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Review Article

Biologically Active Pyrazoles

By RONALD E. ORTH

"No great change occurs in the general nature of the action of a substance if a pyrazole ring be substituted in place of a pyrrole ring" (1).

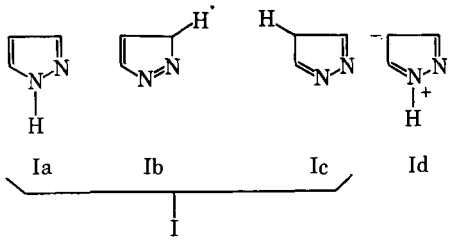
THREE DECADES and the wisdom of this conclusion have vanished since 1937; however, an awareness of changing "truths" is no more amply illustrated than with the bio-active pyrazoles. Although the impact of pyrazole chemistry on biological systems is uneven, the recognized value of a few pyrazoles for even fewer purposes has characterized the past. A rapid leveling of interest, however, is reflected in recent literature, and a review of pyrazole implications on biological systems quickly identifies nearly all activity as a "happening" of the past decade. Kost and Grandberg listed 799 references (2) in an excellent review of pyrazole chemistry and an earlier compilation may also be of interest (3). Pyrazole NMR and UV spectra were reported by Elguero *et al.* (4, 5), and the nonaromatic pyrazolones and pyrazolidones were reviewed (6). Tautomeric pyrazolones, alone, were of sufficient interest that a review was written (7), and certainly, much excitement was generated by the clinical efficacy of phenylbutazone and its analogs (8). Among the well-known compounds are antipyrine and pyramidon, the analgetic-antipyretic pyrazolones. Knorr (9, 10) first synthesized a pyrazole derived compound in 1883, which led to the discovery of antipyrine (11).

Received from the College of Pharmacy, University of Kentucky, Lexington, KY 40506
Present address: College of Pharmacy, University of Houston, Houston, TX 77004

Although the thoroughly investigated 5-pyrazolones and their 3-oxo-isomers react as ketones, the 4-isomers are tautomeric and behave like phenols.

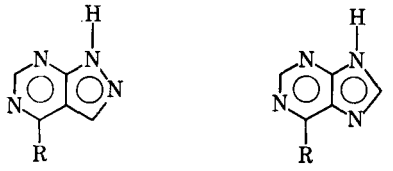
Pyrazole (1) consists of a doubly unsaturated 5-membered ring containing two adjacent N-atoms. Three possible ring-tautomers exist (Ia, Ib, Ic), which have not been separated. The ease of pyrazole-tautomerism may be explained if all the N-H bonds in the associated structures are assumed to be equivalent (12). The polar structure (Id), which contributes much to the resonance hybrid of pyrazole, explains the high degree of electrophilic substitution in the 4-position (13). The presence of the N-H moiety allows pyrazole to ionize as a anion, substitute on this N-atom, and possibly tautomerize. The lone pair of electrons on the secondary N-atom, which is utilized to form an aromatic sextet, is not available for affecting water solubility. The doubly bound N-atom does increase pyrazole solubility over pyrrole because the lone pair of electrons on the N-atom is disengaged and available. Annelation to give indazole decreases water solubility. Pyrazoles with free N-H groups are amphoteric, though more basic than acidic and form associated linear dimers and trimers. Good stability generally characterizes the pyrazoles (14).

The great variety of bio-responses promoted by pyrazoles is illustrated by the insecticidal, anal-



Ia Ib Ic Id

I

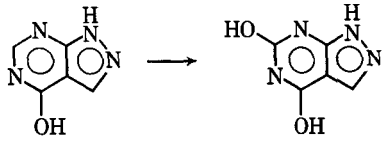


II (when R is H) III (when R is H)
IIa (when R is —OH) IIIa (when R is —SH)
IIb (when R is $-NH_2$)

gesic, sedative, anticonvulsant, antipyretic, and anti-inflammatory activity elicited by only the 1- and 2-dimethylthiocarbamoylpyrazoles (15). The analogous 1-carbamoylpyrazoles effect analgesia, diuresis, antipyresis, sedation, and a bitter taste (16). However, these are selectively toxic medicinal agents, and toxicity is always a concern when these compounds are administered. Hydroxy- and amino-pyrazoles (17) and F.D. & C. yellow No. 5 (an azopyrazole) (18) have been studied and fatty liver was detected following the administration of allopurinol, 4-hydroxypyrazolo[3,4-*d*]pyrimidine (IIa), to four species of warm-blooded animals (19).

BIO-ANTAGONISTIC PYRAZOLES

Pyrazole, pyrazolo[3,4-*d*]pyrimidine (II), and their substitution products include many biologically active agents, which possess enzyme-inhibiting properties of interest. For instance, many xanthine oxidase inhibitors are carcino-



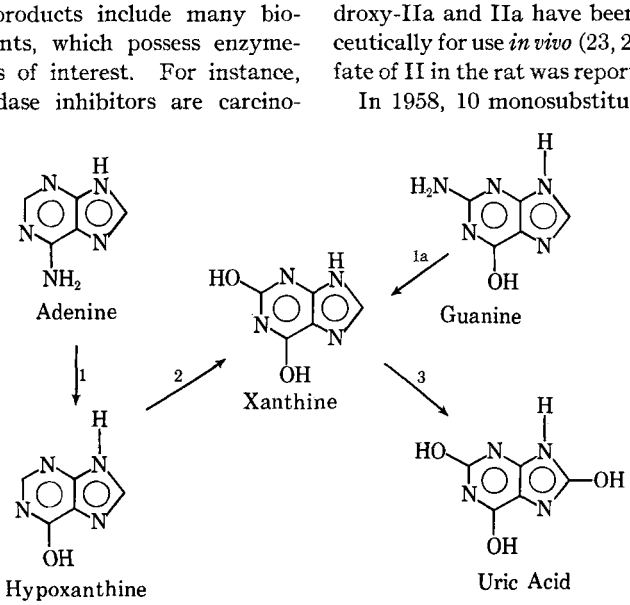
4-Hydroxypyrazolo-[3,4-*d*]pyrimidine (IIa) 4,6-dihydroxypyrazolo-[3,4-*d*]pyrimidine

Scheme II

static or tumor inhibiting, while the effectiveness of pesticides has been correlated with their anticholinesterase activity. Inhibitors of carbonic anhydrase, monoamine oxidase, liver alcohol dehydrogenase, and catalase have been investigated. Some degree of pyrazole activity results from competition with endogenous substances to antagonize an enzyme system. The xanthine oxidase antagonistic pyrazoles, particularly those with antitumor activity, are of great interest. Many of these compounds have been derived from II.

Hypoxanthine and its intestinal metabolites are readily absorbed from the small intestine where xanthine oxidase combines with hypoxanthine, xanthine, and Cu to produce a necessary transport-complex (20). Purine (III) and II-derivatives compete for this common transport process. Although 4-hydroxypyrazolo[3,4-*d*]-pyrimidine (IIa) and 7-hydroxy-IIa strongly inhibited the active transport of uracil across the intestinal wall (Schemes I and II) (21), IIa, uric acid, and adenine form similar transport-complexes with xanthine oxidase. In the chick embryo and chicken, IIa inhibited uric acid formation, but diversion of N to a different end product allowed normal development (22). 6-Hydroxy-IIa and IIa have been developed pharmaceutically for use *in vivo* (23, 24), and the metabolic fate of II in the rat was reported (25).

In 1958, 10 monosubstituted derivatives of II



Scheme I

were prepared and suggested as antimetabolites (26). 6-Hydroxy-IIa and IIa were converted by purinenucleoside phosphorylase to the 1-ribosyl-metabolites and isolated from the urine of treated patients; however, 4-hydroxypyrazolo[3,4-*d*]pyrimidine (IIa) was a better substrate than 6-hydroxy-IIa (27). The sea urchin and other systems have been utilized to investigate the effect of 4-aminopyrazolo[3,4-*d*]pyrimidine (IIb) on purine metabolism (28, 29). Avian glutamine ribosylpyrophosphate 5-phosphate amidotransferase, the first enzyme of purine biosynthesis, was inhibited by IIa-ribonucleotide. A "pseudo-feedback" inhibition of the ribonucleotide may be an important aspect of the *in vivo* biological activity of II derivatives (30).

ANTITUMOR AND CARCINOSTATIC PYRAZOLES

Pyrazole was reported as possessing antitumor activity (31, 32) and 25 courses were given to patients with solid tumors. Bone marrow depression was minimal, while severe thrombocytopenia and hepatotoxic reactions were noted once. Nausea and anorexia were reported, but no objective responses were observed. Pyrazole depressed: adenocarcinoma CA-755 (90–100%); Ehrlich ascites carcinoma (50–60%); and spontaneous mammary tumors in C_3H mice. Crocker sarcoma S-180, leukemia L-1210, and human tumors in conditioned rats, however, did not respond. The i.p. single dose LD_{50} for pyrazole was: 400–600 mg./Kg. for mice and 900 mg./Kg. for rats. Experimentally induced tumors were treated with 4-aminopyrazole (33), and several 1-substituted pyrazoles exhibited significant activity against CA-755 with less effect on S-180. The 1-carboxamide elicited a moderate but consistent action *versus* human tumor HS-1 (34).

The investigation of antitumor activity of II and its substitution products was the most extensive of any for bio-active pyrazoles. The hydrochloride of II showed the greatest activity among 16 pyrimidines tested in 1960.

A xanthine oxidase-inhibiting preliminary screening technique for carcinostatic substances was developed (35) and a large number of II substances were screened *versus* CA-755 and leukemia L-5178 (both were susceptible to inhibition by purine antagonists). Consistent and significant activity was reported using IIb, *N*-alkyl-IIb, *N*-dialkyl-IIb, and their 1-alkyl-derivatives (36). Skipper *et al.* (37), effected antitumor activity with IIb and 1-methyl-IIb. The toxicity of IIb in humans was slight, however, hepatotoxicity and hemorrhage was reported in animals (38). 1-Methyl-IIb and IIb acted on nucleic acid metabolism in ascites carcinoma, but sarcoma S-180 was not sensitive to either material (39, 40).

A Houston team utilized *Neurospora* for screening potential carcinostatic substances and found that 1- and 3-substituted IIb compounds inhibited the growth of this tissue (41). Human HeLa and mouse B-3 adenocarcinoma cells were found to be resistant to IIb (42), but HeLa cell damage was reportedly caused by 13 newer IIb-substances (43). Two of these were more active against *N. crassa* than IIb (44). Active IIb derivatives lower the DNA levels in tumor and liver tissue (45), and 1-methyl-IIb also lowered muscle DNA levels. Interestingly, 12 IIb derivatives gave relief of IIb-inhibition. Since the position of the side chain determines inhibition or relief potential (46), 1-methyl-IIb and IIb were found highly active in recent tumor transplants, while only slightly effective in spontaneous tumors (47). The efficacy of IIb against cultivated human tumor cells, in earlier studies, was greater than for any amino- or 1-substituted-II products (48). Purine synthesis was disrupted in Ehrlich ascites cells by IIb (49), but attempts to establish mutant strains of *N. crassa* with this substance were unsuccessful (50).

Robins (51) reviewed the structure-activity relationship (S-AR) of purines and related compounds (11,300 compounds tested over a 10-year period) against animal tumors (163 references). Similarities of the allowable positions for substitution in II and in purine were most striking. 4-Aminopyrazolo[3,4-*d*]pyrimidine, which is active against CA-755 and numerous other tumors, was the parent compound in that study. Substitution of certain alkyl groups in the 1 position (corresponding to position 9 in purine) provided active compounds, and the presence of a tetrahydropyranyl- or tetrahydrofuryl-group at position 1 also allowed retention of antitumor activity. The 4-alkyl-II derivatives inhibited L-5178 and prolonged L-5178 and L-1210 life span in infected mice. Substitution of alkyl groups on the amino function at position 4 (6 in purine) created less toxic products with superior therapeutic indexes, while substitution at both the 1 and 4 position, simultaneously, usually diminished antitumor activity to a slight degree. 1-Methyl-*N*-*n*-butyl-IIb and *N*-benzyl-IIb were active against Dunnings ascites leukemia, but 1-phenyl-IIb derivatives were inactive. 6-Amino-IIb was active, but the 6-amino moiety (2 in purine) apparently made little difference. The spatial arrangements of II and purine derivatives appear interchangeable, however,

4-mercapto-II and 6-amino-4-mercapto-II, the corresponding analogs of 6-mercaptopurine (IIIa), and 2-amino-IIIa, were without activity *versus* CA-755. An L-1210 azaguanine-resistant strain was found cross-resistant with IIIa, but not with IIb. These results lead to a conclusion that similar steric requirements, alone, were not sufficient to provide antitumor activity. Since IIb cross-resistance did not occur in either case, different mechanisms of action must be involved. Simultaneous administration of IIb with IIIa resulted in potentiation *versus* ascites carcinoma, S-180, and 6C3HED lymphosarcoma. Similar effects were observed with IIb and azaserine or thioguanine (52). This observed potentiation was further evidence favoring separate mechanisms for IIb and IIIa.

The antitumor activity of IIb was probably exerted at the acid-soluble nucleotide level, although it was incorporated readily into nucleic acids of normal and neoplastic tissue. The *de novo* pathway to nucleotide-purines was inhibited, probably by the previously mentioned "pseudofeedback" mechanism. Recent clinical success with *N-n*-propyl-IIb against myeloblastic leukemia has renewed interest in the II tumor inhibitors, and further support for this interest was given by correlation of the pKa values of 4-substituted-II compounds with their antineoplastic activity. Position 5 (1 in purine) may be critical for the adenine-like IIb substances, because a close steric fit was required even at position 3 (7 in purine). 3-Methyl-IIb and the purine analog were devoid of antitumor properties.

Nakajima *et al.* (53), reported correlating the first ionization potential of free doublets of the N-atoms of II and purine and their derivatives with antitumor activity. Electronic structure, chemical reactivity, and the basicity of these agents were related to tumor inhibition (54). Bio-activity was associated with the position of the most basic N-atom and the basic strengths (55). 6-Amino-II was found to be carcinostatic but hepatotoxic, while 5-amino-7-hydroxy-II and a number of trifluoromethyl-derivatives of IIb and *N*-alkyl-IIb were inactive (56–60). Scott and Foye (61) and Sutcliff (62) reported on IIb, which in tumor-bearing mice, decreased formate-^{14}C uptake into polynucleotide purines (DNA, *etc.*) with ^{14}C-accumulation in serine.

The uptake of adenine into the nucleic acids was inhibited by IIb, and nucleic acid synthesis in IIb-sensitive CA-755 and in the less sensitive S-180 ascites was halted for a short period. The S-180 tissue, however, recovers more readily (63), while adenine, given to S-180 ascites-bearing mice prior to IIb, caused a decrease in tumor inhibition (64). 4-Aminopyrazolo[3,4-*d*]pyrimidine was toxic to H. Ep. No. 2 cells, but the "feedback" growth inhibition occurred at much higher concentration and was the mechanism of carcinostasis (65).

Allopurinol (IIa), a powerful xanthine oxidase inhibitor, was found to depress the disappearance rate of ^{32}P-labeled $CrPO_4$ in an attempt to characterize the phagocytic properties of the reticuloendothelial system. Methotrexate, chlorambucil, and thiotepa possessed this facility, while azaserine and busulfan[1] were ineffective (66). A decreased IIIa to thiouric acid oxidation occurred when IIa was given simultaneously to human patients. A severalfold potentiation resulted *versus* CA-755 and in the mouse immune response to sheep erythrocytes. In man, 0.2 to 1.0 Gm. of IIa given daily possessed a higher therapeutic index than other antineoplastic agents (67, 68). When given with IIa or 6-hydroxy-IIa, 6-mercaptopurine was potentiated threefold, while xanthine oxidase oxidation-inhibition of hypoxanthine and xanthine in the liver and kidney gave rise to increased uric acid levels (69). This IIa action was used to test the ability of xanthine to serve as a precursor for nucleic acid purines while being protected from destructive catabolism. The ability of CA-755 (IIIa-resistant)-bearing mice to use xanthine as a precursor was reduced by one-half using IIa (70), and it also inhibited liver and kidney, but not spleen xanthine oxidase in rats (71). Xanthine dehydrogenase-inhibition by IIa was also noted (72).

Pyrazolo[3,2-*c*]-*as*-triazines (IV) were more effective S-180-inhibitors in mice and methylcholanthrene-induced tumorstatic agents in rats than IIIa, but the best of the lot were ethyl-4-amino-IV and 6-iodoacetyl-3-methyl-4-methylene-IV (73,74).

1-Methyl-IIb, given to pregnant rats, produced a high number of malformed and dead fetuses (75). The teratogenic nature of IIa, administered with IIIa at subteratogenic levels, was reported (76).

ANTIVIRAL PYRAZOLES

3-Methylpyrazole-5-carboxylic *n*-hexadecylamide (V) demonstrated virucidal activity *versus* the Japanese encephalitis virus (77). Other studies supported that 1-methyl-*N-n*-propyl-IIb, the *N*-isopropyl- isomer, *N*-isopropyl-IIb and IIb suppressed virus plaque formation with *Herpes simplex*, *Vaccinia*, and West Nile (78). Toxicity,

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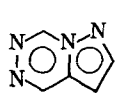
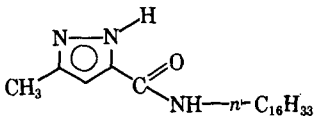
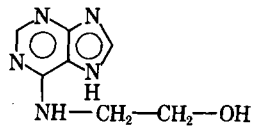


IV



V



VI

but not antiviral activity, decreased when N^6-(2-hydroxyethyl)adenine (VI) was given with IIa (79). In an antiviral formulation (80), one part of the various N^6-(hydroxyalkyl)adenines was combined with 2.5–20 parts of IIa.

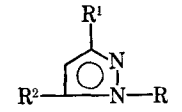
GOUT AND THE PYRAZOLO[3,4-d]-PYRIMIDINES

One of these compounds, allopurinol, is being used in the treatment of patients with gouty conditions. The oxidation of urine xanthine and hypoxanthine was antagonized by the action of IIa on xanthine oxidase (81), which resulted in lower serum and urine uric acid levels (82). Formation of fresh deposits was arrested and mobilization of old deposits occurred, but it was suggested that the best use of IIa was with agents such as colchicine (83, 84). Compound IIa was well tolerated in human patients and was found to be useful in subjects with hyperuricemia who were refractory to uricosuric therapy. Although gouty patients with a low tolerance to other drugs, which lower blood plasma urates, may be helped, no improvement was noted in those with tophaceous gout (85, 86). Further reduction of serum and urine urates and increased urinary hypoxanthines (87) resulted from a sulfinpyrazone and IIa combination. Oxypurinol, 6-hydroxy-IIa, was utilized also in the treatment of gout (88, 90). Toxicity (91), nephropathology (92), human tissue reactions (81), and other pyrazole-gout reports were of interest (93–96).

PYRAZOLES INHIBITING OTHER ENZYME SYSTEMS

One S-A-R report of anti-monoamine oxidase (MAO) 1,3,5-trisubstituted pyrazoles listed several interesting examples (Table I). For instance, transposing of methyl- and the substituted-hydrazide moiety from positions 3 and 5 to 5 and 3, respectively, reduced activity in one series. Activity was found to decrease as R varied, so that when R was aralkyl, separation of the aryl from the hydrazido moiety decreased activity. Benzyl or 2-phenethyl groups produced equal anti-MAO effects, and pyrazole-3,5-dicarboxylic acid hydrazide were ineffective antagonists (97, 98).

TABLE I—MONOAMINE OXIDASE INHIBITORS



Factors Enhancing Inhibition:
- R is benzyl or phenethyl
- R^1 is methyl
- R^2 is benzyl-, β-phenethyl-, or 1-phenethyl-carboxylic acid hydrazide.

Factors That Lower Inhibition or Increase Toxicity:
- R = H
- R^1 = R^2 = CONHNHR
- R^1 and R^2 interchanged
- R^2 alkyl portion > 2 carbon

4-Aminopyrazole *in vitro* and *in vivo* catalase-inhibition was reported, giving the ID *in vitro* as 3.8×10^{-3} *M* (99, 100).

Fundamental biochemical interpretations were derived from the work of Theorell *et al.* (101–103) on liver alcohol dehydrogenase (LADH), and a model of a ternary intermediate in the enzyme reaction LADH-diphosphopyridine nucleotide (DPN)-pyrazole was reported. Pyrazole, the most potent inhibitor of LADH known (1963), adds to the enzyme-coenzyme binary system producing a new complex with a characteristic 290 mμ maximum. The LADH-DPN-pyrazole complex stoichiometry was reported as 1:2:2, respectively. Liberation of one H^+ per complex formed suggested that, following H^+ release, a charged pyrazole carbanion interacted covalently with C-4 of the pyridinium ring of DPN. Binary and ternary complexation increased the stability of LADH toward certain types of inactivation, probably due to conformational changes in the protein molecule. The LADH-NAD-pyrazole and LADH-NAD-4-iodopyrazole complexes have been crystallized to examine "Koshlands Induced Fit Theory." The ternary ligand pyrazoles were found to occupy the active alcoholic binding site and form a bridge between Zn atoms in the LADH and the coenzymic nicotinamide moieties. X-ray crystallography uncovered orthorhombic symmetry for free enzymes and clinic patterns for the ternary complexes. Optical rotatory density data were utilized to calculate Moffitt-Yang plots, and allowance for Cotton effects, introduced by the binding of NAD to the protein, were utilized. The change of Moffitt parameters, b_0, from −100° for the enzyme to −185° in the ternary complex was interpreted as a change of protein conformation due to complex formation.

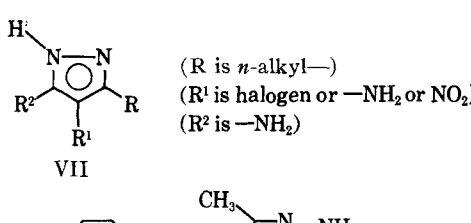
ANTIMICROBIAL PYRAZOLES

The earliest reported anti-infective pyrazole, 5-amino-4-benzeneazo-1-phenyl-3-methyl-

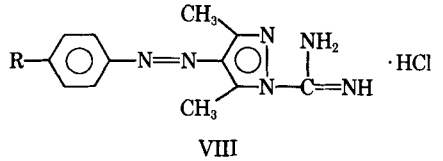
pyrazole, was for use as a urinary antiseptic, but when it was administered orally, albuminuria resulted. A minimum lethal dose (50%) in rabbits was found to be 200 mg./Kg. (104). Grandberg *et al.* (105) tested 96 pyrazoles as effective bactericidal agents, and other investigators reported (106) that 3-nonylpyrazole and its derivatives exhibited bacteriostatic-fungistatic activity. The 3-alkylpyrazoles (VII) reportedly have an extremely specific antibacterial spectrum; *Staphylococcus aureus* and *B. subtilis* were inhibited, but the only sensitive Gram-negative organisms, were *N. gonorrhoeae* and *V. cholerae*. Longer or shorter 3-alkyl chains varied the potency in this series. The *n*-octyl compound possessed the highest surfactant properties (107), while 4-nitro- and 4-halo-3-nonylpyrazoles demonstrated good antimicrobial activity, and the 4-amino-homolog exhibited a marked decrease in efficacy *versus* Gram-positive organisms. Shifting the amino group to the 5 position heightened bacteriostasis, but ring oxidation to the pyrazolone resulted in a loss of activity (108).

1 - Dichloroacetyl - 3 - (*p* - nitrophenyl) - 5 - methylpyrazole inhibited *S. typhosa in vitro* at 500 mcg./ml., but was inactive against several other common organisms (109). 1-Cyclopentyl-*N*-furyl-IIb inhibited the preferential stimulation of the synthesis of DNA, but potentiated kinetin riboside in *D. pneumoniae*. The results indicated a relationship between DNA breakdown products to population changes and DNA synthesis, which illustrated the usefulness of employing a virulent population change system for the study of compounds interfering with DNA synthesis by DNA breakdown products (110).

The adenine isostere 4-aminopyrazolo[3,4-*d*]pyrimidine was effective *versus C. utilis*, *E. coli*, and *B. cereus* (111), inhibiting the growth of *E. coli* and *B. cereus* by about 30%. Adenine or hypoxanthine addition partially relieved the drug-induced inhibition, but a combination of IIb and guanine resulted in potentiated inhibition of cell growth. The formation of 4-amino-5-imidazolecarboxamide, a purine precursor, by an *E. coli* mutant, B-96, was lessened by IIb, resulting in depressed *de novo* purine synthesis. Stimulation of the C-8 guanine, by IIb, to adenosine and ribonucleic acid adenine was observed in *E. coli*, while a depression of the conversion occurred in *B. cereus*. The radio labeling of several purine-containing cell constituents was effected (112). 6-Amino-IIa exhibited good activity *versus B. cereus*, but only slight activity against *E. coli*. Treated *B. cereus* cells elongated, and the RNA content in the cell was reduced, due to the antagonism of an early reaction in purine biosynthesis (113). Three 4-arylazo-1-amidines of 3,5-dimethylpyrazole (DMP) (VIII) were found effective *versus S. aureus* and *S. albus* at $1 \times 10^{-4}M$. They were the 4′-tolyl-, and 4′-chlorophenyl-, and 4-(4′-acetylphenylazo)-3,5-dimethylpyrazolyl-1-amidine aminoguanidine salts, the latter of which possessed good trichomonostatic ($1 \times 10^{-5}M$) and tuberculostatic ($4 \times 10^{-4}M$) activity. Several of these azopyrazoles are also active ascaridostatic agents (114).



VII

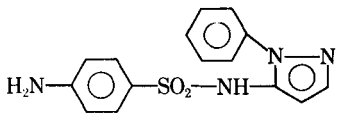


VIII

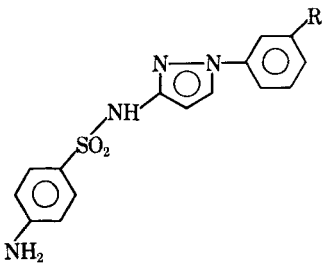
5-Amino-7-methyl-II possessed antitubercular activity and was well absorbed orally in laboratory animals; however, the tuberculostasis produced was less than that shown by streptomycin in the guinea pig and mouse (115, 116). A parallelism was noted between the tuberculostasis and xanthine oxidase inhibition produced by this compound. 4 - (4′ - Acetylphenylazo) - 3,5 - dimethylpyrazolyl - 1 - thiocarbonic acid amide - thiosemicarbazone elicited potent tuberculostatic activity at $1 \times 10^{-4}M$, but unfortunately, the LD_{100} (100 mg./Kg.) in rats was high (114). Certain 4-nitrosopyrazoles were active *in vitro*, but not in the mouse, and some azoxypyrazoles were found to be inactive tuberculostats (118).

Sulfapyrazine, sulfahydantoin, and sulfathiazoline were acclaimed as more promising against *Pneumococcus* than sulfapyrazoles in 1941 (119), however that very year, Jensen introduced 3-sulfanilamidopyrazole as eliciting activity similar to that of sulfathiazole (120). For over 20 years, articles characterizing the chemistry, solubility, microbiology, and toxicity of sulfonamidopyrazoles have been published (121–125).

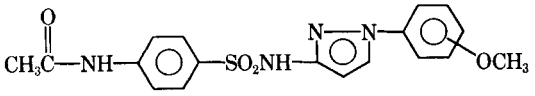
5-(*p*-Aminobenzenesulfonamido)-1-phenylpyrazole (IX) (sulfaphenazole, orisul), was found to lower an induced rabbit fever, but it is less effective and less toxic than pyramidone for this purpose. Each compound in a series of N^1-aryl-3-pyrazolylsulfanilamides inhibited *S. aureus* at 10 mcg./ml. The *m*-methoxy-homolog was the most active *versus E. coli in vitro* (10 mcg./ml.), and it also exhibits a displacement action of various penicillins bound to blood serum proteins. The decrease in bound penicillin G was 49.5%; peni-



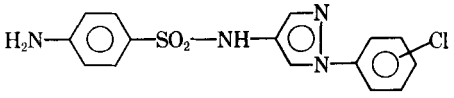
IX



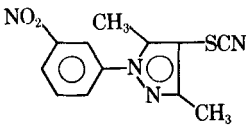
X



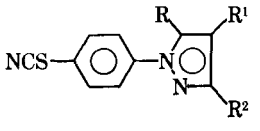
XI



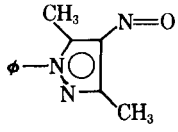
XII



XIII



XIV



XV

cillin V, 39.8%; and ancillin, 35.9%. The relative activity of various sulfonamides as penicillin-displacing agents corresponded closely to the known affinity of each for serum proteins. Over 250 chemicals were tested with ^{14}C-labeled penicillins, and the findings showed that replacement of a 3-methoxyl- group by a 3-methyl- substituent increased the duration of activity (X). Active N^1-aryl-3-pyrazolyl-N^4-acetylsulfanilamides (XI) have been prepared, and a number of chloro-derivatives of 1-phenyl-4-sulfanilamidopyrazole (XII) have been found useful. Padeiskaya *et al.* have contributed to sulfonamide chemotherapeutics (126–135).

Seven of eight fungi tested, including *C. militaris*, converted IIb to the riboside, thus, the fungi may utilize IIb as a nutrient (136). More important is the antifungal activity, which was elicited by a number of pyrazole compounds. Two thiocyanato-, eight 4-(*N,N*-disubstituted-thiocarbamoylthio)-, and five 4-alkoxythiocarbonylthiopyrazoles were effective against *Piricularia oryzae*, *Phytophora infestans*, *Colletotrichum lagenarium*, and *Candida albicans*. The thiocyanato derivatives displayed the greatest fungal inhibition, and of these, 1-(*m*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole possessed the greatest fungal inhibitory activity of all compounds tested (XIII) (137). This same Japanese group found high-level activity in 1-(4-thiocyanatophenyl)pyrazoles (XIV) (138). Maximum fungitoxic activity was attained by substitution of an aryl-group in the 1 position of 3,5-dimethyl-4-nitrosopyrazole (XV). Several of these compounds prevent spore germination at a concentration of 0.1 p.p.m. and provide 95% protection against *Alternaria solani* on tomato foliage at 10–60 p.p.m. (139). Zsolnai has found the nitrosopyrazoles effective *versus* fungi which afflict humans (140, 141); pyrazole was one of 165 *N*-compounds studied for fungitoxicity. 4-Nitrosopyrazole toxicity increased with an increase in the bulk of the hydrocarbon side groups, but the mechanism of action was found to be the same, regardless of the group in this series. Increased fungitoxicity was observed as the oil:water partition coefficient increased for these substances, and generally, lipophilic groups, such as aryl- or alkyl-, increased the toxicity. Amino-, nitro-, nitroso, hydroxyl-, and mercapto-group substitution produced a similar response (142, 143). Six mono-, di-, and tri-substituted 4-nitrosopyrazoles (XVI) are active against *P. oryzae* and *Ophiobolus miyabeanus* (144), and nitrosopyrazoles with 1-substituted cyclic groups are active, particularly against pathogenic fungi. It was found that 1-cyclohexyl-3,5-dimethyl-4-nitrosopyrazole exhibited no dermal irritation and possessed low phytotoxicity (145).

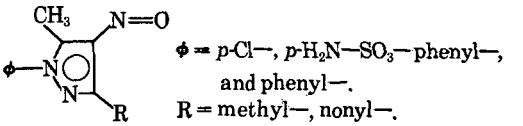
3,5-Dimethyl-4-(4′-chlorophenylazo)pyrazole (XVII), one of 750 chemicals tested, was the most active *versus* 3 selected fungi (146), while a

4-phenylazo-3,5-dimethylpyrazolyl-1-amidine (XVIII) salt was effective *versus T. gypseum*, *E. Kaufman-Wolff*, and *A. quinkeanum* at $2 \times 10^{-4}M$. The 4′-chloro- and 3′-chloro-derivatives (XIX) were effective at $1 \times 10^{-4}M$ against the same fungi. Many of the azopyrazoles were also bacteriostatic, trichomonostatic, and ascaridostatic, but according to Zsolnai, R—N=N—CH— must be present as an intact moiety, in arylazoanti-infective chemotherapeutic agents (114). 3-Nonylpyrazole possessed high antifungal-antibacterial properties (106), and recently, 3-methyl-5-(5-nitro-2-furyl)pyrazole (XX) was introduced for this activity (147). A similar nitrofurylpyrazole was reported in the Netherlands, with claims for effectiveness against a wide spectrum of bacteria and a few fungi (148).

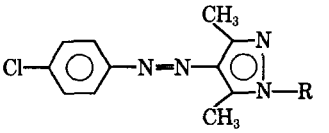
PESTICIDAL PYRAZOLES

Well tolerated 4-aminopyrazoles (XXI) yielded interesting pharmacodynamic spectra; for instance, 1,3,5-trimethyl-4-dimethylaminopyrazole methiodide exhibited a choliomimetic action. Substituting 1-phenyl in place of 1-methyl reversed the action and effected a classical cholinolytic response. Although molecular weight difference was suggested as the underlying factor, the activity of the former substance was attributed to anticholinesterase properties (149). A number of pyrazolyl-carbamates and phosphates, possessing good anticholinesterase activity, were too toxic for use in medicine, but were excellent pesticides. Practical uses of the dimethylcarbamates and dialkylphosphates of 5-hydroxypyrazoles have been studied since 1951 (150–156). 1-Isopropyl-3-methyl-5-pyrazolyl dimethylcarbamate (XXII),[2] and 1-phenyl-3-methyl-5-pyrazolyldimethylcarbamate (XXIII),[3] the 1-phenyl-homolog, were introduced as insecticides in 1952 (157).

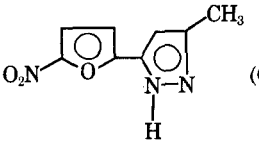
Compound XXII exerted a strong systemic action against aphids (158) and was highly toxic to the honey bee (159), however its selectivity is such that it did not affect the insects natural predators (160). Most organophosphate and carbamate pesticides cause inhibition, followed by recovery, of brain cholinesterase activity in *Musca domestica* (housefly) within 21 hr. Compound XXII was the only pesticide tested that did not allow recovery (161). However, it was a less active systemic insecticide in foliage sprays against the citrus whitefly or gardenia than other pesticides (162). Gaines found XXII more toxic to rats by the dermal route than orally (163). The effects of XXII and XXIII on the



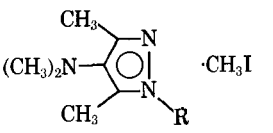
XVI



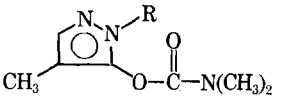
XVII (R = H), XVIII(R = amidino—)
XIX (R = amidino, 3′-Cl–replaces 4′-Cl)



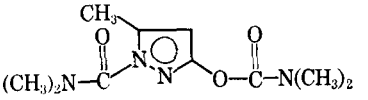
XX



XXI



XXII (R = isopropyl—)
XXIII (R = phenyl)



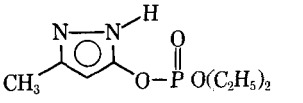
XXIV

stability, toxicity, and reaction mechanisms of human postpartum serum esterase have been reported (164). Aliphatic-esterase activity is inhibited in the housefly by XXII, but resistance to this pyrazole, it was observed, was not related to inhibition of the esterase; mosquito enzymatic activity was not inhibited (165). Many analogs have been reported to have good activity (166, 167). Radio-labeled XXII translocation and persistence in *Theobroma cacao* foliage, and residues in the cacao bean have been studied (168).

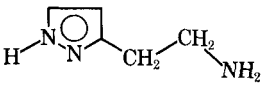
2-Dimethylcarbamoyl-3-methyl-5-pyrazolyl dimethylcarbamate (XXIV),[4] was shown to be toxic to laboratory animals in single oral doses (169, 170), but it was reported that XXIV-^{14}C was detoxified in the cockroach through *N*-methyl hydroxylation. Two out of five of the *N*-hydroxymethyl metabolites have been identified (171). The housefly shows maximum cross-resistance levels between XXII and XXIV (172).

Common commercial aromatic and heterocyclic carbamate pesticides exhibited a tenfold potentiation with piperonyl butoxide, sesoxane, sulfoxide, propyl isome, or sesame oil extracts on the housefly (173). Octachlorodipropyl ether

[2] Isolan.
[3] Pyrolan.
[4] Dimetilan.



XXV XXVI



XXVII

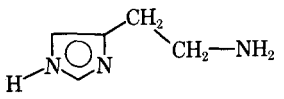
also produced massive potentiation with carbamates on the fly (174), but antagonism, with resultant antidotal protection, was given by atropine and parpanit against all the carbamates tested (175).

Pyrazoxon, containing *0,0*-diethyl-*0*-(3-methylpyrazolyl)-(5)-phosphate (XXV), has become a commercially important foliage spray (176). Phosphoric and thiophosphoric acid derivatives of hydroxy-pyrazolo[1,5-*a*]pyrimidine (XXVI), which were not toxic to warm-blooded animals, acted on insects, red spiders, ticks, nematodes, and fungi (177), and they also exhibited anthelmintic qualities (178). In the Mexican fruitfly, ovaries were affected by IIb sulfate, which reduced oviposition and fertility, acting as a sexual sterilant (179, 180). The screening of various commercial agents against a number of pests has been reported (181).

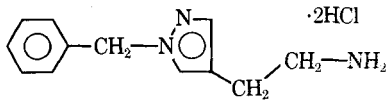
PYRAZOLE HISTAMINE AGONISTS AND ANTAGONISTS

In 1944, Dewar presented histamine-antihistamine models (182), and later, Lee and Jones observed the histamine-like effects produced by several 2-aminoethyl-*N*-heterocyclic compounds. One of these substances 3-(2-aminoethyl)pyrazole, is now known as betazole (XXVII) (183). This isomeric histamine (XXVIII) analog reputedly stimulated gastric acid secretion without producing other histaminic effects (184). Doses of 50 mg. of betazole i.m. elicited a gastric secretory response similar to that for histamine, and like histamine, it was used to study gastric secretions (185). Many clinical studies on betazole HCl have been reported (186–205). Histamine and betazole acted on the same receptors in the guinea pig ileum (206, 207), and additional theoretical histamine-antihistamine models have been reported recently (208, 209).

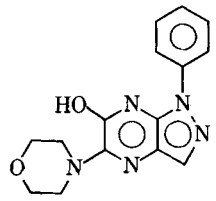
One interesting S-A-R probe indicated that the 1-benzyl-4-(2-aminoethyl)pyrazole·2HCl salt (XXIX) inhibited histamine-stimulated gastric acid secretion. Nevertheless, 4- and 3- (or 5) (2-aminoethyl)pyrazole and bis-2-(3-pyrazolyl)eth-



XXVIII



XXIX

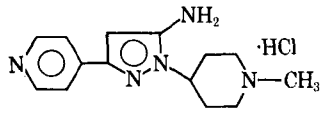


XXX

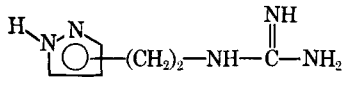
ylamine· 3HCl stimulated acid secretion, even after histamine (210). In one report on the inhibition of histamine, relative to the action of histamine analogs which inhibit histamine methyl transferase, no correlation could be found between antihistaminic activity and enzyme inhibition (211). Alkylamine ethers of 1-phenyl- and 1-benzyl-3-methyl-5-hydroxypyrazole have been prepared as potential antihistaminic substances (212). The 3,5-diphenyl-1-(2-aminoethyl)pyrazole, a diphenyl-substituted analog of betazole, had a procaine-like anesthetic activity and relieved cutaneous pain (213). The allergological significance and toxicity of certain pyrazoles have been reported (214).

DIURETIC, CARDIOVASCULAR, *HYPOCHOLESTEROLEMIC*, AND HYPOGLYCEMIC PYRAZOLES

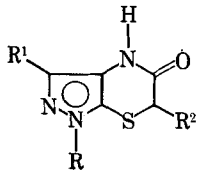
3,5-Dimethylpyrazole (DMP), a true carbonic anhydrase inhibitor with low animal toxicity, given in doses of less than one-half the LD_{50}, only slightly affected blood pressure and respiration (215, 216). Strong K^+ and Cl^- with moderate Na^+ and water excretion patterns were reported (217). It was noted, in a series of DMP relatives, that 3,5-dimethyl-4-bromo- and 1,3,5-trimethyl-4-nitropyrazole caused muscle relaxation and antiedemacious activity (218), while several 3-substituted pyrazolyl-1,2-benzisothiazole-1,1-dioxides showed good hypotensive-diuretic activity. N-Phenethyl-IIb and 1-phenyl-5-morpholino-6-hydroxy-1*H*-pyrazolo-[3,4-*b*]pyrazine (XXX) also produced diuresis. 1-Isopropyl-6-methyl-IIa and 1-isopropyl-6-ethyl-IIa were potent coronary dilators, and 4-mercapto-derivatives of pyrazole and II also elicited strong responses. Ciba-24, 650-Ba suppressed anginose pain, while Ciba-31, 531-Ba, 2-(N-methyl-4-piperidyl)-3-amino-5-(4-



XXXI



XXXII



XXXIII

pyridyl)pyrazole·HCl (XXXI) was a good renal vasodilator. The latter was useful for evaluating renal vascular reactivity to a vasodilating stimulation in various nephropathies. It produced hypotension in conscious dogs and seemed to reduce heart-rate performance in anesthetized unconscious dogs. Pyrazolylguanidines (XXXII) and related substances caused hypotension, sedation, and psychomotor stimulation, and a group of 5-oxo-pyrazothiazines (XXXIII) acted as hypotensive agents (219–224).

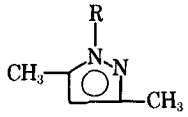
Giachetti *et al.* (225, 226), found that IIb decreased α- and β-globulins, and increased γ-globulins in hepatectomized rats, with a three- to fourfold liver-lipid increase occurring in 24 hr. in mice. Neutral lipids increased 10–16-fold, and the cholesterol level rose by 40%. No significant plasma-phospholipid, free fatty acid, or glucose changes were evident but plasma-triglyceride levels were reduced 40% in 1 hr. 4-Aminopyrazolo[3,4-*d*]pyrimidine (IIb) caused 85% inhibition of orotic-^{14}C acid incorporation into RNA. Hyperlipemia, normally elicited by Triton WR-1339, was inhibited by IIb, which suggested that IIb inhibited the secretion of triglycerides from the liver (227).

Bizzi related the action of DMP to fat and glucose fat, and it was reported that nicotinic acid, salicylic acid, or DMP blocked the mobilization of free fatty acids from adipose tissue. The assertion was made that a new method for preventing or controlling the development of liver triglyceride accumulation is possible. Results indicate that drugs which prevent the release of free fatty acids from adipose tissue could prevent and, in some cases, lower the liver triglyceride accumulation. This was true even if the cause of such an increase of triglyceride was not an increased lipid mobilization. DMP and its metabolite, 3-carboxy-5-methylpyrazole, were effective in lowering the plasma-triglyceride level, with the metabolite proving to be more effective than DMP (228–230). The primary action was on fat metabolism, and the effect on glucose oxidation and blood-sugar depression may be secondary (231). A current review of the effect of drugs on the mobilization of free fatty acid is available (232).

Emphasis on hypoglycemic agents was accelerated by the realization that DMP and its metabolite possessed blood-sugar lowering qualities in addition to hypocholesterolemic properties. DMP increased the glucose oxidation by intact rats and lowered plasma free acids of eviscerate rats, but not their blood-sugar levels. DMP markedly depressed plasma-free fatty acids 15 min. to 3 hr. after administration, and it was assumed that part of the hypoglycemic action may have been due to stimulation of glucose oxidation by the intestines and liver. DMP-^{14}C was utilized in these metabolic fate determinations (233, 234). Vetulani mentioned that an interference with some central mechanism was involved, and species differentiation and diuresis were cited (235). DMP is a "unique tool" when it is used in the study of the carbohydrate-lipid metabolic relationship to aid in understanding normal and abnormal metabolism (associated with diabetes).

Dulin *et al.* (236) have reported on hypoglycemic compositions of 3-carboxy-5-methylpyrazole and closely related 3-substituted analogs. In 1964, they noted that a number of pyrazoles with methyl-groups in both the 3 and 5 positions possessed up to 100 times the hypoglycemic activity of tolbutamide in glucose-primed, intact fasted rats (Table II) (237). DMP was 54 times as active as tolbutamide, suggesting that conversion to the acid metabolite, which has 200 times the activity of tolbutamide, accounted for all of the activity (238, 239). This metabolite had a pronounced effect on plasma free fatty acids and it differs from insulin, sulfonylureas, and biguanide in mechanism of action. Pyrazole-1-carboxami-

TABLE II—HYPOGLYCEMIC PYRAZOLES



R	Hypoglycemic Activity	R	Hypoglycemic Activity
CH_3	4–8	$-CONHNH_2$	16
$CONH_2$	25	$-COC_6H_5$	100
$CONHC_4H_9$	4–8	p-COC_6H_5Cl	25–50
$CONH(CH_3)_2$	30	p-$COC_6H_5NO_2$	25
$CONHC_6H_5$	20–30	Tolbutamide	1

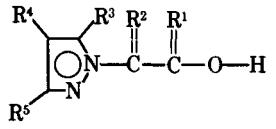
dines (240) and pyrazole-1-ethanol derivatives were reported (XXXIV) (241). The ethanolic substances which are nontoxic acid-addition salts, also affected antiviral and anti-inflammatory responses. 1-Phenylsulfonyl-DMP controlled blood-sugar levels in rats (XXXV) (242) and an excellent hypoglycemic response resulted when approximately 250 mg. of certain sulfanilamidopyrazoles was administered with 500 mg. of tolbutamide (243).

CENTRALLY ACTING PYRAZOLES

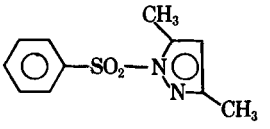
In 1954, a tetra-substituted pyrazole in combination with procaine and a 3,5-dioxopyrazolidine was reported to provoke a strong analgesic-antipyretic response (244). 2-(2-Dimethylaminoethyl)-, 2-alkyl-4,5-DMP homologs, pyrazole, 5-isopropyl-,5-phenyl-, and 4-methyl-5-phenylpyrazoles (XXXVI) caused an analgesic-spasmolytic consequence which paralleled an increase in molecular weight (245). Analgesic 3-hydroxypyrazolecarboxylic acids have been reported (246).

Pyrazole and 3-*n*-alkylpyrazoles (XXXVII) acted as species-selective anticonvulsants in lab animals; optimal convulsion-inhibition occurred with a 4-C side chain in this series (247). Human epileptic seizures were controlled with 4-chloropyrazole or 1 of 3-mono- or 3,4-disubstituted pyrazole·HCl salts (XXXVIII) (248), while a series of 1,4-disubstituted pyrazolecarbinols showed anticonvulsant-muscle relaxant activity (XXXIX) (249).

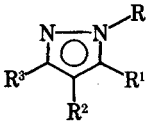
Phemerazole,3-methyl-5-phenylpyrazole (XL), was one of a group of pyrazoles which evoked sharply pronounced sedative, soporific, anticonvulsant, and hypothermic responses. A tenfold species differential was shown in lab animals upon administration of this compound, which inhibited nikethamide, strychnine, and picrotoxin activity in mice and activated camphor. However, when it was given with arecoline and with nicotine, it moderated tremors and convulsions, but increased animal mortality. Phemerazole potentiated the action of diethylstilbestrol on mammary glands (250–254). The anticonvulsant and toxic properties of its 1-allyl- and 1-methyl-4-nitro- analogs (XLI) have been cited. Phemerazole activity has been compared to that of meprobamate on the suppression of a response to an electric stimulus and to nikethamide overdoses (255). It produced no analgesia in rats but did potentiate morphine; however, this combination was more toxic than either substance singly (256). Phemerazole, several of its homologs, and tetrahydroindazole depressed polysynaptic, but not monosynaptic, reflexes. In mice and rats these "mephenesin-type" central relaxants depressed the "turn-over reflex" (257). The distantly related 3-amino-5-(trifluorophenyl)indazole was also a muscle-relaxant analgesic (258). When given in high doses, the majority of aminopyra-



XXXIV

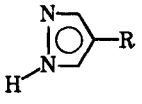


XXXV

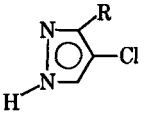


(R = alkyl)
(R′ = H, alkyl)
(R² = H, alkyl)
(R³ = alkyl, phenyl)

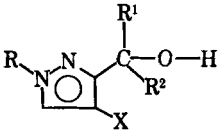
XXXVI



XXXVII

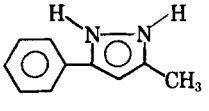


XXXVIII

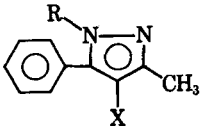


(X = H, halogen)
(R = H, methyl, benzyl)
(R¹ = small alkyl)
(R² = alkyl, *p*-Cl–, and phenyl)

XXXIX

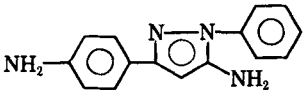


XL

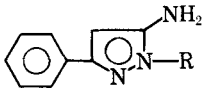


(R = H, methyl, alkyl)
(X = $-NO_2$, halogen)

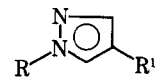
XLI



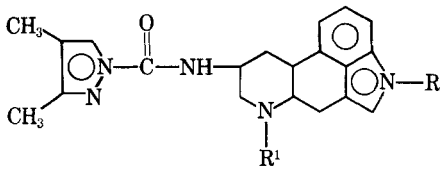
XLII



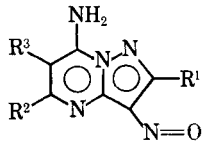
XLIII [R = isopropyl, 1-(2-hydroxyprspyl)]



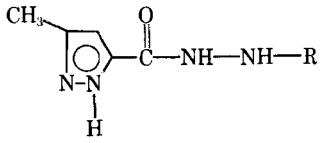
XLIV (R = H; R¹ = ethyl, isopropyl)
XLV (R = phenyl; R¹ = ethyl, isopropyl)



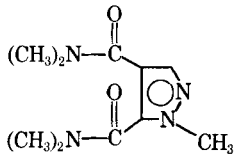
XLVI (R = R¹ = methyl)
XLVII (R = ethyl; R¹ = methyl)



XLVIII



XLIX (R = benzyl)
(R = isopropyl)

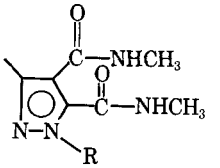


L

zoles depress the CNS; some are capable of potentiating the effect of thiopental, while others eliminate aggression in mice without visibly depressing their behavior. Aminopyrazoles displayed a weak antagonism to the spastic action of pentylenetetrazol[5] and some were classified as tranquilizers, with high activity being attributed to 1-phenyl-3-*p*-amino-phenyl-5-aminopyrazole (XLII). 3-Phenyl-5-aminopyrazole (259) and the 1-isopropyl and 1-(2-hydroxyethyl)-homologs (XLIII) produced distinct muscle relaxation (260). The S-A-R of 13 *N*-substituted 3-amino-4-phenylpyrazoles has been reported, and the parent compound has proved to be the most effective in the series (Table III) (261, 262).

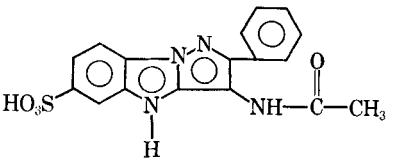
Patients with chronic bronchitis and respiratory failure, who were treated with 2-(*N*-methyl-4-piperidyl)-3-amino-5-(4-pyridyl)pyrazole · HCl (XXXI), showed improvement of some parameters of respiratory mechanics and some indexes of external ventilation. The compound produced bronchospasmolytic effects, but no improvement of internal ventilation was observed (263). Some 4-mono- (XLIV) and 1,4-disubstituted pyrazoles (XLV), which lowered muscle tone, motor activity, and body temperature, antagonized nikethamide and strychnine spasms. The 4-ethyl- and 4-isopropyl- compounds provoked the greatest responses. It was found that the less toxic disubstituted substances were also less active (264). 4-Piperazinoalkylpyrazoles incited a wide range of central responses: central depression, narcosis potentiation, sedation, tranquilization, hypnosis, and narcosis (265). Metoquizine (XLVI) and toquizine (XLVII) were found to be interesting "antiulcer" indolo[3,4-*fg*]quinolinylpyrazoles (266), and 3-nitroso-6-amino-1*H*-pyrazolo[1,5-*a*]pyrimidines (XLVIII) promoted central activity (267).

The clonic convulsions and mortality induced by pentylenetetrazol were promoted by 5-benzyl- and 5-isopropyl-3-methylpyrazole carboxylic acid hydrazides (XLIX), known MAO-inhibitors (268). A 1-methylpyrazole-4,5-diamide (II): prolonged chloral hydrate-induced sleep, antagonized caffeine, intensified the spasmodic effects of corazole, nicotine, and strychnine, stimulated gastric secretion by a central mechanism, was less toxic than the imidazole isomer, and exerted a sedative effect on the cerebral cortex. Several 4,5-



(R = methyl, allyl)

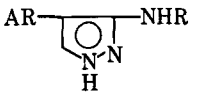
LI



LII

[5] Marketed as Metrazole by Knoll Pharmaceutical Co., Orange, N. J.

TABLE III—MUSCLE RELAXANT 3-AMINO-4-ARYLPYRAZOLES



AR	R	Antistrychnine Activity in Mice: Dose, mg./Kg.	Time, min.	Protection, %	Mortality, %	Preferential Interneuronal Inhibition in Cats: Dose, mg./Kg.	Inhibition, %	Av. Duration, Minimum, min.
Phenyl	H	200	30	144	20	15	70	120 plus
m-Cl-Phenyl	H	150	30	112	..	..	...	...
p-Cl-Phenyl	H	200	30	118	0	..	...	...
3,4-di-Cl-phenyl	H	300	30	175	0	10	12	50
m-Tolyl	H	250	30	155	0	..	...	...
2,3-Xylyl	H	400	30	105	10	..	...	...
3-Thianaphthenyl	H	300	30	115	10	30	100	...
Phenyl	$COOC_2H_5$	350	60	92	0	20	61	188 plus
Phenyl	$CONH_2$	750	30	100	10	20	60	150 plus

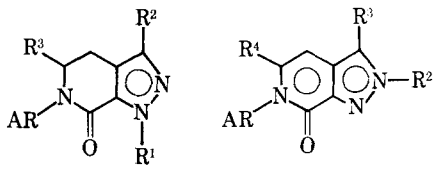
diamides (LI) antagonized caffeine and potentiated amphetamine. The effect of pyrazole dicarboxylic acid on EEG tracings has been reported (269–272). 2-Phenyl-3-acetylaminopyrazolo[1,5-*a*]benzimidazole-6-sulfonic acid (LII) stimulated the nervous system without a growth of spontaneous motricity (273).

Takamizawa *et al.*, who prepared and investigated the pharmacodynamics of a large number of pyrazolo[1,5-*a*]pyrimidines (XXVI), found that 4-substituted homologs possessed antipyretic-antiphlogistic activity. The 7-amino-substances were analgesic, anti-inflammatory, antipyretic, and antiphlogistic, and the 7-carbonyl-amido- and 3-methyl-6-carbethoxy-7-oxo-XXVI products tranquilized, depressed inflammation, and lowered body temperature. The 7-imino-4,7-dihydro-XXVI substances were sedative and antiphlogistic-antipyretic. 2,5-Dimethyl-XXVI was analgetic and antipyretic, and 3-cyanoethyl-2-oxo-5-phenyl-XXVI exhibited anti-inflammatory activity. Also prepared were the 2,3-dialkyl- and 7-formamido-XXVI (274–286). One series of XXVI compounds reduced inflammation (287).

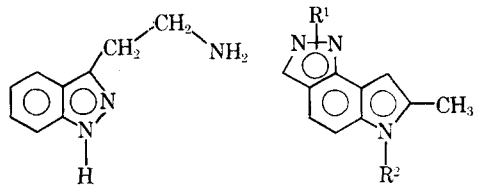
ANTI-INFLAMMATORY AGENTS

Pyrazole demonstrated a reasonable correlation between its antierythemic and antirheumatic activity and this inflammation-inhibiting effect was used in the UV erythema pharmacological assay for anti-inflammatory drugs (288). Activity was apparent in several novel 1-carbamoyl-3-amino-4-nitrilopyrazoles (289). 2*H*- and 1*H*-pyrazolo[3,4-*c*]pyridines (LIII, LIV) reduced inflammation (290) and the indazole (LV) isostere of 5-hydroxytryptamine produced similar responses from isolated smooth muscle preparations (291–293). Several pyrrazoloindazoles (LVI) were analgesic and reduced inflammation (294). Citrates, maleates, and sulfates of 3-dialkylaminoalkyoxyindazoles displayed enhanced activity (295).

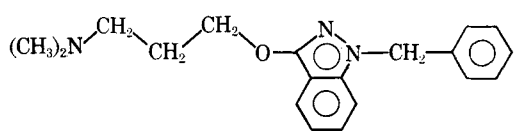
The first therapeutically important indazole was benzydamine, 1-benzyl-3-[3-(dimethylamino)propoxy]1*H*-indazole (LVII). Benzydamine and its salts possessed excellent inflammation-reducing properties, but the hydrochloride salt was the most active of the compounds examined (296). Absorption and elimination studies indicated large quantities of unchanged drug in the blood; 1 mg./Kg., in man, created significant and prolonged blood levels. The drug passed into the



LIII LIV

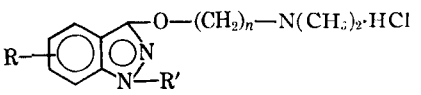


LV LVI



LVII

TABLE IV—BIOLOGICALLY ACTIVE 1-SUBSTITUTED 3-DIMETHYLAMINOALKOXY-1*H*-INDAZOLES[a]

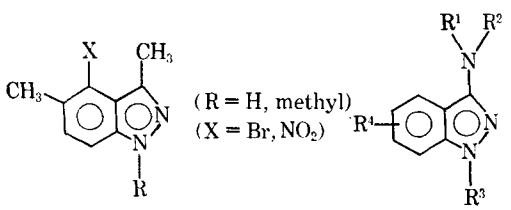


R	R¹	*n*	Analgesia[b]	Anticonvulsants[c]	Antispastic[d]	Anti-inflam.[e]	Local Anesth.[f]	Toxicity[g]
5-NH_2	C_4H_9	3			−			+
5-NH_2	$C_6H_5CH_2$	3					+	+
5-NO_2	C_4H_9	3			−			+
H	CH_3	3	+			+		+
H	C_6H_5	2	+	+		+		
H	C_6H_5	3	+				+	
H	$C_6H_5CH_2$	2	+				+	
H	$C_6H_5CH_2$	3	+	+		+	+	
H	$C_6H_5CH_2CH_2$	2	+	+			+	
6-Cl	$C_6H_5CH_2$	3	+			+		
H	p-$ClC_6H_4CH_2$	2	−			+		
4-Cl	$C_6H_5CH_2$	3	−			+		
5-Cl	C_4H_9	2	−			+		
5-Cl	C_4H_9	3	−	+		+		

[a] These hydrochloride salts produce sedation, muscle relaxation, and motor incoordination at 20–40 mg./Kg. At 80–100 mg./Kg. depression followed by clonic convulsions at near lethal doses occurs. [b] Using the hot plate and phenylquinone tests it is found that the more toxic *n*-2 side chains are least active. ED_{50}'s of 20–40 mg./Kg. are usual. [c] ED_{50}'s 40 mg./Kg. *vs.* strychnine or electroshock induced convulsions. [d] The guinea pig ileum used. A papaverine-like effect produced (0.3 mcg./ml.). [e] ED_{50} 15 mg./Kg. *vs.* plantar edema and induced granuloma. [f] Active at 0.5 mg./ml. *vs.* corneal reflex and tail pinch. [g] Toxicity varies between 120–150 mg./Kg. (LD_{50}) for the series. Compounds with NH_2 and NO_2 in their nucleus are most toxic.

intestinal lumen, in rats, but was not excreted in the feces, suggesting enteric circle. Fifty percent was excreted in the urine of man (297). Liver response, enzyme induction, and resultant increase in liver weight have been cited (298). Benzydamine was compared to codeine and aspirin, using various pain-threshold techniques in mice (299); the local effect and a lack of interference with the adrenals was observed (300). Axerio introduced a new synthesis for benzydamine (301), which was stated to be the most powerful analgetic-anti-inflammatory drug in use (299). Silvestrini has reviewed benzydamine (302).

Low toxicity, reduced inflammation, analgesia, and a decrease of spasms were attributed to 34 homologs of benzydamine (Table IV) (303). Other interesting work on synthetic nonsteroidal inflammation-reducing agents was reported (304), and of these, the 4-bromo- and 4-nitropyrazoles (LVIII) were impressive anti-inflammatory substances (305). The general pharmacology of a few 3-disubstituted-amino-1*H*-indazoles (LIX) was given in another report (306).

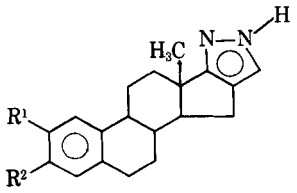


LVIII LIX

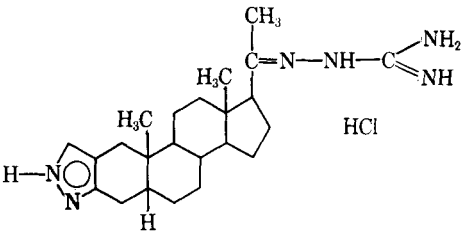
BIOLOGICALLY ACTIVE PYRAZOLOSTEROIDS

Pharmacodynamic interest in steroidal pyrazolo-compounds dates to the 1959 work of Clinton *et al.* (307, 308) with psychopharmacological agents. Hypotensive and hypophyseal-blocking action was observed for a series of estra-1,3,5-(10)-triene[17,16-*c*]pyrazoles (LX) (309) and 20-oxo-4-pregn[3,2-*c*]pyrazole guanylhydrazone · HCl (LXI) (310). Hormonal steroids with pyrazole fused to positions C-2 and C-3 were first reported in the androgen family (311), but some A-aza-steroids (LXII) were found to be inactive androgenic, anabolic, estrogenic, or antiestrogenic substances (312). Rosseels has reviewed LXII (313). Progestation was effected with pyrazolo-[3,2-*c*]-19-nor-4,9-androstadienes (LXIII) (314), and 4-androsteno[3,2-*c*]pyrazoles (LXIV) caused progestational, estrogenic, and lower blood-cholesterol responses (315). Steroidal [17,16-*c*]-pyrazoles reduced cholesterol levels equally as well as estradiol, but their estrogenic potency was only 1/10,000 that of estradiol (316).

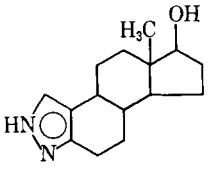
17β-Hydroxy-17α-methylandrostano[3,2-*c*]-pyrazole, stanozolol (LXV), and the 4-eno-analog, when given to human patients, influenced N-retention and electrolyte balance. Chronically ill geriatric mental patients gained weight with stanozolol and 1 to 20 mg. daily for 24–161 days resulted in no hepatotoxicity. Appetites and mental outlook improved without the occurrence of androgenic or other adverse effects. A posi-



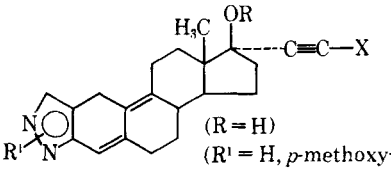
LX



LXI

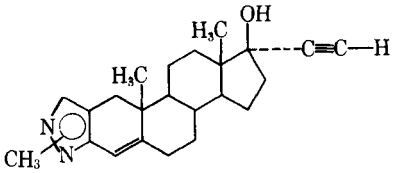


LXII

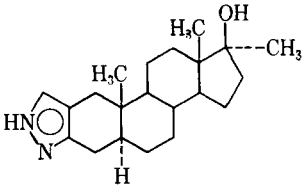


(R = H)
(R^1 = H, *p*-methoxyphenyl)
(X = Br, H)

LXIII



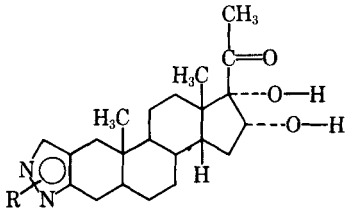
LXIV



LXV

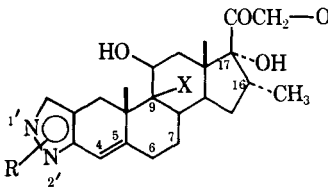
tive N-balance resulted through an unknown mechanism, and calcium metabolism was influenced also. Stanozolol, given orally, was 30 times as potent as methyltestosterone, but had only one-fourth the androgenic activity. This pyrazolosteroid increased hemoglobin and serum-albumin levels with the former being even more dramatically affected than body weight. Serum cholesterol and phospholipid concentration were lowered by stanozolol. Anabolic effects persisted for several weeks following termination of stanozolol therapy. The most serious problems, which were lowering the α-lipoprotein level and the $\alpha:\beta$-lipoprotein ratio, closely paralleled those met with nonpyrazolo anabolic steroids (317–320).

16α,17α-Dihydroxy-2-oxo-4-pregnene[3,2-*c*]pyrazoles (LXVI) were found to be anti-inflammatory compounds. 2′-(*p*-Fluorophenyl)pregn-4-eno[3,2-*c*]pyrazole (LXVII) was the most potent agent in the series (1964) (Table V) and other phenyl-substituted electron-withdrawing groups were found to decrease the activity of the parent phenyl-homolog. One relative was 500 times more active than cortisol for antagonizing granuloma formation and causing adrenal atrophy. Neither this substance, 9α-fluoro-16α-methylcortisol nor LXVII caused Na retention in



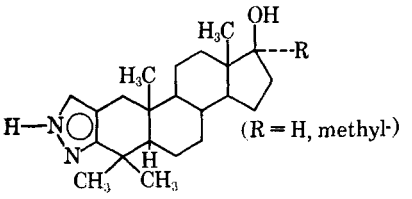
LXVI
LXVII (R = 2′-(*p*-fluorophenyl-))

TABLE V—ANTI-INFLAMMATORY PYRAZOLOSTEROIDS

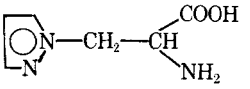


R	R^1	X	Granuloma Inhibition
2′-*p*-C_6H_4F-	H	F	10–12[a,b]
2′-C_6H_5-	Ac	H	60
2′-*p*-C_6H_4F-	Ac	H	100[a,b]
2′-*p*-C_6H_4F-	Ac	F	500[a,b]
1′-C_6H_5-	H	H	2
1′-CH_3-	Ac	H	1.5
2′-CH_3-	Ac	H	5.9
2′-C_6H_5-	Ac	H	1[c,d]
2′*p*-C_6H_4Cl-	Ac	H	15
2′-C_6H_5-	H	H	25[d]
H	H	F	10–12[a]
2′(*o*,*p*-$C_6H_3F_2$)	H	H	115[e]
Cortisol			1

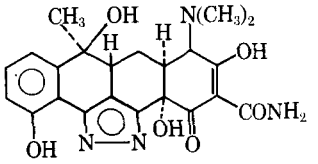
[a] Produces adrenal atrophy. [b] No sodium retention. [c] Saturation of 4–5 bond. [d] A 16 αH replaces the 16α methyl group. [e] The saturated 6–7 bond is replaced to give a delta-6 double bond.



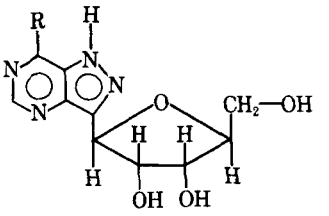
LXVIII



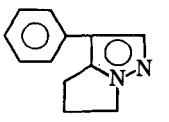
LXIX



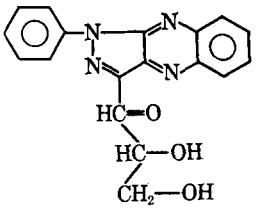
LXX



LXXI (R = NH_2)
LXXII (R = H)
LXXIII (R = NH—NH_2)



LXXIV



LXXV

the rat. While studying the activity of pregn-4-eno and 5α-pregnano-[3,2-*c*]pyrazoles, investigators first made the novel observation that a carbonyl function at C-3 was not required for anti-inflammatory activity. The [3,2-*c*]pyrazole function, unlike the 2-α-methyl-, did not enhance mineralocorticoid activity. These results were intriguing, since the highly potent 2′-phenylpyrazole homolog chemically resembled the biologically inactive isoxazole isostere in its double bond structure; whereas, the nearly inactive 1′-phenylpyrazole homolog, like the natural corticoids, had an exocyclic double bond at C-3 (321–326). Two 17β-hydroxyandrost-5-eno-[3,2-*c*]-pyrazoles (LXVII) were the most effective of 42 androstane derivatives examined as inhibitors of β-hydroxysteroid dehydrogenase. The degree of inhibition was dependent upon the nature of the substituents at positions 2, 3, 4, and 17 of the steroid. Spatial presentation of these groups to the enzyme by the arrangements of double bonds or by their absence also affected inhibition. Estradiol-17β was noncompetitive, while these pyrazolosteroids acted by a competitive mechanism. The 50% inhibitory concentration for estradiol-17β of 5×10^{-5} moles/L. as opposed to 5×10^{-7} moles/L. for LXVIII gave evidence that the pyrazole was more tightly bound to the enzyme (327). Interesting new pyrazolyl- and pyrazolosteroids have been synthesized (328–330).

NATURAL PRODUCTS

Until 1963 pyrazoles of natural origin were unknown but with a little help from Takeshita *et al.* (331), β-(1-pyrazolyl-L-alanine (LXIX) was identified and confirmed. A new enzyme, pyrazolealaninase, which is specific for the L-isomer, has been purified from cells of *Pseudomonas cruciviae* (watermelon juice) grown on the new amino acid. Attempts to activate S-protein at high peptide-protein ratios by replacing the histidine moiety with LXIX or its 3-pyrazolyl homolog have failed. It appears that the ionization behavior of histidine was responsible for the ability of S-peptide to activate S-proteins (332).

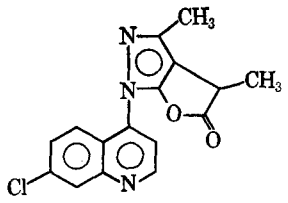
Valcazi *et al.* (333) treated chlortetracycline·HCl with hydrazine in methanol at 20°. The addition product, a conjugated pyrazolotetracycline (LXX), exerted the same action on several organisms as the parent antibiotic. The molecular structure has been established for another natural antimicrobial pyrazolo-compound, formycin, 7-amino-3-(β-D-ribofuranosyl)pyrazolo-[3,4-*d*]pyrimidine (LXXI), and the deaminated product, formycin B (LXXII), also has been identified. 7-Amino- and 7-hydroxypyrazolo-[4,3-*d*] pyrimidine were obtained from LXXI and LXXII, respectively. The semisynthetic hydrazinoformycin (LXXIII) has shown antimicrobial effects (334–337). Withasomnine (LXXIV), isolated from *Withania somnifera* roots, which are used medicinally in India, was structurally proven (338), and 1*H*-pyrazolo[3,4-*b*]quinoxaline "flavones" (LXXV) have been reported (339).

MISCELLANEOUS ACTIVITY

Pyrazole exerted a protective effect on hemin against *in vitro* degradation by ionizing irradiation. A carbamyl-DMP,[6] gave a 50% survival rate at doses of 200 mg./Kg. in mice over a 30-day period (340–342).

DMP stimulated plant growth (343), while 1-aryloxyacylpyrazoles were growth regulators

[6] Dupont-990.



LXXVI

and herbicides (344). 1-Guanyl-DMP·HNO_3, which reacts specifically with the ϵ-amino- groups of lysine (345-347), was utilized for the guanidation of bovine serum albumin, β-lactoglobin, and ovalbumin.

Alkylpyrazoles have been suggested for use in perfumery (348). Pyrazolo[4′,3′:5,6]2-pyrone (LXXVI), a novel annelate, incited no appreciable pharmacodynamic response (349).

CONCLUSIONS

The versatility of action of even the simplest pyrazoles was noteworthy, and pyrazole, itself, was mentioned on several occasions. A dimethylated pyrazole, DMP, and its carboxylic acid metabolite exerted profound effects on diuresis, fat, and glucose metabolism. The simple histamine isomer, betazole, manifested greater specificity on gastric secretions than histamine, while 3-methyl-5-phenylpyrazole, phemerazole, was an excellent central spasmolytic anticonvulsant. The simple pyrazoles, XXII, XXIII, XXIV, and pyrazoxon reportedly are all commercially successful pesticides, and the 1*H*-indazole, benzydamine, has proved to be an excellent nonsteroidal anti-inflammatory agent. Xanthine oxidase inhibitors like allopurinol, used in gout, and its carcinostatic 4-amino analog have been highly effective substances. The androstano-[3,2-*c*]pyrazole, stanozolol, fairly exploded on the scene and has become one of our finest anabolic agents. These drugs were all unknown 10 years ago.

The pyrazoles are exciting entities from which many new biologically active materials have been derived. Unlike the thiophenes (350), there is no slackening of interest in these pi-excessive N-heteroaromatic compounds. Quite to the contrary, the breath-taking pace of discovery of new pyrazolo-ring systems, new substitutions in established nuclei, and the biological responses to these heterocycles and to their modification products has given a momentum to pyrazole researches that has been known to few heterocycles. The widely varied biological activity spectrum is, indeed, unique. Pyrazole has manifested itself, in most instances, as a distinct and accountable portion of any number of diverse chemical structures which effect numerous biological responses. The crest of activity has yet to peak in the vast wave of research in this fertile area of study.

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Keyphrases

Pyrazoles, biologically active—review
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