] Spectral data of XIX, compound **110**, support meta nitration in this pyrazolodiazepinone series also. Similarly, comparison of the spectra of bromo compound **109** with authentic *m*-chloro compound **108** permits meta assignment.[§] The meta substitution of Cl in **108** is established by its synthesis from 4-amino-1-ethyl-3-methylpyrazol-5-yl *m*-chlorophenyl ketone [prepared from the reaction of (*m*-chlorophenyl)magnesium bromide with 4-amino-5-cyano-1-ethyl-3-methylpyrazole] (Tables I and II).

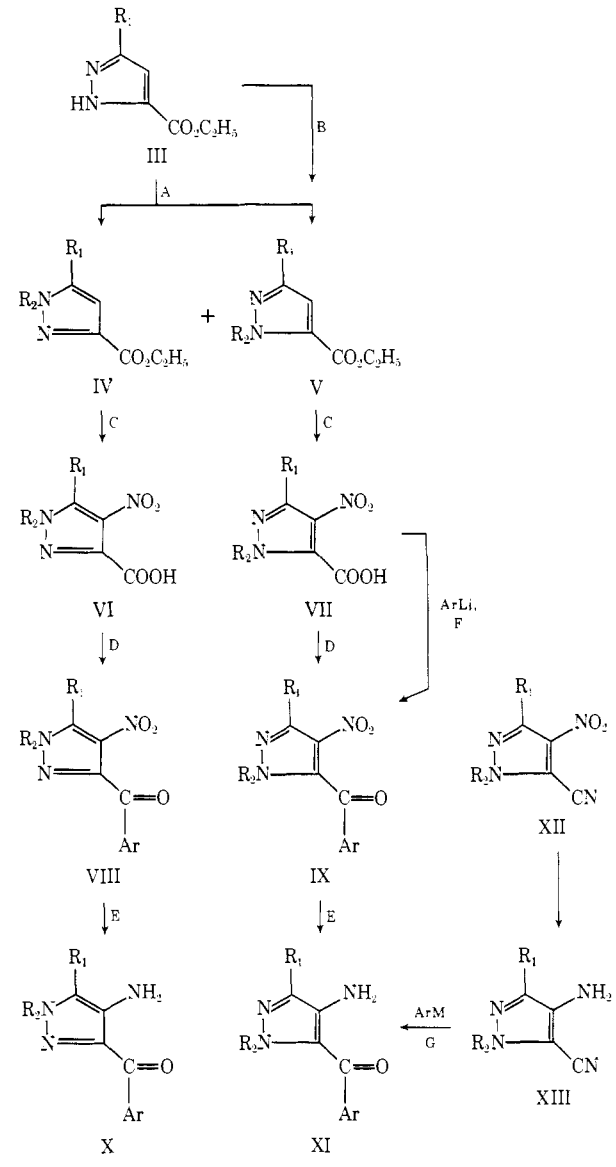
Pharmacology. Many of these pyrazolodiazepinones showed CNS effects in animals qualitatively similar to those seen with chlordiazepoxide, diazepam, oxazepam, and medazepam. In general, the pyrazolo compounds displayed very little acute toxicity in mice, with depression of reflexes and behavior only at high doses. A striking difference between the most potent pyrazolodiazepinones and the clinically effective benzodiazepinones was the absence of sedation observed subjectively by the operators of the animal screens with the pyrazolodiazepinones at pharmacological effective doses.

The compounds were tested for potential mild tranquilizer activity by two primary screens (PM and AX). The PM screen measured the dose required to prevent convulsions in rats that had been administered a subcutaneous dose of 93 mg/kg of pentylenetetrazole in a standard test described by Chen.[11] Results are expressed in the MED required to prevent clonic seizures in 100% of the rats.

‡We are indebted to Dr. C. Kulier for demonstrating that fuming sulfuric acid was not necessary for this nitration.

§The absence of biological activity of compounds **108–110** also supports the structure assignment.

Scheme I

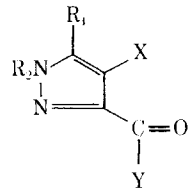


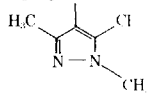
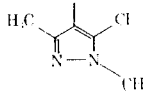
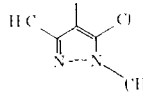
Antianxiety behavior (AX) was measured by a simple specific screen devised by Poschel,[12] where the effect of a drug to overcome inhibited behavior of rats placed in an anxiety-producing situation was measured by consumption of a milk preparation. The effective doses (mg/kg) observed in this novel screen appear to correlate remarkably with the total doses prescribed clinically for the benzodiazepines, and the results of this screen were relied upon heavily for following useful structure–activity relationships (SAR). Because of space limitations, AX results are tabulated here only as the MED to elicit the required minimal response for an active (A) rating. However, it is desirable in this behavioral screen to see the response in terms of *volume* of milk consumed and behavioral side effects over a wide dose in order to obtain a reliable perspective of each compound's merit.

Secondary evaluation of selected compounds included their effect in rats on motor coordination, conditioned conflict in Skinner boxes, and upon intracranial self-stimulation.[13]

The following observations on SAR may be made on the basis of PM and AX results. The 1,3-dialkylpyrazolodiazepinones (Table IV) are superior to the 2,3-dialkyl series (Table III), with ethyl and methyl as the optimal alkyl groups. The 1,3-dialkylpyrazolo system can produce re-

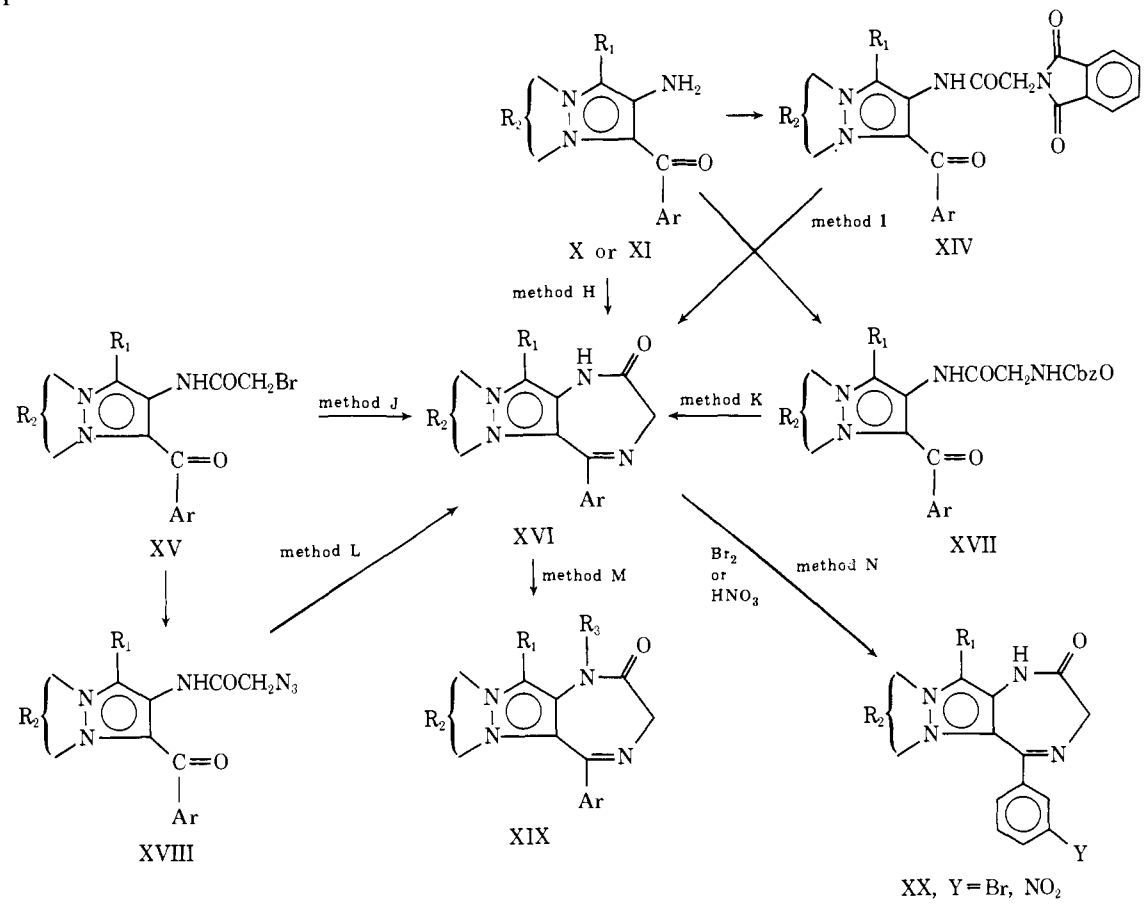
Table I. 1,5-Dialkylpyrazoles



Compd no.	R_1	R_2	X	Y	Yield, %	Mp or bp (mm), °C	Purification solvent	Formula	Analyses[f]
1	CH_3	CH_3	H	OH	63	174–176	H_2O	$C_6H_8N_2O_2$[a]	
2	CH_3	CH_3	NO_2	OH	83	153–155	H_2O	$C_6H_7N_3O_4$[b]	
3	CH_3	C_2H_5	H	OC_2H_5	56	150–154 (12)		$C_9H_{14}N_2O_2$[c]	
4	CH_3	C_2H_5	H	OH	82	136–137	H_2O	$C_7H_{10}N_2O_2$[c]	
5	CH_3	C_2H_5	NO_2	OH	90	106–108	EtOAc–pet. ether	$C_7H_9N_3O_4$	C, H, N
6	CH_3	i-C_3H_7	H	OC_2H_5	45	161–163 (23)		$C_{10}H_{16}N_2O_2$[d]	
7	CH_3	i-C_3H_7	H	OH	86	107–108	EtOAc–pet. ether	$C_8H_{12}N_2O_2$[d]	
8	CH_3	i-C_3H_7	NO_2	OH	70	85–88	H_2O	$C_8H_{11}N_3O_4 \cdot H_2O$	C, H, N
9	CH_3	CH_3	NO_2	C_6H_5	80	74–76	EtOAc–pet. ether	$C_{12}H_{11}N_3O_3$	N; C[e], H[e]
10	CH_3	CH_3	NO_2		22	150–152	EtOH	$C_{11}H_{12}ClN_5O_3$	C, H, N
11	CH_3	C_2H_5	NO_2	C_6H_5	73	90–92	EtOAc–pet. ether	$C_{13}H_{13}N_3O_3$	C, H, N
12	CH_3	i-C_3H_7	NO_2	C_6H_5	82	123–125	EtOH	$C_{14}H_{15}N_3O_3$	C, H, N
13	CH_3	CH_3	NH_2	C_6H_5	97	97–99	EtOAc–pet. ether	$C_{12}H_{13}N_3O$	C, H, N
14	CH_3	CH_3	NH_2		92	130–132	EtOH	$C_{11}H_{14}ClN_5O$	C, H, N
15	CH_3	C_2H_5	NH_2	C_6H_5	95	212–214	i-PrOH	$C_{13}H_{15}N_3O \cdot HCl$	C, H, N
16	CH_3	i-C_3H_7	NH_2	C_6H_5	97	130–132	MeOH	$C_{14}H_{17}N_3O$	C, H, N
17	CH_3	CH_3	$NHCOCH_2NHCbz$	C_6H_5	65	153–155	EtOAc–pet. ether	$C_{22}H_{22}N_4O_4$	C, H, N
18	CH_3	CH_3	$NHCOCH_2NH_2$	C_6H_5	80	203–205	i-PrOH	$C_{14}H_{16}N_4O_2 \cdot HBr$	C, H, N
19	CH_3	CH_3	$NHCOCH_2NHCbz$		65	157–159	EtOAc–pet. ether	$C_{21}H_{23}ClN_6O_4$	C, H, N
20	CH_3	C_2H_5	$NHCOCH_2NHCbz$	C_6H_5	69	150–152	EtOAc	$C_{23}H_{24}N_4O_4$	C, H, N
21	CH_3	C_2H_5	NH_2	C_6H_5	77	170 dec	i-PrOH	$C_{15}H_{18}N_4O_2 \cdot HCl$	C, H, N

[a]Prepared directly from the reaction of the $CH_3COCHNaCOCOOC_2H_5$ with CH_3NHNH_2: C. Rojahn, *Chem. Ber.*, **59**, 608 (1926). [b]U. Papesch and R. Dodson, *J. Org. Chem.*, **30**, 199 (1965). [c]Reference 6. [d]E. Eidebenz and K. Koulen, *Arch. Pharm. (Weinheim)*, **281**, 171 (1943). [e]C: calcd, 58.76; found, 59.20. H: calcd, 4.52; found, 5.09. [f]Analyses were within ±0.4% for the elements indicated.

Scheme II



sults similar to the 7-chlorobenzo moiety (compare **93** and **98** with chlordiazepoxide and diazepam). Substitution in the 8-phenyl ring follows the same SAR pattern as has been shown for the 5-phenyl ring of the benzodiazepinone (*viz.* meta and para substituents of compounds **96** and **104–110** detract from the activity). The 8-(2-thienyl) moiety (**97** and **112**) is an acceptable substitute for the 8-phenyl. In contrast to the benzodiazepinones, alkylation of the amide nitrogen in these 1,3-dialkylpyrazolodiazepinones decreases the activity, often markedly (**95**, **100–102**, **115**, **117**, and **119**).

The pharmacological profile obtained for compound **98** supported its choice for clinical studies. A description of the detailed pharmacological studies of this compound (CI-683, pyrazapon) is in preparation;[=] some preliminary clinical activity has been reported[14] which appears to substantiate the validity of a new antianxiety screen where an increase in milk consumption seems to be related to brain disinhibition rather than mere appetite stimulation.

Experimental Section

The melting points were taken on a calibrated Thomas-Hoover apparatus and need no correction. A Beckman IR-9 spectrophotometer was used to determine the ir spectra. The nmr spectra were obtained with a Varian A-60 spectrometer.

1-Ethyl-3-methyl-5-pyrazolecarboxylic Acid (25). Method B. A mixture of 154 g (1.0 mol) of ethyl 3-methyl-5-pyrazolecarboxylate[15] and 85 g (0.55 mol) of diethyl sulfate was stirred and heated at 150–160° for 2 hr, cooled to 80°, and poured with stirring into 500 ml of 5 *N* NaOH. The mixture was stirred at 80–90° for 0.5 hr, cooled to 50°, acidified with 135 ml of concentrated HCl, cooled to 5°, and filtered. The acid was washed with ice H_2O and air-dried to give 146 g of **25**, mp 135–140°. Pure, dry **25** melted at 143–145°.

1-Ethyl-3-methyl-4-nitro-5-pyrazolecarboxylic Acid (26). Method C. Concentrated H_2SO_4‡ (350 g) was added to 100 ml of 90% HNO_3 and at 75–85°, 146 g (0.95 mol) of **25** was added portionwise with stirring to maintain the temperature at 85°. After completion of the addition, the mixture was heated on the steam bath for 1–2 hr. The nitration mixture was cooled and poured into 0.5 kg of ice. The suspension was filtered cold (10°) and the solid was washed with ice-cold brine and then air-dried to give 180 g of **26**, mp 155° dec (contaminated with 10–12 g of NaCl).

1-Ethyl-3-methyl-4-nitro-5-pyrazolecarbonyl Chloride (27). Compound **26** (180 g) was added in portions to 180 g (0.86 mol) of PCl_5 in 1-l. boiling flask with swirling. When the additions were completed, the mixture was heated on the steam bath *ca.* 4 hr when HCl evolution had stopped. The mixture was filtered (sintered glass) to remove *ca.* 12 g of NaCl and the filtrate was stripped of $POCl_3$ and PCl_5 at the water aspirator. The residual acid chloride could be distilled [bp 147–149° (15 mm)] but was satisfactory for direct use in the next reaction.

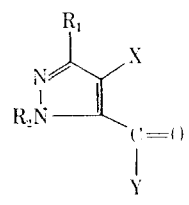
1-Ethyl-3-methyl-4-nitropyrazol-5-yl Phenyl Ketone (45). Method D. The above acid chloride **27** (165 g, 0.76 mol) dissolved in 100 ml of benzene was added in a thin stream to a suspension of 100 g (0.76 mol) of anhydrous $AlCl_3$ in 600 ml of benzene at 20–35°. The reaction mixture was stirred under reflux for 2 hr and decomposed by pouring into 600 ml of cold 10% HCl. The benzene layer was separated and stirred 0.5 hr with 300 ml of 1 *N* NaOH, then washed with brine, and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was crystallized from 250 ml of MeOH to give 156 g (80%) of **45**, mp 56–58°.

1-Ethyl-3-methyl-4-nitropyrazol-5-yl α,α,α-Trifluoro-o-tolyl Ketone (50). Method F. A solution of commercial *n*-butyllithium in heptane (60 ml, 0.1 mol) was added dropwise at 0° under N_2 to a solution of 22 g (0.1 mol) of *o*-bromo-α,α,α-trifluorotoluene in 150 ml of THF. After 15 min, the pale yellow solution was cooled to −40° and added slowly to a cold (−40°) solution of 20 g (0.1 mol) of acid chloride **27** in 120 ml of THF. The red mixture was allowed to warm to 20° and the solvent evaporated *in vacuo*. The residue was stirred 1 hr in a mixture of 250 ml of benzene and 250 ml of 1 *N* NaOH. The benzene layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallized from ethyl acetate–petroleum ether to yield **50**, 20 g (73%), mp 119–121°.

4-Amino-1-ethyl-3-methylpyrazol-5-yl Phenyl Ketone (60). Method E (Fe Reduction). Compound **45** (520 g, 2.0 mol) was dissolved in 1.5 l. of 95% EtOH, diluted with 900 ml of water, and cooled to 25°. Iron powder (reduced) (520 g) was added, followed

[=] B. P. H. Poschel, *et al.*, manuscript in preparation.

Table II. 1,3-Dialkylpyrazoles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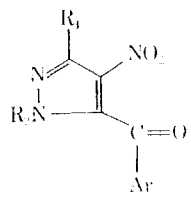
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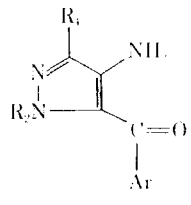
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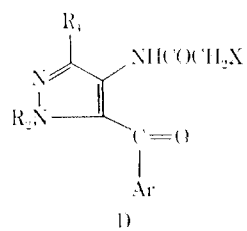
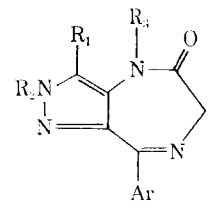

D

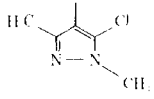
Compd no.	R_1	R_2	X	Y	Yield, %	Mp or bp (mm), °C	Purification solvent	Formula	Analyses[a]
				Compounds of Structure A					
22	CH_3	CH_3	H	OH	93	206–207	H_2O	$C_6H_8N_2O_2$[b]	
23	CH_3	CH_3	NO_2	OH	80[c]	155–158	H_2O	$C_6H_7N_3O_4$[d]	
24	CH_3	C_2H_5	H	OC_2H_5	29	100–105 (12)		$C_9H_{14}N_2O_2$[e]	
25	CH_3	C_2H_5	H	OH	95[c]	143–145	H_2O	$C_7H_{10}N_2O_2$[c]	
26	CH_3	C_2H_5	NO_2	OH	90	157–158	H_2O	$C_7H_9N_3O_4$	C, H, N
27	CH_3	C_2H_5	NO_2	Cl	90	147–149 (15)		$C_7H_8ClN_3O_3$[f]	
28	CH_3	n-C_3H_7	H	OC_2H_5	42	108–115 (10)		$C_{10}H_{16}N_2O_2$	C, H
29	CH_3	n-C_3H_7	H	OH	89	110–111	EtOH	$C_8H_{12}N_2O_2$	C, H
30	CH_3	n-C_3H_7	NO_2	OH	93	129–131	MeCN	$C_8H_{11}N_3O_4$	C, H, N
31	CH_3	n-C_3H_7	NO_2	Cl	90	148–150 (13)		$C_8H_{10}ClN_3O_3$	C, H
32	CH_3	i-C_3H_7	H	OC_2H_5	30	128–141 (23)		$C_{10}H_{16}N_2O_2$[g]	
33	CH_3	i-C_3H_7	H	OH	85	140–141	H_2O	$C_8H_{12}N_2O_2$[g]	
34	CH_3	i-C_3H_7	NO_2	OH	90	163–164	EtOAc	$C_8H_{11}N_3O_4$	C, H, N
35	CH_3	i-C_3H_7	NO_2	Cl	68	79–85 (1)		$C_8H_{10}ClN_3O_3$	Cl
36	C_2H_5	H	H	OC_2H_5	60	125–132 (1)		$C_8H_{12}N_2O_2$[h]	C, H, N
37	C_2H_5	CH_3	H	OH	90	143–145	$CHCl_3$–pet. ether	$C_7H_{10}N_2O_2$	C, H, N
38	C_2H_5	CH_3	NO_2	OH	50	120–123	EtOAc–pet. ether	$C_7H_9N_3O_4$	C, H, N
39	C_2H_5	CH_3	NO_2	Cl	76	94–97 (1)		$C_7H_8ClN_3O_3$[i]	
40	C_2H_5	C_2H_5	H	OH	74	100–102	H_2O	$C_8H_{12}N_2O_2$	H, N; C[j]
41	C_2H_5	C_2H_5	NO_2	OH	80	132–135	H_2O	$C_8H_{11}N_3O_4$	C, H, N
42	C_2H_5	C_2H_5	NO_2	Cl	90	92–98 (1)		$C_8H_{10}ClN_3O_3$[f]	
				Compounds of Structure B					
			Ar	X					
43	CH_3	CH_3	C_6H_5		79	63–65	EtOAc–pet. ether	$C_{12}H_{11}N_3O_3$	C, H, N
44	CH_3	CH_3	4-FC_6H_4		61	90–92	EtOAc-pet. ether	$C_{12}H_{10}FN_3O_3$	C, H, N
45	CH_3	C_2H_5	C_6H_5		80	56–58	MeOH	$C_{13}H_{13}N_3O_3$	C, H, N
46	CH_3	C_2H_5	4-$CH_3C_6H_4$		90	148–150 (0.15)		$C_{14}H_{15}N_3O_3$[j]	
47	CH_3	C_2H_5	4-$CH_3OC_6H_4$		64	154–158 (0.15)		$C_{14}H_{15}N_3O_4$[j]	
48	CH_3	C_2H_5	4-ClC_6H_4		36	165–170 (0.15)		$C_{13}H_{12}ClN_3O_3$[j]	
49	CH_3	C_2H_5	4-FC_6H_4		45	60–62	MeOH	$C_{13}H_{12}FN_3O_3$	C, H, N

50	CH_3	C_2H_5	$2\text{-}CF_3C_6H_4$		63	119–121	EtOAc–pet. ether	$C_{14}H_{12}F_3N_3O_3$	C, H, N
51	CH_3	C_2H_5	$2\text{-}C_4H_3S$		27	79–81	MeOH	$C_{11}H_{11}N_3O_3S$	C, H, N
52	CH_3	C_2H_5	$2\text{-}(5\text{-}ClC_4H_2S)$		50	125–127	*i*-PrOH	$C_{11}H_{10}ClN_3O_3S$	C, H, N
53	CH_3	$n\text{-}C_3H_7$	C_6H_5		94	133–140 (0.15)		$C_{14}H_{15}N_3O_3$	C, H
54	CH_3	$i\text{-}C_3H_7$	C_6H_5		57	148–153 (0.3)		$C_{14}H_{15}N_3O_3$	H, N; C[k]
55	C_2H_5	CH_3	C_6H_5		80	57–59	EtOAc–pet. ether	$C_{13}H_{13}N_3O_3$	C, H, N
56	C_2H_5	C_2H_5	C_6H_5		76	69–72	EtOAc–pet. ether	$C_{14}H_{15}N_3O_3$	C, H, N
					Compounds of Structure C				
57	CH_3	CH_3	C_6H_5		90[l]	192 dec	*i*-PrOH	$C_{12}H_{13}N_3O\cdot HCl$	C, H, N
58	CH_3	CH_3	$4\text{-}FC_6H_4$		66[m]	187–189	*i*-PrOH	$C_{12}H_{12}FN_3O\cdot HCl$	C, H, N
69	CH_3	CH_3	$2\text{-}C_4H_3M$		20[n]			$C_{10}H_{11}N_3OS$[o]	
60	CH_3	C_2H_5	C_6H_5		78,[p] 75[q]	152–162 (1)			
						195–197	*i*-PrOH	$C_{13}H_{15}N_3O\cdot HCl$	C, H, N
61	CH_3	C_2H_5	$4\text{-}CH_3C_6H_4$		69[m]			$C_{14}H_{17}N_3O$[o]	
62	CH_3	C_2H_5	$4\text{-}CH_3OC_6H_4$		85[m]			$C_{14}H_{17}N_3O_2$[o]	
63	CH_3	C_2H_5	$4\text{-}ClC_6H_4$		84[m]			$C_{13}H_{14}ClN_3O$	
64	CH_3	C_2H_5	$4\text{-}FC_6H_4$		90[l]	205–206	*i*-PrOH	$C_{13}H_{14}FN_3O\cdot HCl$	C, H, N
65	CH_3	C_2H_5	$3\text{-}ClC_6H_4$		75[n]			$C_{13}H_{14}ClN_3O$	
66	CH_3	C_2H_5	$3\text{-}NO_2C_6H_4$		73[r]	192–194	*i*-PrOH	$C_{13}H_{14}N_4O_3\cdot HCl$	C, H, N
67	CH_3	C_2H_5	$2\text{-}CF_3C_6H_4$		80[l]	169–171	*i*-PrOH	$C_{14}H_{14}F_3N_3O\cdot HCl$	C, H, N
68	CH_3	C_2H_5	$2\text{-}C_4H_3S$		53[n]			$C_{11}H_{13}N_3OS$[o]	
69	CH_3	C_2H_5	$2\text{-}(5\text{-}ClC_4H_2S)$		67[m]	80–81	EtOH–H_2O	$C_{11}H_{12}ClN_3OS$	C, H, N
70	CH_3	$n\text{-}C_3H_7$	C_6H_5		81[m]	135–142 (0.2)[s]		$C_{14}H_{17}N_3O$	C, H, N
71	CH_3	$i\text{-}C_3H_7$	C_6H_5		90[l]	203–205	*i*-PrOH	$C_{14}H_{17}N_3O\cdot HCl$	H, N; C[t]
72	C_2H_5	CH_3	C_6H_5		50[m]	143–147 (0.2)		$C_{13}H_{15}N_3O$	C, H, N
73	C_2H_5	C_2H_5	C_6H_5		35[l]	170–173	*i*-PrOH	$C_{14}H_{17}N_3O\cdot 0.5H_2O$	C, H, N
					Compounds of Structure D				
74	CH_3	CH_3	C_6H_5	Br	**92**	181–183	EtOH–ether	$C_{14}H_{14}BrN_3O_2\cdot HBr$	H, N; C[u]
75	CH_3	CH_3	C_6H_5	NHCbz	75	112–114	EtOAc–pet. ether	$C_{22}H_{22}N_4O_2\cdot 2HBr$	C, H, N
76	CH_3	CH_3	C_6H_5	NH_2	57	230	*i*-PrOH	$C_{14}H_{16}N_4O_2\cdot 2HBr$	C, H, N
77	CH_3	C_2H_5	C_6H_5	Br	90	130–132	Ether	$C_{15}H_{16}BrN_3O_2$	C, H, N
78	CH_3	C_2H_5	C_6H_5	N_3	83	95–97	EtOAc–pet. ether	$C_{15}H_{16}N_6O_2$	C, H, N
79	CH_3	C_2H_5	C_6H_5	NHCbz	63	91–93	EtOAc–pet. ether	$C_{23}H_{24}N_4O_4$	C, H, N
80	CH_3	C_2H_5	C_6H_5	NH_2	90	203–205	*i*-PrOH	$C_{15}H_{18}N_4O_2\cdot 2HBr$	H, N; C[v]
81	CH_3	C_2H_5	C_6H_5	Phthalimido	89	218–220	CH_2Cl_2–ether	$C_{23}H_{20}N_4O_4$[w]	
82	CH_3	C_2H_5	$2\text{-}CF_3C_6H_4$	Br	71	122–124	Ether	$C_{16}H_{15}BrF_3N_3O_2$	C, H, N
83	CH_3	C_2H_5	$2\text{-}CF_3C_6H_4$	N_3	92	104–105	EtOAc–pet. ether	$C_{16}H_{15}F_3N_6O_2$	C, H, N
84	CH_3	C_2H_5	$4\text{-}FC_6H_4$	Br	82	157–158	EtOAc	$C_{15}H_{15}BrN_3O_2$	C, H, N
85	CH_3	C_2H_5	$4\text{-}FC_6H_4$	N_3	91	164–166	EtOAc	$C_{15}H_{15}N_6O_2$	C, H, N

[a]Table I, footnote *f*. [b]Table I, footnote *a*. [c]By procedure in Experimental Section. [d]Table I, footnote *b*. [e]Reference 6. [f]Only spectral analysis was obtained. [g]Table I, footnote *d*. [h]From ethyl propionylpyruvate [O. Deils, J. Sielisch, and E. Müller, *Chem. Ber.*, **39**, 1328 (1906)] and hydrazine. [i]C: calcd, 57.12; found, 56.67. [j]Only spectral data obtained, used as an oil in the next step. [k]C: calcd, 61.52; found, 60.65. [l]By Raney nickel reduction. [m]By iron reduction. [n]*Via* Grignard, method G. [o]Not analyzed and used directly in the next step. [p]97% by gc. [q]99% by gc. [r]By acid hydrolysis of diazepinone **110**. [s]HCl salt from *i*-PrOH, mp 191–192°. [t]C: calcd, 60.09; found, 59.66. [u]C: calcd, 40.31; found, 40.89. [v]C: calcd, 40.20; found, 40.68. [w]Ir and nmr consistent with structure; single spot in tlc.

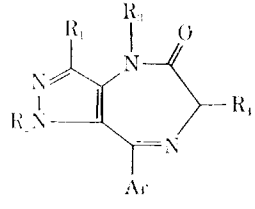
Table III. 2,3-Dialkyl-8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones



Compd no.	R_1	R_2	R_3	Ar	Method	Yield, %	Mp, °C	Purification solvent	Formula	Analyses[c]	PM,[a] MED_{100}, mg/kg	AX,[b] mg/kg
Chlordiazepoxide											4[e]	10[d]
Diazepam											4[e]	1.25[d]
86	CH_3	CH_3	H	C_6H_5	H	55	265–267	EtOH	$C_{14}H_{14}N_4O$	C, H, N	125	>40
87	CH_3	CH_3	CH_3	C_6H_5	M	50	170–173	$CHCl_3$–pet. ether	$C_{15}H_{16}N_4O$	C, H, N	32	80
88	CH_3	CH_3	C_2H_5	C_6H_5	M	71	154–156	EtOAc–pet. ether	$C_{16}H_{18}N_4O$	C, H, N	250	>80
89	CH_3	C_2H_5	H	C_6H_5	H	45	213–215	EtOH	$C_{15}H_{16}N_4O$	C, H, N	32	80
90	CH_3	C_2H_5	CH_3	C_6H_5	M	44	130–132	Benzene–pet. ether	$C_{16}H_{18}N_4O$	C, H, N	32	40
91	CH_3	*i*-C_3H_7	H	C_6H_5	H	30	210–212	MeOH	$C_{16}H_{18}N_4O$	C, H, N	>500	>80
92	CH_3	CH_3	H		K	53	253–255	Toluene	$C_{13}H_{15}ClN_6O$	C, H, N	>500	

[a] Five fasted rats weighing between 100 and 150 g were used for each dose level (500, 250, 125, 63, . . ., mg/kg). MED_{100} represents the minimal effective dose required to prevent clonic seizures in 100% of the rats. [b] Eight Holtzman male rats weighing 200–230 g are treated at each dose level (40, 20, 10, 5, . . ., mg/kg) and are used only once in the procedure. A control group of eight rats treated with water or 0.2% methocel 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). [c] Reference 11. [d] Reference 12. [e] Table I, footnote *f*.

Table IV. 1,3-Dialkyl-8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones



Compd no.	R_1	R_2	R_3	R_4	Ar	Method	Yield, %	Mp, °C	Purification solvent	Formula	Analyses[j]	PM,[k] MED_{100}, mg/kg	AX,[l] MED, mg/kg
Chlordiazepoxide												4	10
Diazepam												4	1.25
93	CH_3	CH_3	H	H	C_6H_5	H[g]	70[i]	267–270[h]	Toluene	$C_{14}H_{14}N_4O$	C, H, N	8	5
94	CH_3	CH_3	CH_3	H	C_6H_5	M	37	213–215	*i*-PrOH	$C_{15}H_{16}N_4O \cdot HCl \cdot H_2O$	C, H, N	32	20
95	CH_3	CH_3	CH_2CF_3	H	C_6H_5	M	50	186–187	Toluene	$C_{16}H_{15}F_3N_4O$	C H N	250	>40
96	CH_3	CH_3	H	H	4-FC_6H_4	H	24	218–222	Toluene	$C_{14}H_{13}FN_4O$	C, H, N	>500	>40
97	CH_3	CH_3	H	H	2-C_4H_3S	H	19	246–247	EtOH	$C_{12}H_{12}N_4OS$	C, H	64	2.5
98	CH_3	C_2H_5	H	H	C_6H_5	H	70[i]	221–223	Toluene	$C_{15}H_{16}N_4O$	C, H, N	4	2.5

99	CH_3	C_2H_5	CH_3	H	C_6H_5	M	72	99–102	Cyclohexane	$C_{16}H_{18}N_4O$	C, H, N	16	10
100	CH_3	C_2H_5	C_2H_5	H	C_6H_5	M	68	91–93	Cyclohexane	$C_{17}H_{20}N_4O$	C, H, N	>500	20[d]
101	CH_3	C_2H_5	$(CH_2)_3N(Me)_2$	H	C_6H_5	M	10	178–180	*i*-PrOH–ether	$C_{20}H_{29}N_5O \cdot HBr$	C, H, N	>500	>40
102	CH_3	C_2H_5	$(CH_2)_2N(Et)_2$	H	C_6H_5	M	48	188–193	i-PrOH–ether	$C_{21}H_{29}N_5O \cdot HBr$	C, H, N	>500	>40
103	CH_3	C_2H_5	H	CH_3	C_6H_5	H	43	223–226	Toluene	$C_{16}H_{18}N_4O$	C, H, N	64	2.5
104	CH_3	C_2H_5	H	H	4-$CH_3C_6H_4$	H	37	199–201	Toluene	$C_{16}H_{18}N_4O$	C, H, N	>500	40[d]
105	CH_3	C_2H_5	H	H	4-$CH_3OC_6H_4$	H	36	198–200	Toluene	$C_{16}H_{18}N_4O_2$	C, H, N	>500	20[d]
106	CH_3	C_2H_5	H	H	4-ClC_6H_4	H	51	240–242	Toluene	$C_{15}H_{15}ClN_4O$	H, N; C[e]	>500	>40
107	CH_3	C_2H_5	H	H	4-F-C_6H_4	L	69	198–200	MeCN	$C_{15}H_{15}FN_4O$	C, H, N		
108	CH_3	C_2H_5	H	H	3-ClC_6H_4	H	30	224–225	Xylene	$C_{15}H_{15}ClN_4O$	H, N; C[f]		>40
109	CH_3	C_2H_5	H	H	3-BrC_6H_4	N	71	227–228	EtOAc	$C_{15}H_{15}BrN_4O$	C, H, N		>40
110	CH_3	C_2H_5	H	H	3-$NO_2C_6H_4$	N	88	155–157	MeOH	$C_{15}H_{15}N_5O_3$	C, H, N	500	>40
111	CH_3	C_2H_5	H	H	2-$CF_3C_6H_4$	H[g]	49[g]	195–197	Toluene	$C_{16}H_{15}F_3N_4O$	C, H, N	16	5
112	CH_3	C_2H_5	H	H	2-C_4H_3S	H	10	205–206	EtOH	$C_{13}H_{14}N_4OS$	C, H	16	2.5
113	CH_3	C_2H_5	H	H	2-(5-ClC_4H_2S)	H	15	189–192	EtOH	$C_{13}H_{13}ClN_4OS$	C, H		>40
114	CH_3	*n*-C_3H_7	H	H	C_6H_5	H	71	168–172	*i*-PrOH	$C_{16}H_{18}N_4O$	C, H, N	8	5–10
115	CH_3	*n*-C_3H_7	CH_3	H	C_6H_5	M	82	82–84	C_6H_6–pet. ether	$C_{17}H_{20}N_4O$	C, H, N	16–32	>40
116	CH_3	*i*-C_3H_7	H	H	C_6H_5	H	34	207–210	Toluene	$C_{16}H_{18}N_4O$	H; C[h]	32	20
117	CH_3	*i*-C_3H_7	CH_3	H	C_6H_5	M	20	145–147	Toluene	$C_{17}H_{20}N_4O$	C, H, N	>250	>40
118	C_2H_5	CH_3	H	H	C_6H_5	H	50	236–239	Toluene	$C_{16}H_{18}N_4O$	C, H, N	16	5
119	C_2H_5	CH_3	CH_3	H	C_6H_5	M	32	91–93	Ether	$C_{16}H_{18}N_4O$	C, H, N	16	10
120	C_2H_5	C_2H_5	H	H	C_6H_5	H	52	212–215	Toluene	$C_{16}H_{18}N_4O$	C, H, N	32	20–40
121	C_2H_5	C_2H_5	CH_3	H	C_6H_5	M	54	79–81	Ether	$C_{17}H_{20}N_4O$	C, H, N	32	5[i]

[a]Method J, 40% yield; method K, 57%. [b]HCl from EtOH, mp 295°. [c]Method I, 63% yield; J, 50%; K, 55%; L, 71%. [d]Weak, unpromising activity. [e]C: calcd, 59.50; found, 60.19. [f]C: calcd, 59.50; found, 60.00. [g]Method L, 50% yield. [h]C: calcd, 68.07; found, 68.52. [i]Inactive <5 and >5, weak activity. [j]Table I, footnote *f*. [k]Table III, footnote *a*. [l]Table III, footnote *b*.

by 20 ml of concentrated HCl, and the mixture was stirred and heated to 60°. An exothermic reaction resulted in a rapid reflux for the next 20 min; after this reaction subsided, the mixture was stirred under reflux for another 2 hr. The cooled reaction mixture was filtered using Supercel. The filter cake was washed well with EtOH, and the filtrate was evaporated *in vacuo*. The residue was diluted with ether, and the solution was extracted with water and dilute NaOH. The ether solution was dried ($MgSO_4$) and the solvent evaporated to give 415 g of **60**. This dark oil was homogeneous by gc and satisfactory for use in the next step. Distillation gave 345 g (75%), bp 152–162° (1 mm) (gc 99%). A 2.5-g sample dissolved in 50 ml of CH_3CN was treated with 1 ml of concentrated HCl to give 2.7 g of the hydrochloride salt, mp 198–199°.

60 by Raney Nickel Reduction. A mixture of 129.5 g (0.5 mol) of **45** in 800 ml of MeOH and 40 ml of concentrated NH_4OH was hydrogenated in the presence of 10 g of 50:50 nickel-H_2 (Raney Catalyst Co). An exothermic reaction to 82° was observed in the first 0.5 hr. The hydrogenation was stopped at the end of 2.5 hr when the temperature had returned to 28° and the theoretical amount of H_2 had been consumed. The mixture was filtered, and the filtrate was concentrated *in vacuo* and distilled to yield 90 g (78%) of **60** (gc 97%).

4-Amino-5-cyano-1-ethyl-3-methylpyrazole. 1-Ethyl-3-methyl-4-nitropyrazole-5-carboxamide (mp 175–176°, CH_3CN) (60 g) (from the reaction of **27** with aqueous NH_4OH) was stirred under reflux in 350 ml of $POCl_3$. The resulting 5-cyano-1-ethyl-3-methyl-4-nitropyrazole (mp 60–62°, $CHCl_3$–ligroine) (45 g) was hydrogenated in a mixture of 100 ml of MeOH and 300 ml of THF in the presence of 5 g of Raney nickel at an initial pressure of 3.5 kg/cm^2 to give 34 g of the aminopyrazole, mp 82–84° (isooctane).

4-Amino-1-ethyl-3-methylpyrazol-5-yl 2-Thienyl Ketone (68). Method G. A solution of 34 g (0.25 mol) of 4-amino-5-cyano-1-ethyl-3-methylpyrazole in 500 ml of THF was added gradually to a stirred solution of 2-thienyllithium prepared by the reaction of 600 ml of commercial butyllithium in heptane (1.0 mol) with 92 g (1.1 mol) of thiophene in 700 ml of THF. The reaction mixture was stirred and heated at 65° for 16 hr, cooled, and treated with 1 l. of water. The organic phase was separated, diluted with ether, and washed with H_2O. The organic layer was extracted with excess dilute HCl; the acidic aqueous extract was made basic with concentrated NaOH and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give 31 g (53%) of **68** as an oil of satisfactory purity to use in the next step.

1-Ethyl-4,6-dihydro-3-methyl-8-phenylpyrazolo[4,3-*e*][1,4]diazepin-5(1*H*)-one (98). Method H. A mixture of 53 g (0.23 mol) of **60**, 56 g (0.4 mol) of glycine ethyl ester hydrochloride, 3 ml of piperidine, and 300 ml of pyridine was stirred under reflux for 4 hr, then *ca.* 120 ml of solvent was distilled out slowly. This was replaced by an equal volume of fresh pyridine, another 8 g of glycine ester hydrochloride was added, and the mixture was stirred under reflux overnight and evaporated *in vacuo*. The residue was stirred in a mixture of 500 ml of CH_2Cl_2 and 400 ml of 4 *N* NH_4OH. The organic phase was separated, washed three times with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to *ca.* 120 ml. The solution was diluted with 250 ml of EtOAc and refrigerated. The precipitate was collected to give 43 g (70%) of **98**, mp 221–223°, after recrystallization from toluene. As measured by uv this diazepinone and close analogs hydrolyzed fairly readily at intermediate pH values (2.5–5) with a half-life of several hours to the open-chain 4-(2-aminoacetamido)5-benzoyl-1,3-dialkylpyrazole (*cf.* **80**). Recyclization to the diazepinone **98** was extremely rapid (minutes) above pH 10. At lower pH (0–1) a half-life of 30–50 hr was observed and at pH 7 and above the pyrazolodiazepinones were quite stable.

98. Method K. Dicyclohexylcarbodiimide (16 g, 0.08 mol) was added to a solution of 18 g (0.08 mol) of compound **60** and 15 g (0.08 mol) of carbobenzoxyglycine in 300 ml of EtOAc, and the mixture was stirred under reflux for 16 hr. The reaction mixture was cooled and filtered to remove 15.5 g of dicyclohexylurea. The filtrate was washed with a $NaHCO_3$ solution and then 1 *N* HCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized from EtOAc–ligroine to give 21 g (63%) of **79**, mp 91–93°. This 4-(2-carbobenzoxyaminoacetamido)-5-benzoyl-1-ethyl-3-methylpyrazole (20 g, 0.048 mol) was dissolved in 200 ml of 20% HBr in glacial HOAc. After standing 2 hr, the brown solution was poured into 1.2 l. of dry ether. The precipitate was collected and dried *in vacuo* to give 23 g of the dihydrobromide salt of **80**, mp 203–205°, from *i*-PrOH–EtOAc. Compound **80**·2HBr (20 g, 0.045 mol) was dissolved in 100 ml of H_2O and made strongly basic with concentrated NaOH, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the sol-

vent was evaporated. The residue was recrystallized from toluene to give 6.6 g (55%) of 98, mp 221–223°.

1-Ethyl-4,6-dihydro-3-methyl-8-(α,α,α-trifluoro-o-tolyl)pyrazolo[4,3-e][1,4]diazepin-5(1 *H*)-one (111). Method L. Compound 83 (11 g, 0.029 mol) was dissolved in 110 ml of glacial HOAc and hydrogenated in the presence of 1 g of 5% Pd/C for 2.5 hr. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed twice with a saturated $NaHCO_3$ solution, and dried ($MgSO_4$), and the solvent was evaporated. The ir spectra suggested the presence of the uncyclized 4-(2-aminoacetamido) derivative, so the oil was refluxed 2.5 hr in toluene containing 1 ml of HOAc. Evaporation of the solvent and crystallization of the residue from toluene gave 5 g (49%) of 111, mp 195–197°.

4-(2-Azidoacetamido)-1-ethyl-3-methylpyrazol-5-yl α,α,α-Trifluoro-o-tolyl Ketone (83). A mixture of 14 g (0.033 mol) of 82 and 3.2 g (0.05 mol) of NaN_3 in 25 ml of DMF was stirred at 40° for 3 hr and poured into 400 ml of ice water. The precipitate was collected, washed with H_2O, and air-dried to give 11.8 g (92%) of 83, mp 104–105° (EtOAc–petroleum ether).

4-(2-Bromoacetamido)-1-ethyl-3-methylpyrazol-5-yl α,α,α-Trifluoro-o-tolyl Ketone (82). A solution of 14 g (0.047 mol) of 67 in 200 ml of $ClCH_2CH_2Cl$ was mixed with 50 ml of H_2O and 10 g of $CaCO_3$ was added. Bromoacetyl bromide (13 g, 0.065 mol) was added dropwise as the temperature rose to 40°. The mixture was stirred another 2 hr and filtered. The organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized from ether to give 14 g (71%) of 82, mp 122–124°.

4,6-Dihydro-2,3,4-trimethyl-8-phenyl-5*H*-pyrazolo[4,3-e]diazepin-5-one (87). Method M. A solution of 7.5 g (0.03 mol) of 86 in 40 ml of DMF was treated portionwise with 1.5 g (0.03 mol) of NaH (50% dispersion in mineral oil). After stirring for 0.5 hr, 3 ml of methyl iodide was added and stirring was continued for 4 hr. The mixture was diluted with 250 ml of H_2O and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was crystallized from $CHCl_3$–petroleum ether to give 4 g (50%) of 99, mp 170–173°.

8-(*m*-Bromophenyl)-1-ethyl-4,6-dihydro-3-methylpyrazolo[4,3-e][1,4]diazepin-5(1*H*)-one (109). Method N. Compound 98 (20 g, 0.075 mol) was dissolved at room temperature in a mixture of 90 ml of concentrated H_2SO_4 and 10 ml of H_2O; then 12 g of bromine and 14 g of silver sulfate[16] were added in portions with vigorous stirring as the temperature rose to 36°. The mixture was stirred for 6 hr, allowed to stand overnight, and filtered. The filtrate was poured into 600 ml of ice water and made basic with concentrated NaOH, and the mixture was extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated. The residue was crystallized from EtOAc to give 18.5 g (71%) of 109, mp 227–228°.

1-Ethyl-4,6-dihydro-3-methyl-8-(*m*-nitrophenyl)pyrazolo[4,3-e][1,4]diazepin-5(1*H*)-one (110). Method N. Compound 98 (15 g, 0.055 mol) was dissolved in 40 ml of concentrated H_2SO_4 and was added dropwise with stirring at 10° to a mixture of 40 g of fuming H_2SO_4 (20% SO_3) and 13 ml of 90% HNO_3 acid. The mixture was stirred at 10° for 1 hr, then an additional 2 hr at 25°, and then added slowly to a mixture of 350 g of ice and 350 ml of concentrated NH_4OH. The yellow precipitate was collected, washed with H_2O, and dried at 50° *in vacuo* to give 15.3 g (88%) of 110, mp 155–157° dec. Hydrolysis gave a single amino ketone 66 in 73% yield whose HCl salt melted at 192–194°.

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References

(1) R. Littell and D. Allen, Jr., *J. Med. Chem.*, 8, 722 (1965).
(2) H. DeWald, U. S. Patent 3,557,095 (1971); Y. L'Italien and I. Nordin, U. S. Patent 3,553,209 (1971).
(3) H. DeWald and D. Butler, U. S. Patent 3,558,605 (1971).
(4) M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumagari, and Y. Takigawa, *J. Med. Chem.*, 16, 214 (1973).
(5) F. Tinney, Belgium Patent 745,560 (1970); U. S. Patent 3,558,606 (1971); and Invag. A. G. Netherlands Patent 6,918,485 (1970).
(6) K. v. Auwers and H. Hollman, *Chem. Ber.*, 59, 601 (1926).
(7) K. v. Auwers and T. Breyhan, *J. Prakt. Chem.*, 143, 259 (1935).
(8) C. Musante, *Gazz. Chim. Ital.*, 75, 121 (1945); *Chem. Abstr.*, 41, 4144*i* (1947).
(9) G. Archer and L. Sternbach, *Chem. Rev.*, 68, 747 (1968); J. Peterson and K. Lakowitz, *Acta Chem. Scand.*, 23, 971 (1969); F. McMillan and I. Pattison, French Patent 1,394,287 (1965).
(10) R. Fryer, B. Brust, and L. Sternbach, *J. Chem. Soc.*, 4977 (1963).
(11) G. Chen, C. Ensor, and I. Clarke, *AMA Arch. Neurol. Psychiat.*, 66, 329 (1951); 68, 498 (1952); G. Chen, R. Porterman, C. Ensor, and A. Bratton, Jr., *J. Pharmacol. Exp. Ther.*, 103, 54 (1951).
(12) B. P. H. Poschel, *Psychopharmacologia*, 19, 193 (1971).
(13) M. Olds, *J. Comp. Physiol. Psychol.*, 62, 136 (1966); B. P. H. Poschel and F. Ninteman, *Life Sci.*, 7, 317 (1968).
(14) R. Santos, C. Bowling, L. Mudgil, and J. Nodine, *Pharmacologist*, 13, 205 (1971).
(15) L. Knorr, *Justus Liebigs Ann. Chem.*, 279, 188 (1894).
(16) D. Derbyshire and W. Walters, *J. Chem. Soc.*, 573 (1950).

1-Polyfluoroalkylbenzodiazepines.[1] 1

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A series of 1-polyfluoroalkylbenzodiazepin-2-ones, -2-thiones, and 1-polyfluoroalkyl-2,3-dihydrobenzodiazepine derivatives was prepared and found to have potent antipentylenetetrazole activity combined with low toxicity. The structure-activity relationships are discussed as well as syntheses and structural determinations.

The medical importance of the benzodiazepines (*e.g.*, diazepam, Ia) as compounds possessing antianxiety, muscle relaxant, and sedative activity[2] encouraged the present studies which were aimed at preparing potent agents with therapeutic advantages over known compounds. Since metabolic studies have shown that with diazepam, for example, the principal phase I reaction is dealkylation and then further oxidation to yield a mixture of compounds each with a mix of activities,[3,4] the idea of preparing compounds more resistant to dealkylation[5] arose and 1,1-dihydroperfluoroalkyl groups, such as trifluoroethyl and pentafluoropropyl, were incorporated into the structure (Ib,c).† It was subsequently found that the main urinary metabolite of halazepam in man (after deconjugation) is

† There is considerable evidence that biological oxidations may involve an oxenoid mechanism (analogous to carbene) according to Hamilton.[5] Thus, the lowered electron density of the methylene in the 1,1-dihydroperfluoroalkyl group would not be expected to facilitate oxygen insertion.