following solvent systems were used for tlc: A, MeOH–C_6H_6 (1:3, v/v); B, Me_2CO–cyclohexane (1:1, v/v).

1-(2-Deoxy-5-*O*-trityl-β-D-ribofuranosyl)-5-trifluoromethyluracil (II).—F_3TDR (I) (4.72 g, 16 mmoles), twice evaporated from dry pyridine (5-ml portions), was dissolved in 45 ml of dry pyridine. Triphenylchloromethane (4.60 g, 16 mmoles) was added and the solution was kept under reflux for 40 min in the absence of moisture. Then the reaction mixture was cooled, and the contents were poured over ice water (400 ml) with constant stirring. This aqueous mixture was extracted with $CHCl_3$ (300 ml), the $CHCl_3$ extract was dried ($MgSO_4$) and filtered, and the filtrate was evaporated to a gum on a rotary evaporator. The gum was dissolved in Et_2O (30 ml) and absorbed on a silicic acid (100 mesh, Mallinckrodt) column (5.5 × 30 cm, packed with Skellysolve B); the column was eluted with C_6H_6, and 40-ml fractions were collected. The first 1200 ml of the eluate gave 1.2 g of a material which on tlc (silicic acid, system A and B) had an R_f similar to that of an authentic sample of triphenylcarbinol. The column was then eluted with 20% MeOH in C_6H_6. The product II came out in a single band of uv-absorbing material, but on tlc it showed slight traces of I as impurity. All fractions containing II were collected and evaporated to a colorless gum. The gum was crystallized from EtOH–H_2O to give II as a colorless crystalline material (6.4 g, 74.4%), which on tlc (silicic acid, system A and B) moved as a single homogeneous uv-absorbing component. It was recrystallized from Et_2O–petroleum ether (bp 30–60°) to give colorless needles: mp 154–156° (softens at 145°); uv, λ_{max}^{MeOH} 262 mμ (ε 9558). *Anal.* ($C_{29}H_{25}F_3N_2O_5$) C, H, N.

1-(2-Deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-ribofuranosyl)-5-trifluoromethyluracil (III).—Dry II (4.03 g, 7.5 mmoles) was dissolved in dry pyridine (25 ml) and the solution was cooled (−5°), treated with $MeSO_2Cl$ (0.93 ml, freshly distilled), and kept in the refrigerator overnight in the absence of moisture. Absolute EtOH (3.5 ml) was added and the solution was maintained in the cold for another 1 hr. Then the pale contents of the reaction mixture were poured over 700 ml of ice–water with vigorous stirring. III precipitated as a pale powder; it was filtered and washed with a large excess of H_2O and dried *in vacuo* over P_2O_5. Crude III moved as a single uv-absorbing component on tlc (silicic acid) in systems A and B. The yield was 4.615 g (100%); III was used as such without further purification; uv, λ_{max}^{MeOH} 258 mμ (shoulder at 262.5), λ_{min}^{MeOH} 243 mμ. The ir spectrum showed a band at 1170 cm^{-1} corresponding to $MeSO_2$.

1-(5-*O*-Trityl-2,3-dideoxy-2,3-didehydro-β-D-*glycero*-pentofuranosyl)-5-trifluoromethyluracil (IV).—Crude III (2.54 g, 4 mmoles) was dissolved in anhydrous DMSO (40 ml) and KO-*t*-Bu (0.929 g, 8.3 mmoles) was added. The reaction mixture was stirred at room temperature (absence of moisture) for 18 min, then the dark yellow solution was gradually poured over stirred ice–water (700 ml). To this solution phenolphthalein (two drops) was added and the solution was made slightly acidic with a few drops of 6 *N* AcOH. The product IV precipitated as a gelatinous mass. It was filtered, washed with excess H_2O, and dried in a vacuum desiccator. IV was recrystallized by dissolving in Et_2O (charcoal) and precipitating with petroleum ether; mp 139–141° (resolidifies at 150°); yield 1.42 g (68.2%); uv, λ_{max}^{MeOH} 260 mμ (ε 8850). The ir spectrum showed no absorption at 1170 cm^{-1} corresponding to $MeSO_2$. The product gave a positive test with molybdate spray, proving the presence of an unsaturated sugar.[4] The nmr spectrum (in $CDCl_3$) showed the presence of two vinyl protons centered at δ 5.85 (3′-proton) and 6.25 (2′-proton); the anomeric proton was a multiplet centered at δ 6.90. *Anal.* ($C_{29}H_{23}F_3N_2O_4 \cdot 0.5H_2O$) C, H, N.

1-(2,3-Dideoxy-2,3-didehydro-β-D-*glycero*-pentofuranosyl)-5-trifluoromethyluracil (V).—Compound IV (0.13 g, 0.25 mmole) was treated with ice-cold 98% formic acid. The mixture was swirled to bring all particles in contact with the acid and then (~1 min) the acid was distilled with an oil pump at room temperature. The last traces of HCO_2H were removed by distillation with dioxane (two 2-ml portions). The residue was extracted with warm H_2O (5 ml) and the aqueous filtrate was evaporated to dryness under reduced pressure (bath temperature 35°). The residue was dissolved in boiling anhydrous Et_2O and filtered, and to the filtrate petroleum ether was added dropwise until slight turbidity. The turbid solution was kept in a referigerator, and V crystallized out during a period of 7 days; mp 103–104°; yield 35 mg (50.3%); uv, λ_{max}^{pH1} 260 mμ (ε 8051), λ_{max}^{pH12} 258.5 mμ (ε 5511). V gave a purple color with molybdate spray.[4] *Anal.* ($C_{10}H_9F_3N_2O_4 \cdot 0.8H_2O$) C, H, N.

1-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-trifluoromethyluracil (IX).—Compound VI (0.36 g, 2 mmoles) was refluxed with hexamethyldisilazane (2 ml) and dichlorodimethylsilane (one drop) (bath temperature 170°) in the absence of moisture. After 2 hr most of the ammonium salt, formed during the reaction, had sublimed into the condenser and a colorless oil was left. This was put on a rotary evaporator (bath temperature 50–60°) and finally fractionated under high vacuum. **Bis(*O*-trimethylsilyl)-5-trifluoromethyluracil (VII)** distilled at 58° (1.5 mm), yield 0.64 g (97%). **2,3,5-Tri-*O*-benzyl-D-ribofuranosyl bromide (VIII)** was prepared according to the method of Barker and Fletcher[12] (obtained from 1.12 g, 1.95 mmoles, of **1-*p*-nitrobenzoyl-2,3,5-tri-*O*-benzylribofuranoside**). To VIII, VII was added (dry CH_2Cl_2 used as a solvent for transfer) and the solvent was removed under reduced pressure. The residue was fused at 180° (bath temperature) for 40 min. The resulting dark green mass was cooled and then triturated with absolute EtOH (25 ml), and some dark insoluble material was filtered. The filtrate was evaporated and the residual gum was again triturated with absolute EtOH (20 ml), when more insoluble material was obtained and filtered. The EtOH filtrate was evaporated to a gum and then triturated with dry C_6H_6 (15 ml). Some insoluble material (shown to be VI by tlc) was filtered, and the filtrate (20 ml) was adsorbed on an alumina (neutral Woelm, activity grade II) column (2 × 28 cm). The column was eluted with C_6H_6 (400 ml), then 10% EtOAc in C_6H_6 (1000 ml), followed by 30% EtOAc in C_6H_6 (400 ml). During this period, most of the sugar derivatives were removed. Finally, IX was eluted with absolute MeOH (the elution was followed by tlc (silicic acid), in 10% EtOAc in C_6H_6). The fractions containing IX were collected, decolorized with charcoal, and evaporated to a gum. The gum gave one homogeneous uv-absorbing component on tlc in three different systems. Compound IX could not be crystallized and was used as such without further purification; uv, λ_{max}^{MeOH} 261 mμ, λ_{min}^{MeOH} 231.5 mμ.

5-Trifluoromethyl-1-(β-D-ribofuranosyl)uracil (X).—Compound IX was dissolved in absolute MeOH (50 ml) and hydrogenolyzed in the presence of Pd catalyst (obtained from 0.5 g of $PdCl_2$) at 2 atm (room temperature) for 40 min. Then the catalyst was filtered and the filtrate was evaporated. The residual gum was dissolved in absolute EtOH (10 ml), some non-uv-absorbing solid remained and was filtered. The filtrate was concentrated and crystallized from EtOH–Et_2O–petroleum ether. Three crops gave 0.188 g of X (over-all yield based on VI, 30.1%). Recrystallization from a small volume of absolute EtOH gave colorless plates, mp 209–210°. The compound gave a positive Na fusion color test for F. A strong and positive Cotton effect in the ORD indicated the β-anomeric configuration. The nmr spectrum showed the anomeric proton as a doublet centered at δ 6.17 (spectrum determined in D_2O); uv, λ_{max}^{pH2} 263 mμ (ε 10,407) and λ_{max}^{pH11} 262 mμ (ε 7002). Hydrolysis with 6 *N* HCl (100°, 3 hr) gave VI as identified by tlc and uv spectra. *Anal.* ($C_{10}H_{11}F_3N_2O_6$) C, H, N.

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Pyrazoles. III. Antileukemic Activity of 3-(3,3-Dimethyl-1-triazeno)pyrazole-4-carboxamide[1]

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Treatment of 3-aminopyrazole-4-carboxamide[2] with nitrous acid yielded 3-diazopyrazole-4-carboxamide.[3]

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(2) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(3) C. C. Cheng, R. K. Robins, K. C. Cheng, and D. C. Lin, *J. Pharm. Sci.*, **57**, 1044 (1968).

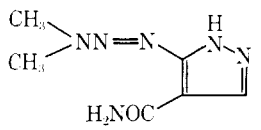
TABLE I

ANTILEUKEMIC ACTIVITY OF 3-(3,3-DIMETHYL-1-TRIAZENO)PYRAZOLE-4-CARBOXAMIDE *vs.* LEUKEMIA L1210[a]

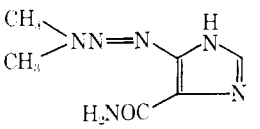
Dose, mg/kg	Day of first injection	Days of once-a-day injections	Mortality	Animal wt dif (T − C)	Survival, days — Test	Control	T/C, %
400	2	1	0/6	−4.9	12.0	8.8	136
200	2	1	0/6	−2.8	11.0	8.8	125
100	2	1	0/6	−1.8	10.0	8.8	113
600	2	1	1/6	−7.9	12.8	8.2	156
400	2	1	0/6	−6.8	11.8	8.2	143
267	2	1	0/6	−5.3	11.7	8.2	142
178	2	1	1/6	−5.3	10.4	8.2	126
300	1	9	0/6	−5.6	9.3	8.4	110
180	1	9	0/6	−4.9	11.3	8.4	134
109	1	9	0/6	−3.7	14.8	8.4	176
65	1	9	0/6	−3.2	12.0	8.4	142

[a] Host, BDF mice; vehicle, saline; route, intraperitoneal.

As in the case of the corresponding imidazole series,[4] I can be caused to couple with Me_2NH to form 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide (I).



I



II

Compound I has now been found to display good antileukemic activity against the leukemia L1210 system in the primary screen of the Cancer Chemotherapy National Service Center (Table I). The antileukemic activity of I and its imidazole analog II are comparable, but the toxicity of I is much less than that of II.[5]

Because of the reported light and heat sensitivity of the imidazole II and other analogous imidazole derivatives,[4-7] the stability of the pyrazole I was examined. Compound I is quite stable to both light and heat under a variety of experimental conditions. The remarkable difference in light and heat sensitivity between the pyrazole I and the imidazole II is indeed of interest. Perhaps the weaker basicity of pyrazole (pK_a = 2.53[8,9] as compared to the pK_a of imidazole, 7.03[9,10]) and the relative electron densities at the 4-carboxamide positions of two systems are important contributing factors.

The current biological interest in the study of triazenoimidazole derivatives,[4-7,11-15] the lower toxicity, and the light and heat stability of the pyrazole derivative I, together with the ease of preparation of the intermediate 3-aminopyrazole-4-carboxamide,[2] as opposed to that of 5-aminoimidazole-4-carboxamide (AIC),[16-18] suggest that I and related pyrazole derivatives would warrant further study.

Experimental Section[19]

3-(3,3-Dimethyl-1-triazeno)pyrazole-4-carboxamide (I).—Ten grams of powdered[20] 3-diazopyrazole-4-carboxamide[3] was added in small portions to 600 ml of EtOAc saturated with anhydrous Me_2NH. After the addition was complete, the reaction mixture was stirred at room temperature for 24 hr and the resulting precipitate was collected, washed (Et_2O), and dried in air to give 12 g of I, mp 200°. One recrystallization from MeOH gave analytically pure product: mp 212–213° dec; λ_{max}^{pH7} 229 mμ (ε 9700), 314 mμ (ε 11,400). *Anal.* ($C_6H_{10}N_6O$) C, H, N.

Stability Tests. (a) An aqueous solution of I buffered at pH 7, stored in a clear volumetric flask, was exposed to daylight and its uv absorption was measured at 1-, 4-, 8-, and 24-hr and 3-day intervals. (b) An analytically pure sample of I was placed in an oven heated at 80° for 72 hr. (c) An analytically pure sample of I, in a clear vial, was placed by the window for 2 weeks. In no case did any of the samples show spectrometric, chromatographic, or melting point changes.

In contrast to the preparation of the corresponding imidazole derivatives,[4-7] all operations, including purifications, can be conducted in the presence of light.

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(4) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2150 (1962).
(5) Y. F. Shealy and C. A. Krauth, *J. Med. Chem.*, **9**, 34 (1966).
(6) Y. F. Shealy, C. A. Krauth, L. B. Holum, and W. E. Fitzgibbon, *J. Pharm. Sci.*, **57**, 83 (1968).
(7) Y. F. Shealy, C. A. Krauth, S. J. Clayton, A. T. Shortnacy, and W. R. Laster, Jr., *ibid.*, **57**, 1562 (1968).
(8) J. Dedichen, *Ber.*, **39**, 183 (1906).
(9) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).
(10) A. H. M. Kirby and A. Neuberger, *Biochem. J.*, **32**, 1146 (1938).
(11) Y. F. Shealy, C. A. Krauth, R. F. Pittillo, and D. E. Hunt, *J. Pharm. Sci.*, **56**, 147 (1967).
(12) K. Hano, A. Akashi, I. Yamamoto, S. Narumi, Z. Horii, and I. Ninomiya, *Gann*, **56**, 417 (1965).
(13) K. Hano, A. Akashi, I. Yamamoto, S. Narumi, and H. Iwata, *ibid.*, **59**, 207 (1968).
(14) Y. F. Shealy, J. A. Montgomery, and W. R. Laster, Jr., *Biochem. Pharmacol.*, **11**, 674 (1962).
(15) Y. F. Shealy, and C. A. Krauth, *Nature*, **210**, 208 (1966).
(16) A Windaus and W. Langenbeck, *Ber.*, **56**, 683 (1923).
(17) A. H. Cook, I. Heilbron, and E. Smith, *J. Chem. Soc.*, 1440 (1949).
(18) Y. Yamada, I. Kumashiro, and T. Takenishi, *Bull. Chem. Soc. Japan*, **41**, 241 (1968).
(19) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The uv spectrum was determined with a Beckman DK-2 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.
(20) The usual precaution for powdering dizao compounds should be exercised. In our laboratory it was found that the best result can be obtained by pressing the diazo compound on a Teflon sheet with a Teflon-coated spatula.