packed with stainless steel helices[8] gave the pure carbamates as colorless to pale yellow liquids. Although there was considerable variation in yields, 60% appeared to be about average.

N,N'-Bis(4-fluoro-3-trifluoromethylphenyl)urea.—This compound was obtained as a by-product from the preparation of the carbamate of 5-amino-2-fluorobenzotrifluoride. It was recovered as an insoluble material from the petroleum ether extraction. Recrystallization from ethanol gave the pure compound, m.p. 223–224°.

Anal. Calcd. for $C_{15}H_8F_8N_2O$: C, 46.89; H, 2.10; N, 7.29. Found: C, 46.66; H, 2.28; N, 7.45.

5-Amino-2-fluorobenzotrifluoride.—To a stirred mixture of 2200 g. (39.4 g.-atoms) of iron filings and 5 l. of 0.78 *N* ammonium chloride solution at reflux temperature was added 2060 g. (9.85 moles) of 5-nitro-2-fluorobenzotrifluoride[9] in a period of 45 min. The amine was steam distilled from the reaction mixture, separated from the water layer, dried over anhydrous magnesium sulfate, and flash distilled, yielding 1512 g. (86%). Fractional distillation gave pure product, b.p. 207–207.5° (microcapillary), $n^{25}D$ 1.4641.

Anal. Calcd. for $C_7H_5F_4N$: C, 46.94; H, 2.81; N, 7.82. Found: C, 46.82; H, 2.95; N, 7.91.

The acetyl derivative was prepared in the usual manner. Vacuum sublimation gave a white solid, m.p. 60–61°.

Anal. Calcd. for $C_9H_7F_4NO$: N, 6.33. Found: N, 6.39.

3-Nitro-2,5-difluorobenzotrifluoride.[10]—To a stirred mixture of 88.6 ml. (2 moles) of fuming nitric acid (sp. gr. 1.49–1.5) and 350 ml. of fuming sulfuric acid (30% SO_3), 183 g. (1 mole) of 2,5-difluorobenzotrifluoride[11] was added dropwise and the exothermic reaction was controlled at 55–60°. After addition, stirring was continued for 1 hr. and the reaction mixture then was allowed to cool to room temperature. Upon pouring slowly over crushed ice, the crude product separated as a heavy oil. Sodium carbonate was added and the mixture was steam distilled, yielding 152 g. 67%). Vacuum fractional distillation gave pure material, b.p. 89° (20 mm.).

Anal. Calcd. for $C_7H_2F_5NO_2$: C, 37.02; H, 0.89; N, 6.17. Found: C, 37.29; H, 0.85; N, 6.28.

Evidence in support of the 3-position for the nitro group is based on the reduction of 3-nitro-2,5-difluorobenzotrifluoride to the amine and a subsequent Schiemann conversion to 2,3,5-trifluorobenzotrifluoride, b.p. 105°. The structure of the latter was verified by nuclear magnetic resonance study. Further evidence is supplied by a nitration study of 2-acetylamino-5-fluorobenzotrifluoride.[12]

3-Amino-2,5-difluorobenzotrifluoride.[10]—An iron reduction of 3-nitro-2,5-difluorobenzotrifluoride by the procedure previously described readily gave the corresponding amine. The crude amine was collected by steam distillation, yielding 97%. Vacuum distillation gave pure material as a heavy, colorless liquid, b.p. 58° (9.6 mm.)

Anal. Calcd. for $C_7H_4F_5N$: C, 42.65; H, 2.04; N, 7.11. Found: C, 42.72; H, 2.21; N, 7.21.

The acetyl derivative was prepared in the usual manner. Recrystallization from petroleum ether (b.p. 90–120°) gave white needles, m.p. 104.5–105.5°.

Anal. Calcd. for $C_9H_6F_5NO$: C, 45.20; H, 2.53; N, 5.86. Found: C, 45.33; H, 2.43; N, 5.82.

(8) Heli-Pak No. 3008, Podbielniak Co., Chicago 17, Ill.
(9) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).
(10) The assistance of H. G. Schneider in this preparation is acknowledged.
(11) G. C. Finger and F. H. Reed, *J. Am. Chem. Soc.*, **66**, 1972 (1944).
(12) G. C. Finger and M. Knell, *Trans. Illinois State Acad. Sci.*, **38**, 71 (1945).

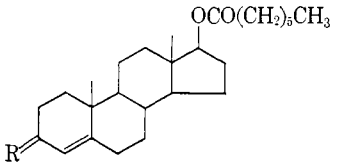
Testosterone 17-Heptanoate 3-Benziloylhydrazone

CLARENCE H. GLEASON

Research Laboratories, Charles E. Frosst & Co., Montreal, Canada

Received March 7, 1964

By converting testosterone 17-heptanoate (I) to its 3-benziloylhydrazone (II) it was observed that the androgenic effects of I could be substantially prolonged.[1] In combination with estradiol 3-monobenzoate and estradiol 3,17-diheptanoate, II was found to be useful for the supression of lactation[2,3] as well as for treatment of the menopausal syndrome.[4,5]



I, R = O
II, R = NNHCOCOH(C_6H_5)$_2$

Experimental

Testosterone 17-Heptanoate 3-Benziloylhydrazone (II).—To a solution of I (10 g.) in benzene (50 ml.) was added glacial acetic acid (0.5 ml.) and benziloylhydrazide (6.1 g.). The mixture was heated under reflux for 2 hr. The solvent was removed by distillation under reduced pressure, and the residue was taken up in ether (50 ml.). The ether solution was washed successively with water, 5% sodium bicarbonate solution, and water. After drying the organic phase over anhydrous sodium sulfate, isopropyl ether (75 ml.) was added, and the solution was chilled. The solid was separated by filtration and purified by recrystallization from ether–isopropyl ether (2:3) to yield 12.1 g. of II, m.p. 114–115°, $[\alpha]^{25}D$ +156° (*c* 1, ethanol), λ_{max}^{EtOH} 282 mμ (ε 34,000).

Anal. Calcd. for $C_{40}H_{52}N_2O_4$: C, 76.88; H, 8.38; N, 4.48. Found: C, 77.08; H, 8.24, N, 4.55.

(2) M. J. A. Kelly and T. Primrose, *Can. Med. Assoc. J.*, **83**, 1240 (1960).
(3) S. M. Dodek, *Clin. Obstet. Gynecol.*, **3**, 1099 (1960).
(4) R. B. Greenblatt, W. E. Barfield, and E. C. Jungck, *Can. Med. Assoc. J.*, **86**, 113 (1962).
(5) M. Bertrand, *Union Med. Canada*, **91**, 291 (1962).

Amides from Nitriles and Alcohols by the Ritter Reaction

JOHN A. SANGUIGNI AND ROBERT LEVINE

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania

Received February 28, 1964

A series of compounds of the type R'CONHR has been synthesized for screening as possible antispasmodics, anticonvulsants, and hypnotics. The amides which have been prepared appear in Tables I–III.

TABLE I
AMIDES, $RCONHCH_2C_6H_5$

R	% yield	M.p., °C.
CH_3	72.5	60–61[a]
CH_3CH_2	45	46–47[b]
CH_2=CH	50	67.6–68.2[c]
$C_6H_5CH_2$	27	119–121[d]
C_6H_5	55	103.2–104.2[e]

[a] J. Shakosch, *Ber.*, **5**, 697 (1872). [b] C. A. Buehler and C. A. Mackenzie, *J. Am. Chem. Soc.*, **59**, 421 (1937). [c] G. Kränzlein and M. Corell, German Patent 752,481 (Nov. 10, 1952); *Chem. Abstr.*, **50**, 10132 (1956). [d] R. Delaby, P. Raynaud, and F. Lilly, *Bull. Soc. Chim. France*, 2067 (1961). [e] E. Beckman, *Ber.*, **23**, 3334 (1890).

Experimental

Two typical experiments are described.

N-Benzhydrylacetamide.—Acetonitrile (0.2 mole, 8.2 g.) and concentrated sulfuric acid (0.1 mole, 10.1 g.) were placed in a 250-ml. flask. To the rapidly stirred mixture, benzhydrol (0.1 mole, 18.4 g.), dissolved in 50 ml. of anhydrous di-*n*-butyl

TABLE II

AMIDES, $RCONHCH(C_6H_5)_2$

R	% yield	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H[a]	86	132–133	$C_{14}H_{13}NO$	79.60	79.75	6.20	6.06	6.63	7.03
CH_3	85	144–146[b]							
CH_3CH_2	97	140.4–141.6[c]							
$CH_2{=}CH$	70	177.8–178.8	$C_{16}H_{15}NO$	80.99	80.87	6.37	6.52	5.89	5.83
$C_6H_5CH_2$	97	161.2–162.4	$C_{21}H_{19}NO$	83.70	84.10	6.36	6.58	4.65	4.90
C_6H_5	86	171–172.4[b]							
d	64	188–192	$C_{20}H_{28}N_2O_2$	80.34	80.58	6.29	6.64	6.25	6.57
CH_2CO_2H[e]	75	94–94.4	$C_{16}H_{15}NO_3$	71.40	71.72	5.61	5.80	5.20	5.42
$CH_2CO_2C_2H_5$[f]	71	92.3–93.2	$C_{18}H_{19}NO_3$	72.71	72.58	6.44	6.39	4.71	5.12

[a] The hydrogen cyanide was prepared *in situ* from sodium cyanide. [b] H. L. Wheeler, *Am. Chem. J.*, **26**, 354 (1901); see also ref. 11. [c] W. Davies, T. H. Ramsay, and E. R. Stove, *J. Chem. Soc.*, 2633 (1949). [d] The product is N,N′-bis(benzhydryl)succinamide. [e] Starting compound, cyanoacetic acid. [f] Starting compound, ethyl cyanoacetate.

TABLE III

AMIDES, $RCONHC(C_6H_5)_3$

R	% yield	M.p., °C.
CH_3	93	206.5–207.2[a]
CH_3CH_2	91	191–192[b]
$C_6H_5CH_2$	68	187.4–188.8[c]
C_6H_5	74	159–160[d]

[a] W. Hemilian and H. Silberstein, *Ber.*, **17**, 744 (1884). [b] *Anal.* Calcd. for $C_{22}H_{21}NO$: C, 84.17; H, 6.71; N, 4.44. Found: C, 84.13; H, 6.39; N, 4.70. [c] *Anal.* Calcd. for $C_{27}H_{23}NO$: C, 85.91; H, 6.14. Found: C, 86.26; H, 6.10. [d] I. Vosburgh, *J. Am. Chem. Soc.*, **38**, 2081 (1916).

ether, was added. The reaction temperature was maintained at 50° by the use of a cooling bath; the mixture was stirred for 3 hr., allowed to stand overnight, and was then poured onto a slurry of ice–water. The solid which precipitated was filtered. In this way, 19.1 g. (85%) of product, m.p. 144–146°, was obtained.

N-Benzylacetamide.—Acetonitrile (50 ml.) and concentrated sulfuric acid (0.2 mole, 20.2 g.) were placed in the reactor; the temperature of the mixture rose to 70°. On the addition of benzyl alcohol (0.2 mole, 21.6 g.) the temperature rose to 85°. The reaction mixture was maintained at the boiling point of the acetonitrile during the addition of the alcohol. The reaction temperature was moderated with an ice bath when this was necessary. The mixture was allowed to cool to room temperature and it then was stirred for an additional 2 hr. It was poured onto a slurry of ice–water, made basic with solid sodium carbonate, and was extracted with several portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, the solvent was removed at atmospheric pressure, and the residue was distilled *in vacuo* to give 21.7 g. (72.5%) of material, b.p. 153–156° (4.5 mm.), m.p. 60–61°.

Substrates for Cytochemical Demonstration of Enzyme Activity. I. Some Substituted 3-Indolyl-β-D-glycopyranosides[1a]

JEROME P. HORWITZ, JONATHAN CHUA, RONALD J. CURBY,[1b] ARTHUR J. TOMSON, MARGARET A. DA ROOGE, BENJAMIN E. FISHER, JOSE MAURICIO, AND IRWIN KLUNDT

The Rollin H. Stevens Memorial Laboratory of the Detroit Institute of Cancer Research, Detroit, Michigan 48201

Received March 6, 1964

The histochemical demonstration of nonspecific esterase in mammalian tissue through the use of substituted indoxyl esters has received considerable attention during the past decade.[2] The enzymatically released indoxyl is oxidized rapidly to an insoluble indigo which can be seen readily at the sites of activity. Recently the "indigogenic principle" was applied successfully to the histochemical localization of mammalian glucosidase through the use of 5-bromo-3-indolyl-β-D-glucopyranoside[3] for which independent syntheses had been recorded both by Anderson and Leaback[4] (method A) and the present authors[5] (method B). The methods have now been extended to some dihalogeno-3-indolyl-β-D-glycosides as part of a search for new substrates for the precise localization of mammalian glycosidases.[6]

Experimental[7]

The following procedure is considered typical of method A by which an acylohalogenoglycose may be coupled with either 1-acetyl-5-bromo-4-chloroindol-3-ol[8] or 1-acetyl-5-bromo-6-chloroindol-3-ol (*vide infra*). Deacylation of the condensation product was effected in the usual manner with catalytic quantities of sodium methoxide in an excess of dry methanol.

1-Acetyl-5-bromo-6-chloro-3-indolyl-tetra-*O*-acetyl-β-D-galactopyranoside.—A mixture of 1.81 g. (6.3 mmoles) of 1-acetyl-5-bromo-6-chloroindol-3-ol and 3.12 g. (7.6 mmoles) of tetra-*O*-acetyl-β-D-galactopyranosyl bromide in 100 ml. of acetone, cooled to 0°, was gassed for 0.5 hr. with a stream of nitrogen. A solution of 7.3 ml. of 1 *N* sodium hydroxide was added dropwise, with stirring, to the cold suspension under an atmosphere of nitrogen. The reaction mixture was stirred overnight (16 hr.) in a cold room (0°). The blue-green solution was evaporated to dryness *in vacuo* at *ca.* 30° and the oily residue solidified after extensive washing with water followed by trituration with cold ethanol. Two recrystallizations (Norit) from ethanol provided an analytical sample in the form of colorless fine needles, 1.89 g. (two crops, 49% yield), m.p. 178–179°, $[\alpha]^{23}D$ −20° (*c* 1.0, acetone).

Anal. Calcd. for $C_{24}H_{25}BrClNO_{11}$: C, 46.58; H, 4.07; N, 2.26. Found: C, 46.62; H, 4.16; N, 2.40.

5-Bromo-6-chloro-3-indolyl-β-D-galactopyranoside.—A solution of 1.0 g. (1.6 mmoles) of the acetylated product in 50 ml. of dry methanol containing 0.1 mmole of sodium methoxide was stirred overnight at 5°. The reaction mixture was neutralized with a drop of glacial acetic acid and the solution was evaporated to dryness *in vacuo* at room temperature. The residue crystallized as an amorphous, colorless powder from ethyl acetate, 0.45 g., m.p. 180–181° dec. The filtrate afforded two additional crops of material after reduction to *ca.* 0.5 of the original volume, 0.12 g. (86% total yield), m.p. 179–181° dec. A single recrystal-

(1) (a) This work was supported in part by research grants CA-02624 and CA-02903 from the National Cancer Institute, Public Health Service, and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation; (b) Deceased 1962.

(2) For a review and key literature references see M. S. Burstone, "Enzyme Histochemistry and Its Application in the Study of Neoplasms," Academic Press, New York, N. Y., 1962, p. 304.

(3) B. Pearson, M. Andrews, and F. Grase, *Proc. Soc. Expl. Biol. Med.*, **108**, 619 (1961).

(4) F. B. Anderson and D. H. Leaback, *Tetrahedron*, **12**, 236 (1961).

(5) See ref. 3.

(6) A portion of the histochemical findings has already been reported: B. Pearson, P. L. Wolf, and J. Vazquez, *Lab. Invest.*, **12**, 1249 (1963).

(7) All melting points were taken with a Thomas-Hoover apparatus and are corrected. Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(8) S. J. Holt, A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 1217 (1958).