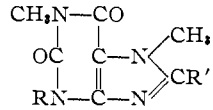
TABLE I

3,8-DISUBSTITUTED PARAXANTHINES



Compounds 1, 15 and 16 were recrystallized from isopropyl alcohol, 2 from water, 3–13 from dilute ethanol, 14, 17 and 18 from dilute methanol, and 15 and 16 from isopropyl alcohol

	R	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Diuresis
1	Ethyl	Chloro	111–112[a]	68	$C_9H_{11}O_2N_4Cl$	44.54	44.82	4.57	4.52	23.09	22.78[b]	Slight in 1 of 4 dogs
2	Ethyl	Amino	293–294	82	$C_9H_{13}O_2N_5$	48.42	48.35	5.87	5.91	31.38	31.20	
3	Ethyl	Methylamino	267–269	85	$C_{10}H_{15}O_2N_5$	50.62	50.55	6.37	6.43	29.52	29.50	None
4	Ethyl	Ethylamino	240–242	78	$C_{11}H_{17}O_2N_5$	52.57	52.39	6.82	6.73	27.87	27.67	Marked in 2 of 4 dogs
5	Ethyl	Dimethylamino	130–132	73	$C_{11}H_{17}O_2N_5$	52.57	52.55	6.82	6.84	27.87	27.99	None
6	Ethyl	Diethylamino	125–127	68	$C_{13}H_{21}O_2N_5$	55.89	56.10	7.58	7.81	25.07	25.03	Mild in 2 of 4 dogs
7	Ethyl	Piperidino	127–129	68	$C_{14}H_{21}O_2N_5$	57.71	58.19	7.27	7.45	24.04	23.97	Mild in 3 of 4 dogs
8	*n*-Butyl	Chloro	69–70	74	$C_{11}H_{15}O_2N_4Cl$	48.80	49.25	5.58	5.73	20.70	20.68[c]	Slight
9	*n*-Butyl	Amino	249–250	76	$C_{11}H_{17}O_2N_5$	52.57	52.56	6.82	6.63	27.87	27.76	
10	*n*-Butyl	Methylamino	230–232	85	$C_{12}H_{19}O_2N_5$	54.32	54.59	7.22	7.00	26.40	26.44	None
11	*n*-Butyl	Ethylamino	206–207	78	$C_{13}H_{21}O_2N_5$	55.89	55.84	7.58	7.61	25.07	25.05	Moderate to marked in all 4 dogs
12	*n*-Butyl	Dimethylamino	69–70	70	$C_{13}H_{21}O_2N_5$	55.89	56.14	7.58	7.63	25.07	24.98	Moderate in 4 dogs
13	*n*-Butyl	Diethylamino	82–83	71	$C_{15}H_{25}O_2N_5$	58.61	58.98	8.20	8.39	22.79	22.76	Mild in 2 of 4 dogs
14	*n*-Butyl	Piperidino	92–93	70	$C_{16}H_{25}O_2N_5$	60.16	60.20	7.89	7.40	21.92	22.07	None
15	Allyl	Chloro	112–114	74	$C_{10}H_{11}O_2N_4Cl$	47.16	47.69	4.35	4.43	22.00	21.89[d]	Mild in 4 of 6 dogs
16	Allyl	Methylamino	233–235	79	$C_{11}H_{15}O_2N_5$	53.00	53.22	6.07	6.32	28.10	28.17	
17	Allyl	Dimethylamino	126–127	68	$C_{12}H_{17}O_2N_5$	54.74	54.69	6.51	6.78	26.60	26.57	
18	Allyl	Piperidino	99–101	65	$C_{15}H_{21}O_2N_5$	59.38	59.99	6.98	6.89	23.09	22.93	Mild in 2 of 4 dogs

[a] H. Biltz and E. Peukert (*Ber.*, **58**, 2109 (1925)), m.p. 112°. [b] Chlorine: calcd. 14.61, found 14.80. [c] Chlorine: calcd. 13.10, found 13.10. [d] Chlorine: calcd. 13.92, found 13.90.

under reduced pressure and the product was recrystallized; yields 65–85%.

Some of the compounds listed in Table I were tested for diuretic activity by oral administration to dogs in the Lilly Research Laboratories. The dose was 200 mg. except in the case of compound 5; in this instance, it was 400 mg.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

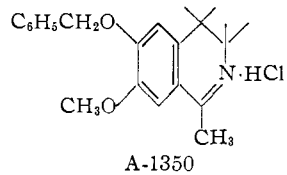
Local Anesthetics. IV.[1] The Synthesis of Local Anesthetic 3,4-Dihydroisoquinolines[2]

BY M. B. MOORE, H. B. WRIGHT, MAYNETTE VERNSTEN, M. FREIFELDER AND R. K. RICHARDS

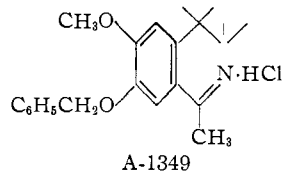
RECEIVED FEBRUARY 27, 1954

Because of the excellent local anesthetic properties of 6(7)-benzyloxy-7(6)-methoxy-3,4-dihydroisoquinolines, their synthesis and pharmacology were extensively studied. Other 3,4-dihydroisoquinolines containing one, two or three substituents, many of them new compounds, were compared with these, but none was found to be superior.

In the course of a pharmacological screening program 6-benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride (A-1350) originally



A-1350



A-1349

synthesized as an intermediate[3] was shown to have powerful local anesthetic properties. It is effective topically as well as by infiltration and is not irritating in the concentrations needed for anesthesia. The isomer (A-1349) in which the positions of the benzyloxy and methoxy groups are interchanged showed only slightly less desirable properties.

Compounds A-1350 and A-1349 were synthesized by Späth, *et al.*,[4] during their proof of structure of salsoline, but neither the bases nor their salts were purified; the crude materials were reduced. The yields by their method are poor, one of the most unsatisfactory reactions being the two-step reduction of the nitrostyrene to the phenethylamine. Other types of hydrogenation were tried here, including a few unsuccessful attempts at one-step electrolytic reduction.[5] A modification of the method of Hahn and Schales[6,7] first applied by Hahn and Rumpf[8] to 3-hydroxy-4-methoxy-ω-nitrostyrene was successful; but the large volumes and careful technique required make it an impractical method for use with large quantities.

The possible routes for synthesis of dihydroiso-

(1) Paper III, THIS JOURNAL, **75**, 1770 (1953).

(2) Presented before the Division of Medicinal Chemistry, 124th Meeting of the American Chemical Society, Chicago, Ill., September 6–11, 1953.

(3) By E. J. Matson, in these laboratories.

(4) E. Späth, A. Orechoff and F. Kuffner, *Ber.*, **67B**, 1214 (1934).

(5) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931). Since this investigation was carried out, two publications have appeared describing successful reductions of nitrostyrenes by lithium aluminum hydride: (a) K. E. Hamlin and A. W. Weston, THIS JOURNAL, **71**, 2210 (1949); (b) F. A. Ramirez and A. Burger, *ibid.*, **72**, 2781 (1950).

(6) G. Hahn and O. Schales, *Ber.*, **67B**, 1486 (1934).

(7) O. Schales, *ibid.*, **68B**, 1579 (1935).

(8) G. Hahn and F. Rumpf, *ibid.*, **71B**, 2141 (1938).

quinolines and their parent phenethylamines have been summarized by Hahn and Schales,[6,7] Slotta and Heller,[9] and in a recent review by Whaley and Govindachari.[10] However, little work has been done on the simultaneous Beckmann rearrangement and ring closure of appropriate oximes to give dihydroisoquinolines. This possibility was explored here with some success, but the satisfactory yields sometimes obtained could not be reproduced, perhaps because of lack of control of the proportions of *syn* and *anti* forms of the oxime.

The method used by Matson[3] included a synthesis of 3-benzyloxy-4-methoxyhydrocinnamazide by a route similar to that used by Schöpf, Perrey and Jäckh,[11] followed by a conventional Curtius reaction by way of the urethan to the desired phenethylamine.[12] The yield from the latter reaction was very low. An attempt was made to substitute a Hofmann rearrangement[13] in spite of the failure reported by Robinson and Sugasawa.[5] Using sodium hypochlorite or hypobromite, yields of 4–5% were realized.

Finally, a greatly improved method was developed for carrying out the Curtius reaction. The azide is converted in one step to the desired acetylated phenethylamine. This avoids losses due to isolation and possible instability of intermediates and gives excellent yields. When 3-benzyloxy-4-methoxyhydrocinnamazide was treated with acetic acid with no other solvent, none of the desired N-(3-benzyloxy-4-methoxyphenethyl)-acetamide was isolated; neither was urea formation observed. It is known that under anhydrous conditions azides may react with acids to give acylated phenethylamines.[11] However, in the case of the lower fatty acids the *sym*-urea may be formed.[14] Refluxing of the azide in benzene led to the expected formation of the *sym*-urea, but none of it was isolated in any rearrangement of this azide in which acetic anhydride or acetic acid was present, with or without the presence of benzene.

Goldstein and Stern[15] were able to convert the azides of some brominated naphthalene carboxylic acids to the acetylated amines by refluxing with acetic anhydride under conditions reported as anhydrous. They explain this result by postulating the formation of the diacetylated amine, with its later hydrolysis to the monoacetylated compound. A paper by Naegeli and Tyabji[16] describes the effects of various solvents upon the reactions of phenyl isocyanates, and reports a good yield of some nitrophenylacetamides by reaction with acetic anhydride in benzene. When our azide was treated with acetic anhydride in benzene under rigorously anhydrous conditions the acetylated amine was not obtained, but when one mole of water was added to the reaction mixture a good yield was realized. In the case of this and other hydrocinnamazides containing two ether substituents in the ring, the surprising discovery was made that a large excess of water did not exert a deleterious effect upon the yield of acetylated amine. One mole of water is of course necessary for the reaction.

$$ArCH_2CH_2CON_3 + (CH_3CO)_2O + H_2O \longrightarrow ArCH_2CH_2NHCOCH_3 + CH_3COOH + N_2 + CO_2$$

It might be expected from the known formation of *sym*-ureas in rearrangements of this type by heating in moist solvents[12,17] that such conditions would tend to form the *sym*-urea at the expense of the substituted acetamide. A high yield of the acetylated amine was isolated in cases in which the azide cake was so moist that two layers were formed when it was added to the solution of acetic anhydride in benzene. Such a procedure makes possible avoidance of the potentially dangerous drying of the azide as well as of the isolation of the relatively unstable phenethylamine. The explanation for this behavior is not apparent from the data at hand. When α-naphthyl isocyanate was heated with moist benzene and acetic anhydride, the only product isolated was the *sym*-urea. Further experiments would be necessary to determine the scope of such facile rearrangement to the substituted acetamide under the conditions used, but the modified reaction as described has given satisfactory yields of acetamides with all of this series of dihydrocinnamazides containing two ether substituents in the benzene ring.

A point of interest in connection with these reactions is that pure 3-benzyloxy-4-methoxyhydrocinnamazide could not be isolated by the methods used. The samples which were dried and purified for analysis gave nitrogen values far below the theoretical for the azide. This was true of those prepared by Matson[3] and by the present authors. The percentages found are consistent with those for a mixture of the azide and the isocyanate, and the good yields of substituted acetamide formed make it seem probable that such is the composition. Naegeli and Stefanovitsch[18] observed a similar phenomenon in the case of the azide of chaulmoogric acid. Such instability of the azide must be quite specific, for 4-benzyloxy-3-methoxyhydrocinnamazide gave an analytical value for nitrogen in fairly good agreement with the theoretical.

Various reagents and conditions were tried for the Bischler–Napieralski ring closure, and the best results were obtained using phosphorus pentachloride in chloroform[11] and maintaining a temperature near 45°. Removal of color from the aqueous solution of the hydrochloride is difficult because of the strong adsorption of the salt by charcoal, but charcoal efficiently removes color from an ether solution of the base without appreciable loss of the product.

Since A-1349 and A-1350 do not contain the functional groups usually found in local anesthetics, it was deemed advisable to attempt to gain information as to the structure necessary for this effect. Accordingly, three series of 3,4-dihydroisoquinolines were synthesized and studied pharmacologi-

(9) K. H. Slotta and H. Heller, *Ber.*, **63B**, 3029 (1930).

(10) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.

(11) C. Schöpf, H. Perrey and I. Jäckh, *Ann.*, **497**, 47 (1932).

(12) P. A. S. Smith, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337.

(13) By A. H. Sommers, in these laboratories.

(14) H. Goldstein and K. Stern, *Helv. Chim. Acta*, **23**, 809 (1940).

(15) H. Goldstein and K. Stern, *ibid.*, **23**, 818 (1940).

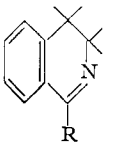
(16) C. Naegeli and A. Tyabji, *ibid.*, **16**, 349 (1933).

(17) H. Lindeman and H. Cissée, *Ann.*, **469**, 44 (1929).

(18) C. Naegeli and G. Stefanovitsch, *Helv. Chim. Acta*, **11**, 609 (1928).

TABLE I

1-SUBSTITUTED 3,4-DIHYDROISOQUINOLINES



A	R	Formula	Anesthesia[f]
1481[a,b]	CH_3	$C_{10}H_{11}N$	+
1483[c]	C_2H_5	$C_{11}H_{13}N$	+
1484[a,b]	C_6H_5	$C_{15}H_{13}N$	++
1058[d]	p-$NH_2C_6H_4$	$C_{15}H_{14}N_2$	++
1488[e]	p-$CH_3OC_6H_4$	$C_{16}H_{15}NO$	++
1486[b]	$C_6H_5CH_2$	$C_{16}H_{15}N$	++

[a] A. Bischler and B. Napieralski, *Ber.*, **26**, 1903 (1893). [b] A. Pictet and F. W. Kay, *ibid.*, **42**, 1973 (1909). [c] E. Späth, F. Berger and W. Kuntara, *ibid.*, **63B**, 134 (1930). [d] V. M. Rodionov and E. V. Yavorskaya, *J. Gen. Chem.* (*U. S. S. R.*), 11, 446 (1941); *C. A.*, **35**, 6592 (1941). [e] Base, m.p. 98°. *Anal.* Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 5.64. Hydrochloride, m.p. 203–204°. *Anal.* Calcd. for $C_{16}H_{15}NO\cdot HCl$: N, 5.11. Found: N, 4.97. [f] +, 1% solution of hydrochloride gave anesthesia in guinea-pig wheals. ++, corneal anesthesia with 2% solution as well as above.

benzene nucleus, and series C of 1-methyl-3,4-dihydroisoquinolines with two ether substituents in the benzene nucleus.

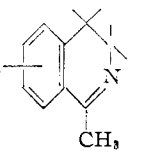
The compounds of groups A and B were synthesized in most cases by well-known methods differing from those used for A-1350. For group C, the synthetic methods followed closely those developed for A-1350.

Table I lists the compounds of series A. The hydrochlorides of all these were local anesthetic to some extent, but the variations gave no compound definitely superior to 1-methyl-3,4-dihydroisoquinoline. Compounds of series B are reported in Table II. Their local anesthetic effects, while definite, were by no means in the range of either of the isomeric 6(7)-benzyloxy-7(6)-methoxy-1-methyl-3,-4-dihydroisoquinolines.

For the first three compounds in Table II, acetylation of the appropriate amines was carried out by short refluxing with acetic anhydride. In all cases only the diacetylated amine was isolated. A search of the literature revealed that it is known that a second acetyl will enter acetamide under

TABLE II

1-SUBSTITUTED 3,4-DIHYDROISOQUINOLINES WITH A SECOND SUBSTITUENT R

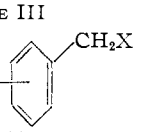


A	R	Cyclized by	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Anesthesia[c]
1147	6-OCH_3	$POCl_3$–$C_6H_5CH_3$	52	207–208	$C_{11}H_{13}NO\cdot HCl$	6.64	6.51	++
1092	7-OCH_3	P_2O_5–$C_6H_4(CH_3)_2$	Very	213–214[b]	$C_{11}H_{13}NO\cdot H_2SO_4$	5.13	4.73	+
		$POCl_3$–$C_6H_5CH_3$	small[a]					
1487	7-i-C_3H_7	P_2O_5–$C_6H_5CH_3$	18	95–99[d]	$C_{13}H_{17}N$	7.48	7.47	++
2620	6-$OCH_2C_6H_5$	PCl_5–$CHCl_3$	Small	175–176	$C_{17}H_{17}NO\cdot HCl$	4.87	5.59 5.54	+

[a] Attempted cyclizations are not described. [b] Picrate. This was converted to the base and precipitated by sulfuric acid in ethereal solution. The sulfate was used for analysis and pharmacological evaluation. [c] + and ++ are used as in Table I. [d] At 0.3 mm.

TABLE III

INTERMEDIATES



R	X	M.p. or b.p., °C.	Mm.	Yield, %	$n^{25}D$	Formula[a]	Nitrogen, % Calcd.	Found
p-iso-C_3H_7	CN	101–104	1	45	1.5110	$C_{11}H_{13}N$	8.80	8.63
p-iso-C_3H_7[b]	CH_2NH_2	97–98	1	71	1.5180	$C_{11}H_{17}N$	8.58	8.47
		198–200				$C_{11}H_{17}N\cdot HCl$	7.01	6.88
p-iso-C_3H_7	$CH_2N(COCH_3)_2$	157–158	1	85	1.5182	$C_{15}H_{21}NO_2$	5.65	5.66
						($C_{13}H_{19}NO$)	(6.82)	5.81
p-OCH_3[c]	$CH_2N(COCH_3)_2$	161–166	1.4	85.5	1.5315	$C_{13}H_{17}NO_3$	5.95	6.08
		170–172	3			($C_{11}H_{15}NO_2$)	(7.25)	
m-OCH_3[c]	$CH_2N(COCH_3)_2$	176–178	3.5	42.5		$C_{13}H_{17}NO_3$	5.95	6.08
o-OCH_3[c]	$CH_2N(COCH_3)_2$	66		Small		$C_{13}H_{17}NO_3$	5.95	5.95
							66.36[d]	66.60[d]
							7.28[e]	7.06[e]
o-OCH_3	$CH_2NHCOCH_3$	93–94		55		$C_{11}H_{15}NO_2$	7.25	7.07
m-$OCH_2C_6H_5$	CH_2COOCH_3	34–35				$C_{17}H_{18}O_3$	75.53[d]	75.78[d]
							6.71[e]	6.71[e]

[a] The figures in parentheses are calculated for the monoacetyl amines. [b] Reference 9 describes this base as boiling at 150° and as probably unstable; the hydrochloride had m.p. 270°. [c] Reference 9 describes the parent bases. [d] Carbon analyses. [e] Hydrogen analyses.

cally. Series A consisted of 3,4-dihydroisoquinolines with a 1-substituent only, series B of 1-methyl-3,4-dihydroisoquinolines with one substituent in the benzene nucleus, and series C of 1-methyl-3,4-dihydroisoquinolines with two ether substituents in the benzene nucleus.

The compounds of groups A and B were synthesized in most cases by well-known methods differing from those used for A-1350. For group C, the synthetic methods followed closely those developed for A-1350.

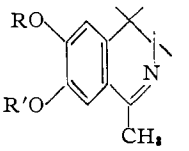
Table I lists the compounds of series A. The hydrochlorides of all these were local anesthetic to some extent, but the variations gave no compound definitely superior to 1-methyl-3,4-dihydroisoquinoline. Compounds of series B are reported in Table II. Their local anesthetic effects, while definite, were by no means in the range of either of the isomeric 6(7)-benzyloxy-7(6)-methoxy-1-methyl-3,-4-dihydroisoquinolines.

For the first three compounds in Table II, acetylation of the appropriate amines was carried out by short refluxing with acetic anhydride. In all cases only the diacetylated amine was isolated. A search of the literature revealed that it is known that a second acetyl will enter acetamide under these conditions,[19] and other diacetylated amines

(19) V. Meyer and P. Jacobsen, "Lehrbuch der organischen Chemie," Vol. I, Walter de Gruyter and Co., Berlin and Leipzig, 1922, p. 616.

TABLE IV

3,4-DIHYDROISOQUINOLINES



A	R	R′	Yield,[a] %	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2562	C_2H_5	C_2H_5	74	205–207	$C_{14}H_{19}NO_2 \cdot HCl$	5.19	5.08				
				65–66	$C_{14}H_{19}NO_2$						
2600	n-C_3H_7	n-C_3H_7	53	174–175	$C_{16}H_{23}NO_2 \cdot HCl$	4.70	4.68				
				52–54	$C_{16}H_{23}NO_2$	5.36	5.59	73.53	73.41	8.87	8.70
2907	i-C_3H_7	i-C_3H_7	73.5	191–192	$C_{16}H_{23}NO_2 \cdot HCl$	4.70	4.71	64.52	64.53	8.12	8.14
2434	n-C_4H_9	n-C_4H_9	5[b]	165–166	$C_{18}H_{27}NO_2 \cdot HCl$	4.30	4.17	66.34	66.16	8.66	8.58
1349	CH_3	$C_6H_5CH_2$	46	193–194 d.	$C_{18}H_{19}NO_2 \cdot HCl$	4.41	4.36				
1350	$C_6H_5CH_2$	CH_3	84	199–200 d.	$C_{18}H_{19}NO_2 \cdot HCl$	4.41	4.35	68.02	67.92	6.34	6.45
2568	CH_3	n-C_4H_9	57.4	179–180	$C_{15}H_{21}NO_2 \cdot HCl$	4.94	5.22	63.48	63.51	7.78	7.72
3048	n-C_4H_9	CH_3	82	197–198	$C_{15}H_{21}NO_2 \cdot HCl$	4.94	4.84	63.48	63.91	7.78	7.85
				63–64	$C_{15}H_{21}NO_2$	5.66	5.85	72.84	72.42	8.56	8.43
3376[c]	CH_3	5-n-C_4H_9	25	149.5–151	$C_{15}H_{21}NO_2 \cdot HNO_3$	9.03	9.09	58.05	57.98	7.15	6.92
3196	CH_3	n-C_6H_{13}	64	154–155	$C_{17}H_{25}NO_2 \cdot HCl$	4.49	4.61				
				25[d]	$C_{17}H_{25}NO_2$	5.09	5.12	74.14	74.21	9.15	8.92
2697	C_2H_5	$C_6H_5CH_2$	75	205–206	$C_{19}H_{21}NO_2 \cdot HCl$	4.22	4.07				
				104.5–105	$C_{19}H_{21}NO_2$	4.74	4.69	77.26	77.30	7.17	7.12
2836	$C_6H_5CH_2$	C_2H_5	49	181–182	$C_{19}H_{21}NO_2 \cdot HCl$	4.22	4.16	68.77	68.89	6.68	6.65
2904	C_2H_5	n-C_4H_9	77.4	174–175	$C_{15}H_{23}NO_2 \cdot HCl$	4.70	4.78				
				49–50	$C_{16}H_{23}NO_2$	5.36	5.44	73.53	73.43	8.87	8.73

[a] The yields refer to salts precipitated from ether solutions of the bases. In many cases further purification was necessary to obtain analytically pure samples. [b] Yield based on the hydrazide. [c] This compound is 5-n-butoxy-6-methoxy-1-methyl-3,4-dihydroisoquinoline. [d] Crystallized from cold pentane; melted at room temperature.

have been described.[17,20] Similar treatment of 3,4-dimethoxyphenethylamine, however, gave only the monoacetylated derivative.

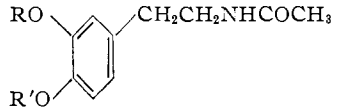
Ring closure of the diacetylated phenethylamines in most cases proceeded to some extent; no similar reaction was found in the literature. Ring closure failed with the diacetyl derivative of *o*-methoxyphenethylamine and yields were extremely low in the case of diacetylated *p*-methoxyphenethylamine. But because of the detrimental effects of *ortho* and *para* substituents in the Bischler–Napieralski reaction, only poor yields might be expected even from the monoacetylated amines.

Table III lists the new intermediates prepared for the dihydroisoquinolines of Table II.

Table IV lists the new compounds of group C prepared for this study. Their syntheses followed the preferred method developed for A-1350, and it is probable that yields of some of them could be improved by changes in the conditions of reaction. The remaining tables (V–X) list the new intermediates in these syntheses, with addition of some previously known members for the sake of clarity.

TABLE V

SUBSTITUTED ACETAMIDES



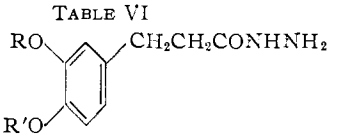
R	R′	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	C_2H_5	80	75–76	$C_{14}H_{21}NO_3$[a]	5.57	5.68
n-C_3H_7	n-C_3H_7	50	80–81	$C_{16}H_{25}NO_3$	5.01	4.98
i-C_3H_7	i-C_3H_7	60	68–69	$C_{16}H_{25}NO_3$	5.01	5.26
n-C_4H_9	n-C_4H_9	Poor	Oil	$C_{18}H_{29}NO_3$	4.56	[b]
CH_3[c]	$C_6H_5CH_2$		116–117	$C_{18}H_{21}NO_3$		
$C_6H_5CH_2$[c]	CH_3		128–128.5	$C_{18}H_{21}NO_3$		
CH_3	n-C_4H_9	87	65–66.5	$C_{15}H_{23}NO_3$	5.28	5.31
n-C_4H_9	CH_3	81	69–70	$C_{15}H_{23}NO_3$	5.28	5.47
CH_3[d]	2-n-C_4H_9	68	86–87	$C_{15}H_{23}NO_3$	5.28	5.35
CH_3	n-C_6H_{13}	52	81–82	$C_{17}H_{27}NO_3$	4.77	4.82
C_2H_5	$C_6H_5CH_2$	72.5	121–123	$C_{19}H_{23}NO_3$	4.47	4.61
$C_6H_5CH_2$	C_2H_5	54	96–98	$C_{19}H_{23}NO_3$	4.47	4.47
C_2H_5	n-C_4H_9	70	79–80	$C_{16}H_{25}NO_3$	5.01	5.04

[a] Calcd.: C, 66.90; H, 8.42. Found: C, 67.59, 67.28; H, 8.53, 8.27. The phenethylamine was previously reported by K. Kindler and W. Peschke, *Arch. Pharm.*, **272**, 60 (1934). [b] Not analyzed; used for ring closure to give A-2434, Table IV. [c] These are reported in ref. 4. [d] This is N-(2-n-butoxy-3-methoxyphenyl)-acetamide.

(20) A. Weizmann, THIS JOURNAL, **70**, 2342 (1948).

TABLE VI

HYDRAZIDES



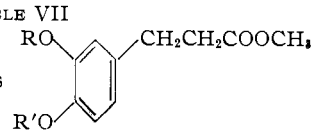
R	R′	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	C_2H_5	51	106–108	$C_{13}H_{20}N_2O_3$	11.10	11.18
n-C_3H_7	n-C_3H_7	49	92.5–94	$C_{16}H_{24}N_2O_3$	9.99	9.70
i-C_3H_7	i-C_3H_7	87	86–87	$C_{15}H_{24}N_2O_3$	9.99	10.02
n-C_4H_9	n-C_4H_9	35	90–91	$C_{17}H_{28}N_2O_3$	9.08	8.88
CH_3	$C_6H_5CH_2$	70	118–120	$C_{17}H_{20}N_2O_3$	9.33	9.51
$C_6H_5CH_2$	CH_3	95	128–129[a]	$C_{17}H_{20}N_2O_3$	9.33	9.48
CH_3	n-C_4H_9	99	107–108	$C_{14}H_{22}N_2O_3$	10.52	10.53
n-C_4H_9	CH_3	70	126–127	$C_{14}H_{22}N_2O_3$	10.52	10.56
CH_3[c]	2-n-C_4H_9	84	62–64	$C_{14}H_{22}N_2O_3$	10.52	10.39
CH_3	n-C_6H_{13}	98	98.5–99.5	$C_{16}H_{26}N_2O_3$	9.52	9.51
C_2H_5	$C_6H_5CH_2$	68	107–108	$C_{18}H_{22}N_2O_3$	8.84	8.43[b]
$C_6H_5CH_2$	C_2H_5	84	103–105	$C_{18}H_{22}N_2O_3$	8.84	8.70
C_2H_5	n-C_4H_9	96	94–96	$C_{15}H_{24}N_2O_3$	9.99	9.88

[a] Reference 11 reports m.p. 138–140°. [b] In spite of this rather poor analysis, a satisfactory final product was obtained. [c] 2-n-Butoxy-3-methoxyhydrocinnamahydrazide.

Pharmacologic tests showed the hydrochlorides of all the compounds of Table IV to be active as

TABLE VII

METHYL HYDROCINNAMATES

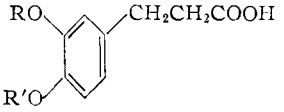


R	R'	Yield, %	M.p. or b.p., °C.	Mm.	n_D^t	t, °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5[a]	C_2H_5		43								
n-C_3H_7	n-C_3H_7	68	144–145	0.6	1.4973	25	$C_{16}H_{24}O_4$	68.54	68.75	8.63	8.63
i-C_3H_7	i-C_3H_7	69	142	0.8	1.4915	25	$C_{16}H_{24}O_4$	68.54	68.30	8.63	8.68
n-C_4H_9	n-C_4H_9	68	177–178	2			$C_{18}H_{28}O_4$	70.10	70.78	9.15	9.25
CH_3	n-C_4H_9	71	132–138	0.4	1.5058	24.5	$C_{15}H_{22}O_4$	67.64	67.77	8.33	8.12
n-C_4H_9	CH_3	98	162	2	1.5064	23	$C_{15}H_{22}O_4$	67.64	67.66	8.33	8.04
CH_3	2-n-C_4H_9[c]	77	152	2.3	1.4975	23.5	$C_{15}H_{22}O_4$	67.64	67.67	8.33	8.31
CH_3	n-C_6H_{13}	71.4	168–169	1.1	1.5012	25	$C_{17}H_{26}O_4$	69.36	69.29	8.90	8.67
C_2H_5	CH_3	84	109	0.2	1.5131	25	$C_{13}H_{18}O_4$	65 53	65.32	7.61	7.60
C_2H_5	$C_6H_5CH_2$	38.5[b]	192–194	1.1	1.5458	24	$C_{19}H_{22}O_4$	72.59	72.46	7.06	7.07
$C_6H_5CH_2$	C_2H_5	68[b]	53–54				$C_{19}H_{22}O_4$	72.59	72.40	7.06	6.79
C_2H_5	n-C_4H_9	72	156	1.2			$C_{15}H_{24}O_4$	68.54	68.54	8.63	8.31
H	C_2H_5	63.5	48–50				$C_{12}H_{16}O_4$	64.27	64.84	7.19	7.22
C_2H_5	H	66.5	132–133	0.2	1.5196	25	$C_{12}H_{16}O_4$	64.27	64.58	7.19	6.98

[a] See reference a, Table V. [b] The yields refer to benzylation of the corresponding hydroxy esters. The others refer to esterification. [c] Methyl 2-n-butoxy-3-methoxyhydrocinnamate.

TABLE VIII

HYDROCINNAMIC ACIDS

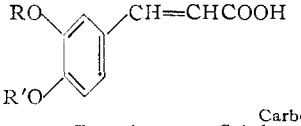


R	R'	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_3H_7	n-C_3H_7	97.5	76–77	$C_{15}H_{22}O_4$	67.64	67.86	8.32	8.31
i-C_3H_7	i-C_3H_7	96.5	Oil[a]	$C_{15}H_{22}O_4$				
n-C_4H_9	n-C_4H_9	91	67–68	$C_{17}H_{26}O_4$	69.36	69.70	8.90	8.89
CH_3	n-C_4H_9	97	86–87	$C_{14}H_{20}O_4$	66.67	66.84	7.99	7.97
n-C_4H_9	CH_3	85.8	80	$C_{14}H_{20}O_4$	66.67	66.77	7.99	7.94
CH_3[b]	2-n-C_4H_9	91	42	$C_{14}H_{20}O_4$	66.67	66.73	7.99	8.03
CH_3	n-C_6H_{13}	97	76–77	$C_{16}H_{24}O_4$	68.54	68.52	8.63	8.49
C_2H_5	n-C_4H_9	93	76	$C_{15}H_{22}O_4$	67.64	67.80	8.32	8.31
H	C_2H_5	Quant.	133–134	$C_{11}H_{14}O_2$	62.86	63.23	6.71	6.72
C_2H_5	H	57	74.5–75	$C_{11}H_{14}O_4$	62.84	63.00	6.71	6.60

[a] The oil was not analyzed; its methyl ester (Table V) was satisfactory. [b] 2-n-Butoxy-3-methoxyhydrocinnamic acid.

TABLE IX

CINNAMIC ACIDS



R	R'	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_3H_7	n-C_3H_7	58	148–149	$C_{15}H_{20}O_4$	68.16	68.28	7.63	7.53
i-C_3H_7	i-C_3H_7	37	117–118	$C_{15}H_{20}O_4$	68.16	68.32	7.63	7.59
n-C_4H_9	n-C_4H_9	88	134–135	$C_{17}H_{24}O_4$	69.84	69.91	8.28	8.15
CH_3	n-C_4H_9	57.4	153–154	$C_{14}H_{18}O_4$	67.18	67.25	7.25	7.33
n-C_4H_9	CH_3	92.5	157–158	$C_{14}H_{18}O_4$	67.18	67.09	7.25	7.05
CH_3[a]	2-n-C_4H_9	85	131–132	$C_{14}H_{18}O_4$	67.18	67.34	7.25	7.29
CH_3	n-C_6H_{13}	96.5	127–127.5	$C_{15}H_{22}O_4$	69.04	69.26	7.97	7.91
C_2H_5	n-C_4H_9	86	150–151	$C_{15}H_{20}O_4$	68.16	68.42	7.63	7.48
H	C_2H_5	74	208–209	$C_{11}H_{12}O_4$	63.45	63.70	5.81	5.85
C_2H_5	$C_6H_5CH_2$	68	189–190	$C_{18}H_{18}O_4$	72.47	72.35	6.08	5.93

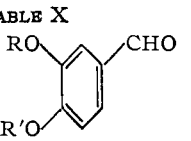
[a] 2-n-Butoxy-3-methoxycinnamic acid.

local anesthetics, in nearly all cases more effective than the simpler dihydroisoquinolines. For comparison, some known members, 6,7-dimethoxy-, -dibenzyloxy-, -methylenedioxy- and 6-ethoxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline hydrochlorides[21] were tested, as well as the 6,7-dihydroxy analog. The phenolic derivative was inactive; and, surprisingly, the 6,7-dimethoxy compound in several experiments proved completely inactive in the concentrations used for screening. This is hard to explain, since the 6-methoxy and 7-methoxy congeners (Table III) showed a fair degree of activity.

(21) Samples kindly furnished by A. W. Weston and R. J. Michaels.

TABLE X

ALDEHYDES



R	R'	Yield, %	M.p. or b.p., °C.	Mm.	$n^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_3H_7	n-C_3H_7	62	137–140	1	1.5479	$C_{12}H_{16}O_3$	70.24	70.50	8.16	7.79
i-C_3H_7	i-C_3H_7	51	109	0.4	1.5397	$C_{12}H_{16}O_3$	70.24	70.20	8.16	7.97
n-C_4H_9	n-C_4H_9	50	165–172	2.5		$C_{15}H_{22}O_3$	71.97	72.14	8.86	8.87
CH_3	n-C_4H_9		140.5–141.2[a]	2						
			29.5–30.5							
n-C_4H_9	CH_3		170–171[b]	20						
CH_3	2-n-C_4H_9[c]	79	126–127	2	1.5389	$C_{12}H_{16}O_3$	69.21	66.75	7.75	6.82
CH_3	n-C_6H_{13}	82.5	166–167	3		$C_{14}H_{20}O_3$	71.16	71.32	8.53	8.60
			37–39							
C_2H_5	n-C_4H_9		38–39[d]							

[a] G. Kubiczek, M. Pohl and A. Smahel, *Monatsh.*, **77**, 52 (1947); *C. A.*, **42**, 4543 (1948). [b] N. Hirao, *J. Chem. Soc. Japan*, **53**, 485 (1932); *C. A.*, **27**, 2776 (1933). [c] 2-n-Butoxy-3-methoxybenzaldehyde. Complete separation from *o*-vanillin could not be achieved by distillation, but the cinnamic acids could be separated. [d] J. Böeseken and J. Greup, *Rec. trav. chim.*, **58**, 528 (1939); *C. A.*, **33**, 6273[4] (1939).

None of the members of Table IV surpassed A-1350 and A-1349 in local anesthetic efficiency coupled with a low degree of tissue irritation. The properties of A-1350 appear slightly better than those of A-1349, and its pharmacology was extensively studied. Its surface anesthetic efficiency approaches that of tetracaine (duration 75–90% at the same concentration). For infiltration a solution containing 0.15% of A-1350 gives a slightly longer duration than 1% procaine. It gave effective spinal anesthesia in all of ten rabbits at 0.25% concentration. The toxicity of A-1350 is significantly less than that of tetracaine in mice, but the difference is not so marked in rabbits.

Experimental[22]

For the most part the compounds listed in the various tables were prepared by common methods. The procedures for 6-benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline and its intermediates are given in detail and these are illustrative of the methods used to prepare the other compounds in Tables IV to X. The synthetic methods for the compounds of Table II are evident from the table and from the intermediates reported in Table III.

3-Hydroxy-4-methoxy-ω-nitrostyrene.—This was synthesized by the method of Hahn and Rumpf[8] in 45% yield, m.p. 155–157° (H. and R. report 154°). Nitrogen analyses by the Dumas method (micro) failed to give satisfactory values, whereas carbon and hydrogen results agreed well with the theoretical. However, Ramirez and Burger[5b] report a satisfactory N analysis for their product, m.p. 161–162°.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18; C, 55.38; H, 4.65. Found: N, 6.27, 6.32; C, 55.45; H, 4.61.

Reduction to 3-Hydroxy-4-methoxyphenethylamine.—For this reduction a modification of the method of Schales[6,7] was used, the "shaking duck" being replaced by a 3-necked flask with a very efficient Hershberg stirrer, a separatory funnel and a hydrogen inlet. The hydrogen was introduced from a reservoir which was also connected to the top of the separatory funnel to equalize the pressure, maintained at about 2 cm.

The addition of the nitrostyrene required about four hours, and any attempt at more rapid addition or any less vigorous stirring gave a colored product of pleasant aromatic odor which resisted all attempts at removal. The precipitate formed by the addition of dry ether to the concentrated filtrate, after washing with dry ether and drying, weighed 3.9 g. (63%). A sample was washed with acetone and again dried in the vacuum desiccator, m.p. 158–160°. Hahn and Rumpf[8] report a melting point of 163°. The product was white, but colored rapidly in contact with moist air.

(22) All melting points are corrected.

3-Benzyloxy-4-methoxybenzylacetone.—Isovanillalacetone was synthesized and reduced to isovanillylacetone by the method of Mannich and Merz.[23] The product melted at 38–41° and was used for benzylation.

Benzylation was carried out according to the directions of Robinson and Sugasawa.[5] For analysis a sample was recrystallized from dry ether, m.p. 65–66°; total yield, 9.6 g. (73%).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09. Found: C, 76.18; H, 7.08.

3-Benzyloxy-4-methoxybenzylacetone Oxime.—The reaction was carried out according to the directions of Merz[24] for obtaining the *syn* form of the oxime of isovanillalacetone.

The crude oxime was recrystallized from acetone–water and dried on a porous plate, m.p. 99–104°; yield 2.45 g (80%). For analysis a sample was dried at the temperature of boiling acetone over phosphorus pentoxide at reduced pressure, but the analytical value for N was always low on such samples.

Anal. Calcd. for $C_{18}H_{21}NO_3$: N, 4.68; C, 72.22; H, 7.07. Found: N, 3.67.

The method of Kamm[25] then was resorted to, and this sample was dried at the temperature of boiling alcohol. This same sample dried at the temperature of boiling acetone gave a low analytical value for N (3.54%).

Found: N, 4.53; C, 72.07; H, 7.06.

For further reactions, the product prepared by the method of Merz[24] was used in the hope that more of the *syn* form would be present.

6-Benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline from the Oxime.—Phosphorus pentachloride (4 g.) was suspended in dry chloroform (70 cc.); the suspension was stirred and 6-benzyloxy-7-methoxybenzylacetone oxime (2.1 g.) was added. The flask was stoppered and allowed to stand at room temperature for three days. The product was worked up as later described. The hydrochloride had m.p. 200–201°, 0.6 g. (27%). For analysis it was dried at the temperature of boiling alcohol *in vacuo*.

Anal. Calcd. for $C_{18}H_{19}NO_2$·HCl: C, 68.02; H, 6.34; N, 4.41. Found: C, 67.97; H, 6.51; N, 4.47.

Variations in solvents and conditions failed to give appreciably better yields and most were lower. Yields from experiments intended as duplicates were not reproducible.

3-Hydroxy-4-methoxyhydrocinnamic Acid.—Isoferulic (hesperetic) acid[5] was reduced catalytically. Three methods were successful: (a) Hydrogenation in methanol with platinum oxide gave a solution of the dihydro acid which could be directly esterified by the addition of hydrogen chloride. (b) Hydrogenation of the aqueous solution of the sodium salt with Raney nickel catalyst was satisfactory. (c) The

(23) C. Mannich and K. W. Merz, *Arch. Pharm.*, **265**, 15 (1927).

(24) K. W. Merz, *Ber.*, **63B**, 2951 (1930).

(25) O. Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1932, p. 172.

preferred method is described in more detail. Isoferulic acid (194 g.) in water (2000 ml.) with sodium hydroxide (45 g.) and 5% palladium-on-charcoal (2 g.) was hydrogenated at 18 pounds pressure at room temperature. Reduction was complete in 45 minutes or less; yield of product melting at 146°,[5] 139.7 g. (98.5%) The same catalyst was used for seven reductions without apparent loss of activity.

Esterification of this acid and its O-benzylation were carried out according to the directions of Robinson and Sugasawa.[5] The use of sulfuric acid in the esterification was also satisfactory.

3-Benzyloxy-4-methoxyhydrocinnamhydrazide.—Methyl 3-benzyloxy-4-methoxyhydrocinnamate was converted to the hydrazide by the method described by Goldstein and Stern.[15] Schöpf, Perrey and Jäckh[11] report m.p. 138–140° for a recrystallized sample.

3-Benzyloxy-4-methoxyhydrocinnamazide.—The above hydrazide was converted to the azide according to the directions of Cheney and Piening.[26] The precipitated azide was filtered and washed with water, and a portion was dried in a vacuum desiccator for analysis.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.70; H, 5.50; N, 13.50. Found: C, 71.20; H, 6.27; N, 8.04 (average of 2 analyses).

The product was probably partially transformed into the isocyanate. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. The azide prepared by Matson[3]: *Anal.* Found: N, 8.10.

If the temperature becomes too high during the addition of nitrite, a considerable proportion of *sym*-diacylhydrazide is formed, m.p. 192–193°.

Anal. Calcd. for $C_{34}H_{36}N_2O_2$: C, 71.81; H, 6.38; N, 4.93; mol. wt., 568. Found: C, 71.88; H, 6.38; N, 4.89; mol. wt., 536 (Rast).

The monoacylhydrazide may be obtained from this by further treatment with hydrazine, m.p. 128–129°.

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: N, 9.33; mol. wt., 300.3. Found: N, 9.48; mol. wt., 303.8.

N-(3-Benzyloxy-4-methoxyphenethyl)-acetamide.—The moist azide from 0.2 mole of 3-benzyloxy-4-methoxyhydrocinnamhydrazide (60 g.) was mixed with benzene (200 ml.) and acetic anhydride (60 ml.) and refluxed for five hours. The solution, after slight cooling, was poured into excess potassium carbonate solution. The layers were separated and the aqueous layer further extracted with benzene until all the solid was dissolved, the substituted acetamide being only sparingly soluble in cold benzene. The combined benzene solution was warmed with charcoal and filtered while hot. After evaporating the filtrate to half its original volume, cooling in ice, filtering and air-drying, the acetamide obtained weighed 45 g. (75% of theoretical from the hydrazide), and melted at 124–125°. The pure amide melts at 128–128.5°,[4] but the above product is satisfactory for ring closure. The residues, containing some of the starting materials, were added to later runs.

6-Benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline from the Acetamide.—The method of Schöpf, Perrey and Jäckh[11] was modified to improve the yield. Phosphorus pentachloride (30 g.) in dry chloroform (200 ml.) was stirred in a 3-necked flask immersed in a bath maintained at about 45°. A solution of N-(3-benzyloxy-4-methoxyphenethyl)-acetamide (30 g.) in dry chloroform (150 ml.) was dropped in at such a rate as to prevent too violent evolution of hydrogen chloride. After all was in, stirring at the same temperature was maintained for an hour. The solvent was removed by distillation under reduced pressure, and the viscous residue was thoroughly extracted with water, the last portions being acidified with hydrochloric acid. The combined aqueous solution was clarified by filtration, made alkaline by addition of 50% potassium hydroxide solution, and the base was shaken out in ether. After drying with potassium hydroxide pellets and filtration with charcoal, the hydrochloride was precipitated from the clear colorless ethereal solution, and dried in a vacuum desiccator. The melting point varies to an unusual extent with the rate of heating and type of bath, perhaps due to the degree of decomposition.

The base was prepared by evaporation of its ether solution and recrystallization from petroleum ether, m.p. 99–100°.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.08; H, 6.80; N, 5.30.

Other salts were prepared by mixing ethereal solutions of the base and the appropriate acid and recovering the precipitated salt. Thus were obtained the acid sulfate, m.p. 185–189°, and the nitrate, m.p. 195–196°. All the salts give evidence of decomposition at the melting point.

All the diether-substituted 1-methyl-3,4-dihydroisoquinolines were synthesized in a manner similar to that described for A-1350, as were their intermediates. The substituted cinnamic acids, including isoferulic acid, were synthesized by condensation of the appropriate aldehyde with malonic acid.[9] The ether substituted benzaldehydes were prepared by alkylation of the hydroxybenzaldehydes.[27]

Acknowledgment.—The authors appreciate the advice and helpful coöperation offered by various members of the Organic Research Department who carried out some of the syntheses as indicated in the text; and by Mr. E. F. Shelberg, Chief Microanalyst, and his staff who furnished the analytical figures herein reported.

NORTH CHICAGO, ILLINOIS

(26) L. C. Cheney and J. R. Piening, THIS JOURNAL, **67**, 731 (1945).

(27) Ethavan and isoethavan were kindly furnished by Monsanto Chemical Co.