methanol was stirred and refluxed for 3 hr, then worked up as in the previous example. The ether solution was evaporated and the residue, 8.1 g of oily crystals, was dissolved in benzene and chromatographed on alumina. Elution with benzene furnished 4.9 g of white needles in the first peak, which were combined and recrystallized from ether and then as shown for **10** in Table I. Elution with 10% ethyl acetate–benzene gave a second peak containing 3.0 g of yellow prisms which were recrystallized as shown for **11**, Table I.

B. Using Diazomethane.—A large excess of diazomethane in 125 ml of ether was added to 4.0 g of 3-phenyl-4-cinnolinol[1b] dissolved in 70 ml of dimethyl sulfoxide. The solution stood for 2 hr and then was concentrated by boiling to 100 ml. It was cooled, decomposed with a small amount of dilute HCl, then made alkaline and extracted with ether. The ether extracts were washed well with water, dried,[8] and concentrated to 50 ml. On cooling 2.2 g of light yellow flakes, mp 105–108°, separated, which when recrystallized from Skellysolve B furnished white needles, mp 107–108°, identical[10] with **10**.

C. By Rearrangement of 4-Methoxy-3-phenylcinnoline.—A 1.3-g. portion of **12** was melted and heated slowly to 160° for 0.5 hr under nitrogen, then sublimed at 200° (0.1 mm). The oily solid was taken up in ether (a fair amount of tar remained) and extracted with dilute NaOH, then the ether was dried,[8] concentrated, and diluted with Skellysolve B.[12] After the ether was boiled off, the solution was stirred with activated charcoal, filtered, and concentrated. On cooling, white needles separated; 0.32 g, mp 107–108°, identical[10] with **10**.

The alkaline extract above furnished on acidification 0.12 g of a white powder, mp 267–269°, identical[10] with 3-phenyl-4-cinnolinol.[1b]

Structure–Hypoglycemic Activity Relationships in 1-Naphthylalkylamines

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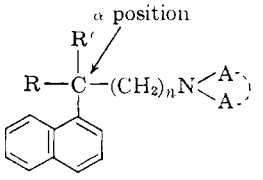
Received March 1, 1966

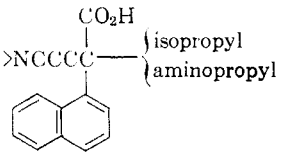
In previous papers we reported hypoglycemic screening results of many 1-naphthylalkylamines.[1] The compounds possessed the general structure **1**, in which R was a hydrogen atom, or an alkyl or aminoalkyl group; R′ was a cyano, substituted or unsubstituted carbamyl, free or esterified carboxy, carbureido, ketimido, or keto group; NAA was a tertiary amino group; n = 2 or 3. During this investigation the most potent compounds were found to be α-isopropyl-α-(3-dimethylaminopropyl)- and α,α-di(3-dimethylaminopropyl)-1-naphthylacetic acids,[1b] which are now undergoing a more detailed pharmacological and toxicological investigation.



1

Some conclusions may be drawn about relationships between hypoglycemic action and the structure of the above compounds and of the substances prepared in the present work. First, the activity is mainly imparted to the compounds by the presence in the α position of an aminoalkyl group of the type shown in **1**. Maximum potency is reached for n = 3; in fact, compounds carrying aminoethyl or aminobutyl chains have been found to be somewhat less active. Another important point is that 1-naphthyl derivatives are, on the whole, more interesting than the corresponding diphenyl, phenyl, and aliphatic compounds, whose activity decreases in this order. As for the radical R, the highest potency is imparted by an isopropyl or aminopropyl group while in the case of R′ optimal activity is shown, on the whole, by the acids, for both the 1-naphthyl and the other series.

The tentative conclusion that, in the series investigated, the skeleton **2** represents the best structure for high-potency hypoglycemic compounds may be drawn from the above considerations.



2

Experimental Section[2]

Chemistry.—The compounds are listed in Table I, along with yields, physical constants, and analytical data. In the majority of cases the synthesis procedures followed the general methods we previously described.[1,3]

α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetonitrile (I).—Sodamide was prepared by adding sodium (18.4 g, 0.8 g-atom) to anhydrous liquid ammonia (360 ml), in small portions and with stirring, in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (0.52 g). α,α-Diisopropylacetonitrile[4] (50.1 g, 0.4 mole) was then cautiously added, followed by 3-(N,N-dimethylamino)-1-chloropropane (97.3 g, 0.8 mole) in ethereal solution (400 ml). The mixture was stirred for 30 hr using a reflux condenser cooled with Dry Ice–acetone. The ammonia was allowed to evaporate and the residue was cautiously decomposed with water. The ethereal layer was extracted with 10% HCl, the acid solution was made alkaline with 30% NaOH, and the oil was separated and extracted with ether and dried (Na_2SO_4). After removal of the solvent, the residue was distilled at 142–143° (15 mm), giving a colorless oil.

α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetamide (II).—I (42 g, 0.2 mole) was hydrolyzed by heating with 85% H_2SO_4 (126 ml) for 36 hr at 90–95°. The crude product was crystallized from petroleum ether (bp 40–70°) giving colorless crystals, mp 85–86°.

α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetic Acid Hydrochloride (III).—Anhydrous HCl was bubbled for 1.5 hr through a cooled solution of II (22.8 g, 0.1 mole) in glacial acetic acid (114 ml). Freshly distilled isoamyl nitrite (28.5 ml) was then added over 2 hr, with stirring, and the mixture was maintained for an additional 2 hr at room temperature and then at 100° for 15 hr. The resulting solution was treated twice more in the same manner, and then the solvent was removed at 50° under reduced pressure. The residue was triturated with ether and crystallized from acetone–ethanol to give colorless crystals, mp 212–213°.

α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetonitrile (V).—Alkylation of IV (60.7 g, 0.3 mole) with 2-bromopropane (73.8 g, 0.6 mole), carried out by refluxing for 18 hr in benzene (600 ml) and in the presence of sodamide (23.4 g, 0.6 mole), gave a colorless oil, bp 115–117° (0.5 mm).

α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetamide (VI).—Hydrolysis of V (48.9 g, 0.2 mole) by heating with 90%

(1) (a) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **9**, 603 (1966); (b) S. Casadio, T. Bruzzese, G. Pala, G. Coppi, and C. Turba, *ibid.*, **9**, 707 (1966).

(2) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(3) G. Pala, S. Casadio, T. Bruzzese, E. Crescenzi, and E. Marazzi-Uberti, *J. Med. Chem.*, **8**, 698 (1965).

(4) M. S. Newman, T. Fukunaga, and T. Miwa, *J. Am. Chem. Soc.*, **82**, 873 (1960).

TABLE I

Compd	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetonitrile (I)	87[a]	142–143 (15)	$C_{13}H_{26}N_2$	74.22	12.46	13.32	73.75	12.42	13.51
α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetamide (II)	68[b]	85–86	$C_{13}H_{28}N_2O$	68.37	12.36	12.27	67.91	12.24	12.28
α,α-Diisopropyl-α-(3-dimethylaminopropyl)acetic acid (III)	90[b]	212–213[c]	$C_{13}H_{27}NO_2 \cdot HCl$	58.73	10.62	5.27	58.82	10.58	5.29
α-(3-Dimethylaminopropyl)phenylacetonitrile[d] (IV)	78[a]	128–130 (0.6)	$C_{13}H_{18}N_2$	77.18	8.97	13.85	76.68	9.15	13.82
α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetonitrile (V)	81[a]	115–117 (0.5)	$C_{16}H_{24}N_2$	78.63	9.90	11.46	79.30	10.04	11.36
α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetamide (VI)	83[b]	81–82	$C_{16}H_{26}N_2O$	73.24	9.99	10.68	72.67	9.98	10.72
α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetic acid (VII)	94[b]	221–222[c]	$C_{16}H_{25}NO_2 \cdot HCl$	64.09	8.74	4.67	63.79	8.75	4.74
α-(3-Dimethylaminopropyl)diphenylacetonitrile[e] (VIII)	85[a]	153–155 (0.5) 71–72	$C_{19}H_{22}N_2$	81.97	7.97	10.06	81.77	9.01	10.05
α-(3-Dimethylaminopropyl)diphenylacetic acid[f] (IX)	56[b]	176–177[g]	$C_{19}H_{23}NO_2 \cdot H_2SO_4$	57.71	6.37	3.54	57.88	6.23	3.53
α-(4-Dimethylaminobutyl)-1-naphthylacetonitrile (X)	62[a]	170–172 (0.5)	$C_{18}H_{22}N_2$	81.16	8.33	10.52	81.67	8.49	10.69
α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetonitrile (XI)	79[a]	161–163 (0.2)	$C_{21}H_{28}N_2$	81.77	9.15	9.08	82.16	9.16	9.03
α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetamide (XII)	78[a]	197–200 (0.3) 97–98	$C_{21}H_{30}N_2O$	77.25	9.26	8.58	76.67	9.21	8.59
α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetic acid (XIII)	86[b]	239–240[c]	$C_{21}H_{29}NO_2 \cdot HCl$	69.31	8.31	3.85	68.59	8.16	3.80

[a] Once distilled. [b] Crude product. [c] Hydrochloride. [d] F. F. Blicke, A. J. Zambito, and R. E. Stenseth [*J. Org. Chem.*, **26**, 1826 (1961)] reported bp 108–109° (0.5 mm), yield 82%. [e] Lit.[d] mp 66–68°, yield 87%. [f] Reported as the free base, mp 211–215° dec, yield 54%, by C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins [*J. Med. Chem.*, **7**, 302 (1964)]. [g] Hydrogen sulfate. *Anal.* Calcd: S, 8.09. Found: S, 8.07.

H_2SO_4 (98 ml) at 90–95° for 6 hr, yielded a solid which on crystallization from petroleum ether (bp 40–70°) gave colorless crystals, mp 81–82°.

α-Isopropyl-α-(3-dimethylaminopropyl)phenylacetic Acid Hydrochloride (VII).—A solution of VI (26.2 g, 0.1 mole) in glacial acetic acid (131 ml) was treated with anhydrous HCl bubbled through for 1.5 hr. Isoamyl nitrite (32.7 ml) was then added over 2 hr and the mixture was maintained at room temperature for additional 2 hr and then at 100° for 15 hr. The above procedure was repeated once again to give a colorless product, melting at 221–222° after crystallization from 2-propanol.

Di-5-cyano-5-(1-naphthyl)amylformal.—Alkylation of 1-naphthylacetonitrile (167.2 g, 1 mole) with di-4-chlorobutylformal[5] (75.5 g, 0.33 mole), carried out by refluxing for 2 hr in toluene (1 l.) and in the presence of sodamide (39 g, 1 mole), gave a viscous brown oil which showed some degree of decomposition on distilling. This product was then heated to 180° (0.4 mm) to remove a certain amount of unreacted material and utilized as such, without further purification (151 g, 93% yield).

α-(4-Hydroxybutyl)-1-naphthylacetonitrile.—The above formal (98 g, 0.2 mole) was hydrolyzed with ethanol (115 ml), water (345 ml), and concentrated HCl (350 ml), heating at 85° for 20 hr with stirring. After cooling and diluting with water, the oil was extracted with ether and submitted to fractional distillation, giving an oily product (61.2 g, 64% yield), bp 203–207° (0.35 mm).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.63; H, 7.18; N, 5.82.

α-(4-Chlorobutyl)-1-naphthylacetonitrile.—Thionyl chloride (35.7 g, 0.3 mole) was added dropwise to a mixture of the above carbinol (47.8 g, 0.2 mole) and N,N-dimethylaniline (60.6 g, 0.5 mole), under stirring and cooling to 15°. The mixture was heated at 80° for 4 hr and afterwards poured into ice–water, acidified, and extracted with ether. Distillation at 180–183° (0.2 mm) gave a colorless oil (41.2 g, 80% yield).

Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; Cl, 13.76; N, 5.43. Found: C, 75.01; H, 6.30; Cl, 13.46; N, 5.48.

(5) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 806 (1948).

TABLE II

PHARMACOLOGICAL DATA

Compd	Approx LD_{50} (mouse), mg/kg ip	Hypoglycemic activity (rat) Blood sugar decrease, %[a]
I	140–160	15
II	290–320	Inactive
III	580–630	Inactive
IV	140–160	14
V	285–320	25
VI	280–310	14
VII	1150–1270	21
VIII	145–160	25
IX	290–315	27
X	145–165	Inactive
XI	75–85	19
XII	150–170	14
XIII	570–605	13
Chlorpropamide		37

[a] Tested orally at 50 mg/kg.

α-(4-Dimethylaminobutyl)-1-naphthylacetonitrile (X).—The above chlorobutyl compound (51.5 g, 0.2 mole) was heated with dimethylamine (27 g, 0.6 mole) in dioxane (120 ml), in a sealed tube at 100° for 26 hr. The mixture was diluted with water, acidified with 10% HCl, washed with ether, and made alkaline with excess K_2CO_3. Extraction with ether followed by distillation gave a colorless oil, bp 170–172° (0.5 mm).

α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetonitrile (XI).—Alkylation of X (53.3 g, 0.2 mole) with 2-bromopropane (32 g, 0.26 mole), carried out by refluxing for 8 hr in benzene (500 ml) and in the presence of sodamide (10.1 g, 0.26 mole), gave a viscous oil, bp 161–163° (0.2 mm).

α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetamide (XII).—Hydrolysis of XI (30.8 g, 0.1 mole), carried out by refluxing for 288 hr with 1:1:1 mixture (120 ml) of concentrated H_2SO_4–glacial acetic acid–water gave a glassy product, bp 197–

200° (0.3 mm). Colorless crystals, mp 97–98°, were obtained on crystallizing from ligroin (bp 75–120°).

α-Isopropyl-α-(4-dimethylaminobutyl)-1-naphthylacetic Acid Hydrochloride (XIII).—XII (32.6 g, 0.1 mole) was treated with isoamyl nitrite (40.7 ml) in glacial acetic acid (163 ml) and in the presence of anhydrous HCl, as described for III. A colorless product, mp 239–240°, was obtained on crystallization from ethanol–ligroin (bp 75–120°).

Pharmacology.—The acute toxicity and hypoglycemic activity were investigated by the techniques previously described;[5a] chlorpropamide was used as standard. The data are listed in Table II.

Acknowledgments.—The authors thank Mr. O. Boniardi for his assistance in preparing the compounds, Dr. G. Sekules for the microanalyses, and Mr. E. Pavesi for the pharmacological tests.

Substituted 2-(5-Nitro-2-furyl)benzimidazoles

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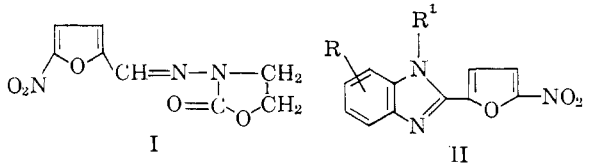
Received November 15, 1965
Revised Manuscript Received May 5, 1966

Although many nitrofurans show *in vitro* and *in vivo* activity against *Trichomonas* species, only 3-[(5-nitrofurfurylidene)amino]-2-oxazolidone (I) has undergone extensive clinical trials.[1,2] 2-(5-Nitro-2-furyl)benzimidazole (IIa), prepared in these laboratories during the evaluation of a synthetic method,[3] was shown to have activity against *T. foetus* in the mouse of an order sufficient to warrant investigation of related compounds.[4]



I

II

	R	R¹
a	H	H
b	5(6)-Cl	H
c	H	CH_2CH_2OH
d	5,6-$(CH_3)_2$	H
e	H	CH_3
f	5-CF_3	CH_2CH_2OH
g	5,6-Cl_2	H
h	H	$CH_2CH_2N(CH_3)_2$
i	H	C_6H_5
j	5(6)-CO_2CH_3	H
k	5-CF_3	$CH_2CH_2N(C_2H_5)_2$

The parent compound IIa had a short duration of activity in the mouse, probably because of rapid metabolism. It seemed unlikely that the benzimidazole ring was involved directly in the activity[6] but rather that it served to transport the nitrofuryl residue, which is well known to exhibit a wide range of antimicrobial ac-

TABLE I
SUBSTITUTED 2-(5-NITRO-2-FURYL)BENZIMIDAZOLES

	R	R¹	Crystn solvent	Mp, °C	Yield,[a] %	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
a	H	H	DMF–methanol	230–231[b]	81	$C_{11}H_7N_3O_3$			18.3				18.05	
b	5(6)-Cl	H	Methanol	236–237	46	$C_{11}H_6ClN_3O_3$	50.1	2.29	15.9	13.45	49.7	2.21	16.2	13.7
c	H	CH_2CH_2OH	DMF–methanol	206–207	69	$C_{13}H_{11}N_3O_4$	57.1	4.06			57.35	4.31		
d	5,6-$(CH_3)_2$	H	Ethyl acetate	285–287	66	$C_{13}H_{11}N_3O_3$	60.7	4.31	16.4		60.4	4.37	16.7	
e	H	CH_3	Acetone–ethanol	218–219.5[c]	9	$C_{12}H_9N_3O_3$	59.3	3.73	17.3		59.3	4.13	17.45	
f	5-CF_3	CH_2CH_2OH	Ethanol	219–220	25	$C_{14}H_{10}F_3N_3O_4$	49.3	2.95	12.3		49.1	3.14	12.4	
g	5,6-Cl_2	H	DMF–ethanol	308–310	17	$C_{11}H_5Cl_2N_3O_3$	44.3	1.69	23.8		44.1	2.02	23.55	
h	H	$CH_2CH_2N(CH_3)_2$	Methanol	140–142	35	$C_{15}H_{16}N_4O_3$	60.0	5.37	18.7		60.2	5.29	18.55	
i	H	C_6H_5	Acetonitrile	244–245	57	$C_{17}H_{11}N_3O_3$	66.9	3.63	13.8		66.7	3.39	13.9	
j[d]	5(6)-CO_2CH_3	H	Chloroform–ethanol	248–250	25	$C_{13}H_9N_3O_5$	54.4	3.16	14.6		54.3	3.43	14.8	
k	5-CF_3	$CH_2CH_2N(C_2H_5)_2$	DMF–methanol	124–125	15	$C_{18}H_{19}F_3N_4O_3$	54.55	4.83	14.1		54.3	4.95	14.2	

[a] Yields refer to analytically pure material and are not maximal. [b] Lit. mp 223–231°, [3] 224–226°, [5] 223–224°; [5] analytical data have not been recorded previously. [c] Lit.[5] mp 213–214°; analytical data have not been recorded previously. [d] The crude acid was too insoluble for crystallization and was esterified with diazomethane in methanol–$CHCl_3$ suspension.

(1) C. W. Collidge, C. S. Glisson, and A. A. Smith, *J. Med. Assoc. Georgia* **48**, 167 (1959).

(2) J. F. Ryley and G. J. Stacey, *Parasitology*, **53**, 303 (1963).

(3) H. F. Ridley, R. G. W. Spickett, and G. H. Timmis, *J. Heterocyclic Chem.*, **2**, 453 (1965).

(4) The author is indebted to Dr. Paul Actor and Miss Irene Rollman of Smith Kline and French Laboratories, Philadelphia, Pa., for the biological results, obtained by the methods described in ref 5.

(5) G. L. Dunn, P. Actor, and V. J. DiPasquo, *J. Med. Chem.*, **9**, 751 (1966).

(6) D. W. Woolley, *J. Biol. Chem.*, **152**, 225 (1944).