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

Synthesis of Potential Anticancer Agents. XXV.[2] Preparation of Some *cis*- and *trans*-2-(6-Substituted 9-Purinyl)cyclopentanols[2]

HOWARD J. SCHAEFFER[3] AND RICHARD D. WEIMAR, JR.

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cis- and *trans*-2-(6-Chloro-9-purinyl)cyclopentanols have been synthesized. Several 6-substituted analogs of these key intermediates have been prepared by nucleophilic displacement of the 6-chlorine atom on the purine moiety.

In the search for effective anticancer agents, numerous modifications of the purine nucleus have been made.[4] In a continuation of this search for effective anticancer agents, a variety of purine nucleosides has been prepared with the aim of inhibiting some stage of nucleotide metabolism in the cell. The modifications which have been made in the nucleosides, as compared to naturally occurring materials, have involved changes in the purine moiety,[5,6] in the sugar moiety,[7,8] or in both[9]; these alterations in structure have caused unpredictable changes in the anticancer activity of the nucleoside compared with the corresponding free purine. Consequently, the preparation of nucleoside analogs which would be sterically similar to, but more stable than, the corresponding nucleoside has been undertaken. In an earlier paper of this series,[10] the syntheses of some 9-(substituted-cyclohexyl)purines were described; the present paper gives details of the syntheses of derivatives of *cis*-and *trans*-2-(9-purinyl)cyclopentanols.

The key intermediates which were necessary for our program were *cis*-and *trans*-2-(6-chloro-9-purinyl)cyclopentanols, whose preparations were accomplished by procedures similar to the ones used in earlier papers of this series; the starting materials, *cis*- and *trans*-2-aminocyclopentanols, were prepared by modifications of previously described procedures.[11] Thus, cyclopentene was allowed to react with *N*-bromosuccinimide in aqueous solvent; the resulting bromohydrin upon reaction with ammonium hydroxide gave a good yield of *trans*-2-aminocyclopentanol.[11] The corresponding *N*-(*trans*-2-hydroxycyclopentyl)benzamide was converted in good yield into *cis*-2-aminocyclopentanol via an oxazolidine intermediate.[11]

Condensation of *cis*-2-aminocyclopentanol with 5-amino-4,6-dichloropyrimidine in the presence of triethylamine resulted in the formation of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol. Ring closure of this pyrimidine to *cis*-2-(6-chloro-9-purinyl)cyclopentanol was accomplished with diethoxymethyl acetate.[12]

Similarly, when *trans*-2-aminocyclopentanol was allowed to react with 5-amino-4,6-dichloropyrimidine, a good yield of *trans*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol was obtained. Attempted ring closure of this pyrimidine to *trans*-2-(6-chloro-9-purinyl)cyclopentanol with diethoxymethyl acetate resulted in considerable decomposition, and only low yields of the desired product could be isolated, especially when the reaction was carried out on a large scale. Subsequently, it was learned that *trans*-2-(6-chloro-9-purinyl)cyclopentanol could be prepared in good yield by allowing *trans*-2-(5-amino-6-chloro-5-pyrimidinylamino)-cyclopentanol to react with triethyl orthoformate at reflux temperature.[13] However, when an attempt was made to prepare *cis*-2-(6-chloro-9-purinyl)-cyclopentanol by ring closure of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol with triethyl orthoformate under identical conditions with those used for the *trans*-isomer, practically no reaction occurred, as evidenced by only a slight change in the ultraviolet absorption spectra of aliquots of the reaction mixture. The reason for the differences in reactivity of the two pyrimidines is probably steric in origin, but a detailed mechanistic interpretation with the limited experimental results at hand is not warranted.

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(2) For paper XXIV of this series, see Y. F. Shealy, *Experientia* (To be published.)

(3) Present address. Department of Medicinal Chemistry, University of Buffalo, Buffalo, New York.

(4) See, for example, D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Research*, **18**, 445 (1958) and the section on purine antagonists in J. A. Montgomery, *Cancer Research*, **19**, 447 (1959).

(5) H. J. Schaeffer and H. J. Thomas, *J. Am. Chem. Soc.*, **80**, 4896 (1958) and earlier papers in this series.

(6) J. Davoll, *J. Chem. Soc*, 1593 (1958).

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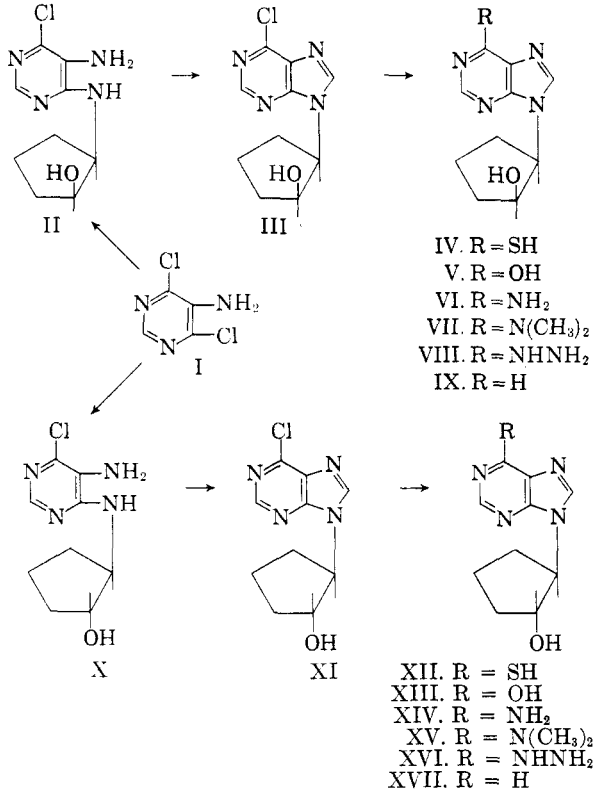
CHART I



The purines (III and XI) were individually converted into analogs in which the 6- position was substituted with a hydrogen, mercapto, hydroxy, amino, dimethylamino, and hydrazino group. In Table I, the pertinent data for the purines prepared are summarized. Typical examples of the procedures employed for the preparation of these compounds are given in the Experimental.

EXPERIMENTAL[14]

cis-2-(5-Amino-6-chloro-4-pyrimidinylamino)cyclopentanol (II). A solution of 79.2 g. (0.487 mole) of 5-amino-4,6-dichloropyrimidine,[15] 51.6 g. (0.509 mole) of *cis*-2-aminocyclopentanol,[11] and 51.6 g. (0.509 mole) of triethylamine in 780 ml. of butyl alcohol was heated under reflux for 23 hr., and then the volatile materials were removed *in vacuo*. The residue on crystallization from water gave a white solid: yield, 101 g. (90.7%). For analysis, a small example was recrystallized from water; m.p. 171° λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 305 (13.0); *p*H 7, 265 (9.13), 290 (9.74); *p*H 13, 264 (8.79), 290 (9.06).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.27; H, 5.73; N, 24.50. Found: C, 47.29; H, 5.74; N, 24.36.

trans-2-(5-Amino-6-chloro-4-pyrimidinylamino)cyclopentanol (X). A solution of 44.2 g. (0.273 mole) of 5-amino-4,6-dichloropyrimidine,[15] 29.8 g. (0.294 mole) of *trans*-2-aminocyclopentanol,[11] and 29.8 g. (0.294 mole) of triethylamine in 400 ml. of butyl alcohol was heated under reflux for 23 hr., and then the volatile materials were removed *in vacuo*. The residual oil after crystallization and recrystallization from water gave the pure product: yield, 45.9 g. (73.7%); m.p. 151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 306 (13.6); *p*H 7, 265 (9.45), 292 (9.97); *p*H 13, 264 (9.57), 293 (10.1).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.27; H, 5.73; N, 24.50. Found: C, 47.35; H, 5.50; N, 24.90.

cis-2-(6-Chloro-9-purinyl)cyclopentanol (III). A solution of 101 g. (0.442 mole) of *cis*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol in 510 ml. of diethoxymethyl acetate[12] was heated in an oil bath at 100° for 4 hr., and then the volatile materials were removed *in vacuo*. The residual oil was allowed to react overnight at 0° with 1 l. of a 21% solution of ammonia in methanol. The reaction mixture was evaporated *in vacuo*, and the residual glass was extracted with boiling water (6 × 300 ml.). Concentration of the combined extracts gave the product in four crops: yield, 52.8 g. (49.7%); m.p. 148°, resolidifies and remelts at 150°. For analysis, a small sample was recrystallized from water; m.p. 158°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (9.00); *p*H 7, 265 (8.80); *p*H 13, 264 (9.00).

The analytical data are recorded in Table I.

trans-2-(6-Chloro-9-purinyl)cyclopentanol (XI).[16] A solution of 2.00 g. (8.76 mmoles) of *trans*-2-(5-amino-6-chloro-4-pyrimidinylamino)cyclopentanol in 20 ml. of triethyl orthoformate was heated under reflux for 63 hr. and then concentrated *in vacuo* to dryness. The residual glass was crystallized from water and gave the pure product in two crops in a 53% yield; m.p. 162–163°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 226 (9.72); *p*H 7, 266 (9.45); *p*H 13, 264 (9.18).

The analytical data are recorded in Table I.

A later, larger run gave material in 88% yield, melting at 162–163°. Its ultraviolet absorption spectrum was practically identical with that of the material described above.

cis-2-(6-Mercapto-9-purinyl)cyclopentanol (IV). A solution of 8.08 g. (33.8 mmoles) of *cis*-2-(6-chloro-9-purinyl)cyclopentanol and 2.59 g. (34.0 mmoles) of thiourea in 160 ml. of propyl alcohol was heated under reflux for 1 hr. and then cooled in an ice bath. The solid was collected by filtration, washed with cold propyl alcohol (5 ml.), and air-dried: yield, 5.76 g. (72.0%); m.p. 307–315° dec. One recrystallization from a mixture of methyl cellosolve and water gave the analytical sample: yield, 3.78 g. (47.3%); m.p. 308–316° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 227 (9.32), 325 (21.2); *p*H 7, 321 (23.4); *p*H 13, 232 (13.5), 311 (22.6).

The analytical data are recorded in Table I.

cis-2-(6-Amino-9-purinyl)cyclopentanol (VI). A mixture of 1.25 g. (5.23 mmoles) of *cis*-2-(6-chloro-9-purinyl)cyclopentanol and 12 ml. of liquid ammonia was heated in a stainless steel bomb at 55° for 24 hr. The ammonia was allowed to evaporate, and the brown residual solid was extracted with boiling acetone (6 × 100 ml.). The combined acetone extracts after evaporation *in vacuo* gave *cis*-2-(6-amino-9-purinyl)cyclopentanol; yield, 0.95 g. (83%); m.p. 225°. The product was purified by sublimation *in vacuo* (190°/0.1 mm.); m.p. 225°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 259 (14.4); *p*H 7, 262 (14.6); *p*H 13, 261 (14.6). The analytical data are recorded in Table I.

cis-2-(6-Dimethylamino-9-purinyl)cyclopentanol (VII). A solution of 1.44 g. (6.02 mmoles) of *cis*-2-(6-chloro-9-purinyl)-cyclopentanol, 30 ml. of ethanol, and 30 ml. of a 25% aqueous solution of dimethylamine was heated under reflux for 1 hr. and then evaporated *in vacuo* to dryness. The residual white solid was recrystallized from 15 ml. of water and gave the pure *cis*-2-(6-dimethylamino-9-purinyl)cyclopentanol: yield, 1.12 g. (75.2%); m.p. 142°. λ_{max} in mμ ($\epsilon \times 10^{-3}$):

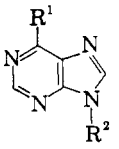
(14) The ultraviolet absorption spectra were determined in aqueous solution with a Beckman model DK-2 spectrophotometer, and the optical densities were determined with a Beckman D.U. spectrophotometer. Melting points below 260° were determined on a Kofler Heizbank and are corrected; melting points above 260° were determined in a capillary tube in an aluminum block and are uncorrected. All compounds were dried at 110°/0.1 mm. over phosphorus pentoxide before analysis.

(15) Krishell Laboratories, Inc., 1735 S. E. Powell Blvd., Portland 2, Oregon.

(16) This experiment was performed by Mr. C. A. Krauth.

TABLE I

cis- AND *trans*-2-(6-SUBSTITUTED 9-PURINYL)CYCLOPENTANOLS



Compound	Recrystn. solvent[a]	Yield, %	M.P., °	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
R^2 = *trans*-2-Hydroxycyclopentyl									
R^1									
Cl	A	53	162–163	50.32	50.60	4.65	4.99	23.47	23.15
SH	A + C	67	303–307 dec.	50.82	50.57	5.12	5.20	23.71	23.46
OH	E	49	282–285 dec.	54.54	54.56	5.49	5.89	25.44	25.44
NH_2	C	51	199	54.78	54.92	5.98	6.00	31.95	32.18
$N(CH_3)_2$	D	88	119–122	58.28	58.28	6.93	6.82	28.32	28.44
$NHNH_2$	E or F	49	182	51.27	51.11	6.02	5.94	35.88	36.19
H	G	87	132	58.81	58.66	5.92	5.90	27.44	27.41
R^2 = *cis*-2-Hydroxycyclopentyl									
R^1									
Cl	A	50	158	50.32	50.55	4.65	4.75	23.47	23.58
SH	A + C	47	308–316 dec.	50.82	50.58	5.12	5.18	23.71	23.76
OH	A	58[b]	276–278 dec.[c]	53.44[b]	53.59	5.61[b]	5.74	24.93[b]	24.81
NH_2	G	83	225	54.78	54.74	5.98	5.75	31.95	31.77
$N(CH_3)_2$	A	75	142	58.28	58.55	6.93	6.94	28.32	28.38
$NHNH_2$	G	58	203	51.27	51.42	6.02	6.21	35.88	35.66
H	G	95	140	58.81	58.53	5.92	5.84	27.44	27.40

[a] A, water; B, benzene and hexane; C, methyl cellosolve; D, extraction with *n*-hexane; E, ethanol; F, benzene; G, sublimation *in vacuo*. [b] Calcd. as 1/4 hydrate. [c] This product melts at 254°, resolidifies and remelts at 276–278° dec.

*p*H 1, 269 (18.1); *p*H 7, 277 (18.5); *p*H 13, 276–277 (17.5). The analytical data are recorded in Table I.

9-(trans-2-Hydroxycyclopentyl)-6-purinol (XIII).[16] A mixture of 500 mg. (2.10 mmoles) of trans-2-(6-chloro-9-purinyl)-cyclopentanol and 10 ml. of 1*N* hydrochloric acid was heated under reflux for 2 hr., during which time solution occurred. To the cooled reaction solution was added 7.5 ml. of 1*N* sodium hydroxide, and the solution was evaporated *in vacuo* to dryness. The crude product was extracted from the residual sodium chloride with hot methyl cellosolve (25 ml.). The methyl cellosolve extract was evaporated *in vacuo* to dryness and the residue was recrystallized from ethanol; crude yield, 360 mg. (78%); m.p. 230–240°. One recrystallization of the crude product from butyl alcohol gave pure material in three crops which was dried at 140° *in vacuo* over phosphorus pentoxide; yield 227 mg. (49%); m.p. 285° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 251 (10.7); *p*H 7, 250 (11.4); *p*H 13, 255 (12.6). The analytical data are recorded in Table I.

trans-2-(6-Hydrazino-9-purinyl)cyclopentanol (XVI). To 13 ml. of anhydrous hydrazine was added over a 3-min. period 1.95 g. (8.16 mmoles) of *trans*-2-(6-chloro-9-purinyl)-cyclopentanol. The reaction mixture was stirred for 4 hr. at room temperature under a nitrogen atmosphere and then evaporated *in vacuo* to dryness. Alternate recrystallizations of the crude product from ethanol and benzene gave the analytical sample; yield, 936 mg. (49%); m.p. 182°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 263 (16.9); *p*H 7, 265 (13.2); *p*H 13, unstable. The analytical data are recorded in Table I.

trans-2-(9-Purinyl)cyclopentanol (XVII). A mixture of 1.64 g. (6.86 mmoles) of *trans*-2-(6-chloro-9-purinyl)cyclopentanol, 0.553 g. (13.7 mmoles) of magnesium oxide, and 0.683 g. of 5% palladium-on-charcoal catalyst in 60 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature until the theoretical amount of hydrogen was absorbed (45 min.). The catalyst was removed by filtration and the filtrate was added to 50 ml. of a 10% aqueous sodium carbonate solution. Evaporation of the solution and extraction of the residue with chloroform (2 × 200 ml.) gave a pure *trans*-2-(9-purinyl)cyclopentanol: yield, 1.22 g. (87.2%); m.p. 132°. If necessary, the product may be purified by sublimation *in vacuo;* m.p. 132°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (6.03); *p*H 7, 264 (7.50); *p*H 13, 264 (7.76). The analytical data are recorded in Table I.

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BIRMINGHAM, ALA.