Cyclopenta[f]isoquinoline Derivatives Designed to Bind Specifically to Native Deoxyribonucleic Acid. 1. Synthesis of 3-Ethoxy-8-methyl-7(5)H-cyclopenta[f]isoquinoline[1,†]

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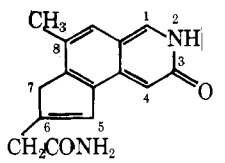
By the use of space-filling models, a novel compound, 6-carbamylmethyl-8-methyl-7(5)H-cyclopenta[f]isoquinolin-3-(2H)-one was devised which would be expected to hydrogen bond specifically to GC pairs in the major groove of the double helix such that (i) the amino group of the cytosine molecule donates a hydrogen bond to the C-3 carbonyl of the isoquinoline moiety and (ii) the amide proton of the side chain donates a hydrogen bond to the N-7 of guanine. 3-Ethoxy-8-methyl-7(5)H-cyclopenta[f]isoquinoline (4) which constitutes the basic ring system of 1 was synthesized in a multistep procedure starting from m-methyl-N-acetylbenzylamine (5). Friedel–Crafts reaction of 5 led to 2,4-bis(chloromethyl)-5-methyl-N-acetylbenzylamine (6) which on treatment with KCN, hydrolysis of the resultant nitrile, and subsequent esterification afforded 6-carbethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (9). Treatment of 9 with triethyloxonium fluoborate followed by dehydrogenation of the product gave 6-carbethoxymethyl-3-ethoxy-7-methylisoquinoline (14). Chain extension of 14 followed by cyclization led to 3-ethoxy-8-methyl-5,6-dihydro-7H-cyclopenta[f]isoquinolin-5-one (19) which on reduction and subsequent dehydration yielded 3-ethoxy-8-methyl-7(5)H-cyclopenta[f]isoquinoline (4).

Many antibiotics bind to cellular DNA in various ways and thereby produce profound biochemical, pharmacological, and chemotherapeutic effects.[2-15] It was of interest to devise *ad hoc*, by the use of space-filling models, a synthetic compound that would be expected (1) to hydrogen bond specifically to guanine–cytosine (GC) pairs in the major groove, across the double helix of DNA; (2) not to be electrostatically attracted to the phosphates of the backbone; and (3) to stack parallel to the base pairs. As shown in Figure 1, the cyclopenta[f]isoquinoline derivative 1 fulfills these criteria on the model, such that the amino proton of cytosine donates a hydrogen bond to the C-3 carbonyl group of the isoquinoline and the amide proton of the side chain donates a hydrogen bond to the N-7 of guanine. This compound, 1, has a novel ring system and does not resemble in structure any of the known DNA-binding antibiotics.



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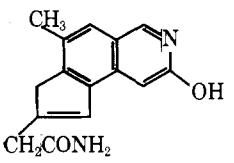

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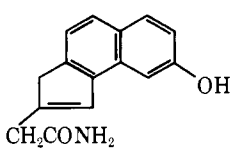

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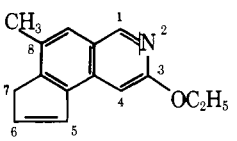

4

Similarly, structure 2, which is the lactim form of 1 and structure 3, the carbocyclic equivalent of 1, from model studies, should bind to adenine–thymine (AT) pairs of DNA such that the C-3 hydroxyl group of 2 or 3, donates a hydrogen bond to the C-4 carbonyl group of thymine and the amide proton of the side chain donates a hydrogen bond to the N-7 of adenine. In order to test these hypotheses, it was desirable to synthesize compounds 1, 2, and 3 and study their interaction with DNA's and poly(deoxyribonucleotides). In the first paper of the series we describe the synthesis of compound 4, which constitutes the basic skeleton of compounds 1 and 2. Some biological properties of 4 and of some of the intermediates involved in its synthesis are also described.

Chemistry. In order to synthesize compound 4, two alternative approaches seemed feasible. One could start with a suitably substituted indene derivative and then build up the isoquinoline moiety, or, from a properly substituted isoquinoline derivative, one could build up the indene part of the molecule. Because of the known chemical[16] and photochemical[17] reactivities of indenes and their tendency to polymerize,[18] the latter approach seemed preferable.

A successful procedure for the synthesis of 4 was developed according to that shown in Chart I. m-Methyl-N-acetylbenzylamine (5), prepared by hydrogenation of commercially available m-toluonitrile following a procedure similar to that of Rupe and Bernstein,[19] was refluxed for 20 hr with excess chloromethyl methyl ether[20] in the presence of anhydrous aluminum chloride to yield 2,4-bis(chloromethyl)-5-methyl-N-acetylbenzylamine (6). The formation of the bis-substituted product instead of the monosubstituted derivative was fortunate, since it not only provided us with proper substituents to build the isoquinoline moiety but also has an additional side chain in the C-6 position of the resultant isoquinoline derivative with which to build the cyclopentane ring. The structure of the Friedel–Crafts product was unequivocally established by its conversion to the known tetramethyl benzene-1,2,4,5-tetracarboxylate (8) by hydrolysis and subsequent oxidation and esterification.

In order to build the isoquinoline ring, 2,4-bis(chloromethyl)-5-methyl-N-acetylbenzylamine (6) was refluxed with potassium cyanide in water–ethanol (3:25) to yield the corresponding cyano compound 7 which on hydrolysis with hydrochloric acid, esterification, and subsequent adjustment of the aqueous ester solution to pH 8 afforded the lactam 9. Dehydrogenation of the lactam with sulfur or palladium/charcoal in diisopropylbenzene gave the isoquinolone 10. Lactam–lactim tautomerism[21] has been observed in the case of nitrogen heterocycles with a hydroxyl group α to the nitrogen. Thus, 3-hydroxyisoxazoles[21] (21) and 3-hydroxypyrazoles[22,23] (22) exist mainly as lactims in nonhydroxylic solvents such as cyclohexane or chloroform; in water or alcohol they are mixtures of comparable concentrations of lactim and lactam. 3-Hydroxyisoquinoline[24,25] was found to be exclusively lactam in water and almost exclusively lactim in diethyl ether, whereas in ethanol it existed as a mixture of the two forms. From uv spectral stud-

† The compound synthesized is a mixture of 7H and 5H isomers; only the structure corresponding to the 7H isomer is shown in the paper. This work was supported in part by Grant CA-07175 from the National Cancer Institute, National Institutes of Health.

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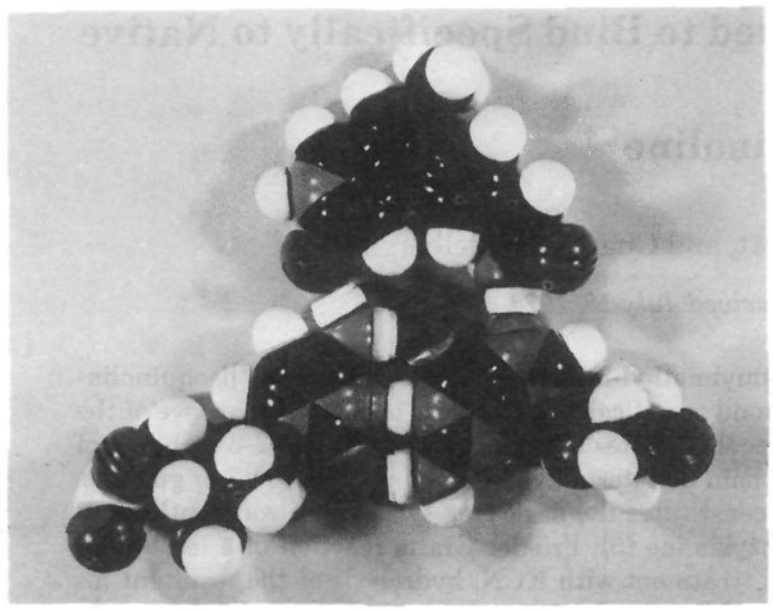
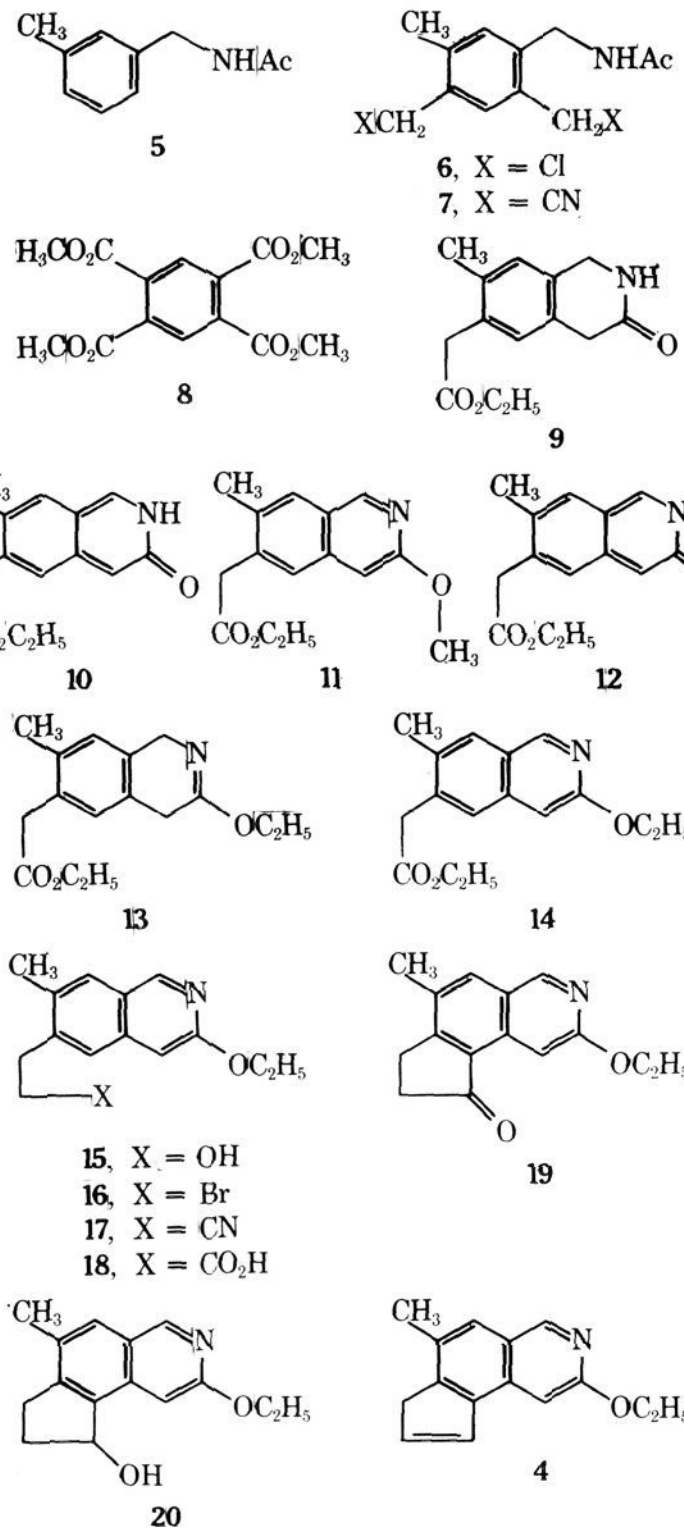


Figure 1. CPK model of the complex between a GC pair of DNA and a cyclopenta[*f*]isoquinoline derivative 1.

Chart I



ies, we found that 6-carbethoxymethyl-3-hydroxy-7-methylisoquinoline exists predominantly in the lactam form (**10**) in aqueous solution but that in 95% ethanol it is a mixture of lactim and lactam isomers. In ether, however, it exists as the lactim form only (see Table I). It is seen from

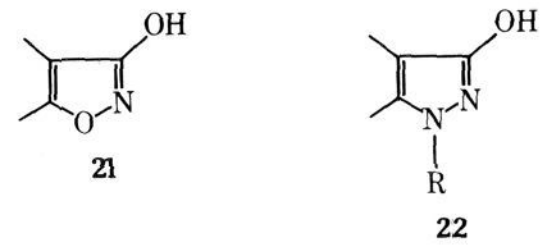


Table I that the highest wavelength absorption for the lactam is around 417 nm whereas that for the lactim lies around 355 nm. The lactam tautomers, in general, since they possess the unstable *o*-quinonoidal structure, are fairly labile[24,26,27] and are good substrates for the Diels–Alder reaction.[28] They dimerize photochemically[29–33] and are known to undergo oxidation in air.[34] Thus, to avoid undesirable reactions during the further building up of the cyclopentene ring, it seemed desirable to stabilize the isoquinoline ring by *O*-alkylation or acylation. Compound **10** could be readily acetylated to the *O*-acetate; however, the *O*-acetate proved very susceptible to hydrolysis. Alkylation, therefore, appeared to be the best method for the protection of the isoquinoline ring. Use of conventional reagents[35] such as methyl iodide or dimethyl sulfate in a variety of solvents and bases invariably led to a mixture of *N*-methyl and *O*-methyl derivatives in which the former predominated. Similarly, treatment with diazomethane in ether[25] gave the *O*-alkyl and *N*-alkyl compounds in the proportions of 1:2.

A more convenient reagent for O-alkylation was found to be triethyloxonium fluoborate.[36] Treatment of **9** with triethyloxonium fluoborate in anhydrous methylene chloride gave 70–85% of the corresponding imino ether **13** which was susceptible to air oxidation and was, therefore, dehydrogenated immediately with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[37] in benzene at room temperature for 10 min. 6-Carbethoxymethyl-3-ethoxy-7-methylisoquinoline (**14**) was obtained in 60% yield as colorless crystals after chromatography over alumina (Merck, 6% water; eluent benzene) and subsequent crystallization from cyclohexane.

The ester **14** was reduced with lithium aluminum hydride in tetrahydrofuran to the corresponding alcohol **15** which on shaking with excess phosphorus tribromide at room temperature for 4 days yielded the corresponding bromide **16.** Reaction of the bromide **16** with magnesium, followed by addition of solid carbon dioxide, failed to give appreciable yields of the expected product (**18**), despite the use of the so-called "entrainment procedure",[38] as used for less reactive alkyl halides. However, the bromide **16,** on reaction with sodium cyanide in dimethylformamide, was easily converted into the corresponding nitrile **17** which on hydrolysis with concentrated hydrochloric acid yielded the acid **18.** Cyclization of **18** with fluorosulfonic acid[39] gave the ketone **19** as light yellow plates. Reduction of the ketone with sodium borohydride and subsequent dehydration of the reduced product **20** with *p*-toluenesulfonic acid in xylene yielded 3-ethoxy-8-methyl-7(5)*H*-cyclopenta[*f*]isoquinoline (**4**). The appearance of two aromatic methyl signals in the nmr shows that **4** may be, at least in solution, a mixture of 7*H* and 5*H* isomers.

Biological Results. The following compounds were tested as growth inhibitors of the following tumor cell lines in culture, according to the previously described assay procedures:[40] HeLa, **9** and **10;** L-5178Y, **4.** None of the compounds showed significant activity in 10^{-5} *M* concentrations. However, compound **6** (10^{-5} *M*) showed more than 60% inhibition of growth in the HeLa cel system.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The uv spectra were record-

Table I. Uv Spectra of 3-Hydroxyisoquinoline and Its Derivatives

Compound	Solvent	λ max, nm (ε)				
3-Hydroxyisoquinoline[a]	Absolute ethanol	405 (1970)	344 (2100)			
	95% ethanol	405 (2560)	347 (1720)			
	Ether		341 (3560)			
3-Methoxyisoquinoline[a]	Absolute ethanol		339 (3660)			
2-Methylisoquinolin-3-one[a]	Absolute ethanol	410 (4490)				
6-Carbethoxymethyl-3-hydroxy-7-methylisoquinoline	Water	400 (4260)			275 (4160)	235 (68,400)
	95% ethanol	410 (3090)	355 (2370)			235 (69,000)
	Chloroform	417 (1030)	345 (2750)			
	Ether		343 (2500)	343 (2520)	277 (2370)	
6-Carbethoxymethyl-3-methoxy-7-methylisoquinoline	95% ethanol		350 (2730)	333 (2420)	263 (4150)	230 (54,800)
	Ether		350 (3960)	333 (3830)	263 (4920)	230 (63,800)
6-Carbethoxymethyl-3-ethoxy-7-methylisoquinoline	95% ethanol		350 (3650)	340 (3670)	264 (4740)	232 (90,400)
	Ether		350 (3190)	340 (3160)	264 (4200)	232 (113,200)

[a] From literature, see ref 26.

ed on a Beckman DB-G and quantitative measurements were done on a Gilford 2400-S. Spectra were usually taken in 95% ethanol unless otherwise mentioned. The ir spectra were taken on a Beckman IR-10 as KBr plates. Nmr spectra (reported in δ) were recorded on a Perkin-Elmer R-12 in deuteriochloroform using tetramethylsilane as internal reference. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or Spang Microanalytical Laboratory, Ann Arbor, Mich. All analytical results were within 0.4% of the theoretical values.

m-Methyl-N-acetylbenzylamine (5). m-Toluonitrile (Aldrich) (38 g, 0.33 mol) was dissolved in 100 ml of acetic anhydride in a Parr hydrogenation bottle and 3 tbs of Raney nickel catalyst (No. 28, W. R. Grace Co., S. Pittsburg, Tenn.) was added. Hydrogenation was carried out in a Parr hydrogenation apparatus at 50° and 50 lb of pressure and was complete in 3 hr. The mixture was cooled and filtered from the catalyst, and the acetic acid–acetic anhydride mixture was evaporated under reduced pressure. The residual colorless oil was distilled to give 30 g (0.18 mol, 54%) of **5**: bp 160–165° (1 mm); nmr 1.83 (s, 3 H), 2.26 (s, 3 H), 4.25 (d, 2 H), 7.2 (m, 4 H), 7.5 (br, 1 H).

2,4-Bis(chloromethyl)-5-methyl-N-acetylbenzylamine (6). m-Methyl-N-acetylbenzylamine (**5**, 30 g, 0.18 mol) was dissolved in 300 g (3.73 mol) of chloromethyl methyl ether (Aldrich) with stirring. The hydrochloride of the amide precipitated. Anhydrous aluminum chloride (50 g, 0.38 mol) was then added little by little with stirring and cooling. At the beginning the reaction was rather violent and there was a momentary brown color which later disappeared. After all of the aluminum chloride had been added, the mixture was refluxed overnight with stirring, was reduced to ⅔ vol by distillation of some of the solvent, cooled, and poured onto ice water. The white precipitate was collected by filtration and dried *in vacuo* at 30–40° over NaOH to give 40 g (0.15 mol, 83%) of 2,4-bis(chloromethyl)-5-methyl-N-acetylbenzylamine (**6**) which crystallized from acetone: mp 174–176°; nmr 2.2 (s, 3 H), 2.5 (s, 3 H), 4.6 (s, 2 H), 4.7 (s, 2 H), 4.5 (d, 2 H), 7.2 (br s, 1 H), and 7.1 (br s, 1 H). *Anal.* ($C_{12}H_{15}NOCl_2$) C, H, N, Cl.

Conversion of 2,4-Bis(chloromethyl)-5-methyl-N-acetylbenzylamine (6) to Tetramethyl Benzene-1,2,4,5-tetracarboxylate (8). 2,4-Bis(chloromethyl)-5-methyl-N-acetylbenzylamine (**6**, 2 g, 0.01 mol) was refluxed with a solution of NaOH (10 g, 0.25 mol) in H_2O (10 ml) and dioxane (100 ml) for 24 hr. The residue after the removal of solvent was treated with H_2O and extracted with $CHCl_3$; the $CHCl_3$ layer was dried and solvent was removed, giving 1.9 g (6 mmol), 58%) of a white residue. The crude diol (1.5 g) was refluxed with concentrated HNO_3 (5 ml) and H_2O (20 ml) for 4 hr, and the material was dried under vacuum. It was then treated with NaOH (1 g, 0.02 mol) and H_2O (20 ml) and brought to a boil, 6 g of $KMnO_4$ (0.04 mol) was added portionwise, and the mixture was then refluxed for 2 hr. Excess $KMnO_4$ decomposed with EtOH and the mixture was filtered. The filtrate was concentrated and the residue strongly acidified with HCl, whereupon a white solid separated, which was filtered and dried. This was esterified with MeOH–H_2SO_4. After the usual work-up and crystallization from MeOH, tetramethyl benzene-1,2,4,5-tetracarboxylate (**8**) was obtained: mp 142–143° (lit.[41] mp 143–144°); mixture melting point with an authentic sample remained undepressed and the ir spectra were identical.

2,4-Bis(cyanomethyl)-5-methyl-N-acetylbenzylamine (7). 2,4-Bis(chloromethyl)-5-methyl-N-acetylbenzylamine (**6**, 26 g, 0.10 mol) was added to a solution of 15 g (0.23 mol) of KCN in 30 ml of H_2O and 250 ml of ethanol. The mixture was stirred and boiled under reflux for 24 hr and filtered, and the filtrate was evaporated to dryness. The residue was treated with H_2O and $CHCl_3$ (3 × 100 ml). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated to yield 23 g (0.096 mol, 96%) of 2,4-bis(cyanomethyl)-5-methyl-N-acetylbenzylamine (**7**), which was crystallized from ethanol as white needles: mp 143–144°. *Anal.* ($C_{14}H_{15}N_3O$) C, H, N.

6-Carbethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (9). 2,4-Bis(cyanomethyl)-5-methyl-N-acetylbenzylamine (0.10 mol) was refluxed in 400 ml of concentrated HCl for 6 hr. HCl and H_2O were removed under vacuum. The residue was then dissolved in a mixture of EOH (500 ml) and concentrated H_2SO_4 (10 ml) and refluxed overnight. EtOH was removed, and the residue was dissolved in H_2O (50 ml), and, after cooling, a saturated solution of sodium carbonate was added until the pH became 8. The solution was stirred for 1 hr, when a solid separated; this was filtered and washed with cold EtOH to yield 12 g (0.05 mol, 50%) of a white solid, which was crystallized from ethanol to give light yellow needles of 6-carbethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**9**): mp 164–166°; ν max 1725, 1670 cm^{-1}; nmr 1.24 (t, 3 H), 2.27 (s, 3 H), 3.5 (br s, 2 H), 3.57 (s, 2 H), 4.13 (q, 2 H), 4.43 (br, 2 H), 6.95 (s, 2 H), 7.43 (br, 1 H). *Anal.* ($C_{14}H_{17}NO_3$) C, H, N.

6-Carbethoxymethyl-3-hydroxy-7-methylisoquinoline (10).
(a) Sulfur Dehydrogenation Method. 6-Carbethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**9**) (1.0 g, 4.05 mmol) and 0.25 g (7.93 mmol) of sulfur were mixed and heated in a sublimation tube at 180–185° in a Wood's metal bath at 50 mm pressure for 15 min and at 1–2 mm of pressure and 240–250° for a further 15 min. The sublimed product was 0.85 g. This was chromatographed through a Florisil column (100–200 mesh) which was eluted with 300 ml of chloroform which contained mostly unchanged tetrahydro derivative and some sulfur, then with 100 ml of a chloroform–methanol 8:2 mixture, 100 ml of a chloroform–methanol 7:3 mixture, and finally with methanol. (The aromatized compound has a brilliant yellow color, while the tetrahydro compound is colorless.) The aromatized compound gives a very strong ferric chloride test (dark purple color) while the tetrahydro derivative does not. The yellow fractions (chloroform–methanol eluents) were combined and evaporated to dryness. The residue was then crystallized from ether to give 0.40 g (1.63 mmol, 40%) of pure 6-carbethoxymethyl-3-hydroxy-7-methylisoquinoline (**10**): mp 238–240°; λ_{max} (95% EtOH) 410 (3090), 355 (2370), 235 (69,900); λ_{max} (H_2O) 400 (4260), 275 (4160), 235 (68,400); nmr 1.25 (t, 3 H), 2.3 (s, 3 H), 3.7 (s, 2 H), 4.1 (q, 2 H), 6.8 (s, 1 H), 7.4 (s, 1 H), 7.5 (s, 1 H), 8.5 (s, 1 H). *Anal.* ($C_{14}H_{15}NO_3$) C, H, N.

(b) Palladium/Charcoal Dehydrogenation Method. 6-Car-

bethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**9**, 10 g, 0.04 mol) was refluxed for 1.5 hr with Pd/C (5 g) in diisopropylbenzene. The mixture was filtered hot and cooled to room temperature, when a yellow solid (5.7 g, 0.02 mol, 57%) separated. The material was purified by chromatography as above and had identical melting point and mixture melting point to the sample made by the sulfur dehydrogenation method.

Reaction of 6-Carbethoxymethyl-3-hydroxy-7-methylisoquinoline (10) with Diazomethane. 6-Carbethoxymethyl-3-hydroxy-7-methylisoquinoline (**10**) was treated with excess of diazomethane in ether and the mixture allowed to stand for 20 hr. Excess diazomethane was decomposed with acetic acid and the ether was removed. The residue on chromatography over Florisil [eluent $CHCl_3$, $CHCl_3$–MeOH(10:1)] yielded fractions containing 11 and 12 in the ratio of 1:2. Fractions containing 11 were combined, evaporated to dryness, and crystallized from Skellysolve **B** to yield 6-carbethoxymethyl-3-methoxy-7-methylisoquinoline as small white needles: mp 57–58°; λ_{max} 350 (2730), 333 (2420), 263 (4150), 230 (54,800); nmr 1.25 (t, 3 H, J = 7 Hz), 2.42 (s, 3 H), 3.75 (s, 2 H), 4.0 (s, 3 H), 4.12 (q, 2 H, J = 7 Hz), 6.9 (s, 1 H), 7.5 (s, 1 H), 7.62 (s, 1 H), 8.8 (s, 1 H). *Anal.* ($C_{15}H_{17}NO_3$) C, H, N. Due to its instability, the *N*-methyl compound **12** could not be crystallized.

6-Carbethoxymethyl-3-ethoxy-7-methyl-1,4-dihydroisoquinoline (13). To a solution of freshly prepared triethyloxonium fluoborate (30 g, 0.16 mol) in 60 ml of anhydrous CH_2Cl_2, a solution of the lactam **9** (5 g, 0.02 mol) in 75 ml of CH_2Cl_2 was added. The mixture was stirred overnight at room temperature; then 50% aqueous K_2CO_3 was added cautiously until no further effervescence occurred. The mixture was filtered and the filtrate dried ($MgSO_4$) and evaporated to dryness *in vacuo*, leaving the product as a cream-colored solid (4.7 g, 0.017 mol, 85%) which was crystallized from Skellysolve B as a white fluffy solid: mp 95–96°. *Anal.* ($C_{16}H_{21}NO_3$) C, H, N.

6-Carbethoxymethyl-3-ethoxy-7-methylisoquinoline (14). A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 5 g, 0.02 mol) in 65 ml of benzene was added dropwise with stirring to a solution of the imino ether **13** in 75 ml of benzene. Each addition of the DDQ produced a transient blue coloration, and addition was stopped when this no longer occurred. Stirring was continued for 10 min; then the solution was filtered through Celite to remove dihydro-DDQ and the clear filtrate passed through a column of alumina (Merck, deactivated with 6% H_2O, 150 g), eluting with more benzene. Combined benzene layers on evaporation yielded **14** (95%). This was crystallized from cyclohexane as small colorless needles: mp 86–87°; nmr 1.25 (t, 3 H, J = 8 Hz), 1.45 (t, 3 H, J = 7 Hz), 2.45 (s, 3 H), 3.78 (s, 2 H), between 4.05 and 4.6 (two overlapping quartets, 4 H), 6.98 (s, 1 H), 7.58 (s, 1 H), 7.72 (s, 1 H), 8.92 (s, 1 H). *Anal.* ($C_{16}H_{19}NO_3$) C, H, N.

3-Ethoxy-6-(β-hydroxyethyl)-7-methylisoquinoline (15). A suspension of $LiAlH_4$ (890 mg, 0.02 mol) in 200 ml of anhydrous tetrahydrofuran was refluxed 30 min, and a solution of the ester **14** (4.93 g, 0.02 mol) in 80 ml of THF was added dropwise to the hot suspension. After cooling, 5 ml of ethyl acetate was added dropwise to remove excess $LiAlH_4$, the mixture was filtered through Celite, and the filtrate evaporated to dryness *in vacuo*. The residue was partitioned between 0.1 *N* H_2SO_4 (250 ml) and chloroform (150 ml). The aqueous layer was neutralized with sodium bicarbonate and then extracted with three further 150-ml portions of chloroform. The combined chloroform layers were dried ($MgSO_4$) and evaporated to dryness *in vacuo*, giving the product as a yellow gum (90%). *Anal.* ($C_{14}H_{17}NO_2$) N.

6-(β-Bromoethyl)-3-ethoxy-7-methylisoquinoline (16). A suspension of the alcohol **15** (2.0 g, 8.65 mmol) in redistilled PBr_3 (12 ml) was shaken for 4 days at room temperature (absence of moisture). The resulting suspension was poured cautiously onto 600 ml of ice-cold saturated $NaHCO_3$ solution with vigorous stirring. The aqueous solution was rapidly extracted with ice-cold chloroform (3 × 75 ml), and the chloroform extracts were washed with bicarbonate (100 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The syrupy residue crystallized on standing (55%). This was further crystallized from $CHCl_3$ to a light yellow solid: mp 221–222°. Due to decomposition of the compound, no satisfactory analysis could be obtained.

6-(β-Cyanoethyl)-3-ethoxy-7-methylisoquinoline (17). A mixture of the bromo compound **16** (1.58 g, 5.37 mmol), NaCN (5.2 g, 0.11 mol), and anhydrous DMF (50 ml) was refluxed for 1 hr, then cooled to room temperature, and diluted with a mixture of water (200 ml) and ether (200 ml). The aqueous layer was extracted twice more with 100 ml of ether, and the combined ether layers were washed with water (150 ml), dried ($CaCl_2$), and evaporated to dryness *in vacuo*, leaving the product (**17**) as a crystalline residue (90%). This was crystallized from ethanol as white needles: mp 113–114°; ν_{max} 2240 cm^{-1}. *Anal.* ($C_{15}H_{16}N_2O$) C, H, N.

6-(β-Carboxyethyl)-3-ethoxy-7-methylisoquinoline (18). A mixture of the nitrile **17** (1.21 g, 5.04 mmol) and concentrated HCl (5 ml) was refluxed for 1 hr. After cooling to 5–10° overnight, the crystalline product was filtered, washed with a little cold water, and dried (80%): mp 188–190°; ν_{max} 1720 cm^{-1}. *Anal.* ($C_{15}H_{17}NO_3$) C, H, N.

3-Ethoxy-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinolin-5-one (19). A solution of the acid **18** (0.90 g, 3.47 mmol) in anhydrous fluorosulfonic acid (6 ml) was allowed to stand 6 hr at room temperature and then was added cautiously to a well-stirred, ice-cold saturated $NaHCO_3$ solution (600 ml). The precipitated solid was filtered, washed with a little water, and dried to give **19** (75%), which crystallized from ethanol in small, pale yellow plates: mp 167°; ν_{max} 1690 cm^{-1}; λ_{max} 356 (6960), 308 (5100), 295 (5000), 262 (11,000); nmr 1.5 (t, 3 H, J = 7 Hz), 2.42 (s, 3 H), between 2.6 and 3.2 (m, 4 H), 4.42 (q, 2 H, J = 7 Hz) 7.75 (s, 1 H), 8.15 (s, 1 H), 8.83 (s, 1 H). *Anal.* ($C_{15}H_{15}NO_2$) C, H, N.

3-Ethoxy-5-hydroxy-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinoline (20). To a solution of $NaBH_4$ (800 mg, 0.021 mol) in 150 ml of EtOH, the ketone **19** (700 mg, 2.9 mmol) was added and the mixture stirred at room temperature for 6 hr. The solution was diluted with 50 ml of H_2O, and EtOH was removed under reduced pressure, when a cream-colored solid separated. This was filtered and crystallized from benzene to yield 700 mg (2.88 mmol, 99.3%) of fine white crystals of **20**: mp 163–164°; ν_{max} 3200, 1630; λ_{max} 270 (1560), 278 (1380), 333 (1370). *Anal.* ($C_{15}H_{17}NO_2$) C, H, N.

3-Ethoxy-8-methyl-7(5)*H*-cyclopenta[*f*]isoquinoline (4). A hot solution of **20** (2.95 g, 12 mmol) in 800 ml of xylene was treated with *p*-toluenesulfonic acid (400 mg, 2.32 mmol) and the mixture was stirred and refluxed under N_2 for 3 hr. Xylene was removed under reduced pressure, and the residue was treated with 50 ml of NaOH (2 *N*) and extracted with $CHCl_3$. The residue obtained after removal of $CHCl_3$ was chromatographed on Florisil (eluent $CHCl_3$). The first fractions on evaporation afforded 2.1 g (9.32 mmol, 77.7%) of **4** as a light brown solid. Crystallization from Skellysolve B yielded fine light yellow needles: mp 81–82°; ν_{max} 1630 cm^{-1}; λ_{max} 353 (4080); nmr 1.45 (t, 3 H, J = 7 Hz), 2.4, 2.5 (s, 3 H, 2:1, $ArCH_3$) 3.33, 3.50 (m, 2 H, 2:1, $ArCH_2C{=}C$), 4.4 (q, 2 H, J = 7 Hz), between 6.5 and 8.9 (5 H). *Anal.* ($C_{15}H_{15}NO$) C, H, N.

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Cyclopenta[*f*]isoquinoline Derivatives Designed to Bind Specifically to Native Deoxyribonucleic Acid. 2. Synthesis of 6-Carbamylmethyl-8-methyl-7(5)*H*-cyclopenta[*f*]isoquinolin-3(2*H*)-one† and Its Interaction with Deoxyribonucleic Acids and Poly(deoxyribonucleotides)‡

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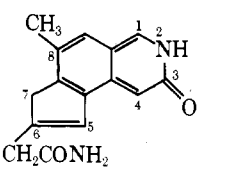
3-Ethoxy-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinolin-5-one (2) was converted to 6-carbethoxymethyl-3-ethoxy-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinolin-5-one (6) through an oxalyl derivative. Treatment of 6 with ammonia gave the corresponding amide 7 which on sodium borohydride reduction and subsequent dehydration yielded 6-carbamylmethyl-3-ethoxy-8-methyl-7(5)*H*-cyclopenta[*f*]isoquinoline (9). The analogous ester 10 was similarly obtained from 6. Numerous attempts to dealkylate the 3-ethoxy group of 9 or 10 failed. However, 6 could easily be dealkylated on heating with 25% hydrochloric acid in a sealed tube. The ester, 6-carbethoxymethyl-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinoline-3(2*H*),5-dione (11), so obtained was converted to the corresponding amide 12 which on reduction with sodium borohydride and subsequent dehydration afforded the desired compound, 6-carbamylmethyl-8-methyl-7(5)*H*-cyclopenta[*f*]isoquinolin-3-(2*H*)-one (1). 1 was found to be mildly cytotoxic against L5178Y mouse leukemia cells in culture. 1 was also found to bind to native calf thymus DNA. 1 inhibited RNA synthesis by a DNA-dependent RNA polymerase and a higher inhibition of RNA synthesis was observed when poly(dG-dC) was used as a template than when poly(dA-dT) was used. A significant increase of thermal transition temperature of calf thymus DNA and poly(dG) · poly(dC) was observed in the presence of 1. The accumulated evidence demonstrates that 1 interacts weakly with calf thymus DNA and interacts preferentially with poly(deoxyribonucleotides)-containing GC pairs.

In the preceding paper,[1] we have described how the compound of structure 1 could bind to guanine–cytosine (GC) pairs of a DNA double helix by hydrogen bond formation. Starting from *m*-methyl-*N*-acetylbenzylamine we have described a multistep synthesis of 3-ethoxy-8-methyl-5,6-dihydro-7*H*-cyclopenta[*f*]isoquinolin-5-one (2) and the corresponding unsaturated compound 3 which constitute the basic skeleton of 1.

In this paper we report the synthesis of compound 1 and its binding to DNA. In order to synthesize 1, it seemed preferable to put the side chain at the C_6 position on compound 2, in the first place, followed by dealkylation. Attempts at the direct alkylation of 2 were not very success-



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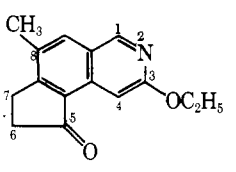

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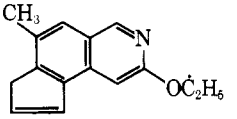

3

† The compound synthesized is a mixture of 7*H* and 5*H* isomers; only the structure corresponding to the 7*H* isomer is shown in the paper.

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