2-Fluoro-2-methylmalonamide (VIb).—A mixture of 100 ml of concentrated NH_4OH, 25 ml of methanol, and 25 g (0.173 mole) of IVb was kept at −10° with intermittent shaking for 22 days. The crystalline product was obtained by filtration and was dried under vacuum at room temperature. The compound melted at 228–230° dec.

Ethyl 2-Cyano-2-fluoropropionate (Vb).—The potassium salt of ethyl 2-cyanopropionate was prepared by adding 26.0 g (0.205 mole) of the ester to a solution of 7.8 g (0.2 g-atom) of K in 100 ml of anhydrous ethanol. The mixture was brought to dryness under vacuum, and the alcohol was replaced with 200 ml of dry DMF. The DMF was flash evaporated under vacuum and replaced twice. The final residue was kept in the flash evaporator for an additional 1 hr at 100° (15 mm). The dry salt was dissolved in 200 ml of dry DMF, purged with dry N_2 and treated with a rapid stream of perchloryl fluoride. The reaction temperature was maintained at 10–15° by means of an ice bath. When no further heat of reaction was apparent, the system was freed of excess perchloryl fluoride by purging with dry N_2. Inorganic materials were removed by filtration, and the liquid was distilled. The product boiling at 50–55° (10 mm) was collected. This was a mixture of the desired fluoro ester and DMF. The mixture was dissolved in ether and was washed free of DMF with H_2O. Compound Vb was obtained in 40% yield by distillation, bp 55° (10 mm).

Ethyl 2-Cyano-2-fluorobutyrate (Vc).—Sodium dispersion[38] (23 g of Na, 1 g-atom) was suspended in 1000 ml of dry toluene and heated to 50°. To the mixture was added 145 g (1.03 moles) of ethyl 2-cyanobutyrate[6] at such a rate as to keep the temperature of the reaction below 90°. The excess ester was necessary to ensure complete consumption of the Na. The system was purged with dry N_2 and kept at 10–15° by external cooling. A rapid stream of perchloryl fluoride was added, and upon completion of the reaction, as evidenced by cessation of heat evolution, the system was again purged with dry N_2. The inorganic salts were removed by filtration, dissolved in H_2O, and extracted with toluene. The combined toluene layers were washed with H_2O and flash evaporated. The residue was distilled, and the product was collected at 65–70° (10 mm).

2-Fluoro-3-methylbutyric Acid (VIIIe).—A mixture of 43.3 g (0.25 mole) of IVe and 100 ml of concentrated HCl was heated under reflux overnight. The hydrolysate was extracted five times with 100-ml portions of ether, and the ether was removed under a stream of air. The residue was freed of water by azeotropic distillation with benzene and distilled. The yield of product was 24 g (80%), bp 80–83° (10 mm). An analytical sample was obtained by redistillating and collecting a middle fraction, bp 82° (10 mm), mp 41°. The neutralization equivalent was 120 (calcd 120) and $\nu_{max}^{C=O}$ 1720 cm^{-1}.

(38) Purchased from Gray Chemical Co., Gloucester, Mass., as 50% sodium in mineral spirits.

Anal. Calcd for $C_5H_9FO_2$: C, 49.99; H, 7.55; F, 15.82. Found: C, 50.03; H, 7.80; F, 15.55.

2-Fluoro-3-methylvaleric acid (VIIIg) was prepared in the same manner as VIIIe in 80% yield, bp 95.5–96.5° (10 mm), neutralization equivalent 134 (calcd 134), $\nu_{max}^{C=O}$ 1732 cm^{-1}.

Anal. Calcd for $C_6H_{11}FO_2$: C, 53.72; H, 8.26; F, 14.16. Found: C, 53.85; H, 8.15; F, 13.99

2-Fluoro-4-methylvaleric acid (VIIIh) was prepared as VIIIe in 75% yield, bp 96.5–98.5°, neutralization equivalent 134 (calcd 134), $\nu_{max}^{C=O}$ 1725 cm^{-1}

Anal, Calcd for $C_6H_{11}FO_2$: C, 53.72; H, 8.26; F, 14.16. Found: C, 53.42; H, 8.31; F, 14.02.

2-Carboxamido-2-fluorobutyramidine (VIIc).—To 1.41 g (0.01 mole) of Vc in a test tube immersed in a Dry Ice–acetone bath was added 5 ml of liquid ammonia. The mixture was allowed to stand overnight and to come to room temperature with concomitant evaporation of the excess NH_3. The yield of residue was 1.5 g (95%) of VIIc, mp 150–151° dec. An analytical sample was obtained by crystallization from an ethanol–H_2O mixture without change in melting point. The product was basic, and the infrared spectrogram was characterized by a broad band at 1590–1725 cm^{-1}.

Anal. Calcd for $C_5H_{10}FN_3O$: C, 40.81; H, 6.85; F, 12.92; N, 28.56. Found: C, 40.76; H, 6.92; F, 12.88; N, 28.45.

2-Ethyl-2-fluoromalonamic Acid (IXc).—A mixture was prepared containing 6.6 g (0.165 mole) of NaOH, 200 ml of H_2O, and 24 g (0.15 mole) of Vc. After stirring for 2 hr a clear solution resulted, and it was allowed to stand overnight. Sodium was removed by passage through a column of Amberlite IR-120 (H^+), and the effluent was flash evaporated below 40° to apparent dryness. The residue was slurried in ether and the crystalline material was removed by filtration and dried under vacuum. A yield of 10 g of product was obtained which melted at 140° dec.

Ammonium 2-Fluoromalonamate Monohydrate (XII).—To a solution composed of 6.0 g (0.15 mole) of NaOH, 60 ml of H_2O, and 30 ml of ethanol was added 26.7 g (0.15 mole) of diethyl fluoromalonate. The mixture was allowed to stand overnight, and the Na^+ was removed by passage through a column of Amberlite IR-120 (H^+). The effluent was evaporated to near dryness, and the syrupy product was dissolved in methanol made alkaline with NH_4OH and treated with decolorizing carbon, and crystallization was induced by addition of acetone followed by refrigeration. The yield of product was 8.2 g (35%) as the monohydrate, mp 209–211° dec. An analytical sample was obtained by crystallization from a H_2O–methanol–acetone mixture and melted at 209–210° dec.

Anal. Calcd for $C_3H_9FN_2O_4$: C, 23.08; H, 5.81; F, 12.17; N, 17.95. Found: C, 23.30; H, 5.96; F, 12.28; N, 17.56.

Ammonium 2,2-difluoromalonamate monohydrate (XVI) was prepared as above in 47% yield, mp 220–221° dec (methanol–acetone mixture).

Anal. Calcd for $C_3H_8F_2N_2O_4$: C, 20.70; H, 4.63; F, 21.82; N, 16.09. Found: C, 21.01; H, 4.47; F, 22.00; N, 16.12.

Antiinflammatory Dialkylaminoalkylureas

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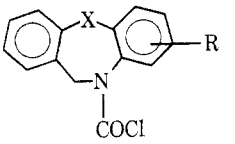
A series of dialkylaminoalkylureas were synthesized from various tricyclic amines and tested for their antiinflammatory activity.

Previous research in these laboratories has indicated that dialkylaminoalkylureas derived from benzylphenylamines possess antiinflammatory activity.[1] In an attempt to increase the potency of these compounds, ureas derived from various tricyclic amines were prepared. The tricyclic amines used as starting materials were essentially benzylphenylamines bridged at the *ortho* positions of the two aryl groups by O, NR, CH_2, CH_2CH_2, CH=CH, and a single bond. These constitute the 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepines, 10,11-dihydro-5H-dibenzo[*b*,*e*][1,4]diazepines, 5,6-dihydrodibenz[*a*,*d*]azepines, 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocines, 5,6-dihydrodibenz[*b*,*f*]azocines, and the phenanthridines, respectively. Dialkylaminoalkylureas prepared from 10,11-dihydrodibenz[*b*,*f*][1,4]thia-

(1) J. W. Cusic, U. S. Patent 2,681,929 (1950).

TABLE I
CARBAMOYL CHLORIDES



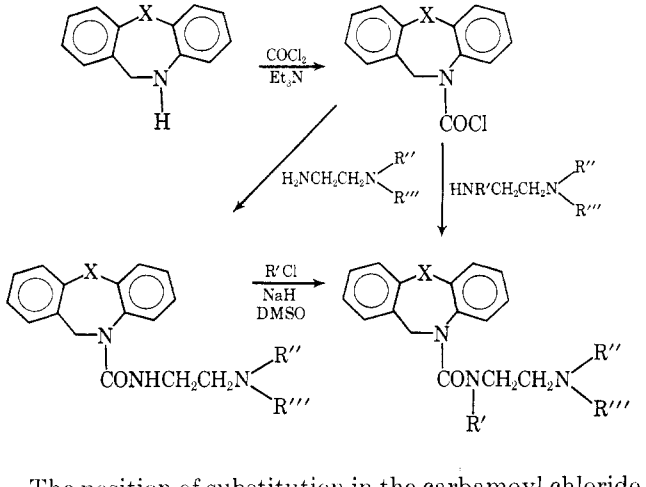
X	R	Crystn solvent	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
O	H	SSB[a]	110–112	64.75	64.80	3.88	4.19	5.40	5.36
O	8-Cl	SSB	101–104	57.17	57.16	3.08	3.40	4.76	4.72
NH	H	EtOH	173–176	64.99	64.82	4.29	4.33	10.83	10.86
NCH_3	H	SSB	117–119	66.05	66.25	4.80	5.25	10.27	10.51
NC_2H_5	H	SSB	162–164	67.01	67.18	5.27	5.36	9.77	9.63
$NCH_2C_6H_4Cl$-*p*	H	C_6H_6	157–159	65.80	65.98	4.21	4.36	7.31	7.31
...[b]	H	SSB	63.5–65.5	69.00	69.08	4.14	4.40	5.75	5.81
CH_2	H	SSB	98–102	69.90	70.16	4.70	4.77	5.44	5.38
CH_2CH_2	H	SSB	95.5–97.5	70.71	70.68	5.19	5.15	5.16	5.14
CH=CH	H	SSB	125–127	71.24	71.35	4.49	4.78	5.19	5.19

[a] SSB = Skellysolve B (petroleum ether fraction bp 60–70°). [b] Denotes single bond between two aryl groups.

zepines have been reported,[2] although no antiinflammatory activity was mentioned.

The synthesis of ureas from these amines proceeded *via* the carbamoyl chlorides (Table I) which could be obtained in high yields by treating the amine with phosgene and triethylamine at <10° to give stable crystalline solids. These carbamoyl chlorides condensed readily with the appropriate diamine to give the desired compounds (Chart I). The tetrasubstituted ureas could be prepared either by reaction of the carbamoyl chloride with a trisubstituted diamine or by alkylation of a trisubstituted urea with an alkyl halide in dimethyl sulfoxide (DMSO) using NaH as a base. The majority of the ureas prepared were oils and were isolated as oxalates or hydrochlorides.

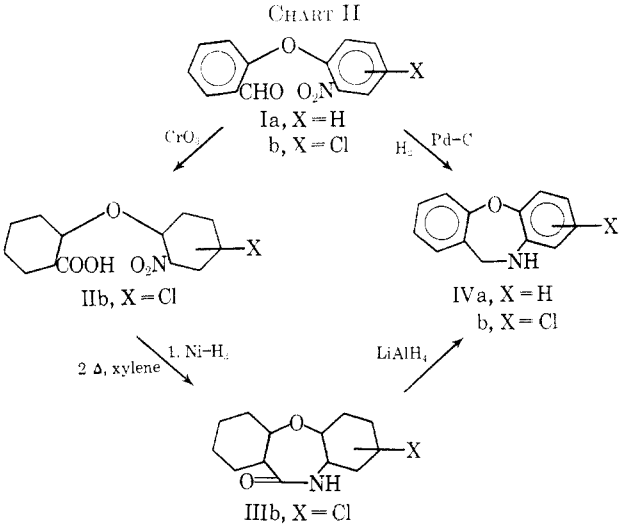
CHART I



The position of substitution in the carbamoyl chloride derived from 10,11-dihydro-5H-dibenzo[*b*,*e*][1,4]diazepine Xa was proven by nmr studies. The paramagnetic shift (*ca.* 50 cps) of the benzyl protons α to the nitrogen observed on formation of the carbamoyl chloride was identical with the shift observed with the other carbamoyl chlorides in which only one product was possible.

At the time this work began, 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine IVa was unknown, although the corresponding lactam had been reported.[3] The first synthetic efforts toward the amine involved a Bischler–Napieralski ring closure of *o*-formalaminodiphenyl ether.[4–6] This reaction, however, proceeds in poor yields except in the preparation of 11-substituted compounds. A two-step synthesis was developed in which O-(*o*-nitrophenyl)salicylaldehyde[3] was hydrogenated over Pd–C to give directly a 77% yield of the 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine IVa (Chart II). The

CHART II



8-chloro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine could not be prepared cleanly in this manner, since the chlorine was hydrogenolyzed during the reduction. Substitution of Raney nickel as catalyst only slightly improved the yield of this compound. The best overall yield was obtained by oxidation of the aldehyde Ib (Chart II) to the carboxylic acid IIb, reduction of the nitro group, ring closure, and reduction of the lactam IIIb to the amine IVb. A synthesis which also gives an excellent yield of 10,11-dihydrodibenz[*b*,*f*][1,4]oxa-

(2) H. L. Yale and F. A. Sowinski, U. S. Patent 3,050,524 (1961).

(3) R. Q. Brewster and F. Strain, *J. Am. Chem. Soc.*, **56**, 117 (1934).

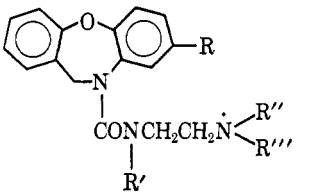
(4) F. Hunziker, F. Künzle, O. Schindler, and J. Schmutz, *Helv. Chim. Acta*, **47**, 1163 (1964).

(5) R. Higginbottom and H. Suschitzky, *J. Chem. Soc.*, 2367 (1962).

(6) J. O. Jilek, J. Pomykáček, J. Metyšová, J. Metyš, and M. Protiva, *Collection Czech. Chem. Commun.*, **30**, 463 (1965).

TABLE II

UREAS FROM 10,11-DIHYDRODIBENZ[*b,f*][1,4]OXAZEPINE



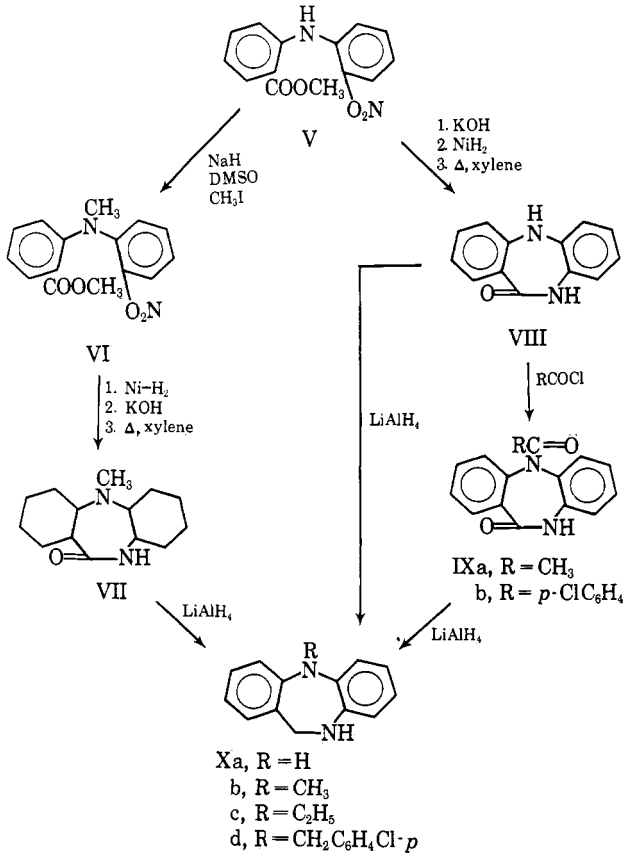
No.	R	R′	R″	R‴	Salt	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	H	H	C_2H_5	C_2H_5	$C_2H_2O_4$	166–168 dec	61.52	61.56	6.34	6.64	9.79	9.88
2	Cl	H	C_2H_5	C_2H_5	$C_2H_2O_4$	158–160 dec	56.96	56.93	5.65	5.79	9.06	8.87
3	Cl	H			$C_2H_2O_4$	156–160 dec	57.20	56.98	5.24	5.47	9.10	8.94
4	H	*i*-C_3H_7	*i*-C_3H_7	*i*-C_3H_7	$C_2H_2O_4$	165–167 dec	64.91	64.98	7.47	7.44	8.41	8.52
5	H		C_2H_5	C_2H_5	$C_2H_2O_4$	138–141 dec	64.58	64.90	6.88	6.92	8.69	8.56
6	H	H			$C_2H_2O_4$	147–150 dec	60.38	60.67	5.95	5.18	9.19	9.40
7	H	$CH_2C_6H_5$	C_2H_5	C_2H_5	...	*a*	75.49	75.24	7.27	7.22	9.78	9.49

[a] Oily product.

zepines was recently reported.[7] This involves an intramolecular Leuckhart amide reaction of an isocyanato diphenyl ether to give the tricyclic lactam. The lactam is further reduced by $LiAlH_4$ to the amine.

The 10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepines X (Chart III) were prepared using a common starting

CHART III



material, methyl N-(*o*-nitrophenyl)anthranilate.[8] Both the 5-unsubstituted Xa and the 5-methyl compounds Xb had been prepared previously,[8] but an improved method for synthesis of the 5-methyl compound was developed. Methyl N-methyl-N-(*o*-nitrophenyl)-anthranilate (VI) had been synthesized by methylation of methyl N-(*o*-nitrophenyl)anthranilate with dimethyl sulfate and KOH in acetone.[9] However, we obtained poor results with this method. An improved methylation procedure, in fact the only one of several attempts which was successful, involved the treatment of V with NaH in DMSO at room temperature followed by addition of CH_3I to give VI in good yield. This procedure was also superior to the preparation of VI by condensation of *o*-bromonitrobenzene with methyl N-methylanthranilate.[10] VI could be converted cleanly to the lactam VII followed by reduction to 5-methyl-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepine (Xb).[4] The 5-ethyl Xc and 5-(*p*-chlorobenzyl) Xd derivatives were synthesized by acylating 10,11-dihydro-5H-dibenz[*b,f*]-[1,4]diazepin-11-one (VIII)[8] with acetyl chloride and *p*-chlorobenzoyl chloride to give the acyl compounds IXa[11] and IXb, respectively. These were reduced ($LiAlH_4$) to give the desired diazepines Xc and Xd.

5,6-Dihydrodibenz[*b,f*]azocine and 5,6,11,12-tetrahydrodibenz[*b,f*]azocine were prepared by a Beckmann rearrangement of the corresponding oximes and $LiAlH_4$ reduction of the resulting lactams.[12]

Biological Activity.—The dialkylaminoalkylureas (Tables II–IV) were tested for their antiinflammatory activity in two biological assays. The inhibition of yeast-induced foot edema was measured in male Badger rats (120 g) both subcutaneously and intragastrically. The minimal effective dose of phenylbutazone in this test was 120 mg/kg sc and 175 mg/kg orally. Compounds active in this test were further tested intragastrically against cotton pellet induced granuloma growth in adrenalectomized, male, Sprague–Dawley

(7) J. Schmutz, F. Künzle, F. Hunziker, and A. Bürki, *Helv. Chim. Acta*, **48**, 336 (1965).

(8) (a) A. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963); (b) A. R. Hanze, R. E. Strube, and M. E. Greig, *ibid.*, **6**, 767 (1963).

(9) D. H. Hay and R. D. Mully, *J. Chem. Soc.*, 2276 (1952).

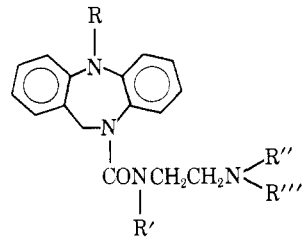
(10) Von F. Hunziker, H. Lauener, and J. Schmutz, *Arzneimittel-Forsch.*, **13**, 324 (1963).

(11) G. R. Clemo, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1751 (1924).

(12) F. Sowinski and H. L. Yale, *Arzneimittel-Forsch.*, **13**, 117 (1963).

TABLE III

UREAS FROM 10,11-DIHYDRODIBENZO[*b*,*e*][1,4]DIAZEPINES

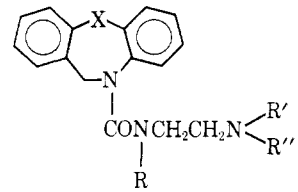


No.	R	R′	R″	R‴	Salt	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
8	CH_3	H	C_2H_5	C_2H_5	HCl	184–185	64.85	65.03	7.52	7.62	14.41	14.52
9	C_2H_5	H	C_2H_5	C_2H_5	...	*a*	72.09	71.83	8.25	7.95	15.29	14.52
10	H	H	C_2H_5	C_2H_5	...	182–185	70.97	71.04	7.74	7.79	16.56	16.34
11	H	H			HCl	214–217	65.18	65.34	7.04	7.20	14.48	14.09
12	H	CH_3	$CH_2C_6H_5$	CH_3	...	102–103	74.96	75.08	7.05	7.16	13.99	13.99
13	$CH_2C_6H_4Cl$-*p*	H	C_2H_5	C_2H_5	...	148–149	69.92	70.03	7.09	6.75	12.07	12.11
14	CH_3	$CH_2C{\equiv}CH$	C_2H_5	C_2H_5	HCl	183–186	67.51	67.26	7.32	7.39	13.12	13.28
15	CH_3	$CH_2C_6H_5$	C_2H_5	C_2H_5	...	*a*	75.98	76.15	7.74	7.94	12.66	12.33

[a] Oily product.

TABLE IV

UREAS FROM TRICYCLICS WITHOUT HETERO BRIDGE



No.	X	R	R′	R″	Salt	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
16	...[b]	H	C_2H_5	C_2H_5	$C_2H_2O_4$	123–126 dec	63.90	63.79	6.58	6.67	10.16	10.01
17	...	*i*-C_3H_7	*i*-C_3H_7	*i*-C_3H_7	...	*a*	76.29	76.06	8.96	8.95	10.68	10.76
18	...	H			$C_2H_2O_4$	170–172 dec	64.22	63.98	6.12	6.32	10.21	10.22
19	CH_2	H	C_2H_5	C_2H_5	$C_2H_2O_4$	141–143 dec	64.62	64.39	6.84	6.89	9.83	9.71
20	CH_2	CH_3	$CH_2C_6H_5$	CH_3	...	*a*	78.16	77.64	7.32	7.53	10.52	10.35
21	CH_2CH_2	H	C_2H_5	C_2H_5	...	*a*	75.17	74.93	8.32	8.36	11.96	11.73
22	CH_2CH_2	H			...	*a*	75.99	75.77	8.04	8.05	11.56	11.55
23	CH=CH	H	C_2H_5	C_2H_5	...	*a*	75.61	75.41	7.79	7.96	12.03	12.26

[a] Oily product. [b] Denotes single bond between two aryl groups.

rats (200 g) for a 2-day period. The minimal effective dose of phenylbutazone is 25 mg/kg orally.

Table V shows the testing results of the most active ureas compared with the open chain compound, N-benzyl-N-phenyl-N′-(3-diethylaminoethyl)urea.[1] The results indicate that the tricyclic derivatives retain the activity of the open-chain ureas, but that an increase in potency was not obtained. The most consistent results were obtained with the ureas derived from 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine.

Several of the compounds (**2**, **3**, **6**, **7**, **9**, **17**, **19**) exhibited activity against *Trichophyton mentagrophytes* and *Candida albicans in vitro* as qualitative tests for antifungal activity. (The compound is placed on the surface of an agar plate inoculated with the test organism and the zone of inhibition caused by test compound is compared with that caused by undecylenic acid and mycostatin, respectively.)

TABLE V

ANTIINFLAMMATORY ACTIVITY OF UREAS[a]

Compd	Foot edema 330 mg/kg sc	Foot edema 160 mg/kg ig	Granuloma 150 mg/kg ig
N-Benzyl-N-phenyl-N′-(3-diethylaminoethyl)urea	A	I	A
1	A	I	I
2	A	I	I
3	A	I	I
4	A	I	I
5	A	I	I
6	A	I	I
8	A	I	I
11	A	A	I
14	A	I	I
16	A	I	I
19	A	I	I
23	A	I	I

[a] A = active, I = inactive.

Experimental Section[13]

Preparation of Ureas from Carbamoyl Chlorides.—A solution of 0.03 mole of the carbamoyl chloride, 0.03 mole of the appropriate diamine, and 0.03 mole of triethylamine in 250 ml of 2-butanone was refluxed 18 hr. The 2-butanone was evaporated *in vacuo*, H_2O was added, and the suspension was extracted with ether. The ether extracts were dried (K_2CO_3) and evaporated, to give the crude urea. The oily ureas were converted to their oxalate or hydrochloride salts by dissolving in a minimum of anhydrous ethanol and adding a saturated solution of oxalic acid or HCl in alcohol. These salts could be recrystallized from anhydrous ethanol or ethanol–ether. Ureas which were oils and did not form crystalline salts were purified by column chromatography on neutral alumina.

Preparation of Carbamoyl Chlorides (Table I).—To a stirred solution of 0.08 mole of $COCl_2$ in 35 ml of toluene at 5° was added 75 ml of ether followed by a solution of 0.06 mole of the amine and 0.06 mole of Et_3N in 130 ml of ether or a 1:1 methylene chloride–ether solution. The suspension was stirred for 1 hr after addition and filtered, the residue was washed with ether, and the combined filtrates were evaporated *in vacuo* to give the carbamoyl chloride.

N-Benzyl-N-(2-diethylaminoethyl)-10,11-dihydrodibenz[*b,f*]-[1,4]oxazepin-10-carboxamide (7).—To a stirred solution of 0.023 mole of N-(2-diethylaminoethyl)-10,11-dihydrodibenz-[*b,f*][1,4]oxazepin-10-carboxamide in 200 ml of DMSO, under N_2, was added 0.023 mole of NaH (56% in mineral oil) and the resulting solution was stirred 0.5 hr. To this solution was added 0.023 mole of benzyl chloride and the reaction was stirred 18 hr. at 25°. The mixture was poured into 1 l. of H_2O, extracted with ether, and dried (K_2CO_3). Evaporation of the ether gave a yellow oil which was extracted with aqueous oxalic acid and washed with ether. The aqueous phase was made basic with K_2CO_3 and extracted with ether; the ether extracts were dried (K_2CO_3) and evaporated. The oily product **7** was purified by charcoaling twice in ethyl acetate.

O-(2-Nitro-4-chlorophenyl)salicylaldehyde.—To 435 g of 2,5-dichloronitrobenzene at 165–170° with stirring was added 218 g of potassium salicylaldehyde portionwise. The temperature was raised to 190° after the addition and kept at 190–200° for 6 hr. A vigorous reaction occurred when the temperature reached 195° and heat had to be removed temporarily. The excess 2,5-dichloronitrobenzene was removed by steam distillation, and the product was extracted with ether and recrystallized from cyclohexane to give 106.0 g of yellow needles, mp 82–90°. The analytical sample from petroleum ether (bp 60–80°) had mp 82–83.5°.

Anal. Calcd for $C_{13}H_8ClNO_4$: C, 56.23; H, 2.90; N, 5.05. Found: C, 56.08; H, 2.92; N, 4.99.

O-(2-Nitro-4-chlorophenyl)salicylic Acid.—To a stirred solution of 103 g of O-(2-nitro-4-chlorophenyl)salicylaldehyde in 500 ml of acetone at room temperature was added 135 ml of chromic acid reagent (100.01 g of chromic acid, 153 g of concentrated H_2SO_4, and sufficient H_2O to make 500 ml) over a period of 0.25 hr. The solution was cooled to keep below reflux temperature and stirred 1.5 hr after addition. The reaction mixture was poured into 2 l. of H_2O and the solid was separated by filtration. The crude acid was recrystallized from ethanol to give 78.0 g of yellow crystals, mp 155–160°.

Anal. Calcd for $C_{13}H_8ClNO_5$: C, 53.17; H, 2.75; N, 4.77. Found: C, 53.32; H, 2.95; N, 4.47.

8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-11-one.—A solution of 78 g of O-(2-nitro-4-chlorophenyl)salicylic acid in 1 l. of methanol was hydrogenated over Raney nickel (18 g) at room temperature and atmospheric pressure. The crude amino acid obtained on evaporation of the methanol was refluxed in 1 l. of xylene for 18 hr with continuous removal of H_2O. The xylene solution was cooled and the solid was filtered to give 58 g of colorless crystals, mp 258–261°. The analytical sample, from ethyl acetate, had mp 260–261°.

Anal. Calcd for $C_{13}H_8ClNO_2$: C, 63.56; H, 3.28; N, 5.70; Cl, 14.43. Found: C, 63.75; H, 3.44; N, 5.62; Cl, 14.38.

8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepine.—To a stirred suspension of 40 g (0.163 mole) of 8-chloro-10,11-dihydrodibenz[*b,f*][1,4]-oxazepin-11-one in 1 l. of ether under N_2 was added 12.4 g (0.326 mole) of $LiAlH_4$ in 200 ml of ether. The mixture was stirred and refluxed for 19 hr and decomposed by the successive addition of 16 ml of H_2O, 16 ml of 15% aqueous NaOH solution, and 48 ml of H_2O. The suspension was filtered, the ether was evaporated, and the solid was recrystallized from petroleum ether (bp 60–80°) to give 34.0 g of colorless crystals, mp 92–97°.

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.45; H, 4.50; N, 6.09.

10,11-Dihydrodibenz[*b,f*][1,4]oxazepine.—A solution of 50 g of O-(2-nitrophenyl)salicylaldehyde was hydrogenated with 5% Pd–C (5.0 g) at atmospheric pressure and room temperature until 4 molar equiv of H_2 were taken up (2.5 hr). The oil obtained on filtration and evaporation was crystallized from petroleum ether (bp 70–90°) to give 29.60 g of light yellow crystals, mp 73–75°.

Methyl N-Methyl-N-(*o*-nitrophenyl)anthranilate.—To a stirred solution of 100 g (0.368 mole) of methyl N-(*o*-nitrophenyl)-anthranilate in 920 ml of DMSO, under N_2, was added 16.8 g of NaH suspension (52.6% in oil) (0.368 mole). The solution was stirred 1 hr at 25° and 100 g (0.7 mole) of MeI was added. The solution was stirred 18 hr at 25° and poured into 3 l. of H_2O. The solid which separated was recrystallized from petroleum ether (bp 70–90°) to give 64.0 g of yellow needles, mp 60–69°. This solid was used directly in the next step.

5-Methyl-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one.—A solution of 60 g of methyl N-methyl-N-(*o*-nitrophenyl)-anthranilate in 2 l. of methanol was hydrogenated at 2.1–3.5 kg/cm² using Raney nickel (12 g) as catalyst. The crude amine, isolated by filtration and evaporation of the methanol, was stirred 18 hr at room temperature in 300 ml of alcohol, 50 ml of H_2O, and 22 g of KOH and 1 hr at reflux. The ethanol was removed *in vacuo*, and the residue was dissolved in H_2O and adjusted to pH 6 with 10% HCl. The solid which separated was removed by filtration and refluxed 20 hr in 500 ml of xylene. The solid which separated on cooling was recrystallized from ethanol to give 29.6 g of colorless crystals, mp 215–216°.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.22; H, 5.47; N, 12.57.

5-Methyl-10,11-dihydro-5H-dibenz[*b,e*][1,4]diazepine.—To a stirred suspension of 14.3 g (0.0635 mole) of 5-methyl-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one in 300 ml of ether, under N_2, was added 6.35 g (0.165 mole) of $LiAlH_4$ in 100 ml of ether. The mixture was refluxed 45 hr and then decomposed by addition of 63.5 ml of 2% aqueous NaOH. The suspension was filtered; the filtrate was evaporated to give 11.50 g of a white solid which on recrystallization from 2-propanol gave colorless needles, mp 115–117°.

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.70; H, 6.60; N, 13.25.

5-Ethyl-10,11-dihydro-5H-dibenz[*b,e*][1,4]diazepine.—To a stirred suspension of 13.35 g of 5-acetyl-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one[11] in 1 l. of ether was added, under N_2, 13.0 g of $LiAlH_4$ in 150 ml of ether. The solution was stirred and refluxed 18 hr, cooled, and decomposed by successive addition of 13.0 ml of H_2O, 13.0 ml of 15% aqueous NaOH, and 39 ml of H_2O. The solid obtained on filtration and evaporation of the ether was recrystallized from 2-propanol to give 9.8 g of colorless crystals, mp 108–110°.

Anal. Calcd for $C_{15}H_{16}N_2$: C, 70.32; H, 7.19; N, 12.49. Found: C, 80.20; H, 6.92; N, 12.77.

5-(*p*-Chlorobenzoyl)-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one.—A solution of 21 g (0.1 mole) of 10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one, 26 g (0.15 mole) of *p*-chlorobenzoyl chloride, and 7 g of N,N-dimethylaniline in 500 ml of dioxane was refluxed 18 hr. The resulting solution was concentrated to *ca.* 100 ml and poured into H_2O. The white semisolid obtained was separated and recrystallized from ethanol to give 12.0 g of white crystals, mp 240–242°.

Anal. Calcd for $C_{20}H_{13}ClN_2O_2$: C, 68.87; H, 3.76; N, 8.03. Found: C, 68.60; H, 3.90; N, 7.85.

5-(*p*-Chlorobenzyl)-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepine.—To a stirred suspension, under N_2, of 10 g of $LiAlH_4$ in 250 ml of dioxane was added 21.25 g of 5-(*p*-chlorobenzoyl)-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-one in 500 ml of dioxane. The suspension was stirred and refluxed overnight and then decomposed by the successive addition of 10 ml of H_2O in 10 ml of dioxane, 10 ml of 15% aqueous NaOH solution, and 30 ml of H_2O. The suspension was filtered and the dioxane was evapo-

(13) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

rated to give 9.36 g of an amber oil. The analytical sample was obtained by distillation at 253° (1.5 mm).

Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.87; H, 5.34; N, 8.73. Found: C, 75.02; H, 5.48; N, 8.85.

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Some Steroidal Cyclic Ethers As Antiestrogens[1]

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The synthesis of four-, five-, and six-membered spiroethers at C-17 and a number of cyclic ethers resulting from rearrangement at C-17 is reported. Several of these steroids exhibit potent antiestrogenicity.

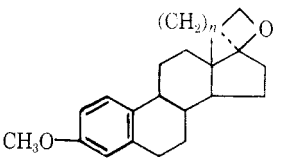
As an extension of work done in these laboratories directed toward the synthesis of steroidal spirolactones as aldosterone antagonists, several steroidal spiroethers were prepared; in addition, some novel cyclic ethers were obtained in a dehydration–rearrangement at C-17. A number of the spiroethers prepared in these laboratories exhibit potent antiestrogenic activity. They have not been found to be of interest as aldosterone antagonists,[2] although Arth and his associates[3] report that the lactone carbonyl is not essential for anti-aldosterone activity.

Steroids containing four-, five-, and six-membered spiroethers at C-17 have been prepared. Reduction of 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-estren-3-one) (**3a**)[3] with lithium aluminum tri-*t*-butoxyhydride gave the 3β-hydroxy-Δ^4 derivative **4a** which was acetylated to give **4c**. Similar treatment of the corresponding compound in the androstane series produced the 3β-hydroxy derivative **4b** and its acetate **4d**.

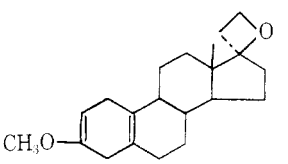
The 19-nor six-membered spiroether was prepared by $LiAlH_4$ reduction of 4-[17β-hydroxy-3-methoxy-1,3,-5(10)-estratrien-17α-yl]butanoic acid lactone[4] to give the diol **6e** which was treated with *p*-toluenesulfonyl chloride, and the product cyclized with potassium *t*-butoxide in refluxing *t*-butyl alcohol to give 3′,4′,-5′,6′-tetrahydrospiro[3-methoxyestra-1,3,5(10)-triene-17,2′(2′H)-pyran] (**1b**). In a modified Birch reduction[5] using Li–NH_3, **1b** was converted to the 1,4-dihydro enol ether and then *via* acid hydrolysis and rearrangement of the double bond to 3′,4′,5′,6′-tetrahydrospiro[estr-4-ene-17,2′(2′H)-pyran]-3-one (**3b**).

Six-membered spiroethers in the androstane series were made beginning with $LiAlH_4$ reduction of 4-(3β,17β-dihydroxy-5-androsten-17α-yl)butanoic acid lactone[4] to the triol **7b**. Reaction of the triol with *p*-toluenesulfonyl chloride was followed by cyclization of the crude product with potassium *t*-butoxide in refluxing *t*-butyl alcohol; chromatographic separation yielded 3′,4′,5′,6′-tetrahydrospiro[androst-5-ene-17,2′-(2′H)-pyran]-3β-ol (**5**). Oppenauer oxidation then yielded the 3-keto-Δ^4 derivative **3c**.

A four-membered spiroether at C-17 was prepared using ethyl 2-[17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17α-yl]acetate (**8**), prepared in a Reformatsky



1a, $n = 1$
b, $n = 3$



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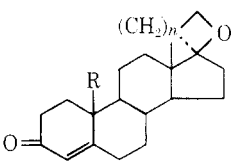
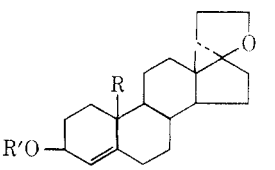
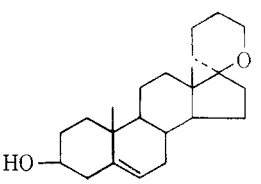


3a, $n = 2$; R = H
b, $n = 3$; R = H
c, $n = 3$; R = CH_3



4a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3CO–
d, R = CH_3; R′ = CH_3CO–



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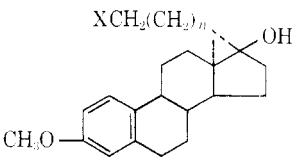
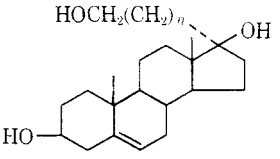
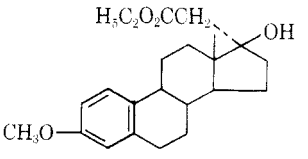


6a, $n = 1$; X = OH
b, $n = 1$; X = Otosyl
c, $n = 1$; X = Cl
d, $n = 2$; X = OH
e, $n = 3$; X = OH



7a, $n = 1$
b, $n = 3$



8

(1) Paper X: Steroidal Aldosterone Blockers. For paper IX see W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966).

(2) None of the compounds reported herein were effective at 2.4 mg/rat in producing a 50% block in the effect of 12μg of deoxycorticosterone acetate. For test details see C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(3) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963).

(4) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(5) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *ibid.*, **26**, 3237 (1961).