(Et_2O), yielding 0.17 g of the diamine **7**, as a colorless product, mp 37–41°; **picrate,** mp 226–228° dec (absolute EtOH). *Anal.* ($C_{34}H_{44}N_8O_{14}$) C, H.

B. From the Diamide 8.—Reduction of the dipiperidide **8**[20] (0.2 g) with $LiAlH_4$ by the same procedure as above gave 0.15 g of a colorless product, mp 38–41°; **picrate,** mp 225–227° dec.

Nmr Spectra. (a) Methyl Adamantane-1-carboxylate.—Peaks[21] at τ 8.10 (−0.12) (β-H), 8.00 (−0.12) (γ-H), 8.28 (+0.06) (δ-H), and 6.41 (CH_3); *cf.* the values in CCl_4 solution:[7] τ 8.12 (−0.10) (β-H), 8.01 (−0.11) (γ-H), 8.29 (+0.07) (δ-H), and 6.40 (CH_3).

(b) 1-(N,N-Diethylamino)methyladamantane (3a).—Peaks[21] at τ 8.51 (+0.29) (β-H), 8.06 (−0.06) (γ-H), 8.31 (+0.09) (δ-H), 9.05 (t) (NCH_2CH_3), 7.56 (q) (NCH_2CH_3), and 7.96 (s) ($CH_2N<$). It is interesting to note that the chemical shifts of the protons in positions β, γ, and δ are practically the same as those of 1-methyladamantane in CCl_4 solution:[7] τ 8.52 (+0.30) (β-H), 8.08 (−0.04) (γ-H), and 8.32 (+0.10) (δ-H).

(c) Methyl 3-(N,N-diethylamino)methyladamantane-1-carboxylate (5a).—The chemical shifts for the protons in positions a–e can be calculated[4] as shown in Table IV. Other peaks

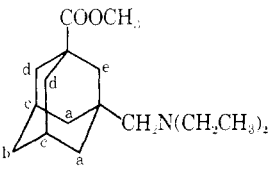

TABLE IV

Proton	Chemical shifts, τ Calcd	Found
$4H_a$	8.22 + 0.06 + 0.29 = 8.57	8.55
$2H_b$	8.22 + 0.06 + 0.09 = 8.37	8.41
$2H_c$	8.12 − 0.12 − 0.06 = 7.94	7.96
$4H_d$	8.22 − 0.12 + 0.09 = 8.19	8.21
$2H_e$	8.22 − 0.12 + 0.29 = 8.39	8.41

are found at τ 9.05 (t) (NCH_2CH_3), 7.96 (s) ($CH_2N<$), 7.56 (q) (NCH_2CH_3), and 6.41 (s) ($COOCH_3$).

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(21) The resonances of the protons are referred as in positions β, γ, and δ relative to the substituent. Values in parentheses are shifts from the values of adamantane in CCl_4 solution, *i.e.*, 8.22 for the CH_2 protons and 8.12 for the bridgehead protons (see ref 4).

Spirans. XVI. 9-Hydroxymethyl-3-azaspiro[5.5]undecanes[1,2]

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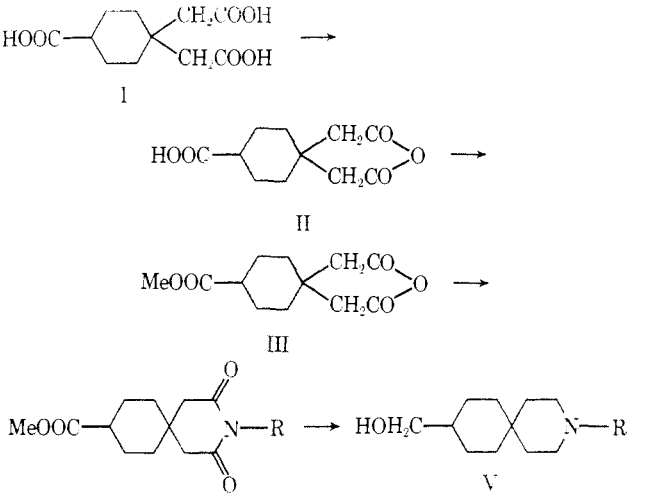
For some time we have been interested in placing a functional group into the 9 position of the 3-azaspiro[5.5]undecane nucleus and studying its pharmacological properties. While substitution by such groups as alkyl, aryl, and trifluoromethyl which are relatively inert chemically have been made accessible from the starting ketones, substitution by more reactive functional groups have not been readily obtainable. We now wish to report a synthesis in which the hydroxymethyl group is present in the 9 position of the 3-azaspiro[5.5]undecane nucleus. This group is amenable to various reactions which could produce other functional groupings.



The key intermediate in our synthesis was 4-carboxycyclohexane-1,1-diacetic acid[3] (I), which could be converted to the anhydride II by mild treatment with acetic anhydride or acetyl chloride. Although the reaction was selective with respect to the 1,1-diacetic acid substitution, some polymeric anhydride was always formed but the quantity could be limited by a short contact time. The polymeric anhydride could also be converted back to the starting acid I with very little loss in over-all yield. The conversion of the anhydride acid II to the anhydride methyl ester III by means of diazomethane was particularly rewarding with no attack on the anhydride moiety. Reaction of the ester anhydride III with 3-dimethylaminopropylamine gave IV without any amide formation from the methyl ester. Cyclization to the imide ester IV was completed at 180°. The product could be distilled easily and was reduced by $LiAlH_4$ to the hydroxymethyl base V.

The hydrochloride salt of V, when screened against mammary cancer cell cultures and KB tissue culture cells, had an activity at about 20 μg ml. The LD_{50} was 175 mg/kg. No remarkable reactions were noted in a general screen using rats for other pharmacological perimeters such as analgesia, sedation, and CNS stimulation, except for more foam cells than normal in the pathological examination of the autopsied animals.

Experimental Section[4]

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.3% of the theoretical values. All compounds conformed to their ir spectra.

4-Carboxycyclohexane-1,1-diacetic Acid Anhydride (II). A.—A mixture of 25 g of acid I and 100 ml of AcCl was heated to

(1) Supported by the Geschickter Fund for Medical Research.

(2) Part XV: L. M. Rice, B. S. Sheth, K. R. Scott, and C. F. Geschickter, *J. Med. Chem.*, **12**, 126 (1969).

(3) L. M. Rice and K. R. Scott, *J. Org. Chem.*, **32**, 1966 (1967).

(4) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

reflux and HOAc was added until a clear solution was obtained. The mixture was refluxed for 2 hr and allowed to cool. After removing the solvents the residue was recrystallized from EtOAc, 20 g, mp 190–192°; recrystallization from EtOAc, mp 195–196°; mmp 173–185° with acid I.

B.—Acid I (20 g) was refluxed with 50 ml of Ac_2O for 5 min and allowed to cool. After cooling petroleum ether (bp 65–75°) was added and the product was filtered, 11 g. After two recrystallizations from EtOAc–petroleum ether, the melting point was 195–196°.

The filtrates from both A and B on removal of the solvents, followed by hydrolysis (NaOH) of the residue and acidifying gave the original acid I. *Anal.* ($C_{11}H_{14}O_5$) C, H.

4-Carbomethoxycyclohexane-1,1-diacetic Acid Anhydride (III).—Acid II (18 g) was dissolved in 250 ml of THF and allowed to cool to 15°. CH_2N_2 (0.15–0.2 mole) in 400 ml of Et_2O at 10° was added, and as the reaction proceeded most of the product precipitated out of solution. After standing 2 hr the crystals were filtered (14 g), mp 128–129°. Recrystallization from EtOAc–petroleum ether gave 13 g, mp 130–131°. *Anal.* ($C_{12}H_{16}O_5$) C, H.

N-Dimethylaminopropyl-9-carbomethoxy-3-azaspiro[5.5]-undecane-2,4-dione (IV).— The ester anhydride (13 g, 0.054 mole) was mixed with 6 g of 3-dimethylaminopropylamine and when homogeneous was heated at 200° for 1 hr. After cooling the product was distilled, bp 193–200° (0.45 mm), yield 7.6 g. *Anal.* ($C_{17}H_{28}N_2O_4$) C, H, N.

The **methiodide** was prepared in the usual manner, mp 229–230° (from EtOH, MeOH). *Anal.* ($C_{18}H_{31}IN_2O_4$) I.

N-Dimethylaminopropyl-9-hydroxymethyl-3-azaspiro]5.5]-undecane (V).–A solution of 7 g of IV in 200 ml of Et_2O was added to 5 g of $LiAlH_4$ dissolved in 500 ml of Et_2O. After 4 hr the mixture was decomposed (H_2O) in the usual manner, filtered, and dried (Na_2SO_4), and the solvent was stripped off. The residue was distilled, bp 133–138° (0.05 mm), yield 5.5 g. *Anal.* ($C_{16}H_{32}N_2O$) C, H, N.

The **hydrochloride** was prepared with alcoholic HCl, mp 295–296° (EtOH, MeOH). *Anal.* ($C_{16}H_{34}Cl_2N_2O$) Cl.

Synthesis of 5-Fluoro-2′-deoxyuridine-5′-carboxylic Acid and Its Derivatives[1]

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Although 5-fluoro-2′-deoxyuridine (FUDR) is an effective antitumor agent, it is easily hydrolyzed to 5-fluorouracil *in vivo* and *in vitro*, both by phosphorylase and by acid.[2,3] Thus in the clinical use of this drug the toxicity to the gastrointestinal system often masks its chemotherapeutic effectiveness. The present work reports the synthesis of 5-fluoro-2′-deoxyuridine-5′-carboxylic acid which is less toxic and more resistant to hydrolysis than FUDR.

Moss, *et al.*,[4] first reported the synthesis of uronic acid derivatives of nucleosides. They successfully oxidized uridine, thymidine, and adenosine to their 5′-carboxylic acids using Pt as a catalyst.[5] More recently, Imai and Honjo[6] reported the oxidation of deoxyuridine and its 5-bromo and 5-iodo derivatives and pointed out the difficulty in obtaining a product as the halogen substituent became more electronegative.

The synthetic scheme for the oxidation of FUDR to give 5-fluoro-2′-deoxyuridine-5′-carboxylic acid (FUDA) was not as simple as the one-step reaction might indicate. Previous workers[4,6] had used decidedly alkaline conditions (pH 8–9); however, no oxidation product was obtained with analogous treatment of FUDR. Our earlier method[7] for the preparation of phenyl-β-D-glucopyruronoside *via* the stepwise addition of $NaHCO_3$ proved to be fruitful. The pH was maintained between 6 and 7 and the reaction was run for 30 hr at 50–60° to give a 60% yield of FUDA.

The structure of FUDA was established by its ir and nmr spectra and by elemental analysis. Comparison of the nmr spectra of FUDA *vs.* FUDR in D_2O confirms the proposed structure of FUDA, both by the integration of nonexchangeable protons, and by the fact that absorption in the methylene region of FUDR at δ 3.8 is completely absent in FUDA.

While FUDR is sensitive to acid hydrolysis, FUDA has been found stable to acid. Although the mechanism of acid hydrolysis of nucleosides is ambiguous, most workers agree that the sugar ring O atom must be protonated.[8] For example, Garrett and co-workers[3] had suggested that the three steps involved in the acid hydrolysis of nucleosides are (1) protonation of the sugar ring O atom, (2) formation of the Schiff base, and (3) decomposition of the Schiff base. Thus, a plausible explanation for the enhanced stability toward acid hydrolysis of FUDA compared to FUDR can be provided. In the case of FUDA, protonation of the carbonyl O atom can greatly diminish the rate of protonation of the sugar ring O atom, thereby retarding hydrolysis.

FUDA has been shown to have only about one-tenth the toxicity of FUDR *in vivo* in mice. Due to the known lower level of esterase in tumor cells compared to normal cells,[9] the esters shown in Table I were prepared in the hope that, if a more cytotoxic ester could be found, such derivatives would become more permeable to tumor cell membrane, whereas normal cells, by virtue of their esterase content, would hydrolyze it back to FUDA.

The method of synthesis was acid catalysis, both by use of H_2SO_4 and ion-exchange resin, thereby taking advantage of the stability of FUDA toward acid hydrolysis. During these syntheses, no 5-fluorouracil could be detected in the reaction mixture by means of tlc. The use of dicyclohexylcarbodiimide (DCC) as a condensing agent for the preparation of esters was attempted. No product could be found with this method and only the anhydride of FUDA was isolated. Its structure was established by its ir spectrum and complete conversion to FUDA upon hydrolysis. On the other hand, DCC was an effective agent in yielding the amide VII from β-naphthylamine. The facile formation of this amide has led us to our present attempts

(1) This work was supported by U. S. Public Health Service Grant CA 07339; presented at the ACS Mid-Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968.

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