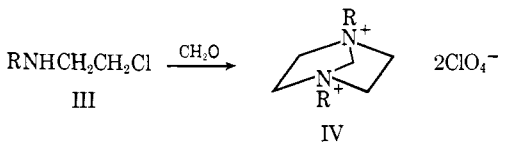
TABLE I



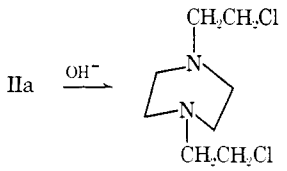
III IV

Compd IV	R	Yield, %	Dec pt, °C	Formula[c]
a	C_2H_5	63	292–294	$C_{11}H_{18}Cl_2N_2O_4$
b		81[a]	271–273	$C_{13}H_{16}Cl_4N_2O_4$
c	$PhCH_2CH_2$	90[a]	256–257.5	$C_{21}H_{24}Cl_2N_2O_4$
d	$3,4,5\text{-}(MeO)_3C_6H_2CH_2CH_2$	90[a]	255–256.5	$C_{21}H_{40}Cl_2N_2O_{14}$
e	$PhCH_2$	61[a]	191–193[b]	$C_{17}H_{14}Cl_2N_2O_4$
f	$m\text{-}ClC_6H_4CH_2$	63[a]	233–235	$C_{17}H_{22}Cl_4N_2O_4$
g	$3,5\text{-}(MeO)_2C_6H_3CH_2$	87[a]	188–189	$C_{23}H_{32}Cl_2N_2O_{12}$
h	$3,4,5\text{-}(MeO)_3C_6H_2CH_2$	79[a]	178–180	$C_{25}H_{36}Cl_2N_2O_{14}$

[a] Calculated as the chloride salt. [b] Lit.[4b] 192°. [c] All compounds were analyzed for C, H, Cl, N. Analytical results were within 0.3% of the calculated values.

Biological evaluations are being performed under auspices of the Cancer Chemotherapy National Service Center. Results available at present indicate that chloroethyl derivative IIa and bromoethyl derivative IIb are the most active of the series, completely inhibiting growth of Walker 256 (subcutaneous) carcinoma in random-bred albino rats at dose levels of 23 and 50 mg/kg, respectively.[6] By comparison, the ethyl derivative IVa and quaternary salts IVf–h (investigated as chlorides) were considerably less active, demonstrating only slight activity at relatively high dose levels.

The greater activity displayed by haloethyl derivatives IIa,b might be explicable in terms of the diazabicyclo[2.2.1]heptane ring chemistry. Böhme and Orth have reported[4b] that basic hydrolysis of salt IIa produced formaldehyde and 1,4-bis(2-chloroethyl)piperazine (V), a potential alkylating agent. When evaluated



as described above, the maleate salt of piperazine V gave approximately 61% inhibition of tumor growth at a dose level of 150 mg/kg. Perhaps the activity of IIa may be due in part to *in vivo* formation of piperazine V.

Experimental Section

Melting points were recorded employing a Kofler melting point apparatus. Purity of analytical samples (colorless) was confirmed by tlc on silica gel HF_{254} (E. Merck, A. G. Darmstadt) spread on microscope slides. Chromatograms were performed with the top layer of a BuOH–H_2O–HOAc (4:5:1) mixture as solvent and developed with I_2. Microanalytical data were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Ir spectra were determined in KBr by Miss K. Reimer (Arizona State University) and Dr. R. A. Hill (University of Maine). Pmr spectra were recorded in D_2O (TMS external standard) with a Varian A-60. The secondary 2-haloethylamines were prepared employing a previously described procedure:[7] **N-(2-chloroethyl)-2-cyclopentylethylamine hydrochloride**, mp 245–246°, ν_{max} 2750 (broad, NH_2^+) cm^{-1} [*Anal.* ($C_9H_{19}Cl_2N$) C, H, Cl, N]; **N-(2-chloroethyl)-2-phenylethylamine hydrochloride**, mp 193.5–194.5°, ν_{max} 2790 (broad, NH_2^+) and 1605 (weak) cm^{-1}, pmr δ 7.5 (s, 5 aromatic protons) and 4.1–3.0 (overlapping A_2B_2 patterns, 8 protons) [*Anal.* ($C_{10}H_{15}Cl_2N$) C, H, Cl].

The N-substituted 2-chloroethylamines were stored as their stable HCl salts and converted to the free bases as described for N-(2-chloroethyl)ethylamine.

N-(2-Chloroethyl)ethylamine (IIIa).—The HCl salt of IIIa (1.44 g) was added to an ice-cold 10% KOH solution (7 ml) and the resulting mixture was quickly extracted (Et_2O, three 10-ml portions). The combined Et_2O extract was dried and concentrated at reduced pressure without heating to yield free base IIIa as a mobile oil.

1,4-Diethyl-1,4-diazabicyclo[2.2.1]heptane Diperchlorate (IVa).—A solution of N-(2-chloroethyl)ethylamine (0.01 mole), 37% formalin (2 ml), and 95% EtOH (3 ml) was stirred at room temperature 24 hr. Treatment of the colorless solution with 70% $HClO_4$ (0.8 ml) followed by chilling (ice bath) led to a crystalline solid (1.03 g, 63%) decomposing at 200–230°. Three recrystallizations from 95% EtOH afforded a pure sample as colorless plates: dec pt 292–294°.

1,4-Bis(2-bromoethyl)-1,4-diazabicyclo[2.2.1]heptane Dibromide (IIb).—Bis(2-bromoethyl)amine (0.008 mole) was left at room temperature in formalin–EtOH solution for 10 hr. After cooling, the salt which deposited was collected (2.3 g, 59%), dec pt 168–171°. A portion was recrystallized three times from aqueous EtOH for analysis, providing colorless plates: dec pt 178.5–179.5°. *Anal.* ($C_9H_{18}Br_4N_2 \cdot H_2O$) C, H, Br, N.

1,4-Bis(2-fluoroethyl)-1,4-diazabicyclo[2.2.1]heptane Diperchlorate.—To a solution of bis(2-fluoroethyl)amine hydrochloride (0.720 g, 0.005 ml)[8] in EtOH (10 ml) was added NaOH (0.2 g, 0.005 ml) in H_2O (3 ml) followed by 37% formaldehyde (2 ml). After 6 days at room temperature, acidification with 70% $HClO_4$ (0.5 ml), dilution with EtOH (2 ml), chilling, and filtration afforded a colorless solid (0.55 g, 55%, dec pt 210–214). Two recrystallizations from aqueous EtOH followed by two from H_2O produced an analytical sample, dec pt 223.5–225°. *Anal.* ($C_9H_{18}Cl_2N_2O_4$) C, H, Cl, F, N.

1,4-Diazabicyclo[2.2.1]heptanes (Table I). General Procedure.—A solution composed of N-[2-chloroethyl-2-(3,4,5-trimethoxyphenyl)]ethylamine (0.014 mole), 37% formalin (3.2 ml), and 95% EtOH (6.6 ml) was allowed to stand at room temperature 24 hr. The solution was concentrated at reduced pressure to an oil which was dried by addition and evaporation of PhH (three 50-ml portions). Upon trituration with dry Et_2O the oil solidified and crystallized as needles (3.5 g, 90%) from EtOH–Et_2O; dec pt 215–220°. Treating a solution of the dichloride salt (0.5 g) in H_2O (3 ml) with 70% $HClO_4$ (0.1 ml) yielded a colorless solid which crystallized from aqueous EtOH (0.47 g). Three recrystallizations from aqueous EtOH afforded a pure sample of IVd as colorless needles, dec pt 255–256.5°.

Acknowledgment.—This investigation was supported in part by Public Health service research grant CA-10115-02 from the National Cancer Institute, and in part by Grant T-79G from the American Cancer Society.

(6) In each case, the substance was given intraperitoneally in saline solution for 5 days following tumor transplant. Evaluation of tumor growth was made on the tenth day.

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Fluorinated Pyrimidines. XXXII. Syntheses of 2′,3′-Dehydro-5-trifluoromethyl-2′-deoxyuridine and 5-Trifluoromethyluridine[1]

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A number of fluorinated pyrimidines and their nucleoside derivatives have been synthesized in this labora-

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(2) American Cancer Society Professor of Oncology.

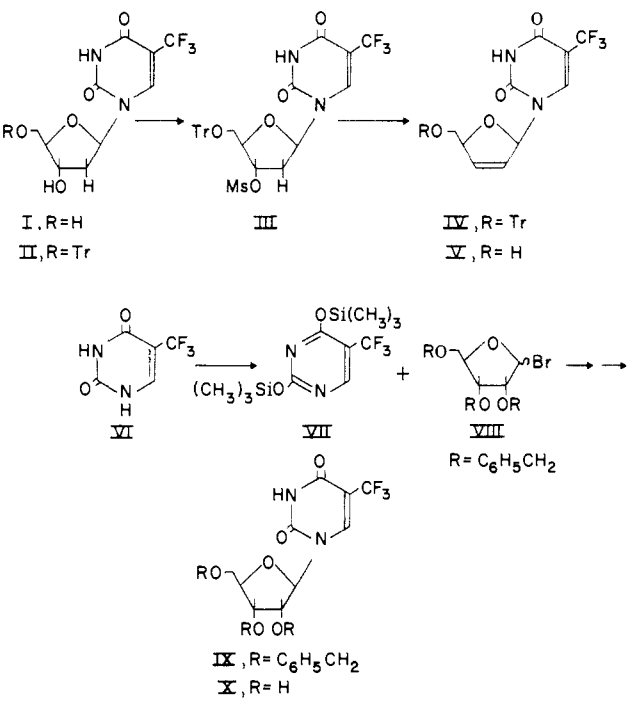
tory.[3,4] Of these, 5-fluorouracil (FU), 5-fluoro-2′-deoxyuridine (FUDR), and 5-trifluoromethyl-2′-deoxyuridine (F_3TDR) are currently used in cancer chemotherapy. In this paper we report the syntheses and properties of two new compounds related to biologically active 5-trifluoromethyl-2′-deoxyuridine (F_3TDR),[5] 1-(2,3-dideoxy-2,3-didehydro-β-D-*glycero*-pentofuranosyl)-5-trifluoromethyluracil (V, 2′,3′-dehydro-5-trifluoromethyl-2′-deoxyuridine, DHF_3TDR), and 5-trifluoromethyl-1-(β-D-ribofuranosyl)uracil (X, 5-trifluoromethyluridine, F_3TR).

We have reported that 2′,3′-dehydro-5-fluoro-2′-deoxyuridine (DHFUDR)[4] is a powerful inhibitor of a variety of transplanted tumors in mice including some that are resistant to FUDR. Consequently it was of interest to synthesize the corresponding derivative (V) of F_3TDR. Furthermore, F_3TDR is mutagenic to bacteriophage T4B,[6] inhibits the growth of several transplanted tumors,[7] is a potent inhibitor of herpes simplex keratitis in the rabbit's eye,[8] and is also effective against vaccinia virus grown in HeLa cell cultures.[9] The antiviral activity of F_3TDR is probably due to its incorporation into viral DNA.[10] Because of this biological activity it was of interest to prepare the ribonucleoside, F_3TR, and determine whether it would have any activity against RNA viruses.

In analogy with the work on 2′,3′-dehydro-FUDR,[4] DHF_3TDR was synthesized by a base-catalyzed elimination of the 3′-mesylate (III) of F_3TDR. F_3TDR (I) was treated with trityl chloride in dry pyridine to give the 5′-*O*-trityl derivative II, which on treatment with methanesulfonyl chloride in pyridine gave the mesylate III (Scheme I). The crude III was treated with slightly more than 2 equiv of KO-*t*-Bu in dry DMSO for 18 min (room temperature) to give 5′-*O*-trityl-DHF_3TDR (IV) in 68% yield. The nmr spectrum of the product IV showed two vinyl protons centered at δ 5.85 and 6.25. The anomeric proton was a multiplet centered at δ 6.90. The presence of an unsaturated sugar moiety was also confirmed because IV gave a purple color with molybdate spray.[4] Detritylation of IV gave DHF_3TDR (V) in good yield. The structure of V was confirmed by its uv spectra, elemental analysis, and the molybdate spray test.[4]

F_3TR was prepared by the fusion method of Nishimura, *et al.*,[11] in 30% yield. F_3T (VI) on refluxing with hexamethyldisilazane at 170° gave bis(*O*-trimethylsilyl)-5-trifluoromethyluracil (VII), which was fused with 2,3,5-tri-*O*-benzyl-D-ribosyl bromide (VIII)[12] at 180° for 40 min. The protected nucleoside IX was isolated by column chromatography and converted to F_3TR (X) by hydrogenolysis in the presence of Pd catalyst. X gave a positive F test and a strong and positive Cotton effect, which, together with the nmr spectrum

SCHEME I



showing the anomeric proton as a doublet centered at δ 6.17, demonstrate that we obtained the β anomer. The uv spectra and elemental analysis also establish its structure as X.

DHF_3TDR, like DHFUDR,[4] is very sensitive to acid, and on mild acid treatment is completely decomposed to F_3T ($t_{0.5}$ = 2 min in 0.1 *N* HCl at 95°). On alkaline treatment V slowly decomposes to a 5-carboxy derivative (5-carboxyuracil and/or 5-carboxy-2′-deoxyuridine), as does F_3TDR.[5] On prolonged treatment with 6 *N* aqueous HCl at 100°, F_3TR gave F_3T as the sole uv-absorbing product. In analogy to F_3TDR, F_3T is extremely sensitive to alkali ($t_{0.5}$ = 2 hr in aqueous 0.1 *M* $NaHCO_3$ at room temperature) and is converted to 5-carboxy derivatives.

Biological Activity.—2′,3′-Dehydro-F_3TDR was $^1/_{50}$ as active as F_3TDR at inhibiting the growth of HeLa cells in culture, $^1/_{100}$ as active against L5178Y leukemia cells in culture, $^1/_{1000}$ as active as F_3TDR at inhibiting vaccinia viral replication in HeLa cells,[13] and was not mutagenic to bacteriophage T4 in *Escherichia coli*.[14]

F_3TR was active only at 10^{-3} *M* in inhibiting the growth of HeLa and L5178Y cells in culture (the same activity as F_3T),[13] was not mutagenic to bacteriophage T4, did not inhibit the burst size of RNA bacteriophage MS-2 in *E. coli*,[14] and at 2×10^{-4} *M* did not inhibit plaque formation by the RNA animal vesicular stomatitis virus in mouse embryo cells.[15] Thus, neither of these compounds exhibited significant biological activity.

Experimental Section

All melting points are corrected. The uv spectra were run on a Cary spectrophotometer Model 15. The nmr spectra were determined on a Varian A 60 instrument. The analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The

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(13) Data obtained in this laboratory by Dr. Y. Fujiwara.
(14) Data obtained in this laboratory by Mr. Thomas Corbett.
(15) Data obtained by Professor H. M. Temin of this university.

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.

Acknowledgment.—We wish to acknowledge the skillful technical assistance of Miss Sharon Ohlhorst and Miss Marian Mitsche.

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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