*o*-chlorobenzaldehyde, *ca.* 243–245°. Based on the yield of semicarbazone obtained fraction I must have been >80% aldehyde—this would represent a 10–15% recovery of the starting aldehyde.

Fractions II, III and IV represent the cinnamonitrile yield. Basing the *cis–trans* composition of each fraction on infrared analyses and using the spectra of the pure isomers as reference, the composition of the three fractions was: II, 51% *trans* and 42% *cis;* III, 64% *trans* and 25% *cis;* IV, 83% *trans* and 7% *cis*.

The total combined yield of II, III and IV was 72 g. (45%) of the cinnamonitrile and this consisted of 56 g. (78%) *trans* and 16 g. (22%) *cis*.

Fraction V, 16 g., probably consisted largely of β-(*o*-chlorophenyl)-glutaronitrile and was not further investigated.

**Amidines.**—All were made essentially by the procedure of Lorz and Baltzly[1] using dried benzene to increase the solubility of the reactants where necessary. Either the hydrochloride or a mixture of hydrochloride with (usually yellow) hydrobromide crystallized during the decomposition. A typical example is given below.

**N,N-Dibutyl-*o*-chlorocinnamamidine Hydrochloride.**—To a Grignard reagent made from 3.09 g. (0.127 mole) of magnesium turnings, 14.2 g. (0.13 mole) of ethyl bromide and 120 ml. of absolute ether was added during 5 minutes 17.05 g. (0.132 mole) of di-*n*-butylamine dissolved in 50 ml. of anhydrous ether. The mixture was boiled for an additional half-hour, and a solution of 14.5 g. (0.089 mole) of *trans-o*-chlorocinnamonitrile of m.p. >40°, dissolved in 50 ml. of absolute ether, was added in a few minutes. The solution was boiled under reflux for 5 hours, and decomposed, after remaining overnight, by the addition of 50 ml. of 4 *N* HCl. The resulting solid was filtered, washed with 4 *N* HCl and then with ether. The residue was 27.7 g. of product, m.p. 210–222°. This was recrystallized from absolute ethanol–ethyl acetate giving a first crop of 15.6 g., m.p. 225–229°. A second crop obtained by addition of ether weighed 8.2 g., m.p. 227–228°.

**N,N-Di-*n*-butyl-β-methylcinnamamidine hydrochloride** was prepared from 59.7 g. of β-methylcinnamonitrile and bromomagnesium dibutylamide, essentially by the procedure given above. Decomposition of the reaction mixture with aqueous hydrochloric acid led to the formation of three layers. The middle one, which was benzene soluble, and the aqueous layer, were treated with an excess of iced aqueous sodium hydroxide and the amidine base so liberated was taken up in ether, dried briefly over magnesium sulfate and distilled. A fore-run of solvent and of dibutylamine (the latter removed *in vacuo*) was followed by 10.07 g. (12% of theory) of distillate, b.p. 120–126° (0.15 mm.). This was acidified in ethyl acetate–ether solution with gaseous hydrogen chloride, and treated with Skellysolve A to give an oil. This was redissolved and, after a week at −15°, a crystalline solid was formed. This was recrystallized from the same solvent mixture, m.p. 148.5–150.3°.

**β-Cyclocitrylideneacetamide.**—To 15.7 g. (0.081 mole) of cyclocitrylideneacetic acid was added 48 g. of thionyl chloride. After the acid had dissolved and the mixture had been heated for 40 minutes under reflux, the excess thionyl chloride was evaporated at the water-pump up to bath temperature 42°. The residual oil was taken up in 80 ml. of absolute ether and added dropwise to 200 ml. of absolute ether kept saturated with ammonia by passing in a rapid stream of gaseous ammonia throughout the addition and for 10 minutes more. The solution then was filtered to remove ammonium chloride, and the ethereal solution was washed with water, dried and concentrated. The residue was 15.4 g., m.p. 143–146°. This was recrystallized from Skellysolve C to give 13 g. of white solid, m.p. 147–148°.

*Anal.* Calcd. for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.54.

**β-Cyclocitrylideneacetonitrile (II).**—A mixture of 11.4 g. (0.059 mole) of β-cyclocitrylideneacetamide and 70 ml. of benzene (dried by azeotropic distillation) was heated under reflux while 7.1 g. (0.065 mole) of thionyl chloride was added dropwise over 10 minutes. An additional 20 ml. of benzene was added and the solution was boiled an additional 2 hours. It was then distilled *in vacuo* collecting 9.94 g. (96% of theory, if pure) of a yellow liquid, b.p. 132–136° (12 mm.). This was redistilled at the same temperature [literature[5] b.p. 141° (17 mm.)].

**N,N-Dibutyl-β-cyclocitrylideneacetamidine Hydrochloride.**—The procedure previously given for cinnamamidines was followed with 9.94 g. of β-cyclocitrylideneacetonitrile except that the reaction mixture was decomposed after 2.5 hours under reflux, by addition of aqueous acid. The precipitate was filtered off, and washed with water and ether to give 17.7 g. of solid, m.p. 195–200°. This was dissolved in 500 ml. of boiling acetone, filtered from some inorganic impurity, and absolute ether was added to incipient turbidity (*ca.* 800 ml.). The first crop of felted needles had m.p. 192–198°, and had a broad absorption maximum at 289–290 mμ, ε 8800.

*Anal.* Calcd. for $C_{20}H_{37}Cl^-N_2$: $Cl^-$, 10.42. Found: $Cl^-$, 10.65.

TUCKAHOE, N. Y.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

# Synthetis of Potential Anticancer Agents. XVI. S-Substituted Derivatives of 6-Mercaptopurine[1a]

BY THOMAS P. JOHNSTON, LEE B. HOLUM AND JOHN A. MONTGOMERY

RECEIVED JUNE 30, 1958

A number of S-substituted derivatives of 6-mercaptopurine have been prepared by a new procedure in which dimethylformamide was used as the reaction medium.

Because both 6-methylthiopurine and 6-benzylthiopurine have shown activity against Adenocarcinoma 755[2] and Sarcoma 180[3] comparable to that of 6-mercaptopurine, an extensive investigation of the anticancer activity of S-substituted derivatives of 6-mercaptopurine is of great interest. For this study we have prepared the varied series of 6-alkyl- and 6-arylthiopurines summarized in Tables I and II. Although the screening of these compounds has not yet reached the stage at which a pattern of the structural effect on anticancer activity can be established, some interesting variations in activity and toxicity already have been noted. Speculation that the activity of the methyl and benzyl derivatives is related to an *in vivo* formation of 6-mercaptopurine by a biological cleavage of the thioether has been advanced.[4] Such a mechanism is

(1) Affiliated with Sloan–Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Contract No. SA-43-ph-1740. Part XV. H. J. Schaeffer and H. J. Thomas, THIS JOURNAL, **80**, 4896 (1958).

(1a) Name in common usage; 6-purinethiol is used by "Chemical Abstracts."

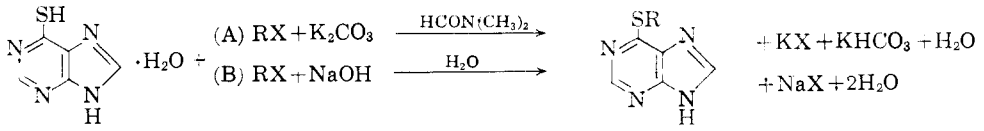
(2) H. E. Skipper, J. A. Montgomery, J. R. Thomson and F. M. Schabel, Jr., *Proc. Am. Assoc. Cancer Research*, **2**, 346 (1958).

(3) D. A. Clarke, G. B. Elion, G. H. Hitchings and C. C. Stock, *Cancer Research*, **18**, 445 (1958).

(4) G. B. Elion, G. H. Hitchings, D. A. Clarke and C. C. Stock, *Proc. Am. Assoc. Cancer Research*, **2**, 199 (1957).

TABLE I

6-ALKYLTHIOPURINES




| R | X | Method | Crude yield, % | Recrystn. solvent[a] | M.p.,[b] °C. | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethyl | I | A-1 | 93[c] | A | 196[d] | 46.66[e] | 46.75 | 4.48[e] | 4.34 | | |
| 2-Propynyl[f] | Br | A-1 | 95[g] | B | 238 d. | 50.51 | 50.53 | 3.18 | 3.19 | 29.45 | 29.37 |
| Cyanomethyl | Cl | A-1 | 95[g] | A | 258 d. | 43.97 | 43.88 | 2.64 | 2.66 | 36.63 | 36.99 |
| Allyl | Cl | A-1 | 84[g] | A | 176 | 49.98 | 49.98 | 4.19 | 4.46 | 29.15 | 29.11 |
| Propyl | Br | A-1 | 93[g] | A | 179[h] | 49.46 | 49.75 | 5.19 | 5.44 | 28.84 | 28.86 |
| Isopropyl | I | A-1 | 88[g] | A | 239.5 | 49.46 | 49.59 | 5.19 | 5.15 | 28.84 | 28.98 |
| 2-Hydroxyethyl | Br | A-2 | 75[g] | A[i] | *ca.* 200 d. | 42.84 | 42.76 | 4.11 | 4.25 | 28.55 | 28.59 |
| Acetonyl | Cl | A-1 | 88[g] | A | 184.5 | 46.14 | 46.11 | 3.87 | 3.89 | 26.91 | 26.85 |
| Butyl | I | A-1 | 93.5[g] | C, D | 152[j] | 51.90 | 51.89 | 5.81 | 5.89 | 26.90 | 26.99 |
| Carbamoylmethyl | Cl | A-1 | 87[g] | A | 264 dec. | 40.18 | 40.60 | 3.37 | 3.54 | 33.47 | 33.62 |
| Carboxymethyl[k] | Cl[l] | A-2 | 96[g,m] | A | Chars >260 | 39.99 | 39.97 | 2.88 | 2.85 | 26.65 | 26.41 |
| 2-Chloroethyl | Br | A-1 | 48[g] | None | 277–279 d.[n] | 39.16[o] | 38.81 | 3.29 | 3.03 | 26.10 | 25.97 |
| Cyclopentyl | Br | A-2 | 96[g] | E | 228 | 54.52 | 54.56 | 5.49 | 5.61 | 25.43 | 25.61 |
| Pentyl | Br | A-1 | 93[g] | F | 115.5[p] | 54.02 | 53.96 | 6.35 | 6.39 | 25.20 | 25.22 |
| Methoxycarbonylmethyl | Br | A-1 | 80[g] | E | 169 d. | 42.84 | 43.12 | 3.60 | 3.68 | 24.99 | 24.83 |
| 2-Carboxyethyl | Cl[q] | A-2 | 73[g,r] | A | 227 d.[s] | 42.84 | 42.58 | 3.60 | 3.59 | 24.99 | 24.66 |
| 2-Ethoxyethyl | Br | A-1 | 69[c] | G, A | 143 | 48.21 | 47.86 | 5.39 | 5.33 | 24.99 | 24.73 |
| 2-Chloroallyl | Cl | A-1 | 90[g] | A | 173 | 42.38 | 42.56 | 3.11 | 3.22 | 24.72 | 24.57 |
| Benzyl | Cl | B | 86 | A, H | 193[t] | 59.50 | 59.57 | 4.16 | 4.24 | | |
| 2-Thenyl | Cl | A-1 | 99[g] | I | 186 | 48.37 | 48.62 | 3.25 | 3.36 | 22.56 | 22.51 |
| Phenethyl | I | A-1 | 99[g] | G | 166.5 | 60.91 | 61.02 | 4.72 | 4.70 | 21.86 | 21.88 |
| *o*-Fluorobenzyl | Cl | B | 70 | None | 161 | 55.50 | 55.36 | 3.46 | 3.81 | 21.45 | 21.66 |
| *m*-Fluorobenzyl | Cl | B | 84 | None | 159 | 55.50 | 55.27 | 3.46 | 3.62 | 21.45 | 21.26 |
| *p*-Fluorobenzyl | Cl | B | 86 | None | 229 | 55.50 | 55.49 | 3.46 | 3.77 | 21.45 | 21.68 |
| Octyl | I | A-1 | 97[g] | J | 87, 100[u] | 59.05 | 59.11 | 7.63 | 7.66 | 21.19 | 21.40 |
| Cinnamyl[v] | Cl | A-1 | 99[c] | I | 210 | 62.68 | 62.58 | 4.51 | 4.53 | 20.89 | 20.63 |
| Benzoylmethyl | Cl | A-1 | 102[g] | E | 170 | 57.76 | 57.58 | 3.73 | 3.70 | 20.73 | 20.34 |
| 2-Phenoxyethyl | Br | A-1 | 103[g] | G | 154 | 57.35 | 57.45 | 4.44 | 4.57 | 20.58 | 20.73 |
| *o*-Chlorobenzyl | Cl | B | 78 | None | 202 | 52.20 | 52.02 | 3.26 | 3.38 | 20.30 | 20.08 |
| *o*-Chlorobenzyl | Cl | A-1 | 100[g] | K | 203 | | | | | | |
| *p*-Chlorobenzyl | Cl | B | 60 | C | 201.5 | 52.20 | 52.15 | 3.26 | 3.36 | 20.30 | 20.29 |
| *p*-Chlorobenzyl | Cl | A-1 | 94[g] | B | 201 | | | | | | |
| *p*-Nitrobenzyl | Cl | B | 76 | None[w] | 262 | 50.18 | 50.32 | 3.16 | 2.98 | 24.38 | 24.27 |
| Decyl | I | A-1 | 98[g] | J | 95, 102[x] | 61.60 | 61.64 | 8.27 | 8.14 | 19.16 | 18.68 |
| 3,4-Dichlorobenzyl | Cl | A-1 | 104[g] | B | 222 | 45.31 | 45.21 | 2.59 | 2.65 | 18.01 | 18.18 |
| Dodecyl | Br | A-1 | 99[g] | J | 98 | 63.70 | 63.49 | 8.81 | 8.52 | 17.48 | 17.46 |

[a] A, water; B, methanol; C, methanol–water; D, chlorobenzene; E, ethyl acetate; F, carbon tetrachloride; G, benzene; H, toluene; I, 2-butanone; J, Skellysolve C; K, chloroform. [b] Taken on Kofler Heizbank except where indicated. [c] An exact 1:1 molar ratio of $K_2CO_3$ to 6-mercaptopurine hydrate used. [d] Lit.[5] m.p. 185°. [e] Analyses given for product, m.p. 196°, prepared by modification of method B. [f] Sensitive to light. [g] A 1.12:1.00 molar ratio of $K_2CO_3$ to 6-mercaptopurine hydrate used. [h] Lit.[5] m.p. 163–165°. [i] Crystallized from water as hydrated plates and needles; water of crystallization removed by evaporating a methanolic solution to dryness *in vacuo* over $P_2O_5$ at 80°. [j] Lit.[5] m.p. 126–127°. [k] Reported by G. Huber, *Angew. Chem.*, 68, 706 (1956). [l] Sodium chloroacetate. [m] Isolated at *p*H 4. [n] Capillary, aluminum block. [o] Calcd.: Cl, 16.9; found: Cl, 16.7. [p] Lit.[5] m.p. 78–79°. [q] Sodium β-chloropropionate. [r] Isolated at *p*H 4. A higher yield (83%) of less pure crude product was obtained from a reaction carried out in dimethyl sulfoxide. [s] On Fisher-Johns block with moderate rate of heating. Fast heating on Kofler Heizbank gives decomposition point as high as 260°. [t] Lit. m.p. 178–180°,[5] 193–194°.[12] [u] Amorphous form melts at 87°, crystallizes and remelts at 100°, lit.[6] m.p. 78–80°. [v] $\bar{\nu}$ in cm.$^{-1}$: 970 (*trans*-1,2-disubstituted ethylene; *cf.* W. Ziegenbein and W. Franke, *Chem. Ber.*, 90, 2291 (1957)); No —CH=$CH_2$ absorption at 995–985, 915–905, 1420–1410. [w] Can be recrystallized from glacial acetic acid. [x] Amorphous form melts at 95°, crystallizes and remelts at 102°, lit.[6] m.p. 84–85°.

not necessarily supported by, for example, the retention of activity by 6-phenylthiopurine and the loss of activity by 6-(methoxycarbonylmethylthio)-purine.

The preparation of a number of 6-alkylthiopurines for testing in other biological areas has been reported by Skinner, *et al.*,[5,6] who treated appropriate alkyl halides with 6-mercaptopurine in aqueous alkaline solution, alcohol being added to increase the solubility of the less soluble halides. This procedure was patterned after that of Elion, Burgi and Hitchings[7] for the methylation of 6-

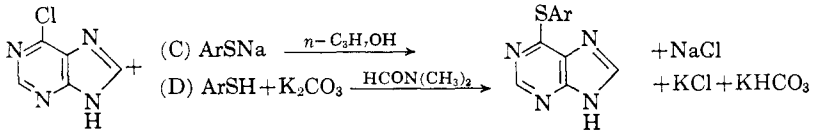
(5) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, THIS JOURNAL, **78**, 5097 (1956).

(6) C. G. Skinner, R. G. Ham, D. C. Fitzgerald, Jr., R. E. Eakin and W. Shive, *J. Org. Chem.*, **21**, 1330 (1956).

(7) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

TABLE II

6-ARYLTHIOPURINES




| Ar | Method | Crude yield, % | Recrystn. solvent[a] | M.p., °C. | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| Phenyl | C | 82 | None | 256–257[b] | 57.89 | 57.57 | 3.53 | 3.68 | 24.55 | 24.38 |
| *o*-Tolyl | C | 88.5 | A | 174[c] | 59.50 | 59.46 | 4.16 | 4.10 | 23.13 | 23.55 |
| *o*-Tolyl | D | 81[d] | B, C | 174[c] | | | | | | |
| *m*-Tolyl | C | 98 | D | 220[c] | 59.50 | 59.55 | 4.16 | 4.24 | 23.13 | 23.14 |
| *p*-Tolyl | C | 78 | None | 254[c] | 59.50 | 59.33 | 4.16 | 4.00 | 23.13 | 23.19 |
| *p*-Chlorophenyl | C | 95 | D | 271.5–272[b] | 50.40 | 50.47 | 2.47 | 2.81 | 21.35 | 21.18 |
| *o*-Carboxyphenyl | C | 59 | E | 242–243[b] | 52.94 | 52.97 | 2.96 | 3.33 | 20.58 | 20.25 |
| *o*-Carboxyphenyl | D | 97.5 | [e] | 238–239[b] | | | | | | |
| *p*-Nitrophenyl | C | 71 | F | 259–260[b] | 48.35 | 48.33 | 2.58 | 2.83 | 25.64 | 26.35 |
| 2-Naphthyl | C | 84 | F | 287–289[b] | 64.74 | 64.42 | 3.62 | 3.83 | 20.14 | 20.00 |

[a] A, water; B, chlorobenzene; C, acetonitrile; D, ethanol; E, acetic acid–water; F, methyl Cellosolve. [b] Taken on Fisher–Johns apparatus. [c] Taken on Kofler Heizbank. [d] Aqueous reaction mixture filtrates not worked up for recovery of additional amounts of crude product. [e] Precipitated from basic solution with dil. HCl.

mercaptopurine. We found this method useful for preparing the 6-benzylthiopurines of Table I (method B), but failed to duplicate the preparation of 6-ethylthiopurine. Only when a large excess of sodium hydroxide and iodoethane was used was a reaction achieved, giving pure 6-ethylthiopurine, m.p. 196°, in 46% yield.

We have found that the reaction of 6-mercaptopurine with appropriate active halogen-containing compounds proceeds readily in dimethylformamide in the presence of 1.0 to 1.1 moles of potassium carbonate per mole of 6-mercaptopurine. With a few exceptions, such as sodium β-chloropropionate and bromocyclopentane, the halides used produced exothermic reactions of varying degree, the temperature maxima being reached in five to twenty minutes. The rates of reaction in dimethylformamide contrast sharply with the long reaction times (six to sixty-eight hours) described for the reaction in aqueous medium.[6] The isolation of relatively pure single products (*cf.* propyl- and isopropyl- of Table I) in high yields and particularly the apparent absence of allylic rearrangement in the preparation of 6-cinnamylthiopurine (see Table I) are indicative of a predominant SN2-type mechanism. The initial concentration of 6-mercaptopurine in dimethylformamide varied between 7 and 25% depending on the fluidity of the reaction mixtures and the solubilities of the reactants and the products. The reactions in which a spontaneous rise in temperature occurred were considered essentially complete when the temperature began to fall, usually within ten minutes after the maximum was reached, but stirring was continued, sometimes with mild external heating, for twenty minutes to an hour or more in order to ensure that no unchanged 6-mercaptopurine remained. Generally the products were isolated by adding the reaction mixture to water, usually five or six volumes per volume of dimethylformamide used, and acidifying the resulting alkaline slurry or solution to *p*H 5–6 with either acetic acid or dilute hydrochloric acid. Additional amounts of the more soluble products could be recovered by evaporation of the aqueous dimethylformamide filtrates to dryness, and then trituration of the residue with water at *p*H 5. A modified procedure involving extraction of the dried residue with benzene was used for the isolation of 6-(2-ethoxyethylthio)-purine (see Experimental).

No qualitative difference was observed in the spontaneous reactivity of simple bromo- and iodoalkanes toward nucleophilic displacement by the 6-purinyl mercaptide ion, whereas 2-chloroethanol required external heating. This difference in reactivity suggested that 1-bromo-2-chloroethane should give 6-(2-chloroethylthio)-purine, a purine analog of mustard gas, under mild reaction conditions. Actually, Hine and Brader[8] found that 1-bromo-2-chloroethane was less reactive toward sodium thiophenoxide in methanol at 20° than was bromoethane. However, 6-(2-chloroethylthio)-purine has been isolated in low yields (up to 48%) from 2.95-mmole runs, the operational range of reaction conditions being quite limited and the nature of the water-soluble side products being as yet unresolved.

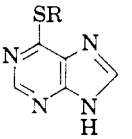
The detection of a strong mercaptan odor during the recrystallization of 6-(2-hydroxyethylthio)-purine from water prompted a qualitative comparison of the relative ease of hydrolysis of three S-substituted 6-mercaptopurines in refluxing 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide solutions. It was found that both 6-ethylthiopurine and 6-benzylthiopurine were subject to rather slow acid-catalyzed hydrolysis to hypoxanthine, but were essentially unaffected by prolonged treatment in basic solution. In contrast, 6-(2-hydroxyethylthio)-purine was hydrolyzed readily in either acid or base, and even in a solution buffered at *p*H 7, though more slowly. This unusual lability of the 2-hydroxyethylthio group may be explained on the basis that hydrogen bonding[9] is available to the sulfur as a negative charge is form-

(8) J. Hine and W. H. Brader, Jr., THIS JOURNAL, **75**, 3964 (1953).

(9) The role of the neighboring hydroxyl group in the easy hydrolysis of monoesters of certain 1,3-diols has been recently discussed by H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

TABLE III

ULTRAVIOLET SPECTRA

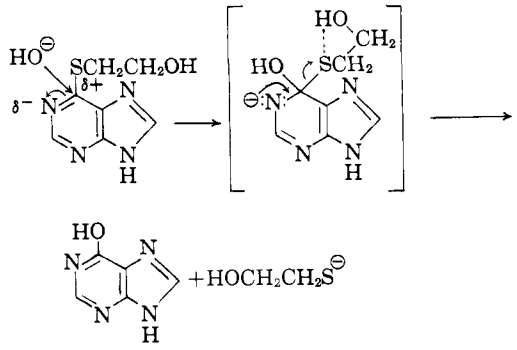


| R | Alcohol[a] λmax, mμ | Alcohol[a] ε × 10⁻³ | 0.1 N HCl λmax, mμ | 0.1 N HCl ε × 10⁻³ | pH 7 λmax, mμ | pH 7 ε × 10⁻³ | 0.1 N NaOH λmax, mμ | 0.1 N NaOH ε × 10⁻³ |
|---|---|---|---|---|---|---|---|---|
| Ethyl | 284(s),[b](e) | | 224 | 9.64 | 292 | 17.4 | 292 | 15.3 |
| | 290 | 17.6 | 297 | 15.1 | | | | |
| 2-Propynyl | 280(e) | 16.5 | 289 | 15.3 | 283(s) | | 290 | 13.8 |
| | 286 | 16.3 | | | 287–288 | 16.1 | | |
| Cyanomethyl | 276(m) | 15.5 | 280 | 14.2 | 279 | 14.4 | 287 | 12.5 |
| | 280(s) | | 283(s) | | 284(s) | | | |
| Allyl | 281–287(p)[c](e) | 18.3 | 294 | 14.9 | 291 | 17.0 | 292 | 14.8 |
| Propyl | | | 224 | 9.38 | 291 | 17.8 | 292 | 15.5 |
| | | | 297 | 15.1 | | | | |
| Isopropyl | | | 298 | 15.3 | 292 | 16.6 | 293 | 14.8 |
| 2-Hydroxyethyl | 284–288(p)(e) | 16.6 | 293 | 14.5 | 290 | 16.7 | 291 | 14.5 |
| Acetonyl | | | 227 | 13.6 | 282(s) | | 289 | 14.0 |
| | | | 300 | 14.6 | 287 | 15.6 | | |
| Butyl | | | 224 | 9.58 | 292 | 18.7 | 293 | 15.6 |
| | | | 297 | 15.4 | | | | |
| Carbamoylmethyl | | | 288 | 15.0 | 281(s) | | 288 | 13.9 |
| | | | | | 286 | 16.1 | | |
| Carboxymethyl | | | 287 | 14.8 | 289 | 17.1 | 223 | 13.5 |
| | | | | | | | 291 | 15.5 |
| 2-Chloroethyl[d] | 281(m) | 15.8 | 292 | 14.5 | 247–248[e] | 5.11 | 291[e] | 12.4 |
| | 286 | 15.9 | | | 288 | 15.4 | | |
| Cyclopentyl | 285–289(p)(e) | 18.1 | 299 | 15.6 | 292 | 17.8 | 293 | 15.7 |
| Pentyl | 283(s)(e) | | 224 | 9.21 | 292 | 17.8 | 293 | 15.7 |
| | 289 | 17.8 | 297 | 15.2 | | | | |
| Methoxycarbonylmethyl | 279(e) | 16.6 | 287 | 15.4 | 281 | 16.2 | 291 | 15.8 |
| | 287 | 16.0 | | | 286 | 16.2 | | |
| 2-Carboxyethyl | | | 293 | 15.2 | 291 | 17.8 | 223–224 | 13.6 |
| | | | | | | | 292 | 16.1 |
| 2-Ethoxyethyl | 281–287(p)(e) | 17.0 | 293 | 15.5 | 289 | 17.3 | 291 | 15.1 |
| 2-Chloroallyl | 280–287(p)(e) | 16.1 | 290 | 15.1 | 288 | 16.2 | 291 | 13.9 |
| Phenyl | | | 294 | 14.6 | 288.5 | 16.7 | 291 | 15.0 |
| Benzyl | | | 295[f] | 15.8[f] | 292 | 18.3 | 293 | 15.8 |
| *o*-Tolyl | | | 292 | 16.6 | 254(s) | | 292 | 16.8 |
| | | | | | 290 | 18.9 | | |
| *m*-Tolyl | | | 294 | 15.0 | 250 | 5.85 | 293 | 15.3 |
| | | | | | 290 | 17.1 | | |
| *p*-Tolyl | | | 295 | 14.7 | 249 | 6.70 | 292 | 15.4 |
| | | | | | 291 | 16.7 | | |
| 2-Thenyl | | | 224 | 14.5 | 291 | 17.2 | 293 | 15.1 |
| | | | 294 | 15.0 | | | | |
| Phenethyl | 283(s)(e) | | 296 | 13.3 | 292 | 16.1 | 293 | 15.0 |
| | 289 | 18.9 | | | | | | |
| *o*-Fluorobenzyl | | | 294 | 15.5 | 290 | 17.6 | 292 | 15.2 |
| *m*-Fluorobenzyl | | | 294 | 15.4 | 291 | 17.9 | 292 | 15.2 |
| *p*-Fluorobenzyl | | | 295 | 15.5 | 291 | 17.8 | 292 | 15.5 |
| *p*-Chlorophenyl | | | 295 | 14.7 | 249 | 6.70 | 292 | 15.4 |
| | | | | | 291 | 16.7 | | |
| Octyl | 285–290(p)(e) | | 225 | 9.38 | 293 | 16.6 | 293 | 15.3 |
| | | | 297 | 15.4 | | | | |
| Cinnamyl | 258–259(m) | 21.3 | 254 | 20.7 | 254 | 20.8 | 255 | 21.3 |
| | 288 | 26.1 | 296 | 19.3 | 293 | 22.9 | 294 | 19.7 |
| Benzoylmethyl | 244(m) | 14.4 | 249 | 14.1 | 250 | 14.9 | 289 | 15.1 |
| | 282 | 16.6 | 289 | 17.3 | 284–285 | 19.1 | | |
| | 286(s) | | | | | | | |
| *o*-Carboxyphenyl | | | 295 | 12.0 | 291 | 13.6 | 295 | 13.1 |
| 2-Phenoxyethyl | 281(e) | 17.8 | 292 | 14.2 | 290 | 16.2 | 291 | 14.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 287 | 17.4 | | | | | | |
| *p*-Nitrophenyl | | | 286 | 14.5 | 285 | 14.6 | 287 | 13.5 |
| | | | | | 322 | 10.8 | 338 | 11.0 |
| *o*-Chlorobenzyl | | | 293 | 16.4 | 291 | 18.4 | 293 | 15.6 |
| *p*-Chlorobenzyl | | | 221 | 20.2 | 292 | 18.3 | 293 | 15.7 |
| | | | 294 | 16.2 | | | | |
| 2-Naphthyl | 290(e) | 20.9 | 293 | 18.7 | | | 292 | 19.6 |
| *p*-Nitrobenzyl | | | 291 | 23.0 | 287 | 24.6 | 289 | 22.1 |
| Decyl | 286(s)(e) | | | | | | | |
| | 290 | 17.8 | | | | | | |
| 3,4-Dichlorobenzyl | | | 293 | 16.8 | 291 | 18.1 | 293 | 15.3 |
| Dodecyl | 285(s)(e) | | | | | | | |
| | 290–291 | 18.3 | | | | | | |

[a] (e) absolute ethanol, (m) methanol. [b] (s) shoulder. [c] (p) plateau. [d] Sample, isolated at *p*H 7.4, was prepared by Dr. R. W. Balsiger. [e] Sample reported to be unstable in *p*H 7 buffer and 0.1 *N* NaOH solutions. [f] Not in agreement with spectrum reported by Bullock, Hand and Stokstad.[12]

ing, thus dissipating the negativity on the sulfur and weakening the sulfur to purine–carbon linkage—a mechanism depicted below for the base-catalyzed hydrolysis



Little attempt has been made to isolate and identify minor side-products from these displacements carried out in dimethylformamide, although small amounts of gummy solids and dark viscous oils have been observed in evaporated filtrates both from reaction mixtures and from recrystallizations of the crude products.[10] Results of recent experiments in this Laboratory indicate that N-alkylation of the imidazole ring of some purines other than 6-mercaptopurine occurs readily in dimethylformamide or dimethyl sulfoxide in the presence of alkali carbonates.[11] However, S-alkylation of 6-mercaptopurine is predominant when a limited amount of carbonate is used—a fact evidenced by the results given in Table I. This conclusion is further substantiated by the results of experiments designed for the dibenzylation of 6-mercaptopurine: (1) one equivalent of 6-mercaptopurine when allowed to react with slightly more than two equivalents of $\alpha$-chlorotoluene in the presence of slightly more than two equivalents of potassium carbonate (*i.e.*, 2.2 moles of potassium carbonate per mole of 6-mercaptopurine) in dimethylformamide at room temperature (24 to 27.5°) for 1.5 hours gave a mixture of products from which 6-benzylthiopurine and a dibenzylated product were separated in approximately equal molar ratios; (2) the above benzylation repeated at a higher temperature (65 to 70° for 45 minutes) gave no monobenzylated product and an 82% yield of dibenzylated product, from which pure 9-benzyl-6-benzylthiopurine and somewhat impure 7-benzyl-6-benzylthiopurine were isolated. These results indicate that N-alkylation occurs to an appreciable extent only when excess carbonate is present and even then occurs less readily than S-alkylation. Thus, dialkylation may very well be responsible for the crude yields of more than 100% reported in Table I; in these runs 1.12 moles of potassium carbonate per mole of 6-mercaptopurine was used. Recrystallization easily removes the more soluble dialkylated materials.

The 6-arylthiopurines of Table II were prepared by nucleophilic displacements on 6-chloropurine by the corresponding sodium thiophenoxide. Similar reactions of 6-chloropurine and sodium mercaptides have been reported,[12] and the reactivity of 6-chloropurine toward other nucleophilic reagents is well-known: *e.g.*, alkoxides,[13] hydrazine[14] and amines.[15,16] The preparation of 6-arylthiopurines in refluxing propanol (method C of Table II) often led to crude products that were difficult to purify. It was found subsequently that by using dimethylformamide and potassium carbonate (Method D of Table II) we could carry out the reaction under milder conditions and obtain products less difficult to purify.

The ultraviolet absorption spectra of 6-alkylthiopurines have been described[5,6] as having characteristic double maxima of about the same intensity between 281 and 292 m$\mu$ in 95% ethanol. The ultraviolet spectra of the S-substituted derivatives described in this paper are given in Table III. The spectra of those unsubstituted alkyl derivatives determined in absolute ethanol show maxima at about 290 m$\mu$ and shoulders of slightly less intensity between 283 and 286 m$\mu$ with the exception of the octyl derivative which showed a plateau extending from *ca.* 285 to *ca.* 290 m$\mu$; at *p*H 1, 7 and 13 these compounds exhibit characteristic maxima without accompanying shoulders at 297–299, 289–293 and 292–293 m$\mu$, respectively. Substitutions on the alkyl group cause in general hypsochromic shifts of varying degree, the greatest shifts being ob-

(10) Elion, Burgi and Hitchings[7] suspected the formation of a small amount of dimethylated product from the reaction of 6-mercaptopurine with dimethyl sulfate.

(11) J. A. Montgomery and Carroll Temple, Jr., to be published.

(12) M. W. Bullock, J. J. Hand and E. L. R. Stokstad, THIS JOURNAL, **78**, 3693 (1956).

(13) G. Huber, *Chem. Ber.*, **90**, 698 (1957).

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(15) A. A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(16) J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956).

served in the spectra of 6-cyanomethylthiopurine. The strong, widely separated maxima in the 250 and 290 mμ region observed in the spectra of the 6-cinnamyl and 6-benzoylmethyl derivatives are believed due to the independent absorption of a phenyl group conjugated with ethylenic and carbonyl unsaturation, respectively.[17] Other substituted phenyl derivatives show weaker absorption in the 250 mμ region.

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## Experimental

Except where indicated, melting points below 264° were determined on a Kofler Heizbank; those between 264 and 300° on a Fisher–Johns melting point apparatus. The ultraviolet spectra were determined with a Beckman model DK-2 spectrophotometer, but the optical densities at the maxima were measured with a Beckman DU. 6-Mercaptopurine and 6-chloropurine were purchased from Francis Earle Laboratories, Inc.

**Method A-1.** (a) **6-Ethylthiopurine.**—Iodoethane (0.6–0.7 ml.) was added to a well-stirred mixture of 1.12 g. (6.58 mmoles) of 6-mercaptopurine monohydrate 0.911 g. (6.58 mmoles) of anhydrous potassium carbonate (dried *in vacuo* over phosphorus pentoxide at 135°) and 4.8 ml. of dimethylformamide at room temperature (30°). The temperature rose rapidly (2 minutes) to a maximum of 41°. Vigorous stirring was continued as the temperature gradually fell to 37° during the next 10 minutes. The mixture then was warmed between 40 and 50° for 30 minutes, cooled a little and poured into water (total of 40 ml.). Much white precipitate formed in a solution of *p*H 7–8.[18] After careful acidification to *p*H 5 with 6 *N* hydrochloric acid, the mixture was refrigerated overnight. The white solid was collected, washed with cold water and dried *in vacuo* over phosphorus pentoxide at room temperature: 0.965 g. of near-white powder, m.p. 196°.

The filtrate (*p*H 5 adjusted to *p*H 6–7 with dilute NaOH solution) was evaporated to dryness *in vacuo* at 60°. The dry residue was triturated with 15 ml. of water, the *p*H adjusted to 5 with 6 *N* HCl, and the mixture refrigerated. An additional 0.135 g. of crude 6-ethylthiopurine, m.p. 195°, was thus obtained; total crude yield 1.10 g. (92.7%). Recrystallization of the combined crude material from *ca.* 70 ml. of water gave 0.83 g. of fine white crystals, m.p. 196°; second crop 0.06 g., m.p. 196°. Analyses and spectral data are recorded in Tables I and III, respectively.

(b) **6-Cinnamylthiopurine.**—A mixture of 3.00 g. (17.6 mmoles) of 6-mercaptopurine monohydrate, 2.73 g. (19.7 mmoles) of anhydrous potassium carbonate and 15 ml. of dimethylformamide was stirred at room temperature (25°) for 15 minutes. With continued vigorous stirring a solution of 3.01 g. (19.7 mmoles) of (3-chloropropenyl)-benzene in 5 ml. of dimethylformamide was added, the temperature rising to 29° in 10 minutes. The mixture then was heated at 45–56° for 40 minutes by a warm water-bath. The reaction mixture was allowed to cool and then poured into 150 ml. of water: a copious white precipitate was formed. The *p*H was adjusted from 9 to 5–6 with acetic acid, and the mixture refrigerated. The precipitate was collected, washed with water and dried *in vacuo* over $P_2O_5$ at room temperature: yield 4.82 g. (102%) of a cream-colored powder, m.p. 203° with pre-softening. The crude solid was crystallized from about 120 ml. of 2-butanone: first crop, 3.31 g. of cream-colored crystals, m.p. 210°; second, 0.20 g., m.p. 208°; and third, 0.41 g., m.p. 208°; total yield of crystallized 6-cinnamylthiopurine, 83%. A final recrystallization of the combined crops from 2-butanone gave the analytical sample of Table I in 76% recovery. Spectral data are given in Tables I and III.

(c) **6-(2-Ethoxyethylthio)-purine.**—A mixture of 4.00 g. (23.5 mmoles) of 6-mercaptopurine monohydrate, 3.25 g. (23.5 mmoles) of anhydrous potassium carbonate and 20 ml. of dimethylformamide was stirred at room temperature (29°) for 15 minutes. 2-Bromoethyl ethyl ether (2.7–2.8 ml.) was added with continued vigorous stirring. The temperature rose to 36° during the first 20 minutes, then gradually fell to 34° during the next 13 minutes. The reaction mixture then was heated at 47–53° for about 45 minutes. The resulting thin slurry was poured into 120 ml. of water, giving a clear straw-colored solution of *p*H 8. Since acidification to *p*H 5 and overnight refrigeration produced no precipitate, the solution was evaporated to dryness *in vacuo* under 60°. Repeated evaporations with methanol and acetone gave a dry tan residue that was extracted with boiling benzene (3 × 80 ml.). The combined benzene extracts were concentrated to about 75 ml. and cooled. The white solid that precipitated was collected, washed with cold benzene and dried *in vacuo* over phosphorus pentoxide; yield 3.31 g. of a soft white powder, m.p. 139°. Further extractions of the residue with boiling benzene (total of 120 ml.) gave an additional 0.32 g., m.p. 142.5°; total yield 68.8%.

Recrystallization of the major portion (3.30 g.) from about 80 ml. of benzene gave 2.95 g. of a white powder, m.p. 141°. The analytical sample was obtained by recrystallizing the smaller sample (0.32 g.) from about 6 ml. of water, recovery as glistening white plates, dried *in vacuo* at 61° over phosphorus pentoxide; 0.18 g., m.p. 143°. Analyses and spectral data are given in Tables I and III, respectively.

The benzene-extracted residue was then treated with 20 ml. of water. The yellowish insoluble material, 0.21 g., was collected and identified as unchanged 6-mercaptopurine by comparison of ultraviolet spectra.

**6-Cyclopentylthiopurine (Method A-2).**—Bromocyclopentane (Eastman practical grade, 3.4 ml., 31.2 mmoles) was added to a well-stirred mixture of 4.00 g. of 6-mercaptopurine monohydrate (23.5 mmoles), 3.64 g. of anhydrous potassium carbonate (26.3 mmoles) and 25 ml. of dimethylformamide. After 15 minutes at room temperature, the mixture was heated gradually to 74° and stirred at 74 to 80° for 3 hours.[19] (Other compounds made by method A-2 required heating periods of 1 hour or less.) The resulting thick suspension was allowed to cool a little and then was mixed with a total of about 200 ml. of water. The resulting slurry of *p*H 8 was acidified with 2.5 ml. of acetic acid, and cooled. The solid was collected, washed with water, air-dried, then dried *in vacuo* over phosphorus pentoxide at room temperature; yield 4.96 g. (96%), m.p. 210–214° with softening from about 202°. Two recrystallizations from ethyl acetate gave near-white crystals of pure 6-cyclopentylthiopurine, m.p. 228°, after drying *in vacuo* over phosphorus pentoxide at 80° for several hours. Analyses and spectral data are given in Tables I and III, respectively.

**6-*m*-Tolylthiopurine (Method C).**—A solution of 2.50 g. (16.2 moles) of 6-chloropurine, 0.88 g. of sodium methoxide[20] and 2.00 g. of *o*-toluenethiol in 50 ml. of *n*-propyl alcohol was allowed to reflux for 1.5 hours. The solid that crystallized during the course of the reaction was collected by filtration, washed with water and air-dried: weight 3.34 g., m.p. 219°. The filtrate was evaporated to dryness *in vacuo*. The residue was triturated with about 20 ml. of water, and the residual solid was collected and air-dried; weight 0.50 g., m.p. 211°; total yield of crude 6-*m*-tolylthiopurine, 3.84 g. (98%). Recrystallization of the combined crops from ethyl alcohol gave a 76% recovery as a white powder, m.p. 220°. Analytical and spectral data are given in Tables II and III, respectively.

(17) For example, *cf.* acetophenone: $\lambda_{max}$ in cyclohexane, 239 mμ (ε × $10^{-4}$, *ca.* 12.5) [L. H. Schwartzman and B. B. Corson, THIS JOURNAL, **76**, 781 (1954)].

(18) Some of the products such as 6-pentylthiopurine can be recovered in high yield at *p*H 7–8 without acidification.

(19) The product isolated from a reaction at 70° for one hour contained as much as 2% of unchanged 6-mercaptopurine as indicated by paper chromatograms developed by descending butanol saturated with water. Bromocyclohexane failed to react appreciably, an observation that parallels the low order of reactivity of bromocyclohexane in other nucleophilic displacements as summarized in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 123.

(20) Metallic sodium dissolved in *n*-propyl alcohol was used in the preparation of 6-naphthylthiopurine by method C.

**6-*o*-Carboxyphenylthiopurine (Method D).**—A mixture of 5.35 g. (38.8 mmoles) of anhydrous potassium carbonate and 3.30 g. of *o*-mercaptobenzoic acid (Eastman technical grade) in 20 ml. of dimethylformamide was stirred mechanically for 5 minutes. 6-Chloropurine (3.00 g., 19.4 mmoles) then was added, and when no temperature rise occurred during 15 minutes of vigorous stirring, the mixture was heated at 40–50° in a warm water-bath for an hour. The resulting thin suspension was poured into 120 ml. of water, and the clear solution was partially neutralized with 5 ml. of concentrated hydrochloric acid. The *p*H now was adjusted to 3 with 1 *N* hydrochloric acid. The tan solid that precipitated was collected by filtration, washed thoroughly with water and dried *in vacuo* over phosphorus pentoxide at 61°; yield 5.15 g. (97.5%), m.p. 235–237°. This material was twice precipitated from 1 *N* sodium hydroxide solution with 1 *N* hydrochloric acid; recovery, 4.12 g. of light tan solid, m.p. 238–239°.

**9-Benzyl-6-benzylthiopurine.**—α-Chlorotoluene (0.12 ml., 1.03 mmoles) was added to a well-stirred mixture of 250 mg. (1.03 mmoles) of 9-benzyl-6-mercaptopurine,[11] 137 mg. (1.03 mmoles) of anhydrous potassium carbonate and 3 ml. of dimethylformamide. The mixture was stirred at room temperature (23–25°) for 15 minutes and then heated between 40 and 53° for about 30 minutes. Then the mixture was cooled and poured into 25 ml. of water: a tan solid precipitated. The resulting mixture (*p*H 8–9) was cooled in an ice–water-bath and the solid was collected, washed with water and dried *in vacuo* over phosphorus pentoxide at room temperature; yield 308 mg. of a tan powder (90%), m.p. 108° with softening from 102°. Recrystallization of *ca.* 295 mg. from *ca.* 20 ml. of cyclohexane gave 240 mg. of matted white needles after drying *in vacuo* at room temperature; m.p., needles fused at 100° forming a solid that melted at 108°; spectral data: $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 295 (18.9); *p*H 7, 289 (shoulder), 294 (20.4); *p*H 13, 289 (shoulder), 294 (20.5); EtOH, 286 (21.3), 290 (shoulder). *Anal.* Calcd. for $C_{19}H_{16}N_4S$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.49; H, 4.84; N, 16.81 (Dumas).

**7-Benzyl-6-benzylthiopurine** was prepared from 74 mg. of 7-benzyl-6-mercaptopurine ($C_{12}H_{10}N_4S \cdot {}^1/_4H_2O$)[11] in a manner similar to that described for the 9-isomer above; the reaction mixture was heated at 50° for one hour; yield 91 mg. (91%) of a tan powder, m.p. *ca.* 120°. Recrystallization from *ca.* 20 ml. of cyclohexane gave 51 mg. of near-white fine matted needles (dried *in vacuo* at 61°), m.p. 120° with collapse of crystal structure at 118° forming an opaque melt; spectral data: $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 305 (13.1); *p*H 7, 252–254 (5.34), 297–301 plateau, 13.8); *p*H 13, 252–254 (5.31), 297–301 (plateau, 13.7); EtOH, 295 (14.9), 299 (shoulder). *Anal.* Calcd. for $C_{19}H_{16}N_4S$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.56; H, 4.81; N, 16.26 (Kjeldahl).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# The Metalation of 1-Phenyl- and 1-Methylpyrazole with *n*-Butyllithium

BY PEGGY W. ALLEY AND DAVID A. SHIRLEY

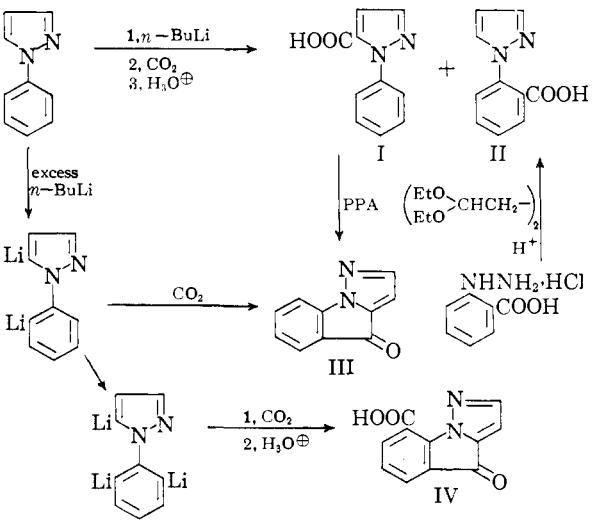
RECEIVED JULY 18, 1958

1-Phenylpyrazole is monometalated in 80% yield. Substitution occurs in the 5-position and in the *o*-position of the phenyl group in a ratio of about 4:1, as shown by reaction of the organolithium compound with carbon dioxide. Treatment of 1-phenylpyrazole with excess *n*-butyllithium gave dimetalation (8%) and trimetalation (26%) as indicated by the formation, upon carbonation, of the cyclic ketone 4-oxopyrazolo[1,5-a]indoline and a monocarboxylic acid derivative of the ketone. 1-Methylpyrazole is metalated in the 5-position with *n*-butyllithium in 54% yield.

The metalation reaction of simple N-substituted pyrazoles with *n*-butyllithium was undertaken to find the position of attack of the metalating agent. Electrophilic substitution of the pyrazole ring occurs predominantly in the 4-position.[1] It is well established[2] that metalation occurs at positions adjacent to heteroatoms. Two such positions (the 3- and 5-positions) are present in the pyrazole nucleus, and it was of interest to determine the points of attack by *n*-butyllithium in the pyrazole ring.

There are few reported examples of metalation of monocyclic systems containing two hetero atoms. These are the metalation of thiazole[3] and 4,5-dimethylthiazole[4] in the 2-position with phenyllithium, the metalation of 1-phenyl-3-methylpyrazole[5] in the 5-position with *n*-butyllithium and the metalation of 1-methyl-, 1-benzyl- and 1-phenylimidazole[6] in the 2-position with *n*-butyllithium.

The metalation of 1-phenylpyrazole with an equivalent of *n*-butyllithium followed by reaction with carbon dioxide gave in 80% yield a mixture of monocarboxylic acid derivatives. The acid mixture gave upon fractional crystallization from water two pure acids, m.p. 185–186.5° (39% yield) and m.p. 140–142° (10%). All possible monocarboxylic acid derivatives of 1-phenylpyrazole are known with the exception of 1-(*m*-carboxyphenyl)-pyrazole. 1-Phenyl-5-pyrazolecarboxylic acid (I) is reported to melt at 183°[7] and 185–186°[8] and none

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