Synthesis and Muscle Relaxant Properties of 3-amino-4-arylpyrazoles

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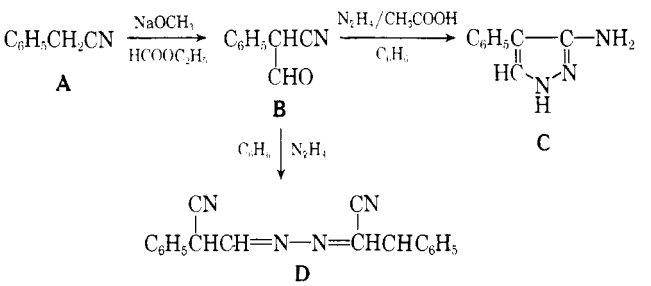
A new synthesis of 3-amino-4-arylpyrazoles involving the acetic acid catalyzed reaction of hydrazine with α-formylarylacetonitriles is described. Seventeen new pyrazoles in this series are reported, as well as thirteen new N-substituted derivatives of 3-amino-4-phenylpyrazole. While a number of these compounds exhibited muscle relaxant activity, 3-amino-4-phenylpyrazole was the most active. Structure–activity relationships are discussed.

In connection with an investigation of the synthesis and pharmacologic action of muscle relaxants, it was necessary to prepare a number of 3-aminopyrazoles unsubstituted in the 1-position. Although numerous synthetic routes for the formation of the pyrazole ring system have been described in the literature,[2] relatively few convenient methods for the preparation of 3-aminopyrazoles are described. Thus, reduction of 3-phenylazopyrazoles[3] and 3-nitropyrazoles,[4] hydrolysis of bispyrazolyl formamidines,[5] and modification of a carboxylic acid derivative in the 3-position *via* the Curtius or Hoffman rearrangements[4a,6] have been used.

A more direct route to 3-aminopyrazoles was suggested by the reaction of hydrazine with an α-substituted-β-ketonitrile to give a 3-amino-4,5-disubstituted derivative.[7] When the enol ether of an α-cyanoketone[8] or an α-cyanoaldehyde[9] was used, similar products were obtained. The preparation of 3-aminopyrazoles by the direct reaction of hydrazine with an α-cyanoaldehyde has not been reported, presumably because of the well known reaction between aldehydes and hydrazine to give excellent yields of azine. Treatment of α-formylphenylacetonitrile (**B**) with hydrazine did, in fact, generate the azide (**D**). However, small yields of 3-amino-4-phenylpyrazole (**C**) could be obtained by using excess hydrazine. Furthermore, yields of up to 88% of the pyrazole (**C**) could be obtained by adding an amount of acetic acid in excess of that required to neutralize the hydrazine. This was found to be a quite general reaction, and the compounds in Table I were prepared using the same procedure and the appropriate α-formylarylacetonitriles.

The α-formylarylacetonitriles were prepared by a modification of the method of Walther and Schickler[10] in which the corresponding arylacetonitriles were



treated with ethyl formate in benzene in the presence of sodium methoxide to give the products in generally good yields. In most cases, these compounds were characterized only by their infrared spectra and converted directly to pyrazoles without further purification. Those compounds which were more fully characterized are listed in Table II.

Extensive deformylation took place during the reaction of hydrazine and α-formyl-2-methylphenylacetonitrile under the usual conditions, probably by hydrolytic cleavage with consequent regeneration of the arylacetonitriles.[11] This occurred to better than 90% with α-formyl-3,4-dichlorophenylacetonitrile. In these two cases good yields of the aminopyrazoles could be obtained in the ring closure reaction by adding acetic anhydride to the reaction mixture, thus assuring anhydrous reaction conditions. The product was not acetylated under these conditions.

The starting arylacetonitriles were available commercially in some cases but were prepared generally from the corresponding benzyl halides by treatment with sodium cyanide in the standard manner. The benzyl halides were prepared conveniently by chloromethylation or by reduction of an appropriately substituted benzaldehyde or benzoic acid to the benzyl alcohol followed by treatment with hydrogen chloride or hydrogen bromide.

Methyl- or phenylhydrazine reacted readily with α-formylphenylacetonitrile to give, respectively, 3(5)-amino-1-methyl-4-phenylpyrazole and 3(5)-amino-1,4-diphenylpyrazole.

Several derivatives were formed from 3-amino-4-phenylpyrazole. Reaction of the compound with formic acid gave 3-formamido-4-phenylpyrazole, and lithium aluminum hydride reduction of this gave the

(1) To whom all inquires concerning pharmacology should be sent.

(2) T. L. Jacobs, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1957, p. 45.

(3) (a) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 408 (1954); (b) R. Fusco and R. Romaini, *Gazz. Chim. Ital.*, **78**, 332 (1948).

(4) (a) W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.*, **73**, 4664 (1951); (b) H. Lund, *J. Chem. Soc.*, 686 (1933); (c) H. Lund, *ibid.*, 418 (1935).

(5) G. F. Duffin and J. D. Kendall, British Patent 743,505 (1956).

(6) (a) L. Knorr, *Ber.*, **37**, 3520 (1904); (b) G. R. Clemo and T. Holmes, *J. Chem. Soc.*, 1739 (1934); (c) M. J. S. Dewar and F. E. King, *ibid.*, 114 (1945); (d) C. Musante and E. Mugnaini, *Gazz. Chim. Ital.*, **77**, 182 (1947); (e) C. Musante, *ibid.*, **78**, 178 (1948).

(7) F. Hoffmann-LaRoche and Co., A.G., British Patent 788,140 (1957).

(8) J. Pascual and F. Serratosa, *Chem. Ber.*, **85**, 686 (1952).

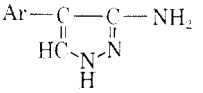
(9) (a) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956); (b) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956); **41**, 306 (1958).

(10) R. Walther and P. G. Schickler, *J. Prakt. Chem.*, **55**, 331 (1897).

(11) R. Walther and P. G. Shickler, *J. Prakt. Chem.*, **55**, 305 (1897), observed the following hydrolysis sequence

TABLE I

3-AMINO-4-ARYLPYRAZOLES



Compd. no.	Ar	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	Phenyl[a]	88	174–176	$C_9H_9N_3$	67.90	67.76	5.70	5.71	26.50	26.62
II	*o*-Chlorophenyl[b]	60	93–94	$C_9H_8ClN_3$	55.82	55.78	4.16	4.08	...	...
III	*m*-Chlorophenyl	69	130–131	$C_9H_8ClN_3$	55.82	55.83	4.16	4.14	...	...
IV	*p*-Chlorophenyl	57	141–143	$C_9H_8ClN_3$	55.82	55.77	4.16	4.39	21.70	21.77
V	3,4-Dichlorophenyl[c]	78	136–138	$C_9H_7Cl_2N_3$	47.39	47.40	3.09	3.26	18.42	18.17
VI	*o*-Tolyl[b,c]	54	93–94	$C_{10}H_{11}N_3$	69.34	68.75	6.40	5.97	24.26	23.94
VII	*m*-Tolyl[b]	65	120–121	$C_{10}H_{11}N_3$	69.34	69.22	6.40	6.58	...	...
VIII	*p*-Tolyl[b]	55	174–175	$C_{10}H_{11}N_3$	69.34	69.35	6.40	6.58	...	...
IX	2,3-Xylyl[b]	66	223–224	$C_{11}H_{13}N_3 \cdot HCl$	59.06	58.83	6.31	6.29	...	...
X	3-Chloro-*o*-tolyl[d]	50	199–200	$C_{10}H_{10}ClN_3 \cdot HCl$	49.20	49.25	4.54	4.60	...	...
XI	5-Chloro-*o*-tolyl[b,d]	37	124–125	$C_{10}H_{10}ClN_3$	57.84	57.90	4.85	4.90	20.24	19.88
XII	*m*-Trifluoromethylphenyl[b]	39	233–235	$C_{10}H_8F_3N_3 \cdot HCl$	45.55	45.36	3.44	3.53	15.94	15.61
XIII	*p*-Trifluoromethylphenyl[b]	40	132–134	$C_{10}H_8F_3N_3$	52.86	52.90	3.55	3.92	18.50	18.45
XIV	*p*-Fluorophenyl	30	225–227	$C_9H_8FN_3 \cdot HCl$	50.60	50.62	4.25	4.41	19.67	19.92
XV	*p*-Methoxyphenyl	71	192–193	$C_{10}H_{11}N_3O$[e]	62.00	62.16	5.96	5.97	21.69	21.35
XVI	*p*-Hydroxyphenyl	60	258–260	$C_9H_9N_3O \cdot HBr$	42.20	42.19	3.94	4.32	...	...
XVII	1-Naphthyl[b]	60	109–110	$C_{13}H_{11}N_3$	74.62	74.67	5.30	5.18	...	...
XVIII	3-Thianaphthenyl	33	131–133	$C_{11}H_9N_3S$[e]	60.11	60.40	4.36	4.45	19.12	19.21

[a] Parham and Bleasdale, lit.[4a] m.p. 173.5–174°. [b] The intermediate α-formylarylacetonitrile was characterized only by infrared spectra and used without purification. [c] These compounds were prepared with acetic anhydride added to the reaction mixture. [d] Prepared by G. S. Forman. [e] These compounds analyzed as quarter hydrates.

TABLE II

α-FORMYLARYLACETONITRILES, ArCH(CHO)CN

Ar[a]	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Phenyl[b]	76	159–160	C_9H_7NO	74.47	74.19	4.16	5.03	9.65	9.39
p-Chlorophenyl	71	160–162	C_9H_6ClNO	60.18	60.00	3.37	3.77	7.80	7.94
p-Fluorophenyl	80	148–150	C_9H_6ClNO	66.26	66.20	3.71	3.47	8.59	8.69
p-Methoxyphenyl	32	116–117	$C_{10}H_9NO_2$	68.56	68.32	5.18	5.35	8.00	7.84
3-Thianaphthenyl	62	119–120	$C_{11}H_7NOS$	65.65	65.56	3.51	3.59	6.96	7.11

[a] Ar = *m*-chlorophenyl, m.p. 169–171°; 3,4-dichlorophenyl, m.p. 166–168°; and 3-chloro-*o*-tolyl, m.p. 143–145°. They were obtained in yields of 83, 82, and 50%, respectively, and used without further purification. [b] See ref. 11.

3-methylamino derivative. 3-Dimethylamino-4-phenylpyrazole was prepared by a Clark–Eschweiler[12] reaction on the primary amine.

Treatment of 3-amino-4-phenylpyrazole with acetic anhydride in varying proportions gave three acetyl derivatives. On the basis of infrared spectra, these have tentatively been assigned the structures corresponding to 3-acetamido-4-phenylpyrazole, 1-acetyl-3-acetamido-4-phenylpyrazole, and 1-acetyl-3-diacetylamino-4-phenylpyrazole. Reduction of the triacetyl derivative with lithium aluminum hydride was accompanied by cleavage of two acetyl groups to give 3-ethylamino-4-phenylpyrazole. Reacetylation with excess acetic anhydride gave 1,3-diacetyl-3-ethylamino-4-phenylpyrazole.

Other derivatives prepared were the 3-ethoxyformamido- and the 3-carbamido-4-phenylpyrazoles, formed by treating the parent compound with ethyl chloroformate and potassium cyanate, respectively (Table III).

Pharmacology.—While it is true that some pharmacological activities may have more bearing on the value of the drug as a practical *muscle relaxant*, and other activities are more significant to the compound's possible *tranquilizing* effects in man, at the present state of our knowledge and with the experience gained with such drugs in medical practice, it is not possible to separate distinctly pharmacological activities under the foregoing aspects. Central muscle relaxant and mild tranquilizing qualities appear to be interrelated and mutually additive.

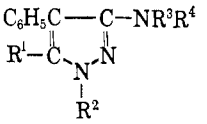
With this basic premise in mind, we have evaluated our potential muscle relaxants in certain laboratory procedures, which we consider to be suggestive of: (1) muscle relaxant activity, and (2) tranquilizing activity.

Among the present animal-testing procedures, the following three tests appear to us to be most indicative of central muscle relaxant activity of a compound: (1) physical examination of intact animals (dose range studies), (2) antagonism to strychnine, and (3) preferential interneuronal inhibition. Although both theoretical and practical objections may be raised against the validity of these tests, experience has shown that these tests serve best to assess the potential value of a centrally acting muscle relaxant.

(12) M. L. Moore, "Organic Reactions," Coll. Vol. 5, John Wiley & Sons, Inc., New York, N. Y., 1949, p. 301.

TABLE III

N-SUBSTITUTED AND 5-SUBSTITUTED PYRAZOLES



Compd. no.	R¹	R²	R³	R⁴	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XIX	CH_3[a]	H	H	H	41	134–136	$C_{10}H_{11}N_3$	69.34	69.57	6.40	6.31	24.26	24.33
XX	H	CH_3	H	H	43	166–167	$C_{10}H_{11}N_3 \cdot HCl$	57.28	57.27	5.77	5.81	20.04	20.37
XXI	H	H	CH_3	H	27	184–185	$C_{10}H_{11}N_3 \cdot HCl$	57.28	57.17	5.77	5.79	20.04	20.04
XXII	H	H	CH_3	CH_3	47	222–223	$C_{11}H_{13}N_3 \cdot HCl$	59.06	59.19	6.31	6.26	...	...
XXIII	H	H	C_2H_5	H	48	137–138	$C_{11}H_{13}N_3$	70.57	70.60	7.00	7.17	...	...
XXIV	H	$COCH_3$	C_2H_5	$COCH_3$	26	116–117	$C_{15}H_{17}N_3O_2$	66.40	66.46	6.32	6.40	...	...
XXV	H	H	$COCH_3$	H	80	155–157	$C_{11}H_{11}N_3O$	65.66	65.57	5.51	5.47	20.88	21.12
XXVI	H	$COCH_3$	$COCH_3$	H	90	152–153	$C_{13}H_{13}N_3O_2$	64.18	64.33	5.39	5.56	17.28	17.63
XXVII	H	$COCH_3$	$COCH_3$	$COCH_3$	58	112–113	$C_{15}H_{15}N_3O_3$	63.15	63.30	5.30	5.56	...	...
XXVIII	H	H	CHO	H	90	167–168	$C_{10}H_9N_3O$	64.16	64.17	4.85	5.00	22.45	23.28
XXIX	H	C_6H_5	H	H	61	137–138	$C_{15}H_{13}N_3$	76.57	76.38	5.57	5.60	17.86	18.15
XXX	CH_3	C_6H_5	H	H	30	77–79	$C_{16}H_{15}N_3$	77.08	76.86	6.06	6.09	16.86	16.73
XXXI	H	H	$COOC_2H_5$	H	18	106–108	$C_{12}H_{13}N_3O_2$	62.32	62.48	5.67	5.70	18.17	18.19
XXXII	H	H	$CONH_2$	H	70	174–176	$C_{10}H_{10}N_4O$	59.39	59.31	4.98	5.11	27.71	27.55

[a] See ref. 6e.

At the present time we are concerning ourselves exclusively with the evaluation of compounds in the muscle relaxant area.

Test Methods

Dose Range Studies.—Dose range studies in the rodent, dog, and monkey can be indicative of central muscle relaxant activity at low nontoxic doses. These indications are: depending upon dose and species, varying degrees of muscular hypotonia and weakness, loss of various polysynaptic reflexes (righting, withdrawal, and pinnal reflexes), low body posture, ataxia, unsteadiness, and at higher doses overt paralysis and prostration. Of particular importance is a muscular weakness of the ascending type, that is, appearing first and being more prominent at the caudal regions of the body (hind drop), with the musculature of the cephalic part of the trunk and neck less or not at all affected. Although animals may appear slightly sedated, depression of higher cerebral centers (hypnosis, stupor, and loss of consciousness) do not accompany the muscular hypotonia and paralysis with most centrally acting muscle relaxants. Likewise, centrally acting muscle relaxants usually do not exhibit restlessness and excitation. These peculiarities of the dose-range effects distinguish the centrally acting muscle relaxants from central depressants of the hypnotic-anesthetic and narcotic type, which may cause a descending type muscular paralysis, and, in the case of hypnotics, initial excitation.

Dose range studies of this sort do not allow one to state easily the relative potency of one muscle relaxant to another, but it is possible to obtain some suggestion of this potency in terms of the comparative doses at which muscle relaxant effects are produced; for example, hypotonia, ataxia, paralysis, and prostration. In each instance the compounds were administered orally (10 ml./kg.) and the animals were observed continually for 5 hr. and again at 24 hr.

Antagonism to Strychnine.—The technique described by Pfeiffer, *et al.*,[13] was employed. It consists in intravenous titration with strychnine of the compound to be tested. A 0.005% solution of strychnine sulfate is intravenously injected into mice at a uniform rate of 0.05 ml. every 10 sec. The end point is the tonic extension of the animals hind legs, that is the peak of the strychnine convulsion. The volume of strychnine solution injected until the end point appears is determined for untreated (control) mice and mice treated with the drug to be assayed. Drug effects are estimated by (1) the difference in amount of strychnine needed for reaching the tonic hind leg extension, and (2) comparing the proportions (or percentages) of mice killed by strychnine.

White male mice (Carwroth F, strain), 18–24 g. were used. The test compounds were suspended in a 0.5% tragacanth gel, which was administered orally. The volume of drug suspension was for all doses 10 ml./kg. bodyweight.

Preferential Interneuronal Inhibition.—The techniques of Lloyd[14] and Greene[15] were employed to evaluate the influence of the agents on the patellar reflex (monosynaptic reflex) and the flexor reflex (polysynaptic reflex) in the anesthetized cat. Cats of either sex were used, ranging in weight from 1.6 to 3.0 kg. All solutions were made up as 10% drug solutions. The drugs were solubilized in 50 to 100% "Carbowax 200," (polyethylene glycol) and injected intravenously; vols. of drug solutions ranged from 0.1 to 2.5 ml., with the majority of doses being under 1.0 ml. The speed of injections was 0.1 to 0.3 ml./min. In all instances, the appropriate Carbowax control was run prior to injection of the test compounds.

Structure-Activity Relationships.—Our current interest in a potential muscle relaxant has centered about structural analogs of 3-amino-4-phenylpyrazole (I). Table IV describes the pharmacological data for I and related compounds and includes data for two standard agents for comparison. There are three major sites in the 3-amino-4-phenylpyrazole molecule that may be varied by substitution. These are the phenyl ring, the pyrazole ring, and the primary amine group. Since the number of possible variations that may be made at a particular site or combination of sites is very large, our approach to the selection of analogs required a method of eliminating many possible structures. At the same time, we desired our choice of analogs to indicate the most advantageous positions in the molecule for substitution. When we had obtained this information we would then vary the substituting group only at these positions.

We chose as our initial substituents the chemically most accessible types for the 3-amino-4-phenylpyrazole molecule, the chlorine atom and the methyl group (see Table I).

The first approach was the preparation of the chloro congeners (II, III, IV, and V). It is our general feeling from studies with these four congeners that the *m*-chloro derivative is the only compound which shows activity that might be considered at least equal to 3-amino-4-phenylpyrazole. The antistrychnine activity of III and IV was about equal to that of the parent compound but V was only about one-fourth as

(13) (a) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exptl. Biol. Med.*, **70**, 254 (1949); (b) E. H. Jenney and C. C. Pfeiffer, *Ann. N. Y. Acad. Sci.*, **64**, 679 (1956); (c) C. C. Pfeiffer, A. J. Ripoelle, R. P. Smith, E. H. Jenney, and H. L. Williams, *ibid.*, **67**, 734 (1957).

(14) D. P. C. Lloyd, *Physiol. Rev.*, **24**, 1 (1944).

(15) L. C. Greene, *Federation Proc.*, **21**, A-322e (1962).

Table IV

Pharmacological Data on Analogs of 3-Amino-4-phenylpyrazole

Compound	Dose range studies[a] Mouse Dose, mg./kg.	Mouse Observation	Monkey[b] Dose, mg./kg.	Monkey Observation	Antistrychnine activity (mice) Dose, mg., kg.	Time, min.	% Protection	% Mortality	Preferential interneural inhibition (cats) Dose, mg./kg.	% Inhibition	Average duration, min.
I	50	Rapid breathing, depr. at 5 min. Effect gone at 30 min.	50	Hypo., mild ataxia (4 hr.)	100	30	63.8	50	5	37	
						60	25.3	80	15	70	120 plus
	100	Pinna reflex gone and hypo. in 5 min. Duration 2 hr.	100	Hypo., mod. ataxia (5 hr.)		120	20.7	50	40	100	
	200	Hypo. in 1 min., depr. then pros., no pinna reflex; still pros. at 1 hr., normal in 2.5 hr.	150	Hypo., marked ataxia (6 hr.)	150	30	90.0	10			
						60	52.5	30			
						120	25.0	70			
	300	Hypo., pros., loss of righting and pinna reflex. Duration 3.5 hr.			200	30	143.9	20			
						60	116.4	30			
						120	96.5	20			
	400	Hypo., pros., loss of pinna and righting reflex. Death 1.5 hr.									
II	100	Loss of pinna, ataxia (30 min.)	300	Slight ataxia							
	200	Loss of pinna, ataxia, depr. (60 min.)									
	300	Ataxia, depr., followed by loss of righting reflex in 15 min. Duration 3 hr.									
	400	Loss of pinna, righting reflex, pros. Duration over 3 hr.									
III	50	Slight reduction in SMA, loss of pinna reflex and slight hypo. (60–90 min.)	150	One monkey, no observable drug effects.	50	30	28.1		80		
					100	30	52.5		25		
				One monkey, no	150	30	111.9		30		
	100	Loss of pinna, and placing reflex, mild ataxia and hypo. Peak 30 min. Duration 90 min.		symptoms till 4 hr. when hypo. and ataxia were seen. Pros. followed in 5 hr.		60	16.9		40		
						90	42.0		70		
						120	20.0		50		
	150	Loss of pinna, placing and righting reflex in 15 min. Extreme hypo. Duration 2 hr.	175	Some hypo., mild ataxia (4 hr.).							
	200	Loss of pinna, placing and righting reflex in 5 min. No corneal reflex at 30 min. Duration 2 hr.	200	Ataxia, hypo., depr., semipros. (6 hr.).							
IV	25	Labored respiration, slight ataxia, depr. (30 min.)	150	No observable effects.	50	30	12.9	30			
			200	Slight hypo. in monkeys (1 of 2).	100	30	45.0	0			
	50	Ataxia, depr., loss of pinna reflex, semipros. (45 min.)			200	30	117.7	0			
	100	Very hypotonic, marked ataxia, followed by pros. in 10 min. Recovery 60–90 min.									
	200	Ataxia, hypo., loss of pinna, placing and corneal reflex in 15 min. Duration 3 hr.									
	300	Loss of righting reflex, pros. in 10 min. Duration 6 hr.									
V	25	Slight ataxia, rapid breathing	150	Slight hypo., ataxia at 2 hr. Duration 6 hr.	50	30	33.2	80	10	12	50 plus
	50	Ataxia and rapid breathing in 5 min. Hypo. and ataxia in 10 min. Duration 30 min.			100	30	71.1	20	20	19	
	100	1 of 2 very hypo. and ataxia in 5 min.; 2 of 2 very hypo., no placing or pinna reflex, pros. in 15 min. Duration 0.5–2 hr., 0.5–3.5 hr.	200–250 300	Mod. to marked hypo., ataxia. Duration 9 hr.	150	60	62.9	30	30	21	
						30	56.0	14			
						120	30.0	22			
				1 of 2 mild hypo., 1 of 2 marked hypo., 2 of 2 emesis		30	175.0	0			
	200	Pros., pinna reflex gone in 15 min. Loss of righting reflex at 30 min. Duration 5.5 hr.									
	400	Loss of righting, placing and pinna reflex in 10 min. 1 of 2 dead overnight									
	600	Loss of pinna, placing, righting reflex in 10 min. 2 of 2 dead overnight									
VI	50	No pinna reflex, depr. for 30 min.	200	Mild ataxia and hypo. Duration 3–4 hr.	100	30	43.3	10	10	24	
	100	Ataxia, hypo., loss of pinna reflex, semipros. at 30 min. Duration 45 min.	250	Very hypo. and ataxia, depr., semipros. Duration 6 hr.	150	30	34.1	40	15	35	120 plus
						60	36.7	44	20	70	
						120	27.6	40			
	200	Ataxia, hypo., loss of pinna reflex; at 12 min. loss of righting reflex, pros. Duration 3 hr.	150	Rabbit Head Drop (i.v. to rabbit produced head drop for 30 min.)	200	30	70.0	10			
						60	119.9	20			
	400	In 5 min. no righting, pinna or corneal reflex. 1 of 2 dead at 20 min. Duration 45 min.									

TABLE IV (*Continued*)

Compound	Dose range studies[a] — Mouse: Dose, mg./kg.	Mouse: Observation	Monkey[b]: Dose, mg./kg.	Monkey: Observation	Antistrychnine activity (mice): Dose, mg./kg.	Time, min.	% Protection	% Mortality	Preferential interneural inhibition (cats): Dose, mg./kg.	% Inhibition	Average duration, min.
VII	100	Loss of placing reflex, hypo. at 5 min. Duration 45-60 min.	300 (Rat)	Mod. ataxia	150	30	35.3	40			
					200	30	77.5	0			
	150	Loss of pinna and placing reflex, hypo. Duration 60-90 min.			250	30	155.0	0			
	250	Pros. loss of placing and pinna reflex. Duration 60 min.									
	300	Loss of placing, righting and pinna reflex in 5 min. Loss of corneal at 60 min. Duration 2 hr.									
VIII	100	Mild hypo.	200 (Rat)	Slight hypo.	50	30	33.8	89			
	200	Loss of placing, pinna reflex in 5 min., extreme hypo. in 5 min. Duration 90 min.			100	30	45.5	64			
					250	30	79.0	10			
	250	No placing, pinna or righting reflex. Extreme hypo. Duration 24 hr.									
	300	Pros., loss of pinna, placing, righting reflex in 5 min. Same at 2 hr. as at 5 min.									
IX	100	Some ataxia	250	No observable drug effects	200	30	27.4	40			
	200	Hypo., depr. (90 min.)			300	30	56.5	10			
	300	Loss of pinna, placing and righting reflex, pros. in 15 min. Peak 60 min. Duration 3 hr.			400	30	104.9	10			
	400	Loss of pinna, righting reflxes, pros. Peak at 60 min. Duration 4.5 hr.									
	500	Pros., loss of righting, pinna, and corneal reflexes in 5 min.									
X	100	No observable drug effects			150	30	18	33			
	150	Loss of pinna reflex, mild ataxia, hypo.			225	30	48	22			
					300	30	61	0			
	200	No placing reflex, hypo., pros. Duration 2.5 hr.									
	300	Loss of placing, pinna, righting reflex, pros.									
	400-500	Loss of placing, pinna and righting reflex, 2 of 2 dead in 24 hr.									
XI	100	10 min. slight hypo. and depr. Mod. at 15 min. Duration 45 min.	200-250	No observable drug effects	100	30	37.7	80			
					150	30	40.0	80			
					200	30	78.6	10			
	200	5 min. 1 of 2 no pinna reflex, 2 of 2 mod. hypo. 1 of 2 pros. at 10 min. Duration 5 hr.									
	300	2 of 2 no pinna, marked hypo. and depr., 15 min. No righting reflex 2 of 2. Duration 5 hr.									
	400	Loss of righting reflex at 10 min. Duration 5 hr.									
XII	500	Slight ataxia and hypo.	250	1 of 2 slight hypo. 1 of 2 marked hypo. 2 of 2 salivation. Duration 6 hr.	100	30	0	90			
	100	Moderate ataxia and hypo., depr. and tachypnea. Duration 30 min.			200	30	52.4	50			
	200	Loss of righting reflex, 1 of 2 loss of pinna reflex, depr. in 5 min. Very hypotonic, almost pros. at 15 min. Duration 2 hr.									
	300	Quite hypotonic, ataxic, tachypnea in 5 min. Semi-pros. 2 of 2, no pinna reflex in 10 min. Duration 2.5 hr.									
	400	Loss of pinna reflex, semi-pros. in 5 min. Loss of placing and righting reflex in 10 min. Duration 5 hr. 1 of 2 dead									
	500	2 of 2 dead in 15 min.									
XIII	50 & 100	Rapid respiration, ataxic, loss	50 & 100	Slight decrease in	50	45	25	100			
	150	of pinna reflex—(90 min.)		spontaneous motor	100	45	34	70			
		1 of 2 no pinna reflex, 2 of 2		activity	150	30	16	90			
		hypo., 2 of 2 ataxic—150	150	1 of 2 hypo., slight		45	53	20			
		min., 2 of 2 pros., 24 hr. 1 of		ataxia		60	46	60			
		2 dead.	300	Same as above		90	11	50			
	200 & 400	Loss of pinna reflex, very depr., hypo., pros., death				120	48	47			
XIV	50	1 of 2 slight decrease in spontaneous motor activity									
	100	1 of 2 marked ataxia, hypo., 1 of 2 normal									

Table IV (*Continued*)

Compound XIV	Dose range studies[a] Mouse Dose, mg./kg.	Mouse Observation	Monkey[b] Dose, mg./kg.	Monkey Observation	Antistrychnine activity (mice) Dose, mg./kg.	Time, min.	% Protection	% Mortality	Preferential interneural inhibition (cats) Dose, mg./kg.	% Inhibition	Average duration, min.
	200	2 of 2 marked ataxia, hypo., 1 of 2 loss of pinna reflex, 1 of 2 semipros., 2 of 2 normal 90 min.									
	300 & 400	Same as above, plus loss of pinna, placing, grasping and righting reflex, 120 min. 2 of 2 normal									
	600	2 of 2 dead within 5 min.									
XV			25, 50, 100 & 200 (Rat)	8 of 8 No observable drug effects							
XVI	50 & 100	No observable drug effect									
	200	Slight tachypnea									
	400	Mod. tachypnea followed by dyspnea. Mod. decrease in spontaneous motor activity.									
	600	Same as above plus hypo., 1 of 2 dead.									
	800	Dyspnea, followed by conv. and death 2 of 2									
XVII	50	Some excitation	250	No observable drug effects	100	30	33.4	80			
	100	Ataxia in 5 min., then ataxia and depr. Duration 60–90 min.			150	30	37.8	60			
					200	30	76.0	20			
						60	96.4	20			
	200	Loss of pinna reflex, ataxia, depr. in 5 min. Pros. at 30 min. Duration 4 hr.				120	40.2	70			
	300	Loss of pinna reflex, ataxia and depr. in 5 min. Pros. at 30 min. Loss of righting reflex at 60 min. Duration over 3 hr.									
	500	Pros., loss of placing and pinna reflex at 15 min. No righting reflex at 30 min. At 19 hr. 2 of 2 pros., no righting reflex. Recovered in 30 hr.									
XVIII	50	No observable drug effects			100	30	40	30	5	0	30
	100	2 of 2 tachypnea, slight decrease in motor activity, slight hypo.			200	30	56	20	10	51	
					300	30	115	10	20	80	
									30	100	
	200	1 of 2 pros., absence of righting reflex, 2 of 2 hypo., decrease in spontaneous motor activity.									
	300 & 500	2 of 2 marked hypo., pros., no righting or pinna reflex									
XIX			300 (Rat)	No observable drug effects. 1 of 3 slight lacrimation							
XX	100	Loss of pinna 1 of 2, 30 min. duration	200	1 of 2 very slight hypo. duration 3 hr., 1 of 2 normal	100	30	50.0	90			
	150	Loss of pinna reflex, ataxia and hypo. at 5 min. Duration 60–90 min.	250	Mild hypo. and ataxia, duration 3 hr., 1 of 2 emesis at 1 hr.	200	30	107.9	20			
					300	30	83.4	30			
	200	Loss of pinna, hypo., depr. in 5 min. Semipros. at 60 min. Duration 4.5 hr.									
	300	Loss of pinna, ataxia, depr., pros. at 15 min. Duration 4 hr.									
	400	Loss of pinna and righting reflex at 5 min. At 19 hr., 1 of 2 no change, 30 hr. 1 of 2 dead									
	500	Loss of pinna, placing reflex 5 min. 1 of 2 dead at 3 hr. 2 of 2 dead at 30 hr.									
XXI	100	Slight depr.			100	30	29.6	70			
	150	Ataxia, hypo., and depr. in 15 min. Duration 45 min.			200	30	41.5	80			
					300	30	87.3	40			
	200	No pinna reflex. pros. in 10 min. Peak at 30 min. Duration 60 min.									
	300	Loss of pinna and placing reflex, pros. in 5 min. Duration 40–120 min.									
	400	Loss of righting, pinna and corneal reflex in 5 min. Recovered overnight.									

TABLE IV (*Continued*)

Compound	Dose range studies[a] — Mouse — Dose, mg./kg.	Mouse — Observation	Monkey[b] — Dose, mg./kg.	Monkey — Observation	Antistrychnine activity (mice) — Dose, mg./kg.	Time, min.	% Protection	% Mortality	Preferential interneural inhibition (cats) — Dose, mg./kg.	% Inhibition	Average duration, min.
XXII	100 & 200	Reduced motor activity									
	300	Slight hypo. at 5 min., marked at 30 min.									
	400	Loss of pinna at 30 min., marked hypo.									
	500	Loss of pinna, hypo., depr. in 5 min. 1 of 2 pros. at 30 min.									
	800	1 of 2 pros. at 60 min., hypo.									
	1200	Extreme hypo., 2 of 2 pros., no righting or corneal reflex									
XXIII	200	Depressed									
	400	Hypo., loss of pinna reflex at 30 min. Recovered at 2 hr.									
	600	Marked depr. and hypo. at 10 min., 30 min. pros. and loss of righting reflex. Duration 5 hr.									
	800	Loss of pinna, placing and righting reflex by 30 min., loss of corneal at 60 min.									
XXIV	200	Very excited and hyperactive for more than 60 min.									
	400	Rapid respiration, stimulation, mild hypo., normal at 45 min.									
	600	Mild hypo., excitation, ataxia at 15 min. Depr., hypo. at 45 min. Duration 2.5 to 4.5 hr.									
	800	Dyspnea, hypo., depr. at 15 min. Semipros., no pinna or righting reflex at 2 hr. Duration over 5 hr.									
	1000	Hypo., depr., ataxia in 15 min. Pros., no righting or pinna reflex in 30 min. 2 of 2 dead overnight									
XXV	50	No observable drug effects									
	100	Slight hypo.									
	200	Mod. hypo., slight decrease in spontaneous motor activity									
	300–400	Same as above plus semipros., loss of pinna, corneal and righting reflex									
	600	Marked hypo., decrease in motor activity, pros., death									
XXVI	100	Excited at 5 min., depr. at 15 min. Loss of pinna reflex at 30 min. Duration 90 min.	250	No observable drug effects	200 300 400	30 30 30	12.2 17.2 89.2	50 20 0			
	200	2 of 2 mild ataxia and hypo., excitation in 10 min. Duration 90 min.									
	300	Mod. hypo., excitation in 5 min. Loss of pinna reflex, 2 of 2 pros. in 60 min. Duration 3 hr.									
	400	2 of 2 almost pros. in 10 min. At 15 min. loss of pinna, placing and righting reflexes 2 of 2. Duration 3 hr.									
	600	2 of 2 very hypo., depr., 1 of 2 no pinna reflex at 10 min. 30 min.—2 of 2 no pinna, placing or righting reflexes, duration 3 hr.									
XXVII	100	No observable drug effects	250	Emesis and hyperactivity at 3 hr. No other observable drug effects	200 500	30 30	39.5 75.6	80 30			
	200	Ataxia, excitation, loss of pinna reflex. Duration 45 min.									
	300	Depr. in 15 min. Ataxia and excitation at 30 min. Duration 45 min.									
	400	Hypo., dyspnea in 20 min. Loss of pinna reflex at 30 min. Depr., ataxia, 2 hr. duration									
	500	Hypo., excitation, loss of pinna reflex in 10 min. Depr., hypo. at 30 min. Duration 2.5 hr.									

TABLE IV (*Continued*)

Compound	Dose range studies[a] Mouse: Dose, mg./kg.	Mouse: Observation	Monkey[b]: Dose, mg./kg.	Monkey[b]: Observation	Antistrychnine activity (mice): Dose, mg./kg.	Time, min.	% Protection	% Mortality	Preferential interneural inhibition (cats): Dose, mg./kg.	% Inhibition	Average duration, min.
XXVII	750	Hypo., pros., loss of righting reflex in 30 min. Duration 3 hr.									
	1000	Same as 750; 1 of 2 dead at 2.5 hr.									
XXIX	125 & 750	No observable drug effects									
	1000	Increase in respiratory rate, decrease in spontaneous motor activity									
	2000–3000	Same as above									
	4000–5000	Increase in respiratory rate, semipros., ataxia, hypo., no pinna reflex									
XXX	250 & 400	No observable drug effects			250	30	0	70	5	70	
	500	Slight decrease in spontaneous motor activity			500	30	3	60	10	85	
	750	Decrease in spontaneous motor activity			1000	30	0	30	15	100	59
									30	75	
	1000	1 of 2 ataxia, pros.; 1 of 2 slight decrease in motor activity									
XXXI	100	No observable drug effects	100 & 150	No observable drug effect	125	30	24	50	5	16	
	200	Rapid respiration, piloerection, 1 of 2 loss of pinna reflex, 1 of 2 loss of righting reflex, 1 of 2 pros.			250	30	60	40	10	37	
			300	Slight decrease in spontaneous motor activity	350	30	99	0	20	61	188 plus
						60	92	0	30	88	
						120	48	30	40	100	
	500	Same as above, labored respiration									
	1500	2 of 2 loss of pinna reflex, hypo., 1 of 2 dead									
	2000	2 of 2 pros., 1 of 2 dead									
XXXII	125	2 of 2 decrease in spontaneous motor activity			125	30	39	50	5	0	
					250	30	64	0	10	58	
	250	Same as above plus 2 of 2 semipros.			500	30	71	40	20	60	150 plus
					750	30	100	10	40	72	
	1000	Same as above plus loss of righting reflex, no pinna or corneal reflex							60	100	
	3000	Same as above									
	5000	Same as above, death 2 of 2 in 1 hr.									
d	200	Ataxia, then depr.	50–200	Mod. hypo. and ataxia	100	30	24.5	30	5	0	20
	300	Pros.		(onset 80 min. duration 6 hr.)	200	30	37.2	22.2	10	20	
					300	30	46.8	0	15	39	
			250	Hypo., ataxia, (onset 80 min.), slight to mod. disorientation 24 hr.					20	21	
									30	51	
									40	67	
e	500	Ataxia, poor righting reflex, decreased SMA	200	2 of 2 slight resistance to pull on chain; 1 of 2 slight ataxia	500	30	32.9	30	5	16	32
	750	No righting reflex, pros., tachypnea, slight opisthotonus			750	30	41.9	50	10	8	
					1000	30	*f*	...	20	−22	
									30	−22	
									40	−80	
	1000	Pros., no righting reflex, twitching, convulsions							50	−100	

[a] Words used frequently in this table have been abbreviated as follows: conv. = convulsions; depr. = depression; hypo. = hypotonia; mod. = moderate; pros. = prostration. [b] Unless otherwise noted. [c] Other doses were run which indicated lack of a consistent dose response. [d] 2-(4-Chlorophenyl)-3-methyl-4-methathiazone-1,1-dioxide (chloromethazanone). [e] N-Isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). [f] Impossible to determine endpoint.

active in terms of preferential inhibition of the flexor reflex. The latter compound also caused emesis on monkeys at 300 mg./kg., orally.

The second approach was the preparation and evaluation of the methyl congeners (VI, VII, VIII, and IX) of 3-amino-4-phenylpyrazole. The *o*-methyl derivative appeared to be the most promising on the basis of its long duration of action. While there appeared to be some decrease in activity, the extraordinarily long duration of action seen in the rabbit head drop test was of particular interest. This was especially interesting, since the effect produced by other muscle relaxants in this test procedure usually lasts for only a few minutes or a matter of seconds at comparable dose. However, this longer duration of action was equal to the activity seen with the parent compound in the monkey. Preferential interneural inhibition in the cat was not greater than that seen with the parent compound.

In view of the activity seen with the *o*-methyl- (VI) and the *m*-chloro- (III) congeners of 3-amino-4-phenylpyrazole, the analogs with the chlorine atom in the *meta* position and the methyl group in the *ortho* position were synthesized as potential skeletal muscle relaxants (X, XI). These compounds were no more active than the parent compound. Compounds with various substituents on the benzene ring (XII–XVI) were prepared but these also were less active. Replacement of the benzene ring by the naphthalene or thianaphthene ring systems (XVII, XVIII) also produced less active compounds, although the latter compound exhibited preferential inhibition of the flexor

reflex which was equal to 3-amino-4-phenylpyrazole. The duration of action, however, was only about one-fourth that of the parent compound.

A series of compounds with nitrogen substituents or a methyl group in the 5-position were also prepared (Table III). In each instance, the compounds exhibited a decrease in muscle relaxant activity as suggested by a dose range study in mice and by the antistrychnine test. In no case did we see muscle relaxant activity which was greater than that seen in 3-amino-4-phenylpyrazole. In general, these congeners were about one-third to one-half as potent as 3-amino-4-phenylpyrazole. Compounds XXIV, XXVI, and XXVII exhibited, in addition to muscle relaxant activity, excitation in the mouse at 200 mg./kg., orally, and in the case of XXVII, excitation in the monkey at 250 mg./kg., orally. Compounds XX and XXVII caused emesis in monkeys at 250 mg./kg., orally; XXX, XXXI, and XXXII exhibited preferential inhibition of the flexor reflex which was about equal to that of the parent compound.

Discussion.—It has been our experience that, in dose range studies, good muscle relaxant activity (hypotonia, ataxia, loss of certain reflexes, etc.) can be manifested in the rodent, but if this activity is not seen in higher animals, like the monkey, this compound will have minimal clinical utility. Likewise, we have never observed the reverse of this relationship. Therefore, if reasonable activity at a fairly low dose level (50 or 100 mg./kg.), suggestive of muscle relaxant activity, is not seen in the rodent, it is unlikely that this compound will have further interest. The congeners of 3-amino-4-phenylpyrazole reported in this communication all exhibited skeletal muscle relaxant activity to a lesser or same degree, as the parent compound in the dose range studies.

The rationale of the antistrychnine test as a method of elucidating muscle relaxant, specifically interneuronal depressant, activity of a compound is based on the excitatory action of strychnine on the cerebrospinal axis. Strychnine is generally believed to facilitate interneuronal transmission on the spinal cord and (in high doses) the brain. If a compound antagonized strychnine, it presumably exerts the opposite action in the spinal cord; that is, it acts as an interneuronal inhibitor. Reviewing the experimental and clinical information on spinal cord depressants, Berger in 1949[16] concluded that there is no quantitative correlation between the antistrychnine (or interneuronal blocking) activity of a compound and its clinical efficacy as a skeletal muscle relaxant. Nor did he find that antistrychnine potency is quantitatively related to interneuronal blocking activity as tested by the effect of such compounds on mono- and multisynaptic reflex responses in cats. Today much more information on muscle relaxants is available, and it seems at least to suggest that the muscle relaxant efficacy in man of such drugs does have a correlation to its antistrychnine potency in mice.

Many central depressants, particularly hypnotics and narcotics, have interneuronal blocking activity on polysynaptic spinal reflexes, some even more so than the muscle relaxants. What makes polysynaptic reflex depression significant for therapeutic usefulness of a muscle relaxant, is that in the latter it stands out among the other actions of the drugs. Particularly the ratio of the polysynaptic reflex depressant potency to the sedative and hypnotic potency of a drug determines whether or not a drug may be promising as a clinical muscle relaxant. Similarly, *preferential* inhibition of multineuronal reflexes (flexor reflex), although not specific for muscle relaxants, is generally considered to be a prerequisite to a compound to be useful as a muscle relaxant.

In general, all of the congeners of 3-amino-4-phenylpyrazole studied exhibited skeletal muscle relaxant activity to the same degree or less than the parent compound. Several of the compounds exhibited, in addition to muscle relaxant activity, stimulatory properties. The parent compound, 3-amino-4-phenylpyrazole, appeared to be the most potent compound in terms of overall activity in dose range studies, antagonism to strychnine, and preferential interneuronal inhibition.

Experimental[17]

The compounds reported in Tables I and II were prepared by essentially the same procedure reported for α-formylphenylacetonitrile and 3-amino-4-phenylpyrazole.

α-Formylphenylacetonitrile.—To a stirred mixture of 27.8 g. (0.515 mole) of sodium methoxide and 40.7 g. (0.55 mole) of ethyl formate in 1 l. of benzene was added over 5 min. 58.5 g. (0.5 mole) of phenylacetonitrile. The temperature rose to 37°, and although the mixture became quite thick, agitation was maintained without difficulty. After the mixture was stirred for an additional hour it was treated with 1 l. of water, and two layers separated. The aqueous layer was drawn off and acidified with 10% hydrochloric acid to give the crystalline α-formylphenylacetonitrile. After the mixture was cooled in an ice bath for 25 min., the white product was filtered, washed well with water, and dried to yield 55.5 g. (76%), m.p. 159–160°.

A 29.2 g. (0.2 mole) portion of the aldehyde dissolved in 100 ml. of hot ethanol was added to 20 g. (0.22 mole) of thiosemicarbazide in 200 ml. of boiling ethanol. The mixture was refluxed with stirring for 1 hr., then cooled to room temperature, filtered, and the solid washed with ethanol. There was obtained 28 g. (64%) of α-formylphenylacetonitrile thiosemicarbazone, m.p. 160–161°; infrared spectrum (Nujol): 2.98, 3.08, 3.15, 3.16 μ (NH bands), and 4.52 μ (CN band).

Anal. Calcd. for $C_{10}H_{20}N_4S$: C, 55.02; H, 4.62; N, 25.67. Found: C, 55.07; H, 4.74; N, 25.83.

3-Amino-4-phenylpyrazole (I).—A 12-l. flask was charged with 8 l. of benzene, 459 g. (7.8 moles) of 85% hydrazine hydrate, 761 ml. of glacial acetic acid, and 880 g. (6.02 moles) of α-formylphenylacetonitrile. The temperature of the benzene solution rose to 43° during the neutralization. The solution was then quickly brought to reflux and maintained at this temperature for 4.5 hr., with water being removed azeotropically. After the mixture was cooled to room temperature, 1100 ml. of 18.5% hydrochloric acid was added with vigorous stirring. The red benzene layer was then separated and washed with two 500-ml. portions of 18.5% hydrochloric acid. The aqueous solutions were combined, treated with Darco, and filtered through Supercel. Neutralization of the light yellow filtrate (to pH 6) with concentrated ammonium hydroxide solution gave a pale yellow solid, which after drying weighed 848 g. (88.5%), m.p. 170–173°. This was redissolved in dilute hydrochloric acid, decolorized with Darco, basified with 40% sodium hydroxide to give 720 g. (75%), m.p. 174–176°; infrared spectrum (Nujol): 2.95, 3.05, and 3.20 μ (NH bands).

α-Cyano-α-phenylacetaldehyde Azine (D).—A mixture of 6.56 g. (0.11 mole) of 85% hydrazine hydrate, 24 g. (0.164 mole) of α-formylphenylacetonitrile, and 230 ml. of benzene was refluxed

(16) F. M. Berger, *Pharmacol. Rev.*, **1**, 243 (1949).

(17) Melting points are corrected. The authors wish to thank Mrs. Doris Rolston and her staff of these laboratories for the microanalyses, and Dr. Walter E. Thompson and Mr. Richard J. Warren for aid in interpreting certain infrared spectra.

with stirring and water separation for 3 hr. After cooling, the mixture was filtered, and the solid was washed well with 10% hydrochloric acid, dissolved in 500 ml. of boiling ethanol, and diluted with 250 ml. of water. The resulting solid, which was fluorescent under ultraviolet light, was collected and dried to yield 4.5 g. (14%), m.p. 203–205°.

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.41; H, 5.16; N, 19.66.

3-Amino-4-(3,4-dichlorophenyl)pyrazole (V).—To a cooled solution of 48.8 g. of 85% hydrazine and 1880 ml. of benzene were added with stirring 88.5 ml. of glacial acetic acid. This was followed by 138 g. of acetic anhydride. The solution was then warmed to 25° and 142.5 g. (0.665 mole) of α-formyl-3,4-dichlorophenylacetonitrile was added. The solution was quickly brought to reflux and refluxing was continued for 4 hr. with the condensate passing through a water separator. The resulting yellow solution was extracted with 6 *N* hydrochloric acid with the hydrochloride salt precipitating as a solid. The aqueous mixture was then basified with 10% sodium hydroxide solution and extracted with three 600-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and then stripped of solvent. An analytical sample was prepared by recrystallizing a portion from benzene and finally from ethanol, m.p. 136–138°.

3-Amino-4-*p*-hydroxyphenylpyrazole Hydrobromide (XV).—A solution of 1 g. of 3-amino-4-*p*-methoxyphenylpyrazole in 15 ml. of 48% hydrobromic acid containing 2 drops of 30% hypophosphorous acid was refluxed for 3.5 hr. After cooling to room temperature, the mixture was filtered and the crystalline salt dried at 70° *in vacuo* to yield 0.95 g. (64.5%), m.p. 258–260°, unchanged by recrystallization from ethanol–ether.

3-Chloromethylthianaphthene.[18]—The yields reported by Blicke and Sheets could not be duplicated. However, by using glacial acetic acid and paraformaldehyde and maintaining the temperature below 58°, yields of 70% were obtained. The product was unstable and was completely decomposed after storage at 0° for 6 weeks. It was also found to be a vesicant and sensitizing agent and caused severe skin irritation.

3-Formamido-4-phenylpyrazole (XXVIII).—A solution of 7.0 g. (0.044 mole) of 3-amino-4-phenylpyrazole and 15 ml. of 98% formic acid was heated slowly to 100°. The sirupy residue was treated twice with 50 ml. of xylene and evaporated to dryness *in vacuo*. The residue was crystallized from acetone to give 7.4 g. (90%) of pure compound, m.p. 167–168°; infrared spectrum (Nujol): 3.05 and 3.15 μ (NH bands).

3-Methylamino-4-phenylpyrazole Hydrochloride (XXI).—A solution of 8.1 g. of 3-formamido-4-phenylpyrazole in 50 ml. of dry ether was added to a slurry of 5 g. of lithium aluminum hydride in 200 ml. of dry ether. After refluxing the mixture for 8 hr., it was treated with methanol and water. The solvents were evaporated *in vacuo*, and the residue was extracted with ether. The combined extracts were dried over anhydrous magnesium sulfate and treated with ethereal hydrogen chloride solution. The crude hydrochloride was removed by filtration and crystallized from alcohol–ether to yield 3 g. of pure material, m.p. 184–185°. A sample of base obtained from the salt melted at 143–144°; infrared spectrum (Nujol): 2.85, 3.15, and 3.70 μ (NH bands).

3-Amino-1-methyl-4-phenylpyrazole Hydrochloride (XX).—A solution of 8 g. of α-formylphenylacetonitrile, 100 ml. of benzene, and 1 *M* equiv. of methylhydrazine was refluxed under azeotropic conditions for 15 hr. The cooled solution was extracted with three 25-ml. portions of 10% sodium hydroxide solution and extracted into 100 ml. of ether. The ethereal solution was dried over magnesium sulfate, filtered, and treated with ethereal hydrogen chloride solution. The crude hydrochloride was collected by filtration and recrystallized from alcohol–ether to yield 6 g. of pure material, m.p. 166–167°; infrared spectrum (Nujol): 2.90 and 2.97 μ (NH bands).

3-Dimethylamino-4-phenylpyrazole Hydrochloride (XXII).—A solution of 3 g. of 3-amino-4-phenylpyrazole, 5 ml. of formic acid, and 10 ml. of 31% aqueous formaldehyde was heated for 1.5 hr. on a steam bath. The solution was concentrated *in vacuo* to a gummy residue which was then treated with 50 ml. of water and made basic with sodium carbonate. The mixture was extracted with two 50-ml. portions of ether and the combined ethereal solution was dried over magnesium sulfate and filtered. The solution was treated with ethereal hydrogen chloride and the precipitated material was removed by filtration and recrystallized from acetone to yield 2 g. of pure material, m.p. 222–223°.

3-Acetamido-4-phenylpyrazole (XXV).—A suspension of 31.8 g. (0.2 mole) of 3-amino-4-phenylpyrazole in 150 ml. of chloroform was treated with 20.4 g. (0.2 mole) of acetic anhydride. A solution was formed immediately, and this was left at room temperature for 3.5 days. A waxy solid was obtained which appeared to be a solvate containing all the chloroform. The solid was dried *in vacuo* to give 39.3 g. of crude amide, m.p. 151–154°. This was dissolved in 120 ml. of warm methanol and diluted with 240 ml. of water. After cooling the solution, a crystalline mass precipitated which was filtered and dried *in vacuo* to constant weight (32 g.), m.p. 155–157°; infrared spectrum (Nujol): 3.15 μ (NH band).

3-Acetamido-1-acetyl-4-phenylpyrazole (XXVI).—A mixture of 31.8 g. (0.2 mole) of 3-amino-4-phenylpyrazole and 44.8 g. (0.44 mole) of acetic anhydride was heated cautiously on a steam bath for 40 min. The amine dissolved and then a solid reprecipitated. Cold water was added to the solid mass, and the product was collected by filtration and dried to yield 47.3 g. After being recrystallized from chloroform, the product weighed 43.7 g. (90%), m.p. 152–153°. This material was also obtained from the mother liquors of the triacetyl compound.

1-Acetyl-3-diacetylamino-4-phenylpyrazole (XXVII).—A solution of 5.8 g. of 3-amino-4-phenylpyrazole and 30 ml. of acetic anhydride was refluxed for 4 hr. The solution was then concentrated *in vacuo* to a small volume and treated with 200 ml. of cold water. The mixture was treated with sodium bicarbonate and extracted with three 75-ml. portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and concentrated to a small volume. The product precipitated from the solution and was collected by filtration. Recrystallization of the material from ether gave 6.1 g. of pure compound, m.p. 112–113°.

3-Ethylamino-4-phenylpyrazole (XXIII).—A solution of 8.6 g. of 1-acetyl-3-diacetylamino-4-phenylpyrazole and 100 ml. of dry ether was added slowly to a stirred suspension of 4.5 g. of lithium aluminum hydride and 350 ml. of ether. The mixture was stirred and refluxed in a nitrogen atmosphere for 16 hr. and then cooled, and the unreacted lithium aluminum hydride was decomposed with methanol–water solution. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml. of ether and extracted with two 30-ml. portions of 10% hydrochloric acid. The acid extracts were made basic with 10% sodium hydroxide solution and extracted with two 100-ml. portions of ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield a crystalline residue which was recrystallized from alcohol–ether to give 2.5 g. of pure product, m.p. 137–138°; infrared spectrum (Nujol): 2.95, 3.20, and 3.70 μ (NH bands).

1,3-Diacetyl-3-ethylamino-4-phenylpyrazole (XXIV).—A solution of 10 g. of 3-ethylamino-4-phenylpyrazole in 50 ml. of acetic anhydride was refluxed for 6 hr. The solution was evaporated to dryness *in vacuo* and the gummy residue recrystallized from alcohol–ether to yield 4.1 g. of pure material, m.p. 116–117°.

3-Ethoxyformamido-4-phenylpyrazole (XXXI).[19]—To a stirred mixture of 17.5 g. (0.11 mole) of 3-amino-4-phenylpyrazole in 75 ml. of pyridine was added dropwise 10.9 g. (0.10 mole) of ethyl chloroformate. The reaction temperature was kept between 25° and 35° during the addition and then for an additional 4 hr. at room temperature. The mixture was poured onto crushed ice, and after 1 hr. the resulting mixture was extracted well with benzene. The combined extracts were washed with cold 5% hydrochloric acid and with water and concentrated at 50° to give 18 g. of crude product, which was purified by recrystallization from isopropyl alcohol.

3-Carbamido-4-phenylpyrazole (XXXII).[19]—To a stirred solution of 58 g. (0.3 mole) of 3-amino-4-phenylpyrazole hydrochloride in 200 ml. of water was added dropwise during 30 min. 30.4 g. (0.38 mole) of potassium cyanate in 100 ml. of water. Precipitated solids were removed from the mixture by filtration and dried. Recrystallization from 2-propanol gave 42 g. (69.5%) of product, m.p. 174–176°.

(18) F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).

(19) Prepared by M. Einas and B. M. Sutton.