groups of compounds (1 and **2f**) are hydrolyzed by liver enzymes to inactive diacids. The difference in activity of pyridines and dihydropyridines containing benzyl and *tert*-butyl ester groups is probably due to their different hydrolysis mechanism and rate.[15]

Replacement of the ethoxycarbonyl substituents of DDC (1a) and the corresponding pyridine derivative **2a** with the methoxycarbonyl substituent (1 and 2e) resulted in decreased activity (Figure 4). When the 4-methyl substituent of methoxycarbonyl compounds was replaced by hydrogen (1 and **2d**) the compounds showed no activity (Figure 4). This inactivity was similar to that previously found when the 4-methyl substituents of DDC (1a) and OX-DDC (2a) were replaced by hydrogen.[3]

It was concluded that the *tert*-butoxycarbonyl compounds would induce higher levels of ALA synthetase in chick embryo than DDC (1a). For this reason these compounds should be valuable in inducing higher levels of ALA synthetase in chick embryo liver prior to attempting to isolate this enzyme.

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Adenosine Cyclic 3′,5′-Monophosphate Phosphodiesterase Inhibitors. 2. 3-Substituted 5,7-Dialkylpyrazolo[1,5-*a*]pyrimidines

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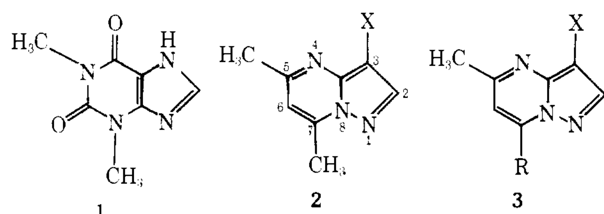
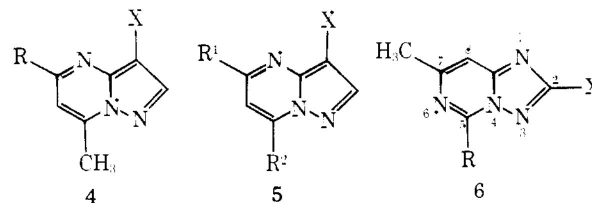
A number of 3-bromo-, 3-nitro-, and 3-ethoxycarbonyl-5,7-dialkylpyrazolo[1,5-*a*]pyrimidines were synthesized and screened as in vitro cAMP phosphodiesterase inhibitors. The condensation of 3-aminopyrazole with symmetrical β-diketones (acetylacetone, heptane-3,5-dione, etc.) afforded symmetrical dialkylpyrazolo[1,5-*a*]pyrimidines (**5**). The reaction of 3-aminopyrazole with unsymmetrical β-diketones (hexane-2,4-dione, heptane-3,5-dione, etc.) gave a mixture of 5-methyl-7-alkylpyrazolo[1,5-*a*]pyrimidine (**3**) and 5-alkyl-7-methylpyrazolo[1,5-*a*]pyrimidines (**4**). The technique for the separation of 3 from 4 is described. The inhibition constants, α (the ratio of the molar I_{50} of theophylline to the molar I_{50} of the test compounds), were subjected to a Hansch correlation analysis. The results indicated that PDE isolated from beef heart tissue was most sensitive to changes in the length of the alkyl group in the 5 position of the pyrazolo[1,5-*a*]pyrimidine ring, whereas the PDE isolated from rabbit lung tissue was more sensitive to changes in the length of the 7-alkyl group. Experimentally and theoretically, the *n*-propyl group was found to approximate the ideal size for the alkyl group in both the 5 and 7 positions; 5,7-di-*n*-propyl-3-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine (**5e**) was the most potent inhibitor of both lung and heart PDE.

It has been reported that the pharmacological effects of theophylline (1) might be due to the inhibition of 3′,5′-AMP phosphodiesterase (PDE) by this compound.[1] Rose and coworkers[2] demonstrated that certain dialkyl derivatives of the triazolo[2,3-*c*]pyrimidines (**6**) [which bear some structural resemblance to theophylline (1)] inhibited PDE from lung tissue to a greater extent than 1. More importantly, derivatives of **6** effectively protected guinea pigs from histamine-induced bronchospasms. Bronchial constriction was known to be accompanied by changes in the intracellular concentrations of 3′,5′-AMP. Others have explored the inhibition of PDE by certain pyrazolo[3,4-*b*]pyridines which were also found to be effective as in vivo antidiabetic agents.[3-5]





We reported on the in vitro PDE inhibition of the dimethyl derivatives of the structurally similar pyrazolo[1,5-*a*]pyrimidine (**2**) in a recent publication.[6] It was found that one of the better PDE inhibitors, 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**2d**, ICN 3009), produced an immediate and moderately prolonged increase in the cardiac output of anaesthetized dogs.[7] The observed lack of

changes in other physiological responses, e.g., heart rate, respiration, serum glucose levels, free fatty acid, and adrenal corticosteroid levels, suggested **2d** might be much more selective and specific as a cardiac PDE inhibitor than theophylline.

In order to explore the structure–activity relationships of this heterocyclic system in greater detail, other 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines (**3**, **4**, and **5**) were synthesized. These compounds were then screened for in vitro inhibition of PDE isolated from both rabbit lung and beef heart tissue. The data, expressed as constants (α) for each compound (α = molar I_{50} of theophylline/molar I_{50} of compound), were then subjected to the Hansch correlation analyses.[8] Such an analysis was expected to reveal the structure–activity relationship between the steric and spatial characteristics of the alkyl groups and the requirements for maximum inhibition of the PDE isolated from each tissue source (heart and lung).

Chemistry. The condensation of 3-aminopyrazole[9] with acetylacetone has been reported[10] to yield 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**2a**). Employing other β-diketones in place of acetylacetone, we obtained the higher alkyl analogs of **2a**, as listed in Table I.

A problem was encountered in the separation of the unsymmetrical pyrazolo[1,5-*a*]pyrimidine isomers, **3** and **4**, when unsymmetrical β-diketones were employed in place of acetylacetone in this synthesis. Dorn and Zubek[11] reported that they obtained a mixture of 5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**3**, R = C_6H_5) and 7-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**4**, R = C_6H_5) from benzoylacetone and 3-aminopyrazole. They were able to identify the correct structure of **3** by an unambiguous synthesis employing 3-amino-2-toluenesulfonylpyrazole. However, we were able to isolate **4a** from the crude mixture of **3** and **4** (from the benzoylacetone condensation) simply by fractional recrystallization.

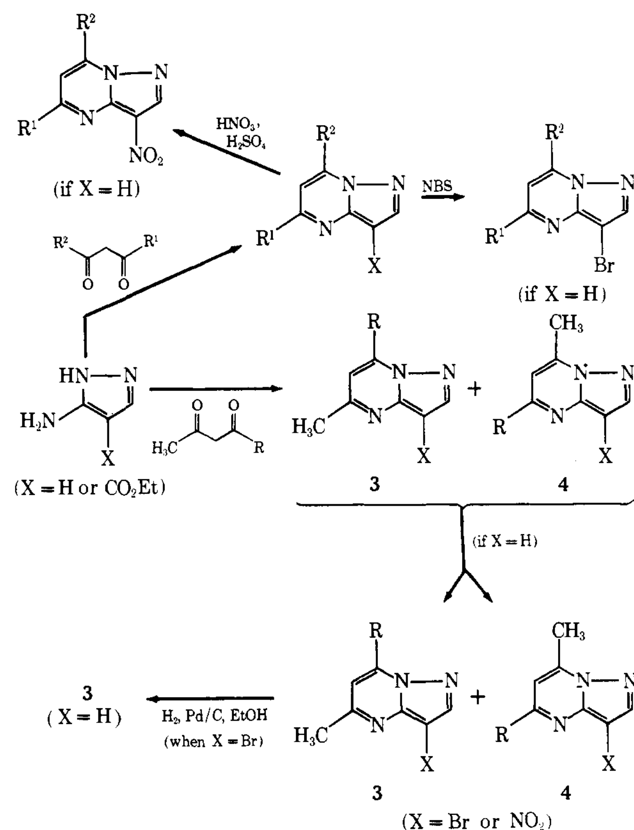
The nonaromatic β-diketones gave liquid isomeric mixtures which posed more of a problem in separation. For example, the condensation of heptane-2,4-dione with 3-aminopyrazole gave 5-methyl-7-*n*-propyl- (**3b**) and 7-methyl-5-*n*-propylpyrazolo[1,5-*a*]pyrimidine (**4**, R = *n*-C_3H_7). Even careful fractional distillation invariably resulted in the contamination of **3b** by **4**.

The problem was solved by brominating the crude isomeric mixture of **3b** and **4** with *N*-bromosuccinimide (NBS). The mixture of unsymmetrical 3-bromo-5,7-dialkylpyrazolo[1,5-*a*]pyrimidines (**3** and **4**, X = Br) was then separated by chromatography on neutral alumina, and the isomer obtained in the greatest amount (**3**) was then recrystallized to afford a pure product with no contamination by the other isomer. Although both of the pyrazolo[1,5-*a*]pyrimidines (**3** and **4**, X = H) were presumably brominated by NBS to yield the corresponding 3-bromo derivatives (**3** and **4**, X = Br), we isolated only the isomers of structure **3** by this technique. Perhaps the reason for the predominance of isomer **3** over isomer **4** (X = Br) is that the longer one alkyl chain of the unsymmetrical β-diketones becomes, the greater the ratio of **3** to **4** (X = H) becomes, by virtue of a steric requirement in the suspected intermediate (in the condensation of the β-diketone with 3-aminopyrazole), as suggested by Dorn and Zubek.[11]

The correct structural assignment of each isomer was determined by ^{1}H NMR, based on the signal for the methyl group at the 5 position of 5-methyl-7-methoxypyrazolo[1,5-*a*]pyrimidine, which was synthesized *via* an unambiguous route.[10,11]

Catalytic reduction of the pure 3-bromo isomers of structure **3** (X = Br), employing palladium on charcoal (Parr hydrogenation apparatus), afforded the corresponding unsymmetrical 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines (**3**, X = H).

Scheme I



Nitration of the symmetrical and unsymmetrical pyrazolo[1,5-*a*]pyrimidines (**3** and **5**, X = H) gave the corresponding 3-nitro derivatives (**3** and **5**, X = NO_2), respectively. The position of the electrophilic substitution by a bromo or nitro substituent in this ring system was established previously by our group.[6]

The condensation of ethyl 3-aminopyrazole-4-carboxylate[9] with the β-diketones employed in this study gave the ethyl 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylates (**3**, **4**, and **5**, X = CO_2Et). In the case of the condensation of the unsymmetrical β-diketones with ethyl 3-aminopyrazole-4-carboxylate, the desired pyrazolo[1,5-*a*]pyrimidine (**3**, X = CO_2Et) was purified by column chromatography and fractional recrystallization, as in the case for the 3-bromo analogs (**3**, X = Br) (Scheme I).

Enzymology. The details of the preparation and assay of the rabbit lung and beef heart phosphodiesterase were described previously.[12] The assay for the inhibition studies of rabbit lung and beef heart enzymes contained the following materials in 0.5 ml of solution: 25 μmol of Tris-HCl, pH 7.5; 5 μmol of $MgCl_2$; 20–200 μg of phosphodiesterase protein; 80 pmol of 8-[^{3}H]-cAMP (3.5 × 10^4 cpm); and varying concentrations of the pyrazolo[1,5-*a*]pyrimidine being tested as an inhibitor. The incubation times (2–10 min) were determined from pilot assays to obtain kinetically valid data. The mixture was heat-inactivated to terminate the reaction. Then the mixture was treated with 5′-nucleotidase (crude *Crotalus atrox* venom) to convert the 5′-nucleotide to a nucleoside. The unreacted 3′,5′-cyclic nucleotide was adsorbed on a Dowex 1 column and the radioactivity of the nucleoside fraction was determined. The results of the inhibition of PDE by each pyrazolo[1,5-*a*]pyrimidine appear in Table I. The data are presented as α values where α = molar I_{50} of theophylline/molar I_{50} for the test compound, where I_{50} for the heart phosphodiesterase was 0.12 m*M* and that for the lung enzyme 0.18 m*M*. Each α value

represents an average of two separate determinations which agreed within ±10%. In each I_{50} determination at least five concentrations of inhibitor were used which produced between 30 and 70% inhibition of the PDE assay. In this range of inhibition a plot of percent inhibition vs. concentration of inhibitor produced straight lines, the slopes of which were parallel with those of different series.

Results and Discussion

The relationship between the structure of the substituents on the pyrazolo[1,5-*a*]pyridine ring and the inhibition constants of these compounds was investigated by multiple regression analysis. The substituent constants used in this analysis were a hydrophobic parameter (the Hansch π constant), an electronic parameter (the Hammett σ constant), and a steric parameter (the Taft E_s constant). It was found, however, that inclusion of the latter two, σ and E_s, did not statistically improve the fit with either set of enzymic data and they were dropped from further consideration.

When the correlation of phosphodiesterase activity with the hydrophobic parameters of the 3, 5, and 7 positions (π_3, π_5, and π_7, respectively) was examined, some interesting relationships began to emerge. The data were fit to the form shown in eq 1.

$$\log (\alpha) = a + b\pi_3 + c\pi_5 + d\pi_7 \quad (1)$$

α (see Enzymology) is directly proportional to the inverse of the molar concentration for 50% inhibition. The π values are the Hansch values from substituted benzene.[13]

The equation derived for heart phosphodiesterase α values (α_H) is given in eq 2 where n is the number of compounds, s is the standard error, and r is the coefficient of multiple correlation and the values in parentheses are the 95% confidence intervals. In eq 2 compounds **5b**, **5e**, and **5h** were eliminated from the fit because they were very poorly predicted.

$$\log (\alpha_H) = -0.49\,(\pm 0.46) + 0.65\,(\pm 0.42)\,\pi_3 + 0.28\,(\pm 0.40)\,\pi_5 + 0.026\,(\pm 0.31)\,\pi_7 \quad (2)$$

$$n = 22, s = 0.40, r = 0.654$$

Although eq 2 gave a poor correlation, it was interesting to note that the determining factors in binding of the pyrazolopyrimidines to the enzyme seemed to be the hydrophobicity of the substituents at the 3 and 5 positions, while the 7-substituents apparently contributed nothing.

The best equation fitting the hydrophobic parameters of all 25 compounds to the lung phosphodiesterase data (α_L) is given by eq 3.

$$\log (\alpha_L) = -1.19\,(\pm 0.72) + 0.45\,(\pm 0.34)\,\pi_3 + 0.11\,(\pm 0.29)\,\pi_5 + 2.12\,(\pm 0.41)\,\pi_7 - 0.70\,(\pm 0.35)\,\pi_7^2 \quad (3)$$

$$n = 25, s = 0.34, r = 0.84$$

The inhibition constants calculated from this equation are given in Table I.

The term π_7^2 in this context is not to be considered the same as the $(\log p)^2$ term which explains the "random walk" of small molecules in whole biological systems.[14] Rather, this π_7^2 term should be interpreted as a limitation in size of the hydrophobic binding area of the alkyl group in the 7 position of the pyrazolo[1,5-*a*]pyrimidines. When the equation was differentiated with respect to π_7 the optimal value of π_7 was found to be 1.55. Thus, the increasing size of the 7-alkyl group contributes to binding up to this value, which ideally approximates the *n*-propyl group. Longer alkyl chains, such as *n*-butyl, cause a loss in binding, which may implicate steric hindrance encountered beyond the length of the propyl group. Thus, those pyrazolo[1,5-*a*]pyrimidines with alkyl chains larger than *n*-propyl (**5d**, **5k**, **5i**, **5j**, and possibly **3i**) bind less effectively to the lung PDE.

Terms for the π values of all three positions have been included in eq 2 and 3 in order to show the relative significance of the contribution of the individual terms to the correlation with α. The poor fit of the heart phosphodiesterase data, given by eq 2, indicates factors other than the simple linear free energy parameters considered (σ, π, and E_s) are determining the binding. It is obvious from eq 3, however, that the hydrophobic interaction of the 7-substituent of the pyrazolo[1,5-*a*]pyrimidine ring is the dominating factor in the binding strength of these compounds to the lung phosphodiesterase. The 5-substituent contributes virtually nothing. If any conclusion at all could be reached from the heart data of eq 2, it would be that the 7-substituent gives no contribution whereas the 5-substituent is slightly contributory. The substituent in the 3 position seems to give about the same contribution in each case.

This type of analysis should greatly aid in the design of potential pharmacological agents to be used in the treatment of cardiac conditions or asthmatic problems. Furthermore, it might be possible to include a polar or ionic group on the alkyl chain that does not participate in hydrophobic binding (e.g., the 7-substituent could be altered for the heart PDE and the 5-substituent could be altered for the lung PDE). This would assist in increasing the solubility of the drug or in modifying the total partition coefficient of the inhibitor without sacrificing the efficiency of the drug or its specificity for the PDE from one or the other tissues.

Work is currently in progress in screening the better in vitro inhibitors in vivo in laboratory animals, to see if these results have application in practice as well as theory.

Experimental Section

The procedures given in this section were representative for each of the analogous compounds presented in Table I. The melting points, which are uncorrected, were taken on a Hoover-Thomas (capillary tube) apparatus. All uv spectra were taken in methanol and recorded on a Cary 15 instrument. The ir spectra of the solid compounds were taken in KBr disks and the liquids were run neat in NaCl cells on a Perkin-Elmer 257 instrument. All NMR spectra were determined in deuteriochloroform on a Hitachi Perkin-Elmer 270 instrument. All analyses for C, H, and N were performed by Heterocyclic Chemical Corp., Harrisonville, Mo., and the elemental composition data were within ±0.4% of the calculated values (the empirical formula for each compound is listed in Table I).

Method A. 5(7)-Methyl-7(5)-*n*-propylpyrazolo[1,5-*a*]pyrimidine (3 and 4, R = *n*-C_3H_7). A solution containing 4.1 g (49 mmol) of 3-aminopyrazole,[9] 6.4 g (50 mmol) of heptane-2,4-dione,[18] 2 drops of piperidine, and 50 ml of absolute ethanol was refluxed for 24 hr. The yellowish colored solution was then cooled to room temperature and evaporated at reduced pressure. The resultant amber oil was extracted several times with boiling petroleum ether (bp 30–60°) and the organic solvent was evaporated to yield 6.0 g of a colorless oil consisting of both isomers **3b** and **4**, which could not be completely separated by distillation.

Method B. 3-Bromo-5-methyl-7-*n*-propylpyrazolo[1,5-*a*]pyrimidine (3g). The foregoing mixture of **3b** and **4**, 6.0 g (30 mmol), was dissolved in 100 ml of chloroform and 6.2 g (32 mmol) of *N*-bromosuccinimide (NBS) was added. The red solution was heated briefly (~15 min) on the steam bath and then poured over 100 g of crushed ice mixed with 20 ml of 2 *N* NaOH. The organic material was extracted with several 50-ml portions of $CHCl_3$ and the organic solvent was dried (Na_2SO_4) and evaporated under reduced pressure. The white solid obtained was then chromatographed on Woelm neutral alumina (activity grade I) with a 9:1 mixture of $CHCl_3$–EtOAc. The eluent was evaporated *in vacuo* to yield a white solid. Recrystallization of the solid from ether–petroleum ether (bp 30–60°) afforded 3.1 g (50% based on the isomeric mixture; 95% based on the pure isomer) of **3b** as white needles, mp 88–89°. The NMR spectrum substantiated the structure, as explained in the text.

Method C. 5,7-Di-*n*-propylpyrazolo[1,5-*a*]pyrimidine (5b).

Table I. Physical and Biological Data on 3,5,7-Trisubstituted Pyrazolo[1,5-*a*]pyrimidines

Compd no.	X	R_5	R_7	Method	Yield, %	Mp or bp (mm), °C	Solvent[d] of recrystn	Empirical formula	α, lung Exptl	α, lung Calcd[g]	α, heart Exptl	α, heart Calcd[i]	Starting materials
2a	H	CH_3	CH_3	C[h]	*h*	*h*	*h*	*h*	0.2	0.6	0.2	0.5	$CH_3COCH_2COCH_3$
3a	H	CH_3	C_2H_5	A, E	54[a]	43–45		$C_9H_{11}N_3$	1.5	1.9	1.3	0.5	$C_2H_5COCH_2COCH_3$
3b	H	CH_3	n-C_3H_7	A, E	57[a]	85–88 (0.5)		$C_{10}H_{13}N_3$	2.1	2.9	1.1	0.5	n-$C_3H_7COCH_2COCH_3$[e]
3j	H	CH_3	i-C_4H_9	A, E	43	75–77 (1.0)		$C_{11}H_{15}N_3$	3.5	2.5	0.5	0.5	CH_3COCH_2CO-i-C_4H_9[f]
4a	H	C_6H_5	CH_3	D	13	70–71	PE	$C_{13}H_{11}N_3$	3.4	0.8	2.4	1.1	$CH_3COCH_2COC_6H_5$
5a	H	C_2H_5	C_2H_5	C	92	43–44	PE	$C_{10}H_{13}N_3$	3.0	2.2	1.1	0.7	$C_2H_5COCH_2COC_2H_5$
5b	H	n-C_3H_7	n-C_3H_7	C	94	100–103 (1.0)		$C_{12}H_{17}N_3$	2.3	3.7	8.0	*j*	n-$C_3H_7COCH_2CO$-n-C_3H_7
5c	H	i-C_3H_7	i-C_3H_7	C	93	85–88 (0.6)		$C_{12}H_{17}N_3$	3.5	3.3	3.0	0.8	i-$C_3H_7COCH_2CO$-i-C_3H_7
5d	H	CF_3	i-C_5H_{11}	C	90	103–105 (0.5)		$C_{12}H_{14}N_3F_3$	0.8	1.2	0.4	0.7	CF_3COCH_2CO-i-C_5H_{11}
5k	H	n-C_4H_9	n-C_4H_9	C	87	110–112 (1.0)		$C_{14}H_{21}N_3$	1.3	2.8	0.5	1.3	n-$C_4H_9COCH_2CO$-n-C_4H_9
2b	NO_2	CH_3	CH_3	F[b]	*b*	*b*	*b*		0.4	0.4	0.2	0.3	
3d	NO_2	CH_3	C_2H_5	F	73	127–128	MeOH	$C_9H_{10}N_4O_2$	2.5	1.4	0.5	0.3	
2c	$CO_2C_2H_5$	CH_3	CH_3	G[b]	*b*	*b*	*b*	*b*	0.6	0.9	0.4	1.0	
3e	$CO_2C_2H_5$	CH_3	C_2H_5	G	62	67–68	PE	$C_{12}H_{15}N_3O_2$	1.5	3.2	0.5	1.0	
5e	$CO_2C_2H_5$	n-C_3H_7	n-C_3H_7	G	93	170–173 (1.0)		$C_{15}H_{21}N_3O_2$	27.0	6.2	9.0	*j*	
2d	Br	CH_3	CH_3	D[b]	*b*	*b*	*b*	*b*	0.7	1.4	1.7	1.7	
3f	Br	CH_3	C_2H_5	B	53	78–79	PE	$C_9H_{10}N_3Br$	7.5	4.7	4.0	1.7	
3g	Br	CH_3	n-C_3H_7	B	50	88–89	PhH–PE	$C_{10}H_{12}N_3Br$	7.5	7.1	6.5	1.8	
3h	Br	CH_3	i-C_4H_9	B	63	127–129 (1.5)		$C_{11}H_{14}N_3Br$	22.0	6.2	1.6	1.8	
5f	Br	C_2H_5	C_2H_5	D	94	64–65	PE	$C_{10}H_{12}N_3Br$	7.4	5.3	6.0	2.4	
5g	Br	n-C_3H_7	n-C_3H_7	D	92	66–67	PE	$C_{12}H_{16}N_3Br$	5.5	9.1	3.0	3.4	
5h	Br	i-C_3H_7	i-C_3H_7	D	89	128–132 (0.7)		$C_{12}H_{16}N_3Br$	3.5	8.1	1.5	2.9	
5i	Br	n-C_4H_9	n-C_4H_9	D	88	47–48		$C_{14}H_{20}N_3Br$	3.5	6.9	0.45	*j*	
5j	Br	CF_3	i-C_5H_{11}	D	75	123–126 (0.5)		$C_{12}H_{13}N_3F_3Br$	5.0	2.8	0.7	2.4	
3i	H	CH_3	CH_2COCH_3	D	85	84–85	PE	$C_{10}H_{11}N_3O_2$	0.1	0.1	0.1	0.5	$CH_3COCH_2COCH_2COCH_3$

[a]Based on the overall yield as described in the Experimental Section. [b]Reported in ref 6. [c]Purchased, see ref 15–17. [d]PE = petroleum ether (bp 30–60°); PhH = benzene. [e]Synthesized, see ref 18. [f]Reference 19. [g]Calculated from eq 3. [h]Reported in ref 10. [i]Calculated from eq 2. [j]Not included in the calculation of eq 2.

The method used to prepare **5b** was identical with that described in method A, except that the oil obtained was distilled (since no isomers were produced) to yield the product (see Table I for data).

Method D. 3-Bromo-5,7-di-*n*-propylpyrazolo[1,5-*a*]pyrimidine (5g). The method employed for **5g** was identical with the method described as method B, except that no isomers were obtained as in the case of the unsymmetrical analogs. Column chromatography was necessary to remove trace impurities and dibrominated compounds.[6]

Method E. 5-Methyl-7-*n*-propylpyrazolo[1,5-*a*]pyrimidine (3b). A solution of 1.8 g (10 mmol) of 3-bromo-5-methyl-7-*n*-propylpyrazolo[1,5-*a*]pyrimidine (**3b**) in 100 ml of absolute ethanol containing 2.0 g of calcium oxide and 0.5 g of 10% palladium-on-charcoal catalyst was hydrogenated in a Parr apparatus at an initial pressure of 38 psi. After the solution had absorbed the theoretical amount of H_2, the reaction was stopped and the solution was filtered and evaporated. The oil remaining on evaporation was distilled to yield the product (see Table I) as a colorless oil, bp 85–88° (0.5 mm).

Method F. 7-Ethyl-5-methyl-3-nitropyrazolo[1,5-*a*]pyrimidine (3d). A solution of 7 ml of concentrated (90%) nitric acid in concentrated (18 *M*) sulfuric acid was cooled to 0° via an ice bath. To this solution was added 3.2 g (20 mmol) of a mixture of 7-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**3**, R = C_2H_5; X = H) and 5-ethyl-7-methylpyrazolo[1,5-*a*]pyrimidine (**4**, R = C_2H_5; X = H), prepared from hexane-2,4-dione[16] (see method A). The addition was carried out carefully to avoid a rise in reaction temperature over 10°. The mixture was stirred for 1 hr at 10° and then poured over 100 g of ice, with manual stirring. The organic material was extracted with several portions of CH_2Cl_2 and the extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the product was chromatographed on neutral alumina (Woelm, activity grade I) with $CHCl_3$–MeOH (5:1) and the eluent was evaporated to afford a solid. The solid was recrystallized (MeOH) to yield 1.3 g of yellow needles, mp 127–128° (see Table I). The procedure for the preparation of 5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**2b**) was similar, as reported previously[6] except that chromatography was unnecessary.

Method G. 3-Ethoxycarbonyl-7-ethyl-5-methylpyrazolo[1,5-*a*]pyrimidine (3e). A mixture of 3.15 g (20 mmol) of ethyl 3-aminopyrazole-4-carboxylate,[13] 2.3 g (20 mmol) of hexane-2,4-dione,[16] and 3 drops of piperidine in 20 ml of ethanol was refluxed for 24 hr. The solution was then cooled and evaporated at reduced pressure to yield an oil. The oil was chromatographed on neutral alumina (Woelm, activity grade I) with $CHCl_3$–EtOAc (4:1). The eluent was evaporated (in vacuo) to yield a solid which was recrystallized from petroleum ether (bp 30–60°). The identification of the isomer **3e** was substantiated by NMR, as discussed in the text (see Table I for physical data).

References and Notes

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