benzene (100 ml) containing ethylene glycol (10 ml) and toluene-*p*-sulfonic acid (from the hydrate, 0.067 g) (Dean–Stark apparatus). The product was refluxed for 3.5 hr with aluminum isopropoxide (0.8 g) in toluene–cyclohexanone (50:10 ml), and the resulting crude ketone was stirred for 2 hr in a stream of acetylene with dimethylacetamide (50 ml) containing lithium acetylide–ethylenediamine complex.[9] The mixture was added to crushed ice and extracted with ether. The product was stirred for 1.5 hr under nitrogen in methanol–3 *N* HCl–water (50:3:2 ml) and the solution was poured into brine and extracted with ether. Chromatography of the product on Florex and recrystallization from ethyl acetate–hexane gave the gonenone (0.55 g), mp 182–184°, λ_{max} 240 mμ (ε 16,500).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.9; H, 9.3. Found: C, 80.6; H, 9.1.

Acknowledgments.—The authors thank Dr. Richard A. Edgren and his staff of the Nutritional and Endocrinological Department, Research Division, Wyeth Laboratories, Inc., for the biological data, Dr. G. Ellis and his staff for analytical data and spectra, and Drs. G. A. Hughes and G. R. Wendt for advice and discussions.

(9) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).

3-Phenylcinnolines. III.[1] Derivatives of Hydroxy-3-phenylcinnolines

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Received April 29, 1966

A few cinnoline derivatives were prepared for pharmacological testing by alkylation of 4- and 4′-hydroxy-3-phenylcinnolines. These are listed in Table I, along with methyl derivatives for comparison of spectral data.

Alkylation of 3-phenyl-4-cinnolinol (**15**) with methyl iodide gave a mixture of the **1** and 2 isomers (**10** and **11**) in about a 5:3 ratio, while diazomethane furnished only the 1 derivative.[2] That these isomers are quite distinct from the 4-methoxy isomer (**12**) is shown by the spectral data and by the large depression of their mixture melting points. Compound **10** was assigned as the 1 isomer on the following evidence: (a) the slightly higher field absorption of its methyl protons in the nmr compared to those of the other isomer has been observed with other similar pairs of cinnoline isomers;[3] (b) the infrared, ultraviolet, and nmr spectra of **10** show great similarity (Table I) to those of the starting material, **15**, which has been assigned structure I,[1b] in common with other 4-hydroxycinnolines;[3] (c) one would expect the less sterically hindered product to predominate,[3] particularly with larger alkyl halides (see below); (d) the isolation of only one isomer using diazomethane which should not isomerize **15** from structure I tends to confirm the assignment; (e) finally, the pattern of aromatic protons in the nmr is interesting. The two 2′-protons on the 3-phenyl ring (which is probably coplanar) are deshielded and appear in several of these compounds at about 475–495 cps.[4] With the 8-proton (about 500–520 cps), there are then three protons from 475 to 520 cps (and the remainder between 400 and 475 cps) for compounds of structure I in Table I. However, **11**, the 2 isomer, has only one proton in the 475–520-cps region. This may be explained by steric interference of the 2-methyl, causing the phenyl ring to twist out of coplanarity and eliminating the deshielding of the 2′-protons. The same effect is also observed with the 1- and 2-oxides of 3-phenylcinnoline,[1b] the latter showing only the 4-proton below 480 cps (the 8-proton is shielded in the 2 isomer[1b]).

The products[4,5] using other alkyl halides were also assigned as 1 isomers having very similar spectra to those of **10**. Lacking the other isomer in these cases, the position of the α-CH_2 protons cannot be used for evidence because of the small difference in the two isomers (5 cps for **10** and **11**), but three aromatic protons in the 475–520-cps region were observed for these derivatives.

Reactions of 4-chloro-3-phenylcinnoline with the sodium salt of the corresponding alcohol furnished the 4-alkyloxy derivatives, **2** and **12**, the former being readily hydrolyzed in acid. On distillation these rearranged to the 1-alkyl-4-cinnolones,[2] **1** and **10**. To our knowledge this type of rearrangement has not been noted before in the cinnoline series, but it is well known for 4-alkoxyquinolines.[5]

Alkylation of **14** gave the corresponding alkoxy derivatives, **3**, **7**, and **9**, whose structures were substantiated by the similarity of their spectra with those of **13** and **14**.

Compound **7** showed about 2% the activity of hydrochlorothiazide as a diuretic in rats. Compounds **4** and **5** had only borderline activity against yeast-induced foot edema in the rat. The most interesting of the series, **3**, was about four times as active orally as phenylbutazone in this latter test, but toxic side reactions in the cotton pellet granuloma test discouraged further study.[6]

Experimental Section[7]

1-(2-Diethylaminoethyl)-3-phenyl-4-cinnolone (Table I, 1). A. By Alkylation of 15.—A solution of 6.6 g of 3-phenyl-4-cinnolinol,[1b] 3.3 g of KOH, and 7.0 g of 2-diethylaminoethyl

(1) (a) Paper I: H. S. Lowrie, *J. Med. Chem.*, **9**, 664 (1966); (b) paper II: H. S. Lowrie, *ibid.*, **9**, 670 (1966).

(2) Spectral data on the crude reaction product indicated predominantly the 1 isomer (I), but the presence of a small amount of the 2-isomer (II) cannot be ruled out. Only in preparation of **10** and **11** with methyl iodide was the 2 isomer actually isolated.

(3) D. E. Ames, R. F. Chapman, and D. White, *J. Chem. Soc.*, 470 (1966), and references therein.

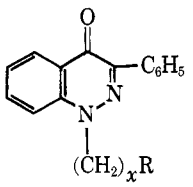
(4) When **1** was prepared by alkylation of **15** it was assumed that the low-field absorption (273 cps) of the α-CH_2 (see Table I) indicated attachment to oxygen rather than nitrogen. In addition, the position of the 8-hydrogen at 500–510 cps seemed to support III rather than I since the 8-H atoms in various 3-phenyldihydrocinnolines[1a] are moved appreciably upfield. Recent papers on the structure and alkylation of cinnolines, summarized in ref 3, forced the reexamination reported here, and the preparation of **2**, Table I, and the methyl derivatives, **10–12**, for comparison. The structures assigned by the author in U. S. Patent 3,239,524 (1966) should be I, not III.

(5) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, 1952, pp 152–153.

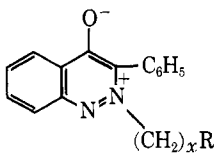
(6) These tests are described in ref 1. The relative potencies given refer to the ratio of the weights of equally effective doses. We are indebted to Drs. F. J. Saunders, E. F. Nutting, and D. L. Cook, and Mr. R. S. Jacobs and their staffs for these screening data.

(7) All melting points are corrected and were taken in a Hershberg apparatus. Microanalyses were performed by the Microanalytical Department under Dr. R. T. Dillon. Infrared spectra were taken in chloroform solution on a Beckman IR-4, and the ultraviolet spectra were taken in methanol on a Beckman DK-2. Nmr, recorded on a Varian A-60, is given in cycles per second (cps) of downfield shift from tetramethylsilane as an internal reference standard in $CDCl_3$.

TABLE I



I



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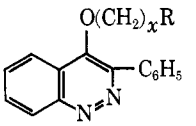
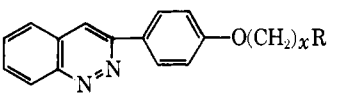
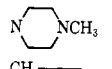


III



IV

No.	Structure	x	R	Crystn solvent[a]	Bp (mm) or mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	λmax, mμ (ε)[b]	Nmr[c] Position, cps	Nmr[c] Apparent J, cps
1[d]	I	2	$N(C_2H_5)_2$		200–230 (0.1)	74.74	74.39	7.21	6.91	13.07	13.26	264 (14,500), 312 (10,300), 360 (13,000)	273 t	7
			$\cdot C_4H_4O_4$[e]	E	160–164	65.89	66.12	6.22	6.10	9.61	9.45			
2[d]	III	2	$N(C_2H_5)_2$			74.74	74.36	7.21	7.11	13.07	13.35	248 (34,400), 288 (6100), 330 (3500)	236 t	6
3[f]	IV	2	$N(C_2H_5)_2$	SKB	67–68	74.74	74.91	7.21	7.39	13.07	13.11	264 (33,400), 295 (20,000)	247 t	6
4[g]	I	2	$N(CH_3)_2 \cdot HCl$	E–Ee	211–214	65.54	65.77	6.11	6.25	12.74	12.43	264 (12,900), 312 (10,000), 361 (12,300)[h]	273 t[h]	7
5[g]	I	3	$N(CH_3)_2 \cdot C_4H_4O_4$[e]	E	190–191	65.23	65.17	5.95	6.05	9.92	9.82	264 (13,500), 312 (10,700)*[h]	273 t[h]	7
6[g]	I	2		Ee	110–111	72.38	72.57	6.94	6.68	16.08	16.25	265 (14,300), 312 (11,200)*	275 t	7
7[f]	IV	2		SKB	102–103	76.05	75.70	7.25	7.46	12.10	12.02	265 (33,000), 297 (19,600)	248 t	6
8[i]	I	1	CO_2H	A	203–204	68.56	68.38	4.32	4.60	10.00	10.04	264 (13,700), 311 (10,400), 358 (12,300)	324 s[j]	
9[d]	IV	1	CO_2H	E–W	230–232	68.56	68.77	4.32	4.46	10.00	9.93	265 (31,600), 296 (18,500)	288 s[j]	
10[d]	I	1	H	SKB	107–108	76.25	76.50	5.12	4.92	11.86	11.97	264 (14,800), 312 (11,600), 360 (12,800)	243 s	
11[d]	II	1	H	Ee	213–214	76.25	76.14	5.12	5.24	11.86	12.03	255 (8500), 356 (15,100), 371 (16,200)	248 s	
12[d]	III	1	H	SKB	106–108	76.25	76.29	5.12	5.10	11.86	11.90[k]	248 (39,000), 288 (6800), 332 (3500)	225 s	
13	IV	1	H	[l]								265 (31,600), 297 (18,800)	232 s	
14[d]	IV	0	H	M–Bz	235–237	75.65	75.48	4.54	4.59	12.61	12.41	266 (29,500), 298 (18,700)	...	
15	I	0	H	[m]								262 (16,700), 310 (11,800), 352 (12,000)	...	

[a] E, ethanol; SK, Skellysolve;[12] A, acetone; W, water; M, methanol; Bz, benzene; Ee, ethyl ether. [b] For principal peaks in the 220–400-mμ range, except the values followed by an asterisk which are in the 220–340-mμ range. [c] Apparent center of main peaks; s, singlet, t, triplet, for the italic hydrogens in the side chain: $CH_2(CH_2)_{x-1}R$. [d] See Experimental Section. [e] Maleic acid salt. [f] Prepared as 1 from the alkyl halide but using butanone as solvent. [g] Prepared as 1 from the alkyl halide. [h] Data taken on the free base.[9] [i] Prepared as **9**. [j] See ref 11. [k] *Anal.* Calcd: OCH_3, 13.13. Found: OCH_3, 12.34. This low result, the same for several different preparations, may reflect rearrangement during analysis to the 1-methyl derivative, **10**, which gave: OCH_3, 0.00. [l] See ref 1a. [m] See ref 1b.

chloride in 400 ml of 2-propanol was stirred and refluxed for 2.5 hr. After cooling, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was taken up in ether, washed with dilute KOH, and extracted with dilute HCl. This was made alkaline and extracted with ether which was dried[8] and evaporated. The brown oil obtained was freed of solvents[9] for spectral analysis;[2] 5.8 g. On cooling a solution of 5.6 g of this oil and 2.1 g of maleic acid in 40 ml of ethanol, 4.7 g of yellow prisms described in Table I were obtained.

B. By Rearrangement of 2.—A portion of **2** (described below) was distilled in a short-path tube at 0.1 mm with the jacket heated at 200–230°. A portion of the yellow oil[2] whose spectra were identical with those in A above, and whose analysis is given in Table I, 1, was converted to the maleate salt, mp 160–164°, which proved identical[10a,11] with that in A above.

4-(2-Diethylaminoethoxy)-3-phenylcinnoline (Table I, 2).—A 50% suspension of 2.6 g of sodium hydride in mineral oil was added portionwise to 24 g of 2-diethylaminoethanol. When the reaction had subsided, the solution was diluted with 500 ml of dry benzene, and 12.0 g of 4-chloro-3-phenylcinnoline[1b] was added. This mixture was stirred and refluxed for 5 hr, then cooled, diluted with ether, and washed thoroughly with dilute NaOH. After drying[8] the solvent was evaporated, finally *in vacuo*. The residue was taken up in Skellysolve A[12] and stirred with activated charcoal. After filtering, the solvent was evaporated and the residue was freed from solvent,[9] yielding the orange oil described in Table I, **2**. A portion of this material dissolved completely in dilute HCl, but a large amount of precipitate quickly formed; this white powder was filtered off and dried, mp 266–268°, undepressed by authentic[1b] 3-phenyl-4-cinnolinol.

3-(4-Hydroxyphenyl)cinnoline (Table I, 14).—A solution of 20 g of 3-(4-methoxyphenyl)cinnoline[1a] in 300 ml of 48% HBr was refluxed for 2 hr, then diluted to 2 l., cooled, and filtered. The red crystals were dissolved in dilute KOH, the solution was filtered, and the filtrate was acidified. The yellow powder was filtered off, dried, and crystallized as shown in Table I.

4-(3-Cinnolinyl)phenoxyacetic Acid (Table I, 9).—A solution of 2.4 g of 3-(4-hydroxyphenyl)cinnoline, 2.4 g of chloroacetic acid, and 5.0 g of KOH in 15 ml of water was heated for 1 hr on a steam bath, then diluted to 50 ml, cooled, and saturated with CO_2. The yellow powder was filtered off, and the filtrate was acidified. The product, filtered off and dried, was crystallized as shown in Table I.

4-Methoxy-3-phenylcinnoline (Table I, 12).—A solution of 6.0 g of 4-chloro-3-phenylcinnoline[1b] and 3.0 g of sodium methoxide in 400 ml of methanol was refluxed for 15 hr. The solvent was evaporated and the residue, taken up in ether, was washed with dilute NaOH. After drying,[8] the solution was concentrated and diluted with Skellysolve B.[12] The ether was boiled off, and the solution was concentrated to 250 ml and cooled. The yellow needles, 5.0 g, mp 105–107°, which separated were recrystallized as shown in Table I. A 1:1 mixture with **10** melted at about 80–90°, and with **11**, at about 100–120°.

1- (and 2-) Methyl-3-phenyl-4-cinnolone (Table I, 10 and 11). A. Using Methyl Iodide.—A mixture of 7.8 g of 3-phenyl-4-cinnolinol,[1b] 6.0 g of KOH, and 14 g of methyl iodide in 400 ml of

(8) The organic layer was shaken with a saturated solution of NaCl, then filtered slowly through anhydrous K_2CO_3.

(9) The oil was heated for several hours at 60° (0.5 mm) on a rotary evaporator.

(10) (a) Mixture melting point and infrared spectrum; (b) ultraviolet and nmr spectra.

(11) Infrared in KBr pellet; nmr in dimethyl sulfoxide solution.

(12) Petroleum ether fraction: A, bp 28–38°; B, bp 60–71°.

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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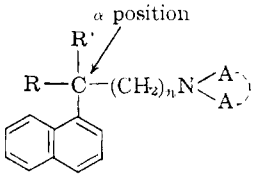
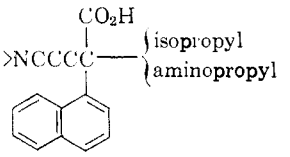
In previous papers we reported hypoglycemic screening results of many 1-naphthylalkylamines.[1] The compounds possessed the general structure **1**, in which R was a hydrogen atom, or an alkyl or aminoalkyl group; R′ was a cyano, substituted or unsubstituted carbamyl, free or esterified carboxy, carbureido, 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).