the carbobenzyloxy group was observed and subsequently no benzyl alcohol could be detected.

Experimental Section§

N-Carbobenzyloxy-L(-)asparaginol (II). Lithium aluminum hydride (1.2 g, 31.6 mmoles) was added to tetrahydrofuran (THF) (160 ml, distilled from $LiAlH_4$) and stirred. *N*-Carbobenzyloxy-L-asparagine[15] (I, 6.0 g, 22.6 mmoles) was added slowly, and the mixture was stirred for 2 days at 25°. To decompose excess $LiAlH_4$, EtOAc (10 ml) was added dropwise, then ether (100 ml), and finally 2 *N* HCl (10 ml). The reaction mixture was filtered after stirring for 15 min. The filtrate was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting oily residue was recrystallized from EtOAc, yielding 0.97 g of colorless needles, mp 142–143°. The precipitate, containing Al oxides and starting material, was treated with 0.5 *N* NaOH (20 ml) and filtered. The filtrate was acidified to pH 1 with concd HCl, upon which unchanged starting material (I) was isolated (1.03 g), yield of *N*-carbobenzyloxy-L(-)-asparaginol (II), 23%. *Anal.* ($C_{11}H_{14}N_2O_3$) C, H, N.

N-Acetyl-L(-)asparaginol (III). A solution of *N*-carbobenzyloxy-L(-)asparaginol (II, 190 mg, 0.85 mmole) in MeOH (2 ml), AcOH (2 ml), and H_2O (2 ml) containing 5% Pd/C (150 mg) was hydrogenated at atmospheric pressure. After absorption of the theoretical amount of H_2, the catalyst was removed by filtration; toluene odor was noticed. The filtrate was evaporated to dryness under reduced pressure. An oily residue was obtained from which, after solution in EtOAc and standing at 0° for 3 days, 57 mg (37%) of colorless needles, mp 126°, was obtained. Recrystallization from EtOAc raised the mp to 134°, ir KBr disk 1050 (OH), 1550 (CH_3CONH), and 1660 cm^{-1} ($CONH_2$). *Anal.* ($C_6H_{12}N_2O_3 \cdot H_2O$) C, H, N.

L(-)-3-Amino-4-hydroxybutyramide (L-Asparaginol) (V). A solution of *N*-carbobenzyloxy-L(-)asparaginol (II, 6.0 g, 0.027 mole) in MeOH (240 ml) with 10% Pd/C (0.4 g) was hydrogenated until H_2 uptake ceased. The solution was filtered and the filtrate was evaporated at 25°, first at 10 mm, then at 0.05 mm. The resulting white crystalline material was taken up in EtOH (30 ml), filtered, and collected (0.3 g), mp 93–95° dec. The filtrate was added to EtOAc (350 ml), and the solution decanted from the yellow oil which separated. This solution was concentrated *in vacuo* until crystallization began to occur. White crystals were collected (1.7 g), mp 95–98° dec. An additional crop (0.4 g), mp 93–95° dec, was obtained by extracting the yellow oil with EtOH, addition of EtOAc, charcoal treatment, and concentration, total yield, 2.4 g (75%). An analytical sample of this material was obtained by recrystallization from EtOAc, mp 98–100° dec, $[\alpha]^{24}D$ −23° (H_2O); ir KBr disk 1050 (OH), 1660 and 1600 ($CONH_2$), 3400 cm^{-1} (NH_2). *Anal.* ($C_4H_{10}N_2O_2$) C, H, N.

Adenosine 5′-L(-)Asparaginol-1-yl Phosphate Na Salt (L-Asparaginol Adenylate) (VI). *N,N′*-Carbonyldiimidazole (DCI) (0.50 g, 3.1 mmoles) was added to a stirred mixture of adenosine 5′-monophosphate, Na salt (NaAMP) (III, 0.50 g, 1.5 mmoles), in dry DMF (15 ml). Solution was effected after 30 min, and *N*-carbobenzyloxy-L(-)-asparaginol (II, 0.36 g, 1.5 mmoles) was added. The solution was kept at 50° for 9 days. The DMF was removed *in vacuo* at 60°, the gummy residue was extracted 3 times with Et_2O, and the ethereal extracts were discarded. The remaining solid was chromatographed on a cellulose column, using 70% aqueous 1-PrOH as an eluent. The solvent from the first 300 ml was removed *in vacuo* and the residue was dissolved in H_2O (3 ml) and precipitated by the addition of EtOH (50 ml) to give white needles (0.40 g, 60%), mp 168–170° dec. A sample was prepared for analysis by futher chromatography, dissolving the resulting residue from evaporation of the eluate in H_2O and reprecipitating with EtOH, $[\alpha]^{25}D$ −26.8° (H_2O); ir KBr disk 1650, 1600 ($CONH_2$), 1570 and 820 (NH_2), 1240 (P=O), 1160, 1100 (POC), 1070 (COH, sugar). *Anal.* ($C_{14}H_{21}N_7O_8PNa$) C, H, N, P.

Isolation of Benzyl Alcohol from the Preparation of VI. A condensation reaction was carried out in the same conditions as above but on a larger scale using 6.5 g of DCI and 6.5 g of NaAMP and 5 g of II. After removal of the DMF from the reaction mixture, the gummy residue was extracted 3 times with Et_2O, the residue being used for the preparation of VI. The ether extracts were combined, and the ether was removed *in vacuo*. The residue was distilled at 10 mm, and the 100–110° fraction was collected (2.5 g, 95%). The uv spectrum of this product was identical with benzyl alcohol; 3,5-dinitrobenzoate, mp 111–112° (lit.[16] 113°) and ir identical with that of an authentic sample.

Reaction of compounds I and II, DCI and DMF (in the absence of NaAMP), in proportions similar to those used for the synthesis of VI failed to yield any benzyl alcohol.

Screening Data. When L-asparaginol (V) and its adenylate (VI) were administered intraperitoneally (ip) in normal BDF_1 mice for 8 days no toxicity was found at dosage levels up to 400 mg/kg.[17,18]

In tissue culture, with P815 leukemia cells resistant to L-asparaginase 100% inhibition was observed when L-asparaginol (V) was administered at 300 μg/ml; at lower dosages compound V was less effective (Table I).

When tested *in vivo* in several mouse leukemias (L5178Y, L5178Y resistant to cytosine arabinoside and L-asparaginase, P815 and P815 resistant to cytosine arabinoside) no antitumor activity up to a dosage of 500 mg/kg, given ip, was observed. No weight loss was encountered.

It can be speculated from the *in vivo* results that V is inactive because it may be oxidized to L-aspartic acid, or be poorly absorbed into the cell and thus could not prevent L-asparagine from being converted to its adenylate. The lack of inhibitory activity of compound VI *in vivo* could be also attributed to its poor absorption.

Acknowledgments. The authors wish to thank Dr. A. Bendich and Dr. C. C. Stock for valuable discussions and continued interest.

§ The infrared data were obtained with a Perkin-Elmer Model 137B infracord spectrophotometer and the uv spectra with a Beckman DBG spectrophotometer. Melting points were determined with a Thomas-Hoover apparatus and were corrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

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Synthesis and Alkylation of Tetrahydrofuro[3,4-*c*]pyrazolols

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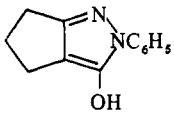
Phenylbutazone and oxyphenbutazone are antiinflammatory-analgetic pyrazoles which are frequently used in the treatment of rheumatoid arthritis.[1] As a continuation

of our work to prepare bicyclic pyrazole analogs such as cyclopentapyrazolol **1**,[2] thienopyrazolol **2**,[3] and pyrrolopyrazolol **3**,[4] we now describe a brief study of some furo[3,4-*c*]pyrazolols.



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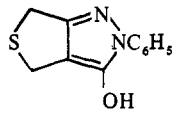

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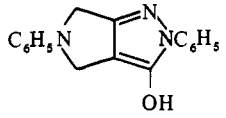
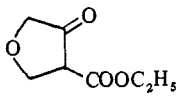


3

Condensation of ethyl 4-oxo-3-furoate (**4**) with arylhydrazines gave the arylhydrazones **5a–5d**. The KBr infrared spectra of compounds **5a–5d** exhibit carbonyl absorptions at 5.85 μ indicating the compounds exist as the arylhydrazones in the solid state.[3]

Cyclization of **5a–5d** in refluxing methanolic NaOMe provided the desired furopyrazolols **6a–6d**. The cyclized



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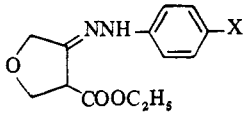

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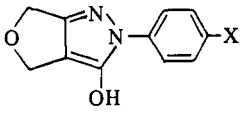
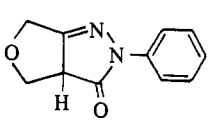


6

a, X = H
b, X = CH_3
c, X = Cl
d, X = Br

products exist in the solid state as the strongly hydrogen-bonded hydroxy tautomers **6**, as shown by the absence of carbonyl absorption below 6.20 μ in the infrared spectra. In $CHCl_3$ soln, typically, the preferred tautomer is the unconjugated lactam **7** (ir 5.83) rather than the conjugated form **8** (no C=O obsd at 5.95 μ). This tautomeric behavior appears to be general for bicyclic 2-substituted pyrazol-3-ols.[2-4]



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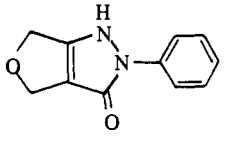
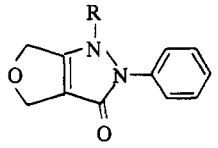


8

Treatment of **6a** with alkyl halides and K_2CO_3 in Me_2CO afforded, as expected,[2-4] mixts of the C- and N-alkylated products. Chromatographic sepn provided the *N*-alkyl products **9** (ir 5.97–5.98 μ) and the *C*-alkyl products **10** (ir 5.82–5.85 μ). The preparation of **11** was accomplished by treatment of **6a** with MeOTs. Reaction of **6a** with MeI in methanolic NaOMe proved to be a more efficient method of obtaining the *N*-Me product **9a**.



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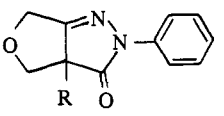

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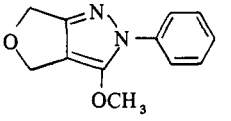

11

a, R = CH_3
b, R = $CH_2CH=CH_2$
c, R = CH_2–C$_6$H$_5$

Oral administration of the furopyrazolols at 250 mg/kg failed to inhibit significantly the carrageenin-induced rat paw edema† when assayed by the method of Winter, *et al.*[5] These findings indicate that this class of compounds is not of interest as antiinflammatory agents.

Experimental Section‡

Ethyl Tetrahydro-4-oxo-3-furoate *p*-X-Phenylhydrazones (5). To 0.01 mole of arylhydrazine was added 0.01 mole of ethyl tetrahydro-4-oxo-3-furoate.§ The reaction was mildly exothermic, and the reaction mixture was stored at room temp for 24 hr. The solid which formed was collected and recrystd; details are furnished in Table I.

Table I. Ethyl Tetrahydro-4-oxo-3-furoate *p*-X-Phenylhydrazones (5)

X	Mp, °C	Recrystn solvent	Formula	Analyses
H	134–135	MeCN	$C_{13}H_{16}N_2O_3$	C, H, N
CH_3	94–97	EtOH	$C_{14}H_{18}N_2O_3$	C, H, N
Cl	106–108	EtOH	$C_{13}H_{15}ClN_2O_3$	C, H, Cl, N
Br	118–121	EtOH	$C_{13}H_{15}BrN_2O_3$	C, H, Br, N

2-*p*-X-Phenyl-2,6-dihydro-4*H*-furo[3,4-*c*]pyrazol-3-ols (6). A soln of 0.01 mole of **5**, 0.62 g (0.011 mole) of NaOMe, and 50 ml of MeOH was heated under reflux for 1 hr and poured into 250 ml of H_2O. The soln was acidified with AcOH, and the solid which pptd was collected and recrystd; details are given in Table II.

Table II. 2-*p*-X-Phenyl-2,6-dihydro-4*H*-furo[3,4-*c*]pyrazol-3-ols (6)

X	Mp, °C	Recrystn solvent	Formula	Analyses
H	169–172 dec	MeCN	$C_{11}H_{10}N_2O_2$	C, H, N
CH_3	193–195 dec	MeCN	$C_{12}H_{12}N_2O_2$	C, H, N
Cl	192–194	MeCN	$C_{11}H_9ClN_2O_2$	C, H, Cl, N
Br	215–220	MeCN	$C_{11}H_9BrN_2O_2$	C, H, Br, N

Alkylation of 2,6-Dihydro-2-phenyl-4*H*-furo[3,4-*c*]pyrazol-3-ol (6a). A. With MeOTs. A mixture of 0.8 g (0.015 mole) of NaOMe and 2.5 g (0.012 mole) of **6a** in 100 ml of anhyd DMF was heated at 80° with stirring, and 2.3 g (0.012 mole) of MeOTs was added. The mixture was heated at 120° for 2 hr, poured into 1.4 l. of H_2O, and extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd under reduced pressure to 1.0 g of brown liquid. This liquid was chromatographed on prep tlc plates to provide 0.49 g of tacky, brown crystals. Two recrystns (hexane) gave 0.08 g (3%) of 4,6-dihydro-3-methoxy-2-phenyl-2*H*-furo[3,4-*c*]pyrazole (**11**) as light brown crystals, mp 91–94°. *Anal.* ($C_{12}H_{12}N_2O_2$) C, H, N.

B. With MeI–NaOMe. A soln of 4.0 g (0.02 mole) of **6a**, 2.2 g (0.04 mole) of NaOMe, and 2.5 ml of MeI in 100 ml of MeOH was heated under reflux for 8 hr. The soln was concd under reduced pressure, and the liquid residue was mixed with 100 ml of H_2O and extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd to

†Animal testing was carried out by Dr. A. E. Sloboda of these laboratories.

‡Melting points were detd in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. All compds were analyzed for C, H, N, and halogen; found values were within ±0.4% of theoretical. Ir spectra were detd by Mr. W. Fulmor and staff.

§Colorless liquid, bp 108–110° (15 mm), prepd from ethyl glycolate and ethyl acrylate using the method of Gianturco, *et al.*[6]

a brown solid which was recrystd (C_6H_6–hexane) to give 2.5 g (58%) of brown crystals, mp 110–115°. A small sample was sublimed at 120° (0.10 mm) to provide 1,2,4,6-tetrahydro-1-methyl-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (9a) as white crystals, 127–128°. *Anal.* ($C_{12}H_{12}N_2O_2$) C, H, N.

C. With MeI-K_2CO_3. A mixt of 2.0 g (0.01 mole) of **6a**, 6 g of K_2CO_3, and 0.7 ml (0.011 mole) of MeI in 50 ml of Me_2CO was stirred at room temp for 24 hr. The mixt was filtered, and the filtrate concd under reduced pressure to 2.6 g of a mixt of crystals and brown liquid. Chromatography on prep tlc plates provided three fractions. The least polar fraction gave 0.23 g of a tacky solid which was recrystd (hexane) to give 0.059 g (2.7%) of straw-colored crystals, mp 56–70°. An additional recrystn (pentane) provided 2,3a,4,6-tetrahydro-3a-methyl-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (10a) as cream-colored crystals, mp 65–70°. *Anal.* ($C_{12}H_{12}N_2O_2$) C, H, N. Pure compounds were not isolated from other fractions. The ir spectrum of the most polar chromatographic band showed it to be the *N*-Me deriv.

D. With $C_6H_5CH_2Br$. A mixt of 2.0 g (0.01 mole) of **6a**, 6 g of K_2CO_3, and 1.5 ml (0.013 mole) of $C_6H_5CH_2Br$ in 50 ml of Me_2CO was stirred at room temp for 20 hr. The mixt was filtered, and the filtrate concd under reduced pressure to 3.1 g of a brown liquid which was chromatographed on prep tlc plates. The most polar fraction was recrystd (C_6H_6–hexane) to give 0.32 g (11%) of cream-colored crystals, mp 163–167°. An additional recrystn (cyclohexane) provided 1-benzyl-1,2,4,6-tetrahydro-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (9c) as cream-colored crystals, mp 163–165°. *Anal.* ($C_{18}H_{16}N_2O_2$) C, H, N.

The least polar chromatographic fraction yielded 0.41 g of a tacky solid which was recrystd (hexane) to give 0.17 g (6%) of 3a-benzyl-2,3a,4,6-tetrahydro-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (10c) as off-white crystals, mp 98–100° dec. *Anal.* ($C_{18}H_{16}N_2O_2$) C, H, N.

E. With Allyl Bromide. A mixt of 8.0 g (0.04 mole) of **6a**, 24 g of K_2CO_3, and 4.8 g (0.04 mole) of allyl bromide in 300 ml of Me_2CO was stirred at room temp for 20 hr. The mixt was filtered, and the filtrate was concd under reduced pressure to 14 g of a mobile, brown liquid which was chromatographed on a silica gel dry column. The more polar fraction provided 2.48 g of a tacky solid which was recrystd (hexane) to give 0.66 g (7%) of straw-colored crystals, mp 110–113°. An additional recrystn (cyclohexane) provided 1-allyl-1,2,4,6-tetrahydro-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (9b) as straw-colored crystals, mp 110–113°. *Anal.* ($C_{14}H_{14}N_2O_2$) C, H, N.

The less polar chromatographic fraction yielded 2.88 g of a mobile, brown liquid. Distn at 0.1 mm gave 1.6 g (16%) of 3a-allyl-2,3a,4,6-tetrahydro-2-phenyl-3*H*-furo[3,4-*c*]pyrazol-3-one (**10b**) as a viscous, brown liquid, bp 132–140°. *Anal.* ($C_{14}H_{14}N_2O_2$) C, H; N; calcd, 11.6; found, 11.1.

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Imidazo[1,2-*a*]pyridine Anthelmintic and Antifungal Agents

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A number of 2-substituted imidazo[1,2-*a*]pyridines have been prepared for anthelmintic and antifungal testing. High anthelmintic activity was found with acylated derivatives of 6-amino-2-(4-thiazolyl)imidazo[1,2-*a*]pyridine. One of the more potent compounds, 6-ethoxycarbonylamino-2-(4-thiazolyl)imidazo[1,2-*a*]pyridine, was orally effective in sheep at a dose of 25 mg/kg against a wide range of helminths. Broad antifungal activity was demonstrated by a variety of compounds but did not correlate well with anthelmintic activity.

2-(4-Thiazolyl)benzimidazole, reported from these laboratories in 1961,[1] has gained wide acceptance as a safe, broad-spectrum anthelmintic agent. In an attempt to extend this activity to other heterocyclic systems, we have synthesized a number of imidazo[1,2-*a*]pyridines of related structure. Early results with simple 2-aryl- or 2-heteroaryl-substituted imidazo[1,2-*a*]pyridines were interesting in that while many compounds demonstrated high *in vitro* anthelmintic activity, little or no activity could be shown *in vivo*. 2-(4-Thiazolyl)imidazo[1,2-*a*]pyridine and 2-methoxycarbonylaminoimidazo[1,2-*a*]pyridine were broadly effective *in vivo* but of low potency. It was speculated that the general lack of activity *in vivo* was not intrinsic but was due to rapid metabolism and excretion. If true, modification of the anticipated sites of metabolism could be expected to lead to more active compounds.

2-Phenylimidazo[1,2-*a*]pyridine is known to undergo electrophilic attack at the 3 position[2] and, since it is common for enzymatic aromatic hydroxylation to occur at the site of electrophilic attack, this position was the first choice for the blockage of metabolism. Derivatives of 2-(4-thiazolyl)imidazo[1,2-*a*]pyridine were prepared in which the 3 position was substituted with nitro, amino, acetamido, diacetylamino, methoxycarbonylamino, chloro, and bromo. In all cases activity was destroyed. The failure of carbamate substitution in the 3 position was particularly disappointing because the carbamate group has been shown, in these laboratories, to be an effective inhibitor of aromatic hydroxylation.[3]

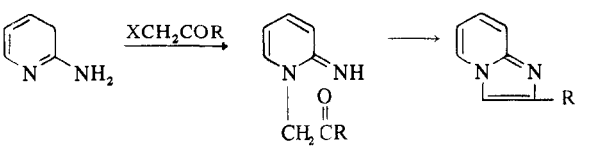
A second possible choice for the site of enzymatic hydroxylation was the 6 position and, in order to test this, derivatives of 2-(4-thiazolyl)imidazo[1,2-*a*]pyridine were prepared in which the 6 position was substituted with methyl, chloro, bromo, cyano, carbamoyl, carboxy, nitro, amino, and acylated amino. Success was attained with acylated 6-amino derivatives and in fact 6-ethoxycarbonylamino-2-(4-thiazolyl)-imidazo[1,2-*a*]pyridine was approximately twenty times as active *in vivo* as the parent compound.

Substitution in the 5, 7, and 8 positions reduced activity.

Oxidation of the 2-(4-thiazolyl)imidazo[1,2-*a*]pyridines with trifluoroperacetic acid gave the thiazole 3-oxide derivatives which were approximately as active as the parent compounds.

Chemistry. The chemistry of imidazo[1,2-*a*]pyridines has recently been reviewed by Mosby.[4] The new compounds prepared are listed in Tables I, II, III, and IV together with some previously described compounds. Synthetic procedures, generalized where possible, are described in the Experimental Section.

2-Substituted imidazo[1,2-*a*]pyridines were synthesized by reaction of 2-aminopyridines with the appropriate haloketones, *e.g.*,



Appropriately substituted 2-aminopyridines similarly yielded 5-, 6-, 7-, and 8-substituted imidazo[1,2-*a*]pyridines.