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Hydrazines, Hydrazides and Hydrazide Esters

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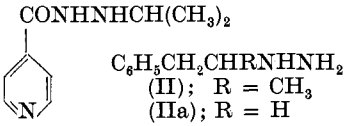
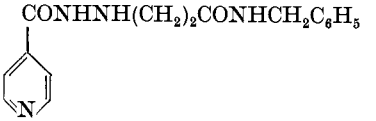
Introduction

Within the past decade, the development of psychopharmacology has made available to the chemist means by which organic compounds can be tested and evaluated for their application at the clinical level. On the one hand, drugs such as reserpine,[1] chlorpromazine[2] and its derivatives, meprobamate,[3] and most recently methaminodiazepoxide,[4] have found important use in the treatment of mental illness and states of anxiety. These drugs have been termed generally as tranquillizers. Of equal concern and interest have been drugs which exert a stimulant effect on the central nervous system. These substances have been known as psychic energizers. An important class of compounds in this genus are the hydrazines and hydrazides; the structures of the clinically effective iproniazid (I),[5] phenylisopropylhydrazine (II) and phenethylhydrazine[6] (IIa), and nialamide (III)[7] are outlined.



(I)

$C_6H_5CH_2CHRNHNH_2$
(II); R = CH_3
(IIa); R = H



(III)

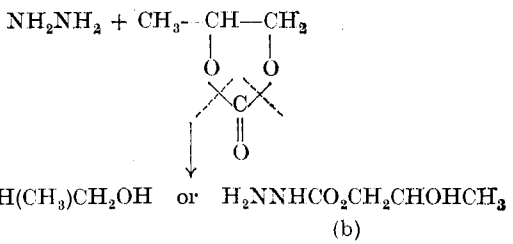
Our principal efforts have been directed toward the alteration of the basic structures I–III in order to elucidate structure–activity relationships. Thus, our study has been divided into three main groups: (A) the arylcarbazate esters, (B) nicotinuric acid derivatives, and (C) the cycloalkylhydrazides and hydrazines. The chemistry of each of these groups comprises the subject matter of this report.

A. *Arylcarbazate esters.* In 1958, Delaby *et al.*[8] reported the preparation of 2-hydroxyethylcarbazate (IV) by treating ethylene carbonate with hydrazine. We have used this highly crystalline substance for condensations with a wide variety of aromatic aldehydes. The resulting arylidene carbazate esters were in turn catalytically reduced to yield the desired hydrazide esters.

$$ArCHO + H_2NNHCO_2CH_2CH_2OH \longrightarrow ArCH{=}NNHCO_2CH_2CH_2OH$$
(IV)

$$\xrightarrow{[H]} ArCH_2NHNHCO_2CH_2CH_2OH$$

When propylene carbonate was allowed to react with hydrazine under the same conditions as previously employed, a light-yellow viscous oil was isolated which resisted crystallization. However, reaction of this oil with an aldehyde gave rise to a crystalline arylidene carbazate ester. These substances were found to be homogeneous by paper chromatography. Thus, one of two possibilities exists. The hydrazine ring cleavage reaction gives rise to either a primary alcohol (a) or a secondary alcohol (b).



The hydrazide esters of (b) should first of all form a chloride under conditions which would not do so for a primary alcohol,[9] and secondly such compounds should give a positive iodoform test. Each of these tests on compounds 6 and 14 (see Table I) was negative, indicating the presence of a primary alcohol.

In Table I are outlined the physical and analytical data for the arylidene carbazate esters and in Table II the data for the saturated hydrazide esters prepared in this group.

B. *Nicotinuric acid derivatives.* In connection with another project under way in our laboratory, it was of interest to prepare a

Table I. Aralkylidenecarbazates

$ArCH=NNHCOOCHRCH_2OH$

No.	Ar	R	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
						C	H	N	C	H	N
1.	*m*-$CH_3C_6H_4$	H	114–115·5	60	$C_{11}H_{14}N_2O_3$	59·46	6·35	12·60	59·05	6·42	12·43
2.	3,4,5-$(OCH_3)_3C_6H_2$	H	110–112	78	$C_{13}H_{18}N_2O_6$	52·34	6·08		52·34	6·11	
3.	*o*-FC_6H_4	H	80–81	45	$C_{10}H_{11}FN_2O_3$			12·38			12·48
4.	*p*-ClC_6H_4	H	119–120	95	$C_{10}H_{11}ClN_2O_3$			11·54			11·80
5.	*p*-$CH_3OC_6H_4$	H	135	40	$C_{11}H_{14}N_2O_4$	55·45	5·92	11·76	55·39	6·08	11·96
6.	*p*-$CH_3OC_6H_4$	CH_3	103–105	45	$C_{12}H_{16}N_2O_4$	57·11	6·39	11·11	56·86	6·37	11·13
7.	*o*-(COOH)—C_6H_4	H	152–154	20	$C_{11}H_{12}N_2O_5$	52·38	4·79	11·11	52·70	4·82	11·16
8.	*o*-(COOH)—C_6H_4	CH_3	127–128	23	$C_{12}H_{14}N_2O_5$	54·13	5·31		53·70	5·50	
9.	*p*-$(C_2H_5)_2NC_6H_4$	H	149–151	55	$C_{14}H_{21}N_3O_3 \cdot HCl$	53·07	7·00	13·27	53·05	7·20	13·06
10.	$C_6H_5(CH_2)_2$	H	80–83	38	$C_{12}H_{16}N_2O_3$			11·88			11·87
11.	$C_6H_5CH_2CH_2—C(CH_3)=$	H	95	15	$C_{13}H_{18}N_2O_3$	62·39	7·25	11·19	62·00	7·34	11·19
12.	2-C_5H_4N[a]	H	134	65	$C_9H_{11}N_3O_2$	51·60	5·30	20·09	51·45	5·26	20·00
13.	3-C_5H_4N	CH_3	168–169	42	$C_{10}H_{13}N_3O_3$	53·81	5·88	18·82	53·46	5·92	18·40
14.	4-C_5H_4N	CH_3	209–210	60	$C_{10}H_{13}N_3O_3 \cdot HCl$	46·25	5·44	16·18	45·97	5·80	16·30
15.	4-C_5H_4N	H	148–150	40	$C_9H_{11}N_3O_3$	51·67	5·30	20·09	51·65	5·40	20·36
16.	2-C_4H_3S[b]	H	112–113	67	$C_8H_{10}N_2O_3S$	44·85	4·71	13·08	44·86	4·80	13·11
17.	5-NO_2–C_4H_3O[c]	H	163–164	55	$C_8H_9N_3O_6$	39·51	3·73		39·75	3·75	

[a] Pyridyl; [b] thienyl; [c] 5-nitro-2-furyl. Compound 11 represents the product of condensing 2-hydroxyethylcarbazate with 1-phenylbutan-3-one.

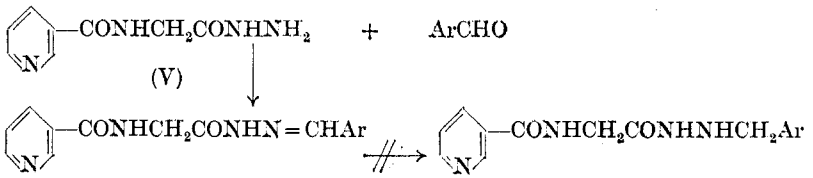
Table II. Aralkyl carbazates

$ArCH_2NHNHCOOCH_2CH_2OH$

No.	Ar	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
					C	H	N	C	H	N
18.	C_6H_5[a]	78	75	$C_{10}H_{14}N_2O_3$	57·13	6·71	13·33	56·94	6·89	13·50
19.	p-$(CH_3)_2NC_6H_4$[a]	99–100	70	$C_{12}H_{19}N_3O_3$	56·90	7·56	16·59	57·02	7·77	16·86
20.	o-$CH_3OC_6H_4$	147–148	25	$C_{11}H_{16}N_2O_4$	55·75	5·21	11·57	55·45	5·41	11·76
21.	$C_6H_5CH_2CH_2$	81–82	80	$C_{12}H_{18}N_2O_3$	60·48	7·61	11·76	60·30	7·68	11·64
22.	2-C_5H_4N	82–84	55	$C_9H_{13}N_3O_3$	51·18	6·20	19·90	51·30	6·49	20·20
23.	4-C_5H_4N	85–87	50	$C_9H_{13}N_3O_3$	51·18	6·20	19·90	50·89	6·60	19·71

[a] These compounds were prepared by reduction of the corresponding benzylidene carbazates reported by Delaby.[8]

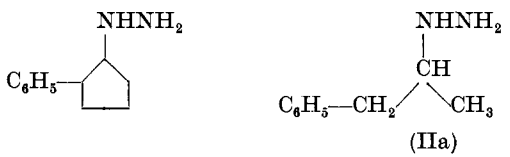
quantity of nicotinuric acid.* The hydrazide V of this acid was in turn condensed with aromatic aldehydes. However, the resulting compounds proved to be remarkably resistant to reduction. Catalytic reduction of the compound in which Ar



= phenyl with palladium on carbon or with platinum oxide at 50 lb hydrogen pressure gave back the starting material almost quantitatively. Reduction with sodium borohydride was also ineffective. An attempt was made to prepare this compound by condensing the ethyl ester of nicotinuric acid with benzyl hydrazine. Only a dark viscous oil of indefinite composition could be isolated from the reaction mixture.

The compounds prepared in this group are characterized in Table III.

C. *Cycloalkyl derivatives.* This phase of our research was concerned with the preparation of cycloalkyl modifications of phenylisopropylhydrazine (IIa). These compounds, of which



(IIa)

2-phenylcyclopentyl hydrazine is an example, were prepared by condensing an α-haloalicyclic ketone with an aromatic Grignard

* Extreme caution must be exercised in preparing one of the intermediates in this synthesis. The method used was that reported by S. W. Fox and H. Field, *J. biol. Chem.*, **147**, 651 (1943). It consists in treating nicotinic acid hydrazide with sodium nitrite to form the azide. The ether solution containing the azide is then evaporated to dryness *in vacuo*. The resulting oil solidifies in long needles (m.p. 46–48°) on standing. The azide is then allowed to react with glycine to yield nicotinuric acid.

This synthesis was carried out on four separate occasions and each time it was noted that the azide was stable. The literature also reports nothing to the contrary. On the fifth run (a 20·0 g batch), the azide violently exploded, seriously injuring one of the chemists and demolishing a considerable part of the laboratory.

Table III. Nicotinuric 2-aralkylidene hydrazides

No.	Ar	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
					C	H	N	C	H	N
24.	C_6H_5	174	60	$C_{15}H_{14}N_4O_2$	63·82	5·00	19·85	64·05	5·20	19·89
25.	m-$CH_3C_6H_4$	158–160	92	$C_{16}H_{16}N_4O_2$	64·85	5·43	18·91	64·70	5·40	18·65
26.	p-$CH_3OC_6H_4$	214–217	73	$C_{16}H_{16}N_4O_3$	61·53	5·16	17·95	61·27	5·36	17·50
27.	p-$(C_2H_5)_2NC_6H_4$	202–202·5	90	$C_{19}H_{23}N_5O_2$	64·57	6·56	19·82	64·71	6·54	19·84
28.	2-C_5H_4N	115	95	$C_{14}H_{13}N_5O_2$	59·35	4·62	24·72	59·04	4·78	24·30
29.	3-C_5H_4N	125·5	45	$C_{14}H_{13}N_5O_2 \cdot H_2O$	55·81	5·02	23·25	56·10	5·14	23·10
30.	4-C_5H_4N	200–202	78	$C_{14}H_{13}N_5O_2 \cdot H_2O$	55·81	5·02	23·25	55·70	5·19	23·50
31.	2-C_4H_3S	170–171	50	$C_{13}H_{12}N_4O_2S$	54·15	4·20	19·44	54·14	4·32	19·67

The compounds reported in this table were recrystallized from 95% ethyl alcohol with the exception of compound 30 which was recrystallized from methyl alcohol.

reagent.[10] The product of this reaction was treated with an acyl or aroyl hydrazide to give a hydrazone. Catalytic reduction of the hydrazone with platinum oxide followed by hydrolysis yielded the hydrazine.[11] It is of interest to note that on hydrolysis of compound 49 no product could be isolated. Repeated attempts to prepare the corresponding hydrazine were unsuccessful. In Tables IV, V and VI are outlined the physical and analytical data for compounds in this group.

D. *Pharmacology.* The compounds described in this paper were tested in rats for their central nervous system stimulation effects. Phenylisopropylhydrazine was used as a control. Under the conditions of our biological test, stimulation of experimental rats in the jiggle cage, only one compound was found to be significantly effective. 2-Phenylcyclopentylhydrazine was one-fifth as potent as phenylisopropylhydrazine.

Experimental

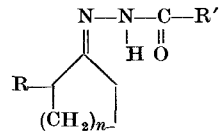
Ethyl nicotinuric acid was prepared according to the method of Meyer and Graf.[12] The 2-arylalicyclic ketones used as intermediates are described in the literature and were prepared as outlined by Mislow and Hamermesh.[10] The method of Delaby *et. al.*[8] was used for the preparation of 2-hydroxyethylcarbazate and 2-hydroxy-1-methylethylcarbazate.

A. *Aralkylidene carbazates.* The compounds outlined in Table I were all prepared in the same manner. The following procedure serves as an example.

2-Hydroxyethyl-p-methoxybenzylidenecarbazate. Anisaldehyde (13·6 g) was added to ethyl alcohol (100 ml) containing 2-hydroxyethylcarbazate (10·6 g). After refluxing the solution on the steam bath for 24 h, half the volume of ethyl alcohol was removed *in vacuo*. The white crystalline powder which precipitated from the solution was collected on a filter and air dried. One recrystallization from ethyl alcohol gave an analytically pure sample, m.p. 134–135°.

The reduction of compounds of the above type to the 2-hydroxyethylaralkylcarbazates was carried out with a palladium on carbon catalyst in ethyl acetate solution at 50 lb hydrogen pressure in an Adams–Parr shaker. Usually the calculated amount of hydrogen

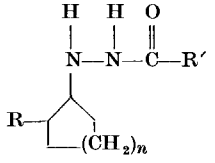
Table IV. 1-Acyl 2-cycloalkylidene hydrazines



No.	R	R′	*n*	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
							C	H	N	C	H	N
32.	C_6H_5	CH_3	1	145	75	$C_{13}H_{16}N_2O$	72·19	7·46	12·95	72·28	7·50	13·01
33.	$C_6H_5CH_2$	CH_3	1	138	95	$C_{14}H_{18}N_2O$	73·01	7·88	12·16	72·81	7·98	12·37
34.	$C_6H_5CH_2$	C_6H_5	1	180–183	65	$C_{19}H_{20}N_2O$	78·05	6·89	9·58	78·05	6·97	9·83
35.	C_6H_5	CH_3	2	152–153	80	$C_{14}H_{18}N_2O$	73·01	7·88	12·16	73·12	7·95	12·51
36.	C_6H_5	C_6H_5	2	142–143	83	$C_{19}H_{20}N_2O$	78·05	6·84		78·38	6·96	
37.	$C_6H_5CH_2$	CH_3	2	128	94	$C_{15}H_{20}N_2O$	73·73	8·25	11·47	74·10	8·34	11·57
38.	4-$CH_3C_5H_9NCH_2$[a]	CH_3	2	130–131	60	$C_{15}H_{27}N_3O$	67·88	10·25	15·84	67·70	10·41	15·66
39.	$NCCH_2CH_2$	CH_3	2	82–84	75	$C_{11}H_{17}N_3O$	63·74	8·27	20·27	63·78	8·46	20·53
40.	H	CH_3	4	127–128	78	$C_{10}H_{16}N_2O$	65·90	9·95	15·37	65·79	10·09	15·10
41.	H	C_6H_5	4	141	65	$C_{15}H_{20}N_2O$	73·73	8·25	11·47	73·50	8·30	11·48
42.	H	4-C_5H_4N[b]	4	105–107	60	$C_{14}H_{19}N_3O$	68·54	7·81	17·13	68·28	7·96	16·95

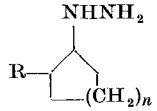
[a] 4-Methylpiperidylmethyl. [b] 4-Pyridyl.

Table V. 1-Acyl 2-cycloalkyl hydrazines



No.	R	R′	*n*	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
							C	H	N	C	H	N
43.	C_6H_5	CH_3	1	110	45	$C_{13}H_{18}N_2O$	71·51	8·38	12·83	71·23	8·20	12·83
44.	$C_6H_5CH_2$	CH_3	1	67–68	35	$C_{14}H_{20}N_2O$	72·37	8·68	12·06	72·31	8·76	12·12
45.	$C_6H_5CH_2$	C_6H_5	1	94–95	50	$C_{19}H_{22}N_2O$	77·52	7·53	9·52	77·23	7·82	9·72
46.	C_6H_5	CH_3	2	105	50	$C_{14}H_{20}N_2O$	72·38	8·68	12·06	72·19	8·85	12·18
47.	C_6H_5	C_6H_5	2	110–112	45	$C_{19}H_{22}N_2O$	77·52	7·53	9·52	77·20	7·68	9·57
48.	$C_6H_5CH_2$	CH_3	2	109–110	80	$C_{15}H_{22}N_2O$	73·13	9·00	11·37	73·37	9·10	11·23
49.	$4\text{-}CH_3C_5H_{11}NCH_2$	CH_3	2	215–217	30	$C_{15}H_{29}N_3O\cdot 2HCl$	52·93	9·18	12·35	52·60	9·27	12·37
50.	H	CH_3	4	56	50	$C_{10}H_{20}N_2O$	65·17	10·94	15·20	65·21	11·00	15·06
51.	H	C_6H_5	4	70	55	$C_{15}H_{22}N_2O$	73·13	9·41	11·37	72·75	9·39	11·37
52.	H	$4\text{-}C_5H_4N$	4	236–237	22	$C_{14}H_{21}N_3O\cdot 2HCl$	52·50	7·24	13·12	52·31	7·30	13·36

Table VI. Cycloalkyl hydrazines



No.	R	*n*	m.p., °C	Yield, %	Formula	Calcd., %			Found, %		
						C	H	N	C	H	N
53.	C_6H_5	1	145–147	45	$C_{11}H_{16}N_2 \cdot HCl$	62·10	8·06	13·17	61·80	8·01	13·19
54.	$C_6H_5CH_2$	1	120	40	$C_{12}H_{18}N_2 \cdot HCl$	63·56	8·45	12·35	63·34	8·61	12·50
55.	C_6H_5	2	179–180	75	$C_{12}H_{18}N_2 \cdot HCl$	63·56	8·45	12·35	63·86	8·45	12·50
56.	$C_6H_5CH_2$	2	210–212	62	$C_{13}H_{20}N_2 \cdot HCl$	64·85	8·79	11·63	64·80	8·76	11·84
57.	H	4	103–105	55	$C_8H_{18}N_2 \cdot HCl$	53·87	10·72	15·68	53·50	10·71	15·56

was taken up within a 10-h period. Filtering the mixture followed by removal of half the volume of solvent resulted in the precipitation of the reduced product which was recrystallized from ethyl acetate or ether. See Table II for the properties of these compounds.

B. *Nicotinuric acid hydrazide.* The ethyl nicotinurate (20 g) was treated with an excess of hydrazine hydrate. Reaction occurred immediately as the temperature rose to 60–65° and a crystalline product separated out. The reaction mixture was maintained at that temperature for 1 h. The mixture was then chilled, and the precipitate collected and recrystallized from ethanol. A 50 per cent yield of product, m.p. 183–185°, was obtained.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49·48; H, 5·19; N, 28·85. Found: C, 49·43; H, 5·21; N, 29·00.

Nicotinuric 2-aralkylidenehydrazide. The general procedure by which this class of compounds was prepared is exemplified in the following preparation:

Nicotinuric acid hydrazide (5·38 g) dissolved in ethanol (250 ml) was treated with benzaldehyde (2·94 g). After heating this solution under reflux for 5 h, the solvent was distilled off *in vacuo*. The remaining oil crystallized on chilling. Two recrystallizations from ethanol yielded analytically pure product.

General Method for the Preparation of 2-Arylcycloalkylhydrazines

These hydrazines were obtained by condensing the particular alicyclic ketone with acetyl, benzoyl or 4-pyridoylhydrazide, followed by catalytic reduction to the substituted hydrazide and finally hydrolysis of this compound to the desired alicyclic hydrazine. The following procedure serves as a general outline for the synthesis of the compounds in Tables IV, V and VI:

A mixture of 2-benzylcyclohexanone (10·0 g)[10] and acetylhydrazide (3·94 g) was dissolved in ethanol (50 ml) and the solution was refluxed on the steam bath for 2 h. On standing, a mass of crystals of 1-acetyl-2-cyclopentylidenehydrazine appeared which was recrystallized from ethyl alcohol.

Platinum oxide catalyst (0·275 g) was added to 100 ml of glacial acetic acid containing the 1-acetyl-2-cyclopentylidenehydrazine (11·0 g). The compound was reduced under 45 lb hydrogen

pressure in an Adams–Parr shaker. The calculated amount of hydrogen was taken up within 40 min. The acetic acid solution, after filtration, was evaporated to dryness *in vacuo*. The residue was taken up in chloroform and washed with 35 per cent sodium hydroxide solution. The chloroform extract was dried over $MgSO_4$. Removal of the chloroform yielded the crude product which was recrystallized for analysis from acetone–hexane.

1-Acetyl-2-cyclopentylhydrazine (4 g) was dissolved in 4·5 per cent hydrochloric acid solution (50 ml). After refluxing under nitrogen for 5 h, the mixture was chilled. The resulting precipitate was collected and recrystallized from ethyl alcohol yielding pure 2-benzylcyclohexylhydrazine hydrochloride.

Summary. A wide variety of hydrazines, hydrazides and hydrazide esters were prepared for pharmacological evaluation, especially as central nervous system stimulants.

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References

[1] Müller, J. H., Schlittler, E. and Bein, H. J. *Experientia*, **8**, 338 (1952)
[2] Charpentier, P., Gailliot, P., Jacob, R., Gandechon, J. and Buisson, P. *C.R. Acad. Sci., Paris*, **235**, 59 (1952)
[3] Ludwig, B. J. and Piech, E. C. *J. Amer. chem. Soc.*, **73**, 5779 (1951)
[4] Sternbach, J. H. U.S. Pat. 2,893,992, July 7, 1959
[5] Feller, E. A. and Barsky, J. *Proc. Soc. exp. Biol., N.Y.*, **81**, 459 (1952)
[6] Biel, J. H., Drukker, A. E., Mitchell, T. F., Sprengeler, E. P., Nukfer, P. A., Conway, A. C. and Horita, A. *J. Amer. chem. Soc.*, **81**, 2805 (1959)
[7] Bloom, B. M. and Carnaham, R. E. U.S. Pat. 2,894,972. Abstracts of Papers, 135th Meeting, American Chemical Society, Boston, Mass., April, 1959, p. 24N.
[8] Delaby, R., Damiens, R. and Capman, M. J. *C.R. Acad. Sci., Paris*, **246**, 3353 (1958)
[9] Lucas, H. *J. Amer. chem. Soc.*, **52**, 802 (1930)
[10] Mislow, K. and Hamermesh, C. J. *J. Amer. chem. Soc.*, **77**, 1590 (1955)
[11] Ebnöther, A., Jucker, E., Lindenmann, A., Rossi, E., Steiner, R., Süess, R. and Vogel, A. *Helv. chim. acta*, **42**, 533 (1959)
[12] Meyer, H. and Graf, P. *Biochem. J.*, **229** 154 (1930)