known previously only to hydroxylate or epoxidize steroids.[7]

EXPERIMENTAL[8]

Preparation of 4,6-pregnadiene-17α,20β-21-triol-3,11-dione. The organism used in this study was a strain of *Curvularia lunata* (NRRL No. 2380), maintained in this laboratory for more than a year on Sabouraud agar slants at 28–30° for 14 to 20 days at each culture generation. In the conversion studies subcultures were prepared from well sporulated slant cultures, 7 to 14 days old. Such a culture was washed with 5–10 ml. of Sabouraud liquid medium and used for inoculation of Erlenmeyer flasks filled with 100 ml. of the following medium: proteose peptone No. 3 (Difco), 0.5 g.; cerelose, 2 g.; soybean oil meal, 0.5 g.; potassium dihydrogen phosphate, 0.5 g.; sodium chloride, 0.5 g.; yeast extract (Difco), 0.3 g.; tap water, 100 ml. The medium had *p*H 5.6 and was sterilized for 15 min. in an autoclave. The inoculated flasks were shaken on a rotary shaker for 48 hr. at 28°. Samples of 25 mg. (1.1 g. total) of 4,6-pregnadiene-17α, 21-diol-3,11,20-trione were dissolved in 2 ml. of ethanol and added to the heavy black 48-hr. culture. After additional shaking for 48 hr., the whole culture was removed, blended with a knife-blade mixer and extracted three times with equal volumes of chloroform. The chloroform extracts were pooled and evaporated on a steam bath. The residue was analyzed by paper chromatography.

Chromatography of the residue on activated Florosil gave a fraction eluted with 25–50% methylene chloride in ether (140 mg.), purified by crystallization from methanol, m.p. 238–240°; λ_{max}^{MeOH} 281 mμ (ε = 24,000); λ_{max}^{Nujol} 2.87 μ, 2.93 (OH), 5.87 (11,20 C=O), 6.10 (3 C=O), 6.17, 6.29 ($\Delta^{4,6}$), identical with starting material.

The major amount of substance (250 mg.) was obtained by elution with 1.5–2% methanol in methylene chloride. Crystallization from methanol gave a methanol solvate of 4.6-pregnadiene-17α,20β,21-triol-3,11-dione, sinters 125°, m.p. 208–209°, $[\alpha]_D^{25}$ 126° (dioxane), λ_{max}^{MeOH} 282 mμ (ε = 22,800), λ_{max}^{Nujol} 2.95 μ, 3.08 (OH), 5.86 (11 C=O), 6.11 (3 C=O), 6.19, 6.28 ($\Delta^{4,6}$).

Anal. Calcd. for $C_{21}H_{28}O_5 \cdot CH_3OH$: C, 67.32; H, 8.22. Found: C, 67.58; H, 8.06.

The molecular rotation change from the starting material is −475°, agreeing in sign with changes which occur on reduction of a C-20 carbonyl to a hydroxyl group.[6] Analysis of the infrared spectrum showed the presence of three hydroxyl groups.

A separate run gave a polymorphic form, m.p. 204–205°, whose infrared spectrum in Nujol mull differed. When observed in bromoform solution, the spectrum was λ_{max} 2.72 μ, 2.81 (OH), 5.84 (11 C=O), 6.04 (3 C=O), 6.17, 6.25 ($\Delta^{4,6}$), identical with that of the other form.

4,6-Pregnadiene-17α,20β,21-triol-3,11-dione 20,21-diacetate. A sample of 100 mg. of the purified transformation product was treated with 3 ml. of acetic anhydride in 4 ml. of pyridine at room temperature for 18 hr. The solution was poured into dilute acid and extracted with methylene chloride. The residue from evaporation of the dried solution was crystallized from aqueous methanol to give a solvate, which, on drying *in vacuo*, had a melting point of 208.5–210°, $[\alpha]_D^{25}$ 237° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.34; H, 7.39.

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(7) G. M. Shull, 130th Meeting of the AMERICAN CHEMICAL SOCIETY, September, 1956, Atlantic City, N. J., reported that E. J. Agnello, *et al.*, had found a similar reduction as a by-product of the action of *C. lunata*.

(8) All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry and Microanalytical Departments of these laboratories. Interpretations of infrared spectra were performed by Dr. Jo-Yun Chen.

Synthesis of Spirolactams from Nitrocycloalkanes

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During an investigation of the Beckmann rearrangement of spiroketoximes,[1] it became necessary to prepare authentic samples of a series of spirolactams with the nitrogen atom bound directly to the spiro carbon. Two methods of preparation of such compounds have been reported; one is that of Lukes and Blaha,[2] who obtained 1-methyl-1-azaspiro[5,5]undecanone-2 in low yield by the action of the Grignard reagent of 1,5-dibromopentane on *N*-methylglutarimide. The other, which appeared to be more capable of extension to a variety of ring sizes, is the reduction of suitable nitroesters. Three foreign patents[3–5] and more recent work by Moffett[6] report the preparation of 1-azaspiro[4,5]decanone-2 by the hydrogenation of ethyl β-(1-nitrocyclohexyl)propionate.

In extending this second method, nitrocyclopentane and nitrocyclohexane were reacted with methyl or ethyl acrylate, using Triton B as the catalyst,[7] to yield the addition products I and V. Hydrogenation over Raney nickel at room temperature and subsequent cyclization by heating gave good yields of the spiropyrrolidones IX and XII.

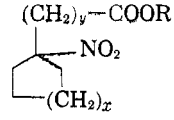
To increase the size of the lactam ring, it was necessary to extend the length of the ester side chain. In one trial, the nitro-ester V was reduced with lithium aluminum hydride and the resulting amino alcohol converted to its *O*,*N*-di-*p*-toluenesulfonate. Heating this with potassium cyanide in an attempt to displace the *O*-tosylate gave no nitrile, however.

The chain lengthening was readily accomplished by the Arndt-Eistert homologation. Hydrolysis of the nitro-esters gave the corresponding acids, II and VI, which were converted successively to the

(1) R. K. Hill and R. T. Conley, *Chemistry and Industry*, 1314 (1956).
(2) R. Lukes and K. Blaha, *Chem. Listy*, 46, 726 (1952).
(3) Swiss patent 227,125 (1942).
(4) French patent 880,400 (1943); *Chem. Zentr.*, 114, 218 (1943 II).
(5) Dutch patent 57,433 (1946).
(6) R. B. Moffett, abstracts of papers, 130th Meeting, ACS, Atlantic City, N. J., September, 1956, 4N.
(7) H. A. Bruson, U. S. Patent 2,390,918; *Chem. Abstr.* 40, 2456 (1946).

TABLE I

NITRO ACIDS AND ESTERS

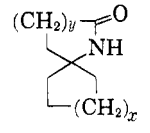


No.	X	Y	R	Formula	M.P. or B.P., °C.	% Nitrogen Calcd.	% Nitrogen Found
I	1	2	CH_3	$C_9H_{15}NO_4$	B.p. 100/0.4 mm.	6.96	6.95
II	1	2	H	$C_8H_{13}NO_4$	M.p. 59.5–60.5[a]	7.48	7.47
III	1	3	C_2H_5	$C_{11}H_{19}NO_4$	B.p. 108–109/0.2 mm.	6.11	6.36
IV	1	4	C_2H_5	$C_{12}H_{21}NO_4$	B.p. 95–97/0.01 mm.	5.76	5.70
V	2	2	C_2H_5	$C_{11}H_{19}NO_4$	B.p. 117–118/0.6 mm.	6.11	6.00
VI	2	2	H	$C_9H_{15}NO_4$	M.p. 93.7–94.2	6.96	6.65
VII	2	3	C_2H_5	$C_{12}H_{21}NO_4$	B.p. 128/0.1 mm.	5.76	6.03[b]
VIII	2	3	H	$C_{10}H_{17}NO_4$	M.p. 96.5–97	6.51	6.29[c]

[a] Recrystallized from 60–70° pet. ether. [b] Calcd.: C, 59.24; H, 8.70. Found: C, 59.21; H, 8.60. [c] Calcd.: C, 55.80; H, 7.96. Found: C, 56.18; H, 8.09.

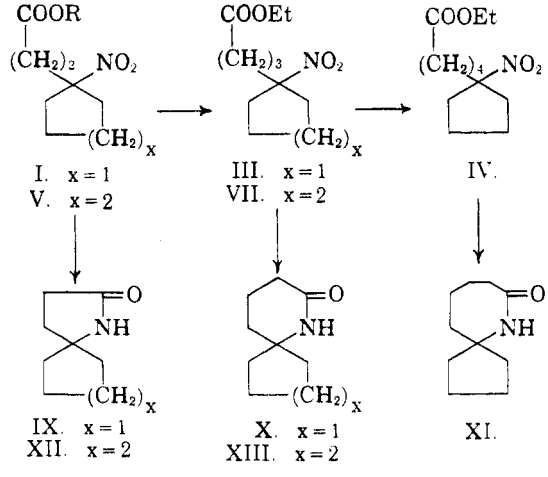
TABLE II

SPIROLACTAMS



Lactam	X	Y	M.P., °C.	Calculated % C	Calculated % H	Calculated % N	Found % C	Found % H	Found % N
IX	1	1	125.6–126.2	69.03	9.41	10.06	69.28	9.37	9.80
X	1	2	106.5–107	70.55	9.87	9.14	70.78	9.72	8.85
XI	1	3	112.7–113.5	71.81	10.25	8.38	71.66	10.17	8.13
XII[a]	2	1	132.2–132.3[b]	70.55	9.87	9.14	70.41	9.84	9.12
XIII	2	2	117–118	71.81	10.25	8.38	71.71	10.05	8.10

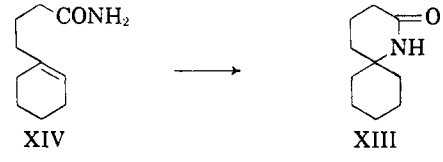
[a] References 3–6. [b] Lit.[4] m.p. 132–133°.



acid chloride, diazoketone, and ethyl esters III and VII. Raney nickel hydrogenation, followed by refluxing in ethanol, again gave good yields of the spiropiperidones X and XIII.

A repetition of the Arndt-Eistert reaction on the nitro-acid II gave the corresponding valerate IV, which on reduction and cyclization yielded the homopiperidone XI.

A second possible approach to the synthesis of these spirolactams was briefly tested. Analogous to the acid-catalyzed lactonization of β,γ-, γ,δ-, or δ,ϵ-unsaturated acids would be the cyclization of the corresponding amides to lactams. In the one experiment tried, γ-(1-cyclohexenyl)butyramide, XIV, was quantitatively converted by heating briefly in polyphosphoric acid to the spiropiperidone XIII. It appears that this reaction may offer a convenient synthesis of lactams, and experiments are in progress to test its generality.



XIV XIII

The properties of the nitro-acids and esters and the spirolactams prepared in this work are shown in Tables I and II.

Lactams XII and XIII were tested for analgesic activity through the courtesy of Dr. Howard J. Glenn of Abbott Laboratories. In a modified Wolff, Hardy, and Goodell procedure in dogs, neither showed any increase in pain threshold.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns hot stage microscope, and are uncorrected. Microanalyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. Since the same procedure was often used to prepare several compounds, details are given below for representative experiments.

Ethyl-β-(1-nitrocyclohexyl)propionate (V). To a mechanically stirred solution of 129.2 g. (1.0 mole) of nitrocyclohexane, 50 ml. of *t*-butyl alcohol, and 12 g. of a 35% methanolic solution of Triton B was added dropwise, over 2 hr., 100.1 g. (1.0 mole) of redistilled ethyl acrylate. The reaction was mildly exothermic, and the temperature was maintained at 35–40° with a cold water bath. When the addition was completed, the mixture was stirred at room temperature for 5 hr. and allowed to stand overnight. The mixture was acidified with dilute hydrochloric acid and extracted with chloroform. After washing with water and drying over magnesium sulfate, the extracts were concentrated and the residue distilled through a short Vigreux column. The nitroester distilled as a pale green oil at 139–141°/3 mm., 117–118°/0.6 mm., and weighed 210.5 g. (91.6%).

β-(1-nitrocyclohexyl)propionic acid (VI).[8] The nitro-ester (54 g.) was refluxed with a solution of 40 g. of sodium hydroxide in 350 ml. of water for 10 hr. After cooling in ice, the solution was acidified with concentrated hydrochloric acid and allowed to stand in the refrigerator. The collected solid weighed 39 g. (83%). Recrystallized from water, it yielded white plates, m.p. 93.0–93.6°. Recrystallization from ethanol-water raised the melting point to 93.7–94.2°.

Ethyl γ-(1-nitrocyclohexyl)butyrate (VII). Thionyl chloride was purified by successive distillations from cholesterol, quinoline, and linseed oil. The nitro-acid (20 g.) was refluxed with 100 ml. of thionyl chloride for 4 hr., and the excess thionyl chloride was evaporated, finally by distilling 50 ml. of dry benzene from the solution. The acid chloride was generally used without further purification; in one run it was distilled *in vacuo*, b.p. 105–109°/0.1 mm. When a sample was treated with water, it regenerated the original acid.

A solution of the acid chloride in 60 ml. of anhydrous ether was added to an ethereal solution of excess diazomethane. After standing overnight, the ether was removed at reduced pressure, leaving the diazoketone as an orange oil. It was heated to reflux in 200 ml. of absolute ethanol, while over a period of 48 hr. a slurry of silver oxide (from 10 g. of silver nitrate) in ethanol was added in portions. The mixture was filtered and the filtrate distilled. The nitro-ester was collected at 128–131°/0.1 mm., and weighed 17.8 g. (73.6%).

1-Azaspiro[4,5]decanone-2 (XII).[3-6] A solution of 40 g. (0.175 mole) of ethyl-β-(1-nitrocyclohexyl)propionate in 125 ml. of ethanol was hydrogenated over Raney nickel at 38 pounds pressure and room temperature. After 6 hr., 0.55 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate refluxed overnight. Distillation of the alcohol left a solid residue, which was collected and washed with a little ether. The crystals weighed 22 g. and melted at 132–132.5°. A second crop of 3.9 g. was isolated from the filtrate by sublimation, bringing the total yield to 96%. The lactam was easily purified by recrystallization from 60–70° petroleum ether or by sublimation at 100°/0.03 mm., though the melting point remained unchanged.

3-(1-Aminocyclohexyl)propanol-1. A solution of 25.9 g. (0.113 mole) of ethyl β-(1-nitrocyclohexyl)propionate in 25 ml. of anhydrous ether was added with stirring over 2 hr. to a solution of 11.8 g. (0.31 mole) of lithium aluminum hydride in 200 ml. of ether. After stirring and refluxing for 2 hr., the mixture was treated with 20 ml. of ethyl acetate, then with saturated aqueous sodium sulfate. Magnesium sulfate was added to coagulate the alumina, and the mixture filtered and washed with hot ethanol. The filter cake was digested three times with hot alcohol, and the combined filtrates dried over magnesium sulfate. Concentration and vacuum distillation gave the amino-alcohol as a pale green oil, b.p. 98–100°/0.15 mm., weighing 11.0 g. (62%). After standing for a few hours, it crystallized to white plates, which, recrystallized from ether, melted at 69.5–70.5°.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.80; H, 12.01; N, 8.97.

The *O,N-diacetate*, prepared with acetic anhydride in pyridine, melted at 96.5–97.5° after successive recrystallizations from cyclohexane and ether.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 65.54; H, 9.41; N, 5.93.

The *O,N-di-p-toluenesulfonate* was prepared by the Hinsburg procedure.[9] After two recrystallizations from ethanol, it melted at 176.5–177.5°.

Anal. Calcd. for $C_{23}H_{31}NO_5S_2$: C, 59.33; H, 6.71; N, 3.01; S, 13.77. Found: C, 59.49; H, 6.63; N, 2.95; S, 13.53.

γ-(1-cyclohexenyl)butyramide (XIV). γ-(1-cyclohexenyl-butyric acid[10] (8.2 g.) was esterified with an ethereal solution of diazomethane from 25 g. of nitrosomethylurea. After removal of the ether, the residual ester was taken up in 60 ml. of methanol, saturated at 0° with dry ammonia, and heated at 125° overnight in a sealed bomb. After charcoal treatment and filtration, the methanol was evaporated to a small volume and the amide precipitated with water. Recrystallized from ethyl acetate-petroleum ether, it melted at 97–98°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.66; H, 10.04; N, 8.05.

Acid cyclization of amide. Two hundred fifty mg. of γ-(1-cyclohexenyl)butyramide was stirred into 12 g. of polyphosphoric acid and heated at 120–130° for 10 min. This solution was poured into a mixture of ice and sodium hydroxide solution, stirred until homogeneous, and extracted with chloroform. The extracts were washed with water, dried over sodium sulfate, and evaporated. The solid residue weighed 250 mg., and after recrystallization from 60–70° petroleum ether, melted at 116.5–118°, alone or admixed with a sample of 1-azaspiro[5,5]undecanone-2 (XIII).

Acknowledgments. It is a pleasure to thank Dr. R. W. H. Gentry of the Explosives Department, E. I. du Pont de Nemours & Company, for generous gifts of the nitrocycloalkanes used in this work.

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(8) H. Hopff, O. von Schickh, and G. Wiest, German patent 851,342 (1952).

(9) No evidence was found for the formation of a spiropyrrolidine tosylate analogous to the cyclization reported by R. F. Brown and N. M. Van Gulick, *J. Am. Chem. Soc.*, 77, 1079 (1955).

(10) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1637 (1935).

Preparation of Dialkylanilines by the Reaction of Bromobenzene with Sodium Amide and Dialkylamines[1]

J. F. BUNNETT AND T. K. BROTHERTON[2]

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Reactions have been reported[3] of the monobro-

(1) Financial assistance from the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(2) American Enka Fellow, 1954–55; R. J. Reynolds Fellow, 1955–56. This note is based on the Ph.D. thesis of T. K. Brotherton, October, 1956.

(3) Bunnett and Brotherton, *J. Am. Chem. Soc.*, 78, 155 (1956).