2,8-Dimethyl-6-purinethiol.—To 50 ml. of absolute ethanol and 1.8 g. of 6-chloro-2,8-dimethylpurine was added 2 g. of thiourea. This mixture then was refluxed for 3 hr., treated with Norite, filtered and the filtrate allowed to cool. The precipitate was filtered and dried at 110° to yield 1.2 g. of an analytically pure product; ultraviolet absorption spectra exhibited at *p*H 1: λ_{max} 232 mμ, ε 14,200; λ_{max} 329 mμ, ε 14,200; at *p*H 11: λ_{max} 235 mμ, ε 20,000; λ_{max}, 314 mμ, ε 14,600.

Anal. Calcd. for $C_7H_8N_4$: C, 46.7; H, 4.5; N, 31.1. Found: C, 46.2; H, 4.6; N, 31.1.

2-Ethoxy-6-methylpurine (XIX, R = OC_2H_5). Method 1.—4,5-Diamino-2-ethoxy-6-methylpyrimidine (XVIII, R = OC_2H_5), obtained after reducing 4 g. of 4-amino-2-ethoxy-6-methyl-5-nitropyrimidine (XVII, R = OC_2H_5) by sponge nickel catalyst in absolute ethanol, was used directly for cyclization after removal of the nickel by filtration and the evaporation of the ethanol under reduced pressure. The dry powdered residue of 4,5-diamino-2-ethoxy-6-methylpyrimidine (XVIII, R = OC_2H_5) was mixed with about 15 ml. of an equimolar mixture of triethyl orthoformate and acetic anhydride and refluxed for 4 hr. The solvent was removed under reduced pressure using a steam-bath as the source of heat. The residue was warmed with dilute potassium hydroxide on the steam-bath. The filtrate, after neutralization and cooling, deposited a brown crystalline product which was filtered, dried and extracted with 5 × 30 ml. of boiling benzene. The nearly colorless benzene extract was concentrated to 100 ml. and allowed to cool to yield 0.8 g. of cream-colored product, m.p. 236°.

Anal. Calcd. for $C_8H_{10}N_4O \cdot \frac{1}{2}H_2O$: C, 51.3; H, 5.9. Found: C, 51.7; H, 5.8.

Method 2.—Five-tenths gram of sodium was dissolved in 60 ml. of absolute ethanol. Then 1 g. of 2-chloro-6-methylpurine (XIX, R = Cl) in 25 ml. of absolute ethanol was added. The solution was refluxed for 24 hr. Toluene now was added, and the ethanol was replaced slowly by toluene in the refluxing mixture. The excess toluene was boiled off to give a deep-brown substance which was treated with about 50 ml. of boiling water. The solution was treated with charcoal, filtered and acidified with glacial acetic acid. On cooling, the product which separated was recrystallized from an alcohol–benzene mixture to yield white crystals, m.p. 230°. A mixed m.p. determination with the product obtained by method 1 showed no depression.

Anal. Calcd. for $C_8H_{10}N_4O \cdot \frac{1}{2}H_2O$: C, 51.3; H, 5.9. Found: C, 51.1; H, 5.9.

2,8-Dimethylpurine (VII).—One gram of 6-chloro-2,8-dimethylpurine was shaken at room temperature with 0.5 g. of 5% palladium–charcoal catalyst in 40 ml. of water and 0.5 ml. of 28% ammonium hydroxide under 1 atm. of hydrogen for 3 hr. The isolation and purification procedure was identical to that employed for the preparation of 2-methylpurine. The yield of 2,8-dimethylpurine was 0.3 g., m.p. 217°.

Anal. Calcd. for $C_7H_8N_4$: C, 56.8; H, 5.4; N, 37.8. Found: C, 56.8; H, 5.4; N, 37.6.

TEMPE, ARIZ.

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

Synthesis of Potential Anticancer Agents. XVII. Preparation of 9-(Substituted-cycloaliphatic)-purines[2]

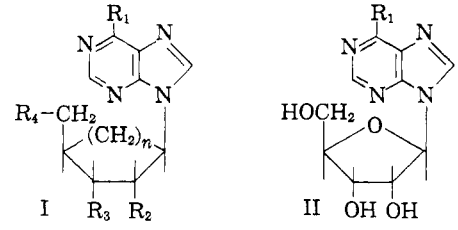
BY HOWARD J. SCHAEFFER AND RICHARD D. WEIMAR, JR.

RECEIVED JULY 24, 1958

The syntheses of 6-chloro-9-(2-cyclohexenyl)-purine, *cis*- and *trans*-2-[9-(6-chloropurinyl)]-cyclohexanols have been completed. From these compounds, several 6-substituted analogs have been prepared. The stereochemical relationship of these compounds with nucleosides is discussed.

In earlier papers of this series,[3,4] we discussed the reasons for our interest in the area of purine ribonucleosides as potential anticancer agents and reported the preparation of a wide variety of these ribonucleosides. Preliminary screening results on some of these ribonucleosides against Adenocarcinoma 755 have shown unpredictable differences in antitumor activity between them and the corresponding free purines.[5] The differences observed were variations in the chemotherapeutic index, in the toxicity, or in both. Nevertheless, the results are encouraging since the differences in activity between the ribonucleosides and the free purines establish that the ribonucleosides remain at least partially intact in the test animals.

Since we were concerned that the sugar moiety of a ribonucleoside might easily be removed hydrolytically or enzymatically in the test animals, we have devised a novel approach for the preparation of compounds related to nucleosides that should be stable under the test conditions. This novel class of compounds are purines which are substituted at the 9-position with a substituted cyclohexyl or cyclopentyl nucleus (I).



n = 1 or 2
R_1 = H, Cl, OH, NH_2, SH or $NHNH_2$
R_2, R_3, R_4 = H or OH

Because this new series of compounds will have a normal C–N bond from the 1-position of the cycloaliphatic group to the 9-position of the purine, it is obvious that this bond will be stable toward hydrolysis in the test animals and, in addition, the cycloaliphatic group should not easily be removed enzymatically. Furthermore, it may be concluded[6] that the substitution of a carbon atom for

(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 Number SA-43-ph-1740.

(2) For Paper XVI of this series, see T. P. Johnston, L. B. Holum and J. A. Montgomery, to be published.

(3) (a) J. A. Johnson, Jr., H. J. Thomas and H. J. Schaeffer, THIS JOURNAL, **80**, 699 (1958); (b) H. J. Schaeffer and H. J. Thomas, *ibid.*, **80**, 3738 (1958).

(4) H. J. Schaeffer and H. J. Thomas, *ibid.*, in press.

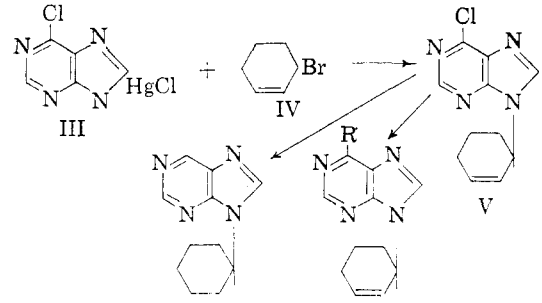
(5) H. E. Skipper and J. R. Thomson, private communication.

(6) A. Maccoll, in W. Klyne, ed., "Progress in Stereochemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1954, pp. 361–365.

the oxygen atom in tetrahydropyran causes only a slight distortion of the ring. Therefore, the preparation of some analogs of I containing a substituted cyclohexyl nucleus will produce compounds which have the same steric size as pyranosylnucleosides. Similar conclusions hold for the 5-membered rings, *i.e.*, the replacement of the sugar moiety in nucleosides (II) by a properly substituted cyclopentyl nucleus will produce analogs of I which have the same steric size as furanosylnucleosides. Initially, we plan to prepare compounds related to structure I in which R_2, R_3 or R_4 may be H or OH. If these compounds exhibit interesting biological activity, we plan to prepare compounds where R_2, R_3 and R_4 may be various combinations of H, OH, NH_2, SH or other related groups. The present paper describes the syntheses of some compounds related to I in which the substituents at the 9-position are the 2-cyclohexenyl, the *trans*-2-hydroxycyclohexyl and the *cis*-2-hydroxycyclohexyl groups.

6-Chloro-9-(2-cyclohexenyl)-purine (V) appeared to be an ideal starting material for the synthesis of compounds related to I, since the double bond in the cyclohexenyl nucleus might offer a convenient entry into the preparation of various mono- and disubstituted cyclohexylpurines, after which the 6-chlorine atom could be caused to undergo nucleophilic substitution. By these procedures, a wide variety of products would be available.

Our initial synthesis of 6-chloro-9-(2-cyclohexenyl)-purine (V) was effected by the condensation of chloromercuri-6-chloropurine (III) with 3-bromocyclohexene (IV) under reaction conditions similar to the conventional nucleoside synthesis.[7a-d] In order to establish whether alkylation had occurred at the 7- or the 9-position of the purine nucleus, the reaction product V was reduced with two moles of hydrogen; the product of catalytic



hydrogenation was 9-cyclohexylpurine (VI), which previously has been prepared in an unambiguous manner by Montgomery and Temple[8] by the cyclization of 5-amino-6-chloro-4-cyclohexylaminopyrimidine with diethoxymethyl acetate, and then catalytic hydrogenolysis of the 6-chlorine atom.

A second synthesis of 6-chloro-9-(2-cyclohexenyl)-purine (V) was found which is more convenient than the first synthesis in that it avoids the necessity of preparing chloromercuri-6-chloropurine[9] (III). The reaction of 6-chloropurine, anhydrous potassium carbonate and 3-bromocyclohexene in dimethylformamide resulted in the formation of a 26% yield of 6-chloro-9-(2-cyclohexenyl)-purine (V).[10] In addition, a second product was isolated from the reaction mixture which was shown to be a cyclohexenyl-6-chloropurine by its infrared and ultraviolet spectra. Since the 9-substituted product V has been identified with certainty, this new product must be 6-chloro-7-(2-cyclohexenyl)-purine.

Treatment of 6-chloro-9-(2-cyclohexenyl)-purine (V) with methanolic ammonia at 100° resulted in the formation of 6-amino-9-(2-cyclohexenyl)-purine (VII). The nucleophilic displacement of the 6-chlorine atom of V with hydrazine, however, occurred at room temperature, and a good yield of 6-hydrazino-9-(2-cyclohexenyl)-purine (VIII) was obtained. 6-Mercapto-9-(2-cyclohexenyl)-purine (IX) was prepared by the reaction of V with thiourea in refluxing *n*-propyl alcohol. The basic hydrolysis of 6-chloro-9-(2-cyclohexenyl)-purine (V) proceeded well, and a good yield of the 6-hydroxy analog X was obtained.

Numerous attempts have been made to prepare some intermediates from 6-chloro-9-(2-cyclohexenyl)-purine (V) by reactions which involve the double bond in the cyclohexenyl nucleus, but, unfortunately, the double bond is extremely unreactive toward several reagents. When V was allowed to react with perbenzoic acid, in an attempt to prepare the corresponding epoxide, over one equivalent of peracid was consumed. However, the reaction mixture was complex, and the desired product could not be isolated. An attempted *cis*-hydroxylation of V with potassium permanganate in acetone resulted in the recovery of unchanged starting material (V). When an attempt was made to *cis*-hydroxylate V by the modification developed by Sarett,[11] there was isolated 6-(N-piperidyl)-9-(2-cyclohexyl)-purine in approximately a 50% yield, in addition to a 10% recovery of unchanged starting material V. The synthesis by different procedures of analogs of I which are disubstituted on the cycloaliphatic group will be the subject of a future paper.

The preparation of the two other key intermediates XIII and XX required for this series of compounds was accomplished by an adaptation of a recently described procedure.[8] 5-Amino-4,6-dichloropyrimidine (XI) was condensed with *cis*- and with *trans*-2-aminocyclohexanols. The resulting 5-amino-4-(substituted amino)-6-chloropyrimidines (XII and XIX), without isolation, were converted to the respective 2-[9-(6-chloropurinyl)]-cyclohexanols (XIII and XX) by the action of diethoxymethyl acetate.[8] From the cyclization of XII with diethoxymethyl acetate, in addition to the desired product XIII, there was isolated a 10% yield of a

(7) (a) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914); (b) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948); (c) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951); (d) H. M. Kissman, C. Pidacks and B. R. Baker, *ibid.*, **77**, 18 (1955).

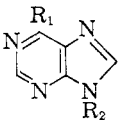
(8) J. A. Montgomery and C. Temple, Jr., *ibid.*, **80**, 409 (1958).

(9) (a) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953); (b) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(10) 6-Chloropurine has been alkylated by a variety of less reactive alkyl halides using dimethylformamide or dimethyl sulfoxide as the reaction solvent; J. A. Montgomery and C. Temple, Jr., *to be published*.

(11) G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, THIS JOURNAL, **76**, 5031 (1954).

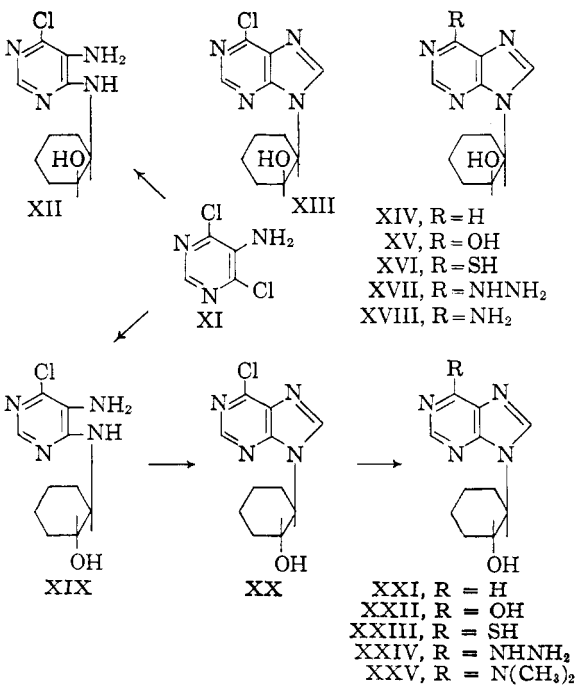
TABLE I



R_2 = 2-Cyclohexenyl, R_1 =	Yield, %	Recrystn. solvent[a]	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Cl	26	A	134–136	56.29	56.51	4.73	4.89	23.87	23.52
SH	96	B	291–294 d.	56.87	56.75	5.21	5.09	24.12	23.90
OH	67	A	261	61.09	61.04	5.59	5.69	25.91	25.81
NH_2	84	B	196	61.37	61.20	6.09	6.15	32.54	32.33
$NHNH_2$	74	C	146	57.37	57.04	6.13	5.88	36.53	36.45
R_2 = *cis*-2-Hydroxycyclohexyl									
Cl	27	A + D	174	52.28	52.43	5.18	5.10	22.17	22.39
SH	57	E	311–315 d.	52.78	52.38	5.64	5.34	22.40	22.68
OH	67	A + D	316–318	56.40	56.06	6.02	5.92	23.92	23.54
NH_2	55	A + F	267	56.63	56.66	6.48	6.55	30.03	29.97
$NHNH_2$	73	A + D	253	53.21	52.81	6.50	6.65	33.85	33.87
H	48	C	163	60.53	60.29	6.47	6.48	25.67	25.60
R_2 = *trans*-2-Hydroxycyclohexyl									
Cl	68	A + B	215 d.	52.28	51.83	5.18	4.99	22.17	22.18
SH	73	D	325–327 d.	52.78	52.68	5.64	5.58	22.40	22.26
OH	53	A or D	325–329 d.	56.40	56.09	6.02	5.59	23.92	23.93
$NHNH_2$[b]	64	A	248[c]	52.26	52.13	6.58	6.43	33.25	33.24
H	58	C	168	60.53	60.88	6.47	6.06	25.67	25.45

[a] A, water; B, methanol; C, benzene; D, methyl Cellosolve; E, precipitated from dil. NaOH with acetic acid; F, ethanol. [b] Calculated as $^1/_4H_2O$. [c] This product melts at 228°, resolidifies and remelts 248°.

second product which was shown to be the acetate of *cis*-2-[9-(6-chloropurinyl)]-cyclohexanol by the presence of absorption in the infrared spectrum at 1710 cm.$^{-1}$ and by its conversion to XIII by reaction with methanolic ammonia at 0°. A similar



product probably was formed in the preparation of the *trans*-purine XX, but no attempt was made to isolate this material. For synthetic purposes, the most convenient reaction conditions for the preparation of XIII or XX consist of the treatment of the crude cyclization product with methanolic ammonia, in order to ensure the highest yield of the desired purines (XIII and XX). The purines XIII and XX were individually converted by known procedures[3,4,8] into analogs in which the 6-position was substituted with a hydrogen, hydroxy, mercapto, hydrazino or amino group. In the case of XX, the corresponding 6-amino analog was not isolated in pure form, but the crude product had the expected spectral properties. The corresponding 6-dimethylamino analog XXV, however, was obtained from XX in high yield.

The pertinent data of the compounds prepared are listed in Table I. Typical examples of the procedures employed for the preparation of these compounds are given in the Experimental section.

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for the microanalytical results reported and to Mr. W. A. Rose and Mr. L. D. Norton for the spectral determinations. The authors wish to express their appreciation to Dr. J. A. Montgomery for his encouragement in this research. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville.

Experimental[12]

6-Chloro-9-(2-cyclohexenyl)-purine (V). a. By Condensation of Chloromercuri-6-chloropurine and 3-Bromocyclohexene.—To an azeotropically dried suspension of 0.749 g. (1.92 mmoles) of chloromercuri-6-chloropurine[9] and 0.746 g.

(12) The ultraviolet spectra were determined in aqueous solution with a Beckman model DK-2 spectrophotometer, and the optical densities were determined with a Beckman DU spectrophotometer. The infrared spectra were determined in a potassium bromide pellet with a Perkin–Elmer model 21 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.

of Celite in 40 ml. of xylene was added 0.33 g. (0.24 ml., 2.0 mmoles) of 3-bromocyclohexene. The mixture, protected with a calcium chloride tube, was heated under reflux for 2.5 hours and filtered. The filter cake was washed with chloroform (15 ml.), and the combined filtrates were concentrated *in vacuo*. A solution of the residue in 10 ml. of hot benzene was washed with 20% potassium iodide solution (3 × 25 ml.), dried with anhydrous magnesium sulfate, concentrated *in vacuo* and gave a yellow crystalline solid: yield 0.21 g. (47%), m.p. 131°. After recrystallization from Skellysolve C, a white crystalline solid was collected and dried over phosphorus pentoxide at 78° and 0.1 mm., yield 0.124 g. (28%), m.p. 136°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 265 (9.93); *p*H 7, 267 (10.0); *p*H 13, 267 (10.0).

b. By Condensation of 6-Chloropurine and 3-Bromocyclohexene in N,N-Dimethylformamide.—To a solution of 0.519 g. (3.36 mmoles) of 6-chloropurine in 10 ml. of N,N-dimethylformamide were added 0.464 g. (3.36 mmoles) of anhydrous potassium carbonate and 0.540 g. (0.386 ml., 3.36 mmoles) of 3-bromocyclohexene; the mixture was stirred for two hours at room temperature while protected with a calcium chloride tube. The mixture was added to 40 ml. of water, and the aqueous solution was extracted with chloroform (3 × 25 ml.). The combined chloroform layers were washed with water (2 × 20 ml.), dried with anhydrous magnesium sulfate, concentrated *in vacuo*, and gave a tan oil, which solidified; yield 0.57 g. (72%), m.p. 90–112°. The crude product was recrystallized from water, and a white crystalline solid was obtained; yield 0.207 g. (26.2%), m.p. 134–136°. A mixed melting point with an authentic sample of 6-chloro-9-(2-cyclohexenyl)-purine prepared by the procedure described above showed no depression.

The filtrate from the recrystallization gave, after concentration, a tan oil which was crystallized from hexane. After several recrystallizations of the crude product from hexane, a pure sample of 6-chloro-7-(2-cyclohexenyl)-purine was obtained; m.p. 79–80°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 267 (8.24); *p*H 7, 269 (8.28); *p*H 13,264 (7.78).

Anal. Calcd. for $C_{11}H_{11}N_4Cl$: C, 56.29; H, 4.73; N, 23.87. Found: C, 56.20; H, 5.21; N, 23.81.

Catalytic Hydrogenation of 6-Chloro-9-(2-cyclohexenyl)-purine.—To a solution of 0.100 g. (0.426 mmole) of 6-chloro-9-(2-cyclohexenyl)-purine in 13 ml. of ethanol and 8 ml. of water were added 52 mg. of magnesium oxide and 49 mg. of 5% palladium-on-charcoal catalyst. The mixture was hydrogenated at room temperature and atmospheric pressure; after 19 minutes, the theoretical amount of hydrogen was absorbed (0.852 mmole). The reaction mixture was filtered through Celite, and the filter cake was washed with hot methanol (3 × 10 ml.). The filtrate was added to 10 ml. of 5% sodium carbonate solution and concentrated *in vacuo* to dryness. The white solid residue was extracted with ether (3 × 25 ml.), and the ether extracts were concentrated *in vacuo* to dryness. Sublimation of the crude product from an oil-bath (80–83°) at 0.1–0.5 mm. gave a white crystalline solid; yield 59 mg. (82%), m.p. 92°. The melting point, mixed melting point, infrared and ultraviolet spectra were identical with an authentic sample of 9-cyclohexylpurine.[8]

***cis*-2-[9-(6-Chloropurinyl)]-cyclohexanol (XIII).**—A mixture of 82.6 g. (0.720 mole) of *cis*-2-aminocyclohexanol and 59.6 g. (0.363 mole) of 5-amino-4,6-dichloropyrimidine in 550 ml. of *n*-butyl alcohol was heated under reflux for 19 hours. The reaction mixture was concentrated *in vacuo*, and the crude 5-amino-6-chloro-4-(*cis*-2-hydroxycyclohexyl)-aminopyrimidine was crystallized from water; yield 60.3 g. (68.4%), m.p. 184°. A solution of 350 ml. of diethoxymethyl acetate and 60.3 g. of crude 5-amino-6-chloro-4-(*cis*-2-hydroxycyclohexyl)-aminopyrimidine was heated at 110° for 3.5 hours, and the volatile materials were removed *in vacuo*. The residual oil was allowed to react overnight at 0° with 350 ml. of an 18% solution of ammonia in methanol. The volatile materials were removed *in vacuo;* the crude product was crystallized from a mixture of methyl Cellosolve and water and gave *cis*-2-[9-(6-chloropurinyl)]-cyclohexanol; yield 29.3 g. (31.9%), m.p. 171–172°. For analysis, a small sample was recrystallized from a mixture of methyl Cellosolve and water; m.p. 174°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 265 (9.66); *p*H 7, 266 (9.67); *p*H 13, 264 (9.02).

***trans*-2[9-(6-Chloropurinyl)]-cyclohexanol (XX).**—A mixture of 118 g. (1.02 moles) of *trans*-2-aminocyclohexanol and 80.0 g. (0.488 mole) of 5-amino-4,6-dichloropyrimidine in 500 ml. of *n*-butyl alcohol was heated under reflux for 6 hours, and then the solution was concentrated *in vacuo* (bath 90°). Diethoxymethyl acetate (500 ml.) was added to the residual gum, and the solution was heated under reflux for 160 min. The volatile materials were removed *in vacuo* (bath 90°); the residual oil was crystallized from 1 l. of water; yield 62.0 g. (50.4%), m.p. 213–214° dec. Concentration of the filtrate gave a second crop of crystals; yield 21.6 g. (17.5%, total yield 67.9%), m.p. 212° dec. One recrystallization from a mixture of methanol and water gave the pure product, m.p. 215° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 266 (9.66), *p*H 7, 266 (9.55); *p*H 13, 266 (9.66).

6-Mercapto-9-(2-cyclohexenyl)-purine (IX).—To a suspension of 4.00 g. (17.0 mmoles) of 6-chloro-9-(2-cyclohexenyl)-purine in 120 ml. of *n*-propyl alcohol was added 1.29 g. (17.0 mmoles) of thiourea. The mixture was heated under reflux for one hour and then cooled in an ice-bath. The light yellow solid was collected by filtration, washed with 20 ml. of cold *n*-propyl alcohol, and dissolved in 90 ml. of 1.0 *N* sodium hydroxide. The solution was filtered, chilled in an ice-bath, and acidified to *p*H 5–6 with 7 ml. of glacial acetic acid. The white product was collected by filtration and dried overnight *in vacuo* over phosphorus pentoxide at 78°; yield 3.79 g. (95.8%), m.p. 290–292° dec. For analysis, a small sample was recrystallized from methanol; m.p. 291–294° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 224 (9.75), 326 (21.0); *p*H 7, 322 (25.0); *p*H 13, 232 (14.5), 311 (23.4).

6-Hydroxy-9-(2-cyclohexenyl)-purine (X).—To a mixture of 1.00 g. (4.28 mmoles) of 6-chloro-9-(2-cyclohexenyl) purine in 60 ml. of water was added 8 ml. of 1.1 *N* sodium hydroxide; the mixture was heated under reflux for four hours. The reaction mixture was decolorized with charcoal, and the filtrate was acidified with acetic acid and cooled. The white solid which precipitated was collected by filtration and air-dried; yield, 623 mg. (67.2%), m.p. 260°. One recrystallization from water gave the analytical sample, m.p. 261°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 250 (11.9); *p*H 7, 251 (12.7); *p*H 13, 255 (13.6).

***cis*-2-[9-(6-Aminopurinyl)]-cyclohexanol (XVIII).**—A solution of 0.559 g. (2.21 mmoles) of *cis*-2-[9-(6-chloropurinyl)]-cyclohexanol in 10 ml. of liquid ammonia was heated in a stainless steel bomb at 50° for 16 hours. The reaction mixture was evaporated in a nitrogen stream, and the crude product was recrystallized from a mixture of ethanol and water; yield 0.281 g. (54.6%), m.p. 263–265°. For analysis, a small sample was recrystallized from a mixture of ethanol and water; m.p. 267°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 260 (14.8); *p*H 7, 261 (15.1); *p*H 13, 261 (15.2).

***cis*-2-[9-(6-Hydrazinopurinyl)]-cyclohexanol (XVII).**—To 3 ml. of anhydrous hydrazine was added over a 2-minute period 0.523 g. (2.07 mmoles) of *cis*-2-[9-(6-chloropurinyl)]-cyclohexanol. The reaction solution was cooled with an ice-bath for one minute and then stirred at room temperature for 2.5 hours. The solid was collected from the cold reaction mixture by filtration, washed with cold *n*-propyl alcohol, and dried at 110° (0.1 mm.) for one hour over phosphorus pentoxide; yield 0.374 g. (72.6%), m.p. 251°. A small sample was recrystallized from a mixture of water and methyl Cellosolve and then sublimed *in vacuo;* m.p. 253°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 263 (16.5); *p*H 7, 267 (15.0); *p*H 13, unstable.

***trans*-2-(9-Purinyl)-cyclohexanol (XXI).**—To 0.989 g. of 5% palladium-on-charcoal catalyst, which was wetted with water, were added 0.453 g. of magnesium oxide and a solution of 4.33 g. (17.1 mmoles) of *trans*-2-[9-(6-chloropurinyl)]-cyclohexanol in 20 ml. of ethanol. The mixture was hydrogenated at atmospheric pressure and room temperature until the theoretical amount of hydrogen was absorbed (approximately 1.5 hours). The catalyst was removed by filtration through a Celite pad, and the filter cake was washed with ethanol (4 × 25 ml.). The filtrate was added to 180 ml. of a 10% aqueous sodium carbonate solution, and the mixture was concentrated *in vacuo* to dryness. The residue was extracted with hot chloroform (3 × 50 ml.); concentration of the chloroform extracts gave a yellow solid; yield 3.51 g. (94.0%), m.p. 163–165°. Alternate recrystallizations from benzene and from dioxane gave a white solid, m.p. 168°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (9.96); *p*H 7, 264 (7.75); *p*H 13, 264 (7.91).

***trans*-2-[9-(6-Dimethylaminopurinyl)]-cyclohexanol (XXV).**—A solution of 0.537 g. (2.12 mmoles) of *trans*-2-[9-(6-chloropurinyl)]-cyclohexanol in 10 ml. of ethanol and 10 ml. of 25% dimethylamine in water was heated under reflux for one hour. Concentration of the reaction solution *in vacuo* left a yellow solid; recrystallization of the crude product from methanol and water gave a white crystalline solid,

which was dried at 100° (0.1 mm.) for 3 hours over phosphorus pentoxide; yield 0.318 g. (57.3%), m.p. 178°; λ_{max} in mμ ($\epsilon \times 10^{-3}$); *p*H 1, 270 (27.0); *p*H 7, 277 (28.3); *p*H 13, 277 (28.2).

Anal. Calcd. for $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N 26.80. Found: C, 60.15; H, 7.64; N, 27.17.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Local Anesthetics. I. Esters of 2-(Dialkylamino)-1-phenylethanols

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The bisesters of succinic, terephthalic and phthalic acids, and the esters of mono-, di- and trichloroacetic acids have been synthesized with the use of alcohols of the type $R_1R_2NCH_2CH(C_6H_5)OH$ and these esters have been examined for pharmacological activity. The bisesters derived from succinic acid were potent anesthetic agents and showed curarimimetic activity.

This paper evaluates the effect of substitution of $R_1R_2NCH_2CH(C_6H_5)$–[1] groups for $R_1R_2NCH_2CH_2$– in pharmacologically active systems in compounds of the type I and II

$$Y\begin{matrix}\diagup \text{COOCH}(C_6H_5)CH_2NR_1R_2 \\ \diagdown \text{COOCH}(C_6H_5)CH_2NR_1R_2\end{matrix}$$

I

$$X_3CCOOCH(C_6H_5)CH_2NR_1NR_2$$

II

where Y is a residue derived from a dicarboxylic acid such as succinic, phthalic and terephthalic acid, and X_3C– represents mono-, di- and trichloromethyl groups.

Although esters of aliphatic acids[2] have generally been associated with poor anesthetic efficiency, it was of interest to explore the bisesters derived from succinic acid, particularly since the bismethyl quaternaries of structure I would be structural analogs of the clinically effective muscle relaxant, succinylcholine.[3,4]

Selected bisesters of terephthalic acid[5] have shown anesthetic potencies comparable to procaine, and similar compounds were prepared in this series. Finally, the effect of a small "fat soluble," aliphatic, hydrophobic[6] group as provided by the X_3C– substituent, was evaluated in preparation of products of the type II.

The compounds prepared of type I are described in Table I, and those of type II in Table II.

The synthesis of the compounds listed in Table I proved to be unexpectedly difficult. In general, yields were poor, ranging from 4–41%. Method A entailed treatment of succinyl chloride with the requisite 2-dialkylamino-1-phenylethanol[1] in benzene, while method B utilized the more polar solvent, acetonitrile. Method C utilized condensation of the amino alcohol with phthalic anhydride and subsequent conversion to the bisester with hydrogen chloride. Method D employed the procedure of Fusco, *et al.*,[7] wherein the hydrochloride of the amino alcohol was allowed to react with succinyl chloride in refluxing chlorobenzene.

The esters of the chloroacetic acids (II) formed readily from the corresponding acid chlorides and were obtained in 50–65% yields.

The compounds were studied for anesthetic potency using the method of Chance and Lobstein,[8] and for curare-like action using the method of Chou.[9] It was of particular interest to establish whether or not a compound would exhibit both an anesthetic and a curare effect. The pharmacological findings are reported in Table III.

In view of the marked enhancement in toxicity noted with the bis-quaternaries (compounds 5 and 6 *vs.* 4, 12 *vs.* 11), this phase of the work was not explored too extensively.

The derivatives of succinic acid (compounds 1, 4) showed excellent anesthetic activity, relative to that noted with xylocaine, while compound 3 was approximately equal to xylocaine in contrast to the derivatives of the aromatic dicarboxylic acids, which were without anesthetic effect (compounds 9, 10, 11). Compounds 1 and 4 showed good curare activity and thus make available compounds which showed both anesthetic and curare-like properties. Compound 5, the methobromide of compound 4, also showed curare-like properties but, interestingly, while it was far more toxic, it required higher levels for the curare ED_{30} than the non-quaternized structure.

The findings of significant curare-like activity in bis-tertiary amino esters is in direct contrast to the presumptive requirement of a bis-onium structure.[10,11]

The esters of the chloroacetic acids (Table II) were without significant anesthetic activity.

Experimental[12]

Di-(2-[N-isopropyl-N-methylamino]-1-phenylethyl) Succinate. Method A (Table I, Compound 2).—A solution of 7.7 g. (0.04 mole) of 2-(N-isopropyl-N-methylamino)-1-

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(12) Data shown in Table I are not reproduced in the Experimental section. Typical preparations are described.