Pyrazolopyrimidine Nucleosides. Part VIII (1)
The Synthesis of Certain 4-Substituted Pyrazolo[3,4-*d*]pyrimidine Nucleosides

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1-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**6**), obtained by a three-step synthesis from allopurinol riboside (**3**), was treated with certain alkyl and aryl halides to provide the corresponding 4-alkylthio derivatives. The nucleoside 4-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) has served as the precursor for the preparation of the 4-methylamino (**11**), 4-dimethylamino (**12**), 4-hydrazino (**13**), and the 4-hydroxylamino (**14**) analogs.

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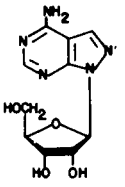
The chemical preparation of pyrazolo[3,4-*d*]pyrimidine nucleosides has been sparse (1-3) and with two exceptions (1,2a) limited to the synthesis of 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (4-APP riboside, **1**) (2) and 1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (allopurinol riboside), (**3**) (3). In all but one (2a) case, the reported pyrazolo[3,4-*d*]pyrimidine nucleosides had either an amino or oxo substituent residing on the four position (C4) of the heterocyclic aglycon. It has been well documented (4) that certain 6-substituted purine ribosides *e.g.*, 9-(β-D-ribofuranosyl)purine-6-thione (6-MP riboside, **2a**) and 6-hydrazino-9-(β-D-ribofuranosyl)purine (**2b**), possess anticancer activity. Therefore, we initiated an investigation which would provide certain 4-substituted



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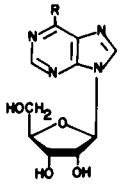

2a, R = SH
b, R = NHNH$_2$

pyrazolo[3,4-*d*]pyrimidine ribosides (isomeric with the purine ribosides) in ample quantity for evaluation as anticancer agents.

Using allopurinol riboside (**3**) (3) as our starting material, we have now synthesized a number of selected 4-substituted pyrazolo[3,4-*d*]pyrimidine nucleosides. Allopurinol riboside (**3**) was acetylated with pyridine-acetic anhydride at 5° for four days. This procedure furnished a quantitative yield of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (**4**). Complete acetylation of the β-D-ribofuranosyl moiety occurred and this was substantiated by pmr spectroscopy, *i.e.*, three sharp

Scheme I

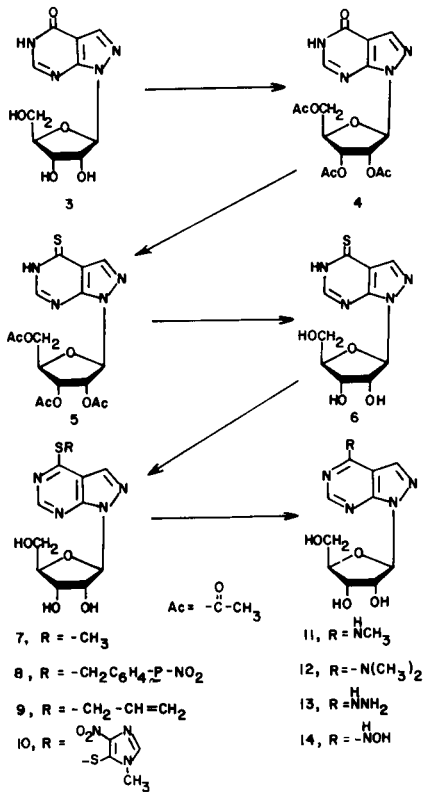

Table I

Ultraviolet Spectral Data [λ /nm (ϵ x 10^{-3})] for Certain Pyrazolo[3,4-*d*]pyrimidine Nucleosides (a)

Compound	λ max (*p*H 1)	λ min (*p*H 1)	λ max (water)	λ min (water)	λ max (*p*H 11)	λ min (*p*H 11)
6	321 (23.6)	271.5 (2.4)	322 (b) (22.7)	271 (b) (2.4)	320 (19.6)	268.5 (2.3)
	236.5 (9.1)		237.5 (b) (7.9)	229 (b) (8.6)	232 (22.1)	
7	302sh (14.9)	252 (4.2)	302sh (13.6)	250 (2.6)	302.5 (13.8)	251 (3.3)
	294 (16.5)		293 (16.1)		292.5 (16.7)	
8	303.5sh (20.1)	242.5 (7.3)	301sh (b) (17.7)	238.5 (b) (6.6)	303.5 (20.5)	242.5 (6.4)
	292.5 (23.4)		284.5 (b) (24.1)		293 (23.9)	
9	303.5sh (13.6)	251.5 (3.7)	303sh (11.7)	250 (2.7)	302.5sh (13.5)	249.5 (2.6)
	294 (16.1)		293 (14.6)		293 (16.3)	
10	276 (13.1)	250 (7.4)	274 (b) (13.0)	250 (b) (7.0)	276 (12.1)	250 (6.1)
11	263 (12.5)	242 (7.1)	280.5 (11.8)	240.5 (3.4)	280.5 (12.7)	240.5 (3.9)
			262sh (8.2)		261.5sh (8.8)	
12	266 (14.9)	243.5 (7.8)	287 (14.4)	242.5 (4.1)	287 (14.9)	242.5 (4.7)
			265sh (10.2)		265sh (10.5)	
13	262.5 (8.8)	242 (5.5)	278.5 (10.0)	240.5 (3.9)	278.5 (9.9)	240.5 (3.5)
			260.5sh (7.6)		260.5sh (7.3)	
14	265 (11.2)	244 (6.9)	228 (b) (13.9)	252 (b) (6.1)	230 (7.4)	257 (4.0)
			264 (6.8)		299 (9.4)	

(a) Shoulder. (b) Methanol.

singlets between δ 2.14 and 2.08 which integrated for nine protons, and elemental analysis. Thiation of **4** with phosphorus pentasulfide-dioxane (5) provided 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**5**) in high yield (90%). The acetyl groups on **5** were removed with methanolic ammonia to furnish 1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**6**); a new isomer of 6-mercaptopurine riboside. Treatment of **6** with either methyl iodide, *p*-nitrobenzyl bromide, allyl bromide, or 5-chloro-4-nitro-1-methylimidazole under basic reaction conditions afforded **7**, **8**, **9**, and **10**, respectively.

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidine (**7**) proved to be a useful intermediate for other 4-substituted 1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidines since the 4-methylthio group was found to be amenable toward nucleophilic displacements. The extreme ease with which this functional group underwent chemical reaction with certain amines reflects the greater reactivity of this position in the pyrazolo[3,4-*d*]pyrimidine ring when compared to its purine counterpart (6,7). This is exemplified by the treatment of **7** with either 40% aqueous methylamine or dimethylamine on a steam bath to provide a near quantitative yield of **11** or **12**, respectively. Careful monitoring of the forementioned reactions with tlc revealed that displacement of the 4-methylthio group occurred in approximately ten minutes. Similarly, treatment of **7** with 40% aqueous hydrazine provided a rapid conversion to 4-hydrazino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyr-

imidine (**13**), a target nucleoside in this series (8). In addition, when **7** was treated with hydroxylamine (9) in ethanol at reflux, a smooth conversion to 4-hydroxylamino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**14**) occurred.

The site of substitution and β-configuration of all nucleosides synthesized in this study was confirmed by the conversion of **7** to 4-APP riboside (**1**); a nucleoside whose structure has already been rigorously established (2d).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The proton magnetic resonance spectra were obtained on a Jeol C60h spectrometer and an EM-390 90MHz (compounds **9** and **14**) spectrometer using DSS as an internal standard and chemical shifts are expressed as parts per million (δ) from DSS. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrophotometer. The ultraviolet absorption spectra were recorded on a Beckman Acta CIII spectrometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Thin layer chromatography was run on glass plates coated (250-μ) with SilicAR 7 GF (Mallinckrodt).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (**4**).

1-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (**3**) (26.8 g., 100 mmoles) was dissolved in dry pyridine (200 ml.) and the solution cooled to ice bath temperature. Acetic anhydride (150 ml.) was then slowly added to this solution with swirling. When addition was complete, the flask (2 liter) containing the solution was tightly stoppered and refrigerated (5°) for 4 days (during this time the reaction solution was periodically hand-shaken). The excess solvents were removed *in vacuo* (water bath 50°) and the resulting syrup was dissolved in chloroform (400 ml.). The organic layer was washed in turn with cold water (150 ml.), a cold 10% aqueous hydrochloric acid solution (100 ml.), cold water (150 ml.), and then dried over anhydrous magnesium sulfate. The chloroform phase was evaporated *in vacuo* (40°) to provide **4** as a solid white foam (41.0 g., quantitative yield), m.p. 136-138°; $[\alpha]_D^{25}$ -34.6 (*C* 1.01, chloroform); pmr (deuteriochloroform): δ 12.00 (bs, 1, NH), 8.13 and 8.00 (2s, 2, H3 and H6) (10), 6.44 (d, 1, $J_{1',2'}$ = 3 Hz, H1'), 2.13 and 2.08 (2s, 9, COCH_3).

Anal. Calcd. for $C_{16}H_{18}N_4O_8 \cdot H_2O$: C, 46.60, H, 4.85, N, 13.59. Found: C, 46.60; H, 4.87; N, 13.41.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**5**).

Purified phosphorus pentasulfide (11) (5.64 g., 25.4 mmoles) was dissolved in a hot dioxane (200 ml.) solution containing 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (**4**) (10 g., 25.4 mmoles) and the mixture was heated at reflux for 25 minutes. At the end of this time, a second charge of phosphorus pentasulfide (5.64 g.) was added and the solution was heated at reflux for an additional 40 minutes. After cooling, the mixture was concentrated (*ca.* 40 ml.) and then poured over cracked ice. The aqueous mixture was extracted with chloroform (800 ml.) and a saturated sodium chloride (NaCl) solution was used to disperse the resulting emulsion. The chloroform layer was washed with a saturated aqueous sodium chloride solution (2 x 300 ml.), a cold, saturated sodium bicarbonate solution (300 ml.), and then dried over anhydrous magnesium sulfate. The dried chloroform phase was evaporated *in vacuo* to furnish **5** as a light yellow foam (9.37 g., 90%). A small portion of this material (100 mg.) was placed on a silica gel CC7 dry-packed column (10 g.) and the column was eluted with chloroform methanol (9:1, v/v) to provide **5** as a colorless foam; $[\alpha]_D^{25}$ -52.7 (*C* 1.01, chloroform); pmr (deuteriochloroform): δ 8.24 and 7.92 (2s, 2, H3 and H6), 6.29 (d, 1, $J_{1',2'}$ = 3 Hz, H1'), 2.17, 2.13, 2.08 (3s, 9, COCH_3).

Anal. Calcd. for $C_{16}H_{18}N_4O_7S$: C, 46.83; H, 4.42; N, 13.65. Found: C, 46.35, H, 4.41; N, 13.31.

1-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**6**).

A solution of **5** (0.75 g., 1.8 mmoles) in methanolic ammonia (30 ml., saturated at -5°,) was allowed to stand at room temperature for 16 hours in a sealed pressure bottle. After removal of the solvent, the residual solid was coevaporated twice with methanol (2 x 10 ml.) and filtered. The solid was recrystallized from water to provide 0.48 g. (92.5%) of **6**, m.p. 209-210°; $[\alpha]_D^{26}$ -67.8 (*C* 1.02, water); pmr (DMSO-d_6): δ 8.30 and 8.23 (2s, 2, H3 and H6), 6.10 (d, 1, $J_{1',2'}$ = 3.5 Hz, H1').

Anal. Calcd. for $C_{10}H_{12}N_4O_4S$: C, 42.27; H, 4.26; N, 19.71. Found: C, 42.25; H, 4.29; N, 19.81.

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**).

1-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**6**) (1.0 g., 3.52 mmoles) was suspended in dry methanol (10 ml.) and to this stirred suspension was added AR sodium methoxide (0.38 g., 7.0 mmoles). When solution was effected, methyl iodide (2.5 ml., 7.7 mmoles) was added and the solution was stirred at room temperature for 12 hours with the exclusion of moisture. The *p*H of the solution was adjusted to 6 using Amberlite IRC-50 (*ca.* 1 ml.). The resin was removed by filtration and washed with hot methanol (3 x 10 ml.). The washings and filtrate were combined and evaporated to dryness under diminished pressure to give a crystalline solid which was recrystallized from methanol, 0.99 g. (94%), m.p. 163-164°; $[\alpha]_D^{26}$ -73.8 (*C* 0.98, water), -76 (*C* 0.98, methanol); pmr (DMSO-d_6): δ 8.75 and 8.38 (2s, 2, H3 and H6); 6.20 (d, 1, $J_{1',2'}$ = 4 Hz, H1'), 2.72 (s, 3, SCH_3) (12).

Anal. Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78. Found: C, 44.21; H, 4.72; N, 18.91.

4-*p*-Nitrobenzylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**8**).

1-(β-D-Ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-4-thione (**6**) (0.285 g., 1 mmole) was dissolved in dry methanol (15 ml.) which contained sodium methoxide (0.192 g., 3.55 mmoles). To this solution was added *p*-nitrobenzyl bromide (0.26 g., 1.2 mmoles) and the mixture was stirred at room temperature for 18 hours. The *p*H of the solution was adjusted with Amberlite IRC-50 (*ca.* 2 ml.) to *p*H 6, the resin was then removed by filtration and washed with hot methanol (2 x 10 ml.). The methanol was removed under diminished pressure to provide a light yellow crystalline solid. Recrystallization from ethanol furnished **8** (0.398 g.) in 91% yield, m.p. 164-165°; $[\alpha]_D^{26}$ -66.0 (*C* 0.96, methanol); pmr (DMSO-d_6): δ 8.85 and 8.45 (2s, 2, H3 and H6), 8.17 and 7.73 (AB q, 2, J = 8 Hz, $SCH_2C_6H_4NO_2$), 6.24 (d, 1, $J_{1',2'}$ = 5 Hz, H1'), 4.83 (s, 2, -S$CH_2C_6H_4NO_2$).

Anal. Calcd. for $C_{17}H_{17}N_5O_6S$: C, 48.68; H, 4.09; N, 16.70. Found: C, 48.77; H, 4.14; N, 16.74.

4-Allylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**9**).

Similar reaction conditions as described for **8** were used for the

synthesis of **9** with one exception, Amberlite IRC-50 was not used. From **6** (0.9 g., 3.17 mmoles), allyl bromide (0.77 g., 6.32 mmoles) and sodium methoxide (9.47 g., 8.66 mmoles), there was obtained, after crystallization from ethanol-water (1:20, v/v), pure **9** (0.9 g., 87.5%) as needles, m.p. 125-126°; $[\alpha]_D^{26}$ -76.7 (*C* 1.02, methanol); pmr (DMSO-d_6): δ 8.90 and 8.51 (2s, 2, H3 and H6), 6.29 (d, 1, $J_{1',2'}$ = 4.5 Hz).

Anal. Calcd. for $C_{13}H_{16}N_4O_4S$: C, 48.14; H, 4.97; N, 17.27. Found: C, 48.23; H, 4.93; N, 17.43.

4-Thio-(1-methyl-4-nitroimidazol-5-yl)-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**10**).

To a well stirred mixture of 1-(β-D-ribofuranosyl)pyrazolo-[3,4-*d*]pyrimidine-4-thione (**6**) (1.4 g., 4.91 mmoles) in absolute methanol (200 ml.) was added sodium methoxide (560 mg., 10.36 mmoles) and stirred at room temperature for 0.5 hour. To the resulting clear solution was added 1-methyl-4-nitro-5-chloroimidazole (0.8 g., 4.95 mmoles) and the mixture was stirred at room temperature for an additional 48 hours (completion of the reaction was detected by tlc). Powdered Dry Ice was added to the reaction mixture to maintain the *p*H at ≃ 7. The excess solvent was removed *in vacuo* and the residue stirred with a mixture of alcohol and water (60 ml., 1:1, v/v) for 0.5 hour. The solid was collected by filtration, washed with cold water (20 ml) and then with ethanol (20 ml.) to furnish 1.3 g. (64%) of **10**, m.p. 239-240° dec.; $[\alpha]_D^{28}$ -36.74 (*C* 1.044, DMF); pmr (DMSO-d_6): δ 8.34 and 8.3 (2.0, two aromatic protons), 8.83 (s, 1, aromatic proton), 6.33 (d, 1, $J_{1',2'}$ = 4.5 Hz, H1').

Anal. Calcd. for $C_{14}H_{15}N_7O_6S$: C, 41.06; H, 3.69; N, 23.95. Found: C, 41.12; H, 3.76; N, 23.67.

4-Methylamino-1-(β-D-ribofuranosyl) pyrazolo[3,4-*d*]pyrimidine (**11**).

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) (1 g., 3.35 mmoles) was dissolved in 40% aqueous methylamine (100 ml.) and heated at reflux for 0.5 hour. The reaction was monitored by tlc (chloroform-methanol, 8:2, v/v) and was shown to be complete in 10 minutes. After cooling, the excess solvent was removed *in vacuo* and the resulting solid was recrystallized from ethanol to provide crystalline **11** (0.9 g.) in 95.5% yield, m.p. 232-233°; $[\alpha]_D^{26}$ -67.5 (*C* 1.05, water); pmr (DMSO-d_6): δ 8.28 and 8.18 (2s, 2, H3 and H6), 6.13 (d, 1, $J_{1',2'}$ = 4 Hz, H1'), 3.04 (d, 3, HNC*H*$_3$).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.90; H, 5.45; N, 24.71.

4-Dimethylamino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**12**).

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) (1.1 g., 3.35 mmoles) was dissolved in 40% aqueous dimethylamine (50 ml.) and heated at reflux on a steam bath for 0.5 hour. The reaction was monitored by tlc (chloroform-methanol, 8:2 v/v) and shown to be complete in 15 minutes. After cooling, the excess solvent was removed *in vacuo* and the resulting solid was recrystallized from 90% ethanol to furnish crystalline **12** (0.95 g.) in 93% yield, m.p. 192.5-193°; $[\alpha]_D^{26}$ -58.8 (*C* 0.99, water); pmr (DMSO-d_6): δ 8.25 (s, 2, H3 and H6), 6.16 (d, 1, $J_{1',2'}$ = 4.5 Hz, H1'), 3.33 [s, 6, N(C*H*$_3$)$_2$].

Anal. Calcd. for $C_{12}H_{17}N_5O_4 \cdot 0.5H_2O$: C, 47.36; H, 5.96; N, 23.01. Found: C, 47.45; H, 6.06; N, 23.28.

4-Hydrazino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**13**).

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) (100 mg., 0.34 mmoles) was dissolved in 40% aqueous hydrazine (25 ml.) and the mixture was heated at reflux for 10 minutes. The excess solvent was removed *in vacuo* and the residual solid was coevaporated with absolute ethanol (3 x 10 ml.) and then recrystallized from ethanol. This procedure furnished **13** (76 mg.) in 76% yield, m.p. 220-222°; $[\alpha]_D^{26}$ -63.2 (*C* 0.95, water); pmr (DMSO-d_6): δ 9.27 (bs, 1, NH), 8.38 and 8.15 (2bs, 2, H3 and H6), 6.15 (d, 1, $J_{1',2'}$ = 4.5 Hz, H1').

Anal. Calcd. for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.40; H, 5.17; N, 29.74.

4-Hydroxylamino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**14**).

To a solution of 4-methylthio-1-(β-D-ribofuranosyl)pyrazolo-[3,4-*d*]pyrimidine (**7**) (1.2 g., 4.02 mmoles) in absolute ethanol (40 ml.) was added hydroxylamine (1.2 g., 36.33 mmoles) and the mixture was gently heated at reflux with stirring for 30 hours. The solvent was removed *in vacuo*, the residual oil was coevaporated with absolute ethanol (4 x 10 ml.) and then crystallized from ethanol to furnish 0.8 g. (70%) of pure **14**, m.p. 172-173°; $[\alpha]_D^{25}$ -63.34 (*C* 0.862, methanol); pmr (DMSO-d_6): δ 9.8 and 11.13 (2 bs, 2, O*H* and/N*H*), 6.02 (d, 1, $J_{1',2'}$ = 4.5 Hz, H1'), 7.86 (b, 2, H3 and H6).

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.62, N, 24.32. Found: C, 42.08; H, 4.57; N, 24.44.

4-Amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**1**, 4-APP Riboside).

4-Methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) (150 mg.) and concentrated ammonium hydroxide (10 ml., 28%) were mixed and heated at 100° for 10 hours in a sealed reaction vessel. The reaction mixture was then cooled and the excess solvent was evaporated to dryness *in vacuo*. The residue was coevaporated with ethanol (2 x 10 ml.) and recrystallized twice from ethanol to furnish 60 mg. (44%) of **1**. The nucleoside (**1**) obtained from this method was found to be identical with the authentic sample (2d) (uv, mixed melting point and tlc).

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