parative scale experiments. A mixture of 48 g. (0.20 mole) of 1-iodoöctane, 24.2 g. (0.35 mole) of sodium nitrite (or 18.6 g. of lithium nitrite), and 250 ml. of the solvent was stirred at room temperature (or higher if noted). The undissolved solid was isolated by filtration, washed, dried, and weighed. The filtrate was dried and rectified. In this way the data of Table III were obtained.

The Influence of Urea on the "Solubility" of Alkali Nitrites in DMF.—The "solubility" of sodium and potassium nitrite in DMF–urea solutions was determined by placing 10 g. of the alkali nitrite in 100 ml. of DMF containing varying amounts of urea. The mixtures were sealed, shaken for 24 hours at room temperature, the undissolved nitrite isolated by filtration, washed with anhydrous ether, dried and then weighed.

TABLE IV

"SOLUBILITY" OF NITRITES IN DMF

Nitrite	Composition of "solvent" DMF, ml.	Composition of "solvent" Urea, g.	Grams of nitrite dissolved
$NaNO_2$	100	...	1.88
$NaNO_2$	100	4.35	4.41
$NaNO_2$	100	8.7	7.6
$NaNO_2$	100	19.4	7.27
KNO_2	100	...	0.64
KNO_2	100	7.1	3.49

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Reaction of Aliphatic Nitro Compounds with Nitrite Esters[1,2]

BY NATHAN KORNBLUM, ROBERT K. BLACKWOOD AND DAVID D. MOOBERRY

RECEIVED SEPTEMBER 9, 1955

Although primary nitroparaffins, secondary nitroparaffins and α-nitroesters are inert toward nitrite esters, the joint action of a nitrite ester and sodium nitrite destroys the nitro compound. Primary nitro compounds give the carboxylic acid, secondary nitroparaffins yield ketones and α-nitroesters are converted to α-oximinoesters. The course of these reactions is described.

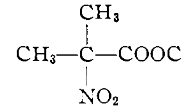
In the preceding paper of this series[3] it was found that if a nitroparaffin, an alkyl nitrite and sodium nitrite are allowed to stand at room temperature, the nitro compound is destroyed. The nature of the destructive process is the subject of the present communication.

As shown in Table I, when 1-nitroöctane is treated with sodium nitrite it is quantitatively recovered (expt. 1 to 3). Nor is there any reaction when 1-nitroöctane is exposed to nitrite esters (expt. 4 and 5). In contrast, when 1-nitroöctane is exposed to the combined influence of sodium nitrite and an alkyl nitrite it is converted into caprylic acid (expt. 6 to 9).

Table IB summarizes a series of experiments using 2-nitroöctane. Here again the nitro compound is completely stable toward either sodium nitrite or alkyl nitrites but is destroyed by their joint influence, 2-octanone being produced.

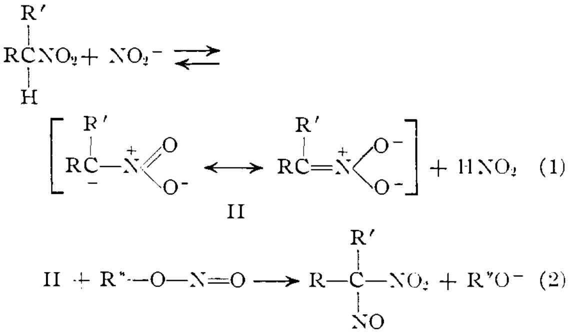
In Table IC are recorded the data of experiments involving ethyl α-nitropropionate. After 24 hours contact with sodium nitrite the α-nitroester is recovered in 93% yield[4] (expt. 17). And after 45 hours there is no reaction between the α-nitroester and *n*-propyl nitrite (expt. 19). But treatment with both sodium nitrite and *n*-propyl nitrite results in complete destruction of the ethyl α-nitropropionate in 22 hours, ethyl α-oximinopropionate being formed.

Thus, for reaction to occur, all three reagents—the nitro compound, the alkyl nitrite and sodium nitrite—are needed. It is also necessary to have a hydrogen atom on the carbon holding the nitro group as is shown by the failure of ethyl α-nitroisobutyrate (I) to react. From these facts, and the



$$CH_3-\underset{NO_2}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-COOC_2H_5 \qquad I$$

data which follow, it is apparent that the reaction proceeds first to give nitrosated nitro compounds (III) which, being unstable, break down to form the products isolated. As will be seen, the nitrite ion simply functions as a base.[5]



$$R\underset{H}{\overset{R'}{C}}NO_2 + NO_2^- \rightleftarrows \left[R\overset{R'}{\underset{-}{C}}-\overset{+}{N}\begin{smallmatrix}\nearrow O \\ \searrow O^-\end{smallmatrix} \longleftrightarrow R\overset{R'}{C}=\overset{+}{N}\begin{smallmatrix}O^- \\ O^-\end{smallmatrix} \right] + HNO_2 \qquad (1)$$

$$\text{II}$$

$$\text{II} + R''-O-N=O \longrightarrow R-\underset{NO}{\overset{R'}{C}}-NO_2 + R''O^- \qquad (2)$$

$$\text{III}$$

$$R''O^- + HNO_2 \longrightarrow R''OH + NO_2^- \qquad (3)$$

The reactions of III vary with the nature of the substituents. When R = alkyl and R′ = hydro-

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[1] Paper XIII in the Series "The Chemistry of Aliphatic and Alicyclic Nitro Compounds."

[2] This research was supported, in part, by grants from The Explosives Department of E. I. du Pont de Nemours and Co., and, in part, by the United States Air Force under Contract No. AF 18 (600)-310 monitored by the Office of Scientific Research, Air Research and Development Command.

[3] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, THIS JOURNAL, **78**, 1497 (1956).

[4] Given 168 hours in which to act, sodium nitrite alone is able to destroy a perceptible amount of the α-nitroester (expt. 18). This is understandable since α-nitroesters are distinctly more acidic than nitroparaffins. It is interesting to note that the conversion of an α-nitroester to the α-oximinoester by the agency of sodium nitrite is much slower in DMF than in aqueous ethanol [N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1494 (1956)].

[5] Although nitrosation of nitroparaffins by nitrite esters has apparently not been reported previously one would have anticipated that, in the presence of a strong base, *e.g.*, ethoxide ion, nitrosation would take place readily. It is surprising, however, that a base as weak as nitrite ion is able to act as an effective catalyst.

TABLE I

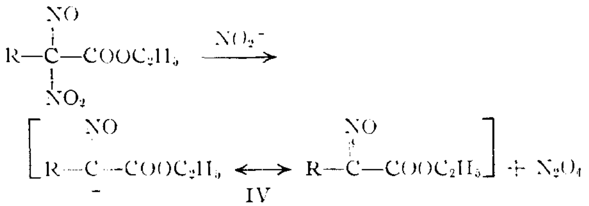
Expt.	Initial amounts: RCH$_2$NO$_2$, g. (mole)	Initial amounts: Nitrite ester, R″ONO, g. (mole)	Initial amounts: NaNO$_2$, g. (mole)	Reacn. time, hr.	Recovery, %: RCH$_2$NO$_2$	Recovery, %: R″ONO	Yields, %: RCOOH	Yields, %: R″OH
				A. With 1-nitroöctane[a]				
1	30 (0.19)			8	90–93			
2	30 (.19)		20 (0.29)	8	88–89			
3	32 (.20)		20 (.29)	26	92			
4	30 (.19)	*n*-Hexyl, 20 (0.15)		8	87–91	70–72		
5	32 (.20)	*n*-Propyl, 18 (.20)		25	89	77		
6	30 (.19)	*n*-Hexyl, 20 (.15)	20 (.29)	8	57–58	[b]	9–15	64–66
7	30 (.19)	*n*-Octyl, 30 (.19)	20 (.29)	24	0	[b]	52	74
8	32 (.20)	*n*-Propyl, 4.5 (.05)	20 (.29)	36	27	[b]	29	[b]
9	32 (.20)	*n*-Propyl, 4.5 (.05)	20 (.29)	64	0	[b]	40	[b]
10	32 (.20)	*n*-Propyl, 18 (.20)	[c]	24	58	50	16	[b]
				B. With 2-nitroöctane[d]				
	RCHNO$_2$CH$_3$				RCHNO$_2$CH$_3$	R″ONO	RCOCH$_3$	
11	32 (0.20)		36 (0.52)	64	96			
12	32 (.20)	2-Octyl, 32 (0.20)		65	91	84		
13[e]	48 (.30)	2-Octyl, 48 (.30)	54 (.78)	64	0	*ca.* 26[g]	47	
14	32 (.20)	*n*-Propyl, 18 (.20)	36 (.52)	65	0	29	83	
15	32 (.20)	*n*-Propyl, 4.5 (.05)	36 (.52)	65	33	[b]	54	
16	32 (.20)	*n*-Propyl, 18 (.20)		65	32	29	58	
				C. With ethyl α-nitropropionate[h]				
	α-Nitroester	*n*-Propyl nitrite			α-Nitroester	*n*-Propyl nitrite	α-Oximinoester	
17	32 (0.22)		36 (0.52)	24	93			
18	30 (.20)		36 (.52)	168	72		6	
19	30 (.20)	15 (0.17)		45	91	82		
20	30 (.20)	15 (.17)	36 (.52)	22	0	25	26	
21	30 (.20)	3 (.03)	36 (.52)	50	15	[b]	12	
22	30 (.20)	15 (.17)		28	13	[b]	21	

[a] All experiments conducted in 400 ml. of DMF. [b] Isolation not attempted. [c] In place of sodium nitrite, 57 g. (0.30 mole) of sodium *m*-nitrobenzoate was added. [d] All experiments in 600 ml. of DMF + 40 g. of urea (except expt. 13). This experiment in 900 ml. of DMF containing 60 g. of urea. [f] In place of sodium nitrite, 94.5 g. (0.50 mole) of sodium *m*-nitrobenzoate was added. [g] 2-Octanol (26 g., 67% yield) was isolated as the acid phthalate ester, m.p. 55–55.5°, mixed m.p. with an authentic sample 55–55.5°. [h] All experiments in 600 ml. of DMF. [i] In place of sodium nitrite, 94.5 g. (0.50 mole) of sodium *m*-nitrobenzoate was added.

gen the compound is the tautomer of a nitrolic acid, R—C(NO$_2$)=NOH. Nitrolic acids (and their salts) are unstable and readily give the corresponding carboxylic acids.[6] The formation of caprylic acid from 1-nitroöctane is, then, fully consistent with the chemistry of nitrolic acids.

According to eq. 1 and 2 the reaction of a secondary nitro compound with an alkyl nitrite will yield a pseudonitrole III, R and R′ = alkyl. In those experiments in which 2-nitroöctane was destroyed (Table IB) visual evidence of pseudonitrole formation was provided by a transient, but easily discerned, blue color.[7] Since the blue color did not persist, it occasioned no surprise that the pseudonitrole could not be isolated. Instead, an excellent yield of 2-octanone was obtained (Table IB). That the ketone is formed *via* the pseudonitrole is strongly supported by the fact that, in a comparatively short time (15 hours), propyl pseudonitrole (2-nitroso-2-nitropropane) is converted to acetone (76% yield) by a DMF solution of sodium nitrite at room temperature.[8]

With α-nitroesters the combined action of an alkyl nitrite and sodium nitrite yields an α-nitroso-α-nitroester (III, R = alkyl, R′ = carbethoxy) which breaks down under the influence of a base, nitrite ion or water, to give the salt of the α-oximinoester (IV)[9,10]



$$\mathrm{R{-}\overset{NO}{\underset{NO_2}{C}}{-}COOC_2H_5} \xrightarrow{NO_2^-} \left[\mathrm{R{-}\overset{NO}{\underset{-}{C}}{-}COOC_2H_5} \longleftrightarrow \mathrm{R{-}\overset{NO}{C}{-}COOC_2H_5}\right] + \mathrm{N_2O_4}$$

IV

(4)

The claim that the nitrite ion simply functions as a base in the initial step (eq. 1, *cf.* footnote 5) is placed on a firm footing by experiments in which a base of comparable strength,[11] the *m*-nitrobenzoate ion, is used in place of nitrite ion. The results of

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(6) V. Meyer, *Ann.*, **175**, 104 (1875); **180**, 160 (1880).

(7) When cyclopentyl bromide is treated with sodium nitrite in DMF, at room temperature, for a relatively short time (seven hours) a 5% yield of analytically pure cyclopentyl pseudonitrole is isolated. The pseudonitrole is unquestionably formed *via* nitrocyclopentane for, when phloroglucinol is present to act as a nitrite ester scavenger, the nitro compound is obtained in 57% yield (*cf.* ref. 3).

(8) This, and a number of other reactions of pseudonitroles, is currently under investigation.

(9) N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1494 (1956).

(10) The relatively poor yield of α-oximinoester (26%) may well be due to partial conversion into the α-ketoester under the influence of N$_2$O$_4$ (or a derived substance).

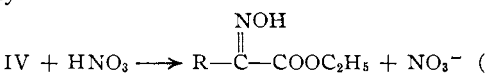
(11) *m*-Nitrobenzoic acid has a pK_a of 3.45 (G. Briegleb and A. Bieber, *Z. Elektrochem.*, **55**, 250 (1951)) while nitrous acid has a pK_a of 3.3 (G. Klemenc and A. Hayek, *Monatsh.*, **54**, 407 (1929)). Thus, in water, and presumably in DMF, nitrite ion and *m*-nitrobenzoate ion will have about the same basicity; since neither ion possesses any special steric requirements, they should have comparable abilities to ionize nitro compounds.

experiments 10, 16 and 22 (Table I) clearly show that sodium *m*-nitrobenzoate is also a catalyst for the reaction of aliphatic nitro compounds with nitrite esters.[12]

From the stoichiometry of eq. 1 to 3 one would anticipate that for each mole of nitro compound destroyed a mole of alkyl nitrite is also used up. But this is not true. Experiments 8, 9, 15 and 21 (Table I) unambiguously show that a mole of nitro compound is destroyed by considerably less than a mole of alkyl nitrite. The explanation lies in the instability of the nitrosated compounds (III). For example, when an α-nitroester is employed the initially formed α-nitroso-α-nitroester undergoes further reaction as shown in eq. 4. One of the products is N_2O_4 and this reacts with the alcohol formed in eq. 3.

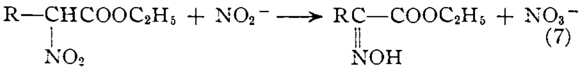
$$N_2O_4 + R''OH \longrightarrow R''ONO + HNO_3{}^{13} \quad (5)$$

Finally



$$\text{IV} + HNO_3 \longrightarrow R{-}\overset{\overset{\displaystyle NOH}{\|}}{C}{-}COOC_2H_5 + NO_3^- \quad (6)$$

Summation of eq. 1 to 6 gives eq. 7 for the overall reaction



$$R{-}\underset{\underset{\displaystyle NO_2}{|}}{C}HCOOC_2H_5 + NO_2^- \longrightarrow R\underset{\underset{\displaystyle NOH}{\|}}{C}{-}COOC_2H_5 + NO_3^- \quad (7)$$

i.e., the alkyl nitrite is a true catalyst.[14]

The destructive path with primary nitroparaffins diverges from that of the α-nitroester system since nitrolic acids are intermediates and carboxylic acids are the final products. It is quite possible that nitrolic acids are strong enough to convert a significant fraction of the sodium nitrite present into nitrous acid (which is, of course, in equilibrium with nitrogen trioxide), but the data which would permit this point to be settled do not appear to be available. In any case, the carboxylic acids produced on breakdown of the nitrolic acids are certainly sufficiently acidic to transform sodium nitrite into a working supply of nitrous acid.[15,16]

Experimental

Experiment numbers refer to those in Table I. Since much of the relevant information is provided in the table these items will not be repeated here. All the experiments listed in Table I were conducted in a bath maintained at room temperature and the reaction flask was covered with a cloth to minimize exposure to light (nitrite esters are photochemically unstable). The working-up process was also carried out with minimal exposure to light. Reaction mixtures were stirred throughout the entire course of the reaction.

Reagents.—Dimethylformamide, du Pont technical grade, was dried over calcium hydride. Analytical grade sodium nitrite, dried at 115°, was used. The urea was Baker and Adamson Purified Grade which had been dried at 105° for several hours. The compounds employed had the following properties and "% Recovery" is based on material of the same, or very nearly the same, properties.

1-Nitroöctane (b.p. 60° (1 mm.), $n^{20}\mathrm{D}$ 1.4324), 2-nitrooctane (b.p. 67° (3 mm.), $n^{20}\mathrm{D}$ 1.4280), ethyl α-nitropropionate (b.p. 55° (1 mm.), $n^{20}\mathrm{D}$ 1.4209), *n*-hexyl nitrite (b.p. 62° (76 mm.), $n^{20}\mathrm{D}$ 1.3997), *n*-octyl nitrite (b.p. 60° (10 mm.), $n^{20}\mathrm{D}$ 1.4127), *n*-propyl nitrite (b.p. 50°, $n^{20}\mathrm{D}$ 1.3592), 2-octyl nitrite (b.p. 44° (6 mm.), $n^{20}\mathrm{D}$ 1.4090).

Expt. 1.—This was worked up by pouring the DMF solution into an equal volume of water and extracting with petroleum ether (b.p. 35–37°). The extracts were dried over sodium sulfate, the ether removed under reduced pressure and the residue rectified.

Expt. 5.—The reaction mixture (after 25 hours), while still being stirred, was subjected to a vacuum of 20 mm. for 3 hours. Of the three dry ice traps interposed between the pump and flask only the one next to the flask contained any material. Distillation of the trap contents gave a 77% recovery of *n*-propyl nitrite.

Expt. 6.—Rectification of the product gave 11.0 g. (64% yield) of 1-hexanol (b.p. 60° (8 mm.), $n^{20}\mathrm{D}$ 1.4181); lit. values[17] b.p. 63° (8 mm.), $n^{20}\mathrm{D}$ 1.4179. This was followed by 17.72 g. (58%) of 1-nitroöctane and, finally, 2.4 g. (9% yield) of caprylic acid (b.p. 85–87° (1 mm.), $n^{20}\mathrm{D}$ 1.4288–1.4292) was obtained, lit.[18] $n^{20}\mathrm{D}$ 1.4280. The caprylic acid was completely soluble in 10% aqueous sodium bicarbonate and gave a *p*-bromophenacyl ester of m.p. 67°, mixed m.p. with an authentic sample 67°. The residue from the rectification weighed 5.4 g.; on extraction with 10% sodium bicarbonate about half dissolved. The bicarbonate-soluble material also gave a *p*-bromophenacyl ester, m.p. 67°, mixed m.p. 67°. The total yield of caprylic acid was *ca.* 4.3 g. (15%).

Expt. 7.—The 1-octanol isolated (18.1 g., 74%) had b.p. 79–82° (7 mm.), $n^{20}\mathrm{D}$ 1.4290–1.4296, and gave a 3,5-dinitrobenzoate of m.p. 62°; mixed m.p. with an authentic sample 62°. The caprylic acid had $n^{20}\mathrm{D}$ 1.4285–1.4287, froze at 12°, and gave a *p*-bromophenacyl ester, m.p. and mixed m.p. 67°.

Expt. 8.—The caprylic acid had $n^{20}\mathrm{D}$ 1.4285–1.4287; neut. equiv. calcd. 144, found 143.

Expt. 9.—The caprylic acid had $n^{20}\mathrm{D}$ 1.4284–1.4287; neut. equiv. calcd. 144, found 143. Rectification of the bicarbonate-insoluble material gave no 1-nitroöctane, there being obtained, instead, 5.3 g. of a dark brown, alkali-insoluble oil.

Expt. 10.—A solution of 50 g. of *m*-nitrobenzoic acid in methanol was titrated with sodium methoxide in methanol to a phenolphthalein end-point. The methanol was removed under reduced pressure, the salt being brought to complete dryness by heating on the steam-bath. The caprylic acid isolated had $n^{20}\mathrm{D}$ 1.4284–1.4287, neut. equiv. 143.

Expt. 13.—The initially pale yellow solution went through the following color sequence: → blue → green → dark yellow. Small amounts of colorless gas were evolved during the reaction. The recovered 2-octyl nitrite fractions had $n^{20}\mathrm{D}$ 1.4102 to 1.4132 and were contaminated with 2-octanone. The 2-octanone in the nitrite ester fractions (and in the others also) was precipitated and weighed as the 2,4-dinitrophenylhydrazone, m.p. 56–57°, mixed m.p. with authentic sample undepressed.

Expt. 14.—The use of *n*-propyl nitrite gave a much easier mixture to separate. The 21.3 g. (83% yield) of 2-octanone had b.p. 44° (3 mm.), $n^{20}\mathrm{D}$ 1.4153, and was derivatized as the 2,4-dinitrophenylhydrazone (yield 91%, m.p. 56–57°, mixed m.p. 56–57°).

Expt. 15 and 16.—The 2-octanone had $n^{20}\mathrm{D}$ 1.4152–1.4153 and gave an 88–89% yield of the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 57–57.5°.

Expt. 17.—The reaction mixture was poured into water and extracted with diethyl ether. The ether solution had a faint blue color but on drying and rectifying there was obtained 29.7 g. (93% recovery) of ethyl α-nitropropionate.

Expt. 18.—The residue remaining after rectification was recrystallized from petroleum ether; yield 1.6 g. (6%) of ethyl α-oximinopropionate, m.p. and mixed m.p. 94°.

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[12] That sodium *m*-nitrobenzoate is not quite as effective a catalyst may be due to a difference in solubility of these salts in DMF.

[13] A. D. Yoffe and P. Gray, *J. Chem. Soc.*, 4112 (1951); M. Anbar and H. Taube, THIS JOURNAL, **77**, 2993 (1955).

[14] Precisely the same conclusion is reached if one substitutes water for NO_2^- in eq. 4 or water for R″OH in eq. 5. Instead of regenerating R″ONO, this raises the concentration of N_2O_3 which, like R″ONO, is an excellent nitrosating agent.

[15] Many instances are known in which acetic acid brings about reaction of aliphatic amines with sodium nitrite. It is also of interest that the decomposition of nitrolic acids into carboxylic acids is reported to produce nitrogen dioxide (V. Meyer, ref. 6).

[16] Until the study[8] of the reactions of pseudonitroles is completed there seems little point to discussing the reactions of secondary nitroparaffins with alkyl nitrites in any further detail.

[17] J. Timmermans and F. Martin, *J. chim. phys.*, **25**, 411 (1928).

[18] A. Dorinson, M. R. McCorkle and A. W. Ralston, THIS JOURNAL, **64**, 2739 (1942).

Expt. 20.—The reaction mixture was poured into water, extracted with diethyl ether and, after drying, the ether was removed by distillation under reduced pressure. The residue was recrystallized from petroleum ether; the 6.8 g. of ethyl α-oximinopropionate obtained had m.p. and mixed m.p. 94.5°. From the petroleum ether mother liquors 8.7 g. of a high-boiling, orange liquid was obtained which, on attempted rectification, gave no ethyl α-nitropropionate.

The Reaction of Propyl Pseudonitrole with Sodium Nitrite.—Propyl pseudonitrole was prepared in 42% yield by treating the sodium salt of 2-nitropropane, in aqueous methanol, at −15°, with nitrosyl chloride. The precipitate was isolated by filtration, washed with water, with absolute ethanol, and then air-dried (in the dark). The white powder melted with decomposition to a blue liquid at 74–75°, lit. m.p. 76°.[19]

To 600 ml. of DMF in a flask equipped with a sealed stirrer was added 50 g. of propyl pseudonitrole (0.42 mole). A small aliquot (A) was removed to observe color changes. Urea (40 g.) was then added and, once again, an aliquot (B) removed. Finally 36 g. of sodium nitrite (0.52 mole) was added after which the mixture was allowed to stir in the dark.

Color Changes Observed at Room Temperature

Time, hr.	Aliquot A	Aliquot B	Reaction mixture
0	Deep blue	Deep blue	Deep blue
3	Deep blue	Deep blue	Deep blue-gr.
15	Deep blue	Deep blue	Light yellow
40	Deep blue	Deep green	....
65	Pale green	Light yell.	....
75	Pale yellow	Light yell.	....

After 15 hr. the reaction mixture was subjected to a vacuum of 10 mm. for 3 hr.; traps held at −80° were interposed between the pump and the reaction product. The 25 g. of a very pale yellow liquid which collected in the traps was rectified. The first material to distil was a pale yellow liquid, b.p. 21°, probably $N_2O_4 + NO_2$, which was lost by accident. After a very small interfraction (b.p. 21–52°) there was obtained 18.2 g. (76% yield) of acetone, b.p. 52–54°, $n^{20}D$ 1.3586–1.3589. The 2,4-dinitrophenylhydrazone (89% yield) had m.p. 124–125°, mixed m.p. with an authentic sample 124–125°.

Isolation of Cyclopentyl Pseudonitrole from the Reaction of Cyclopentyl Bromide with Sodium Nitrite.—Cyclopentyl bromide, 45 g. (0.3 mole), was treated with sodium nitrite in the manner described for the preparation of 4-nitroheptane from 4-iodoheptane[3] (reaction time 7 hours). The blue petroleum ether extracts were concentrated *in vacuo* and the deep blue residual liquid was allowed to stand at −5°. White crystals precipitated out and the intensity of the blue color diminished considerably. At the end of a week the pale blue solution was filtered and the white solid collected (see below). (The filtrate, on rectification, gave a 32% yield of nitrocyclopentane and a 12% yield of cyclopentyl nitrite.) When the white crystals were recrystallized from diethyl ether there was obtained 2.2 g. (5% yield) of white crystals, m.p. 89.5–90.5° (sealed tube). At the melting point the solid formed a blue liquid which decomposed on further heating.

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.93. Found: C, 41.61, 41.56; H, 5.70, 5.86; N, 20.01, 20.28.

Lafayette, Indiana

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[19] V. Meyer, *Ann.*, **175**, 120 (1875).

[Contribution from the Chemistry Department, Northwestern University Dental School]

Some New Halogen-substituted Pressor Amines of the Synephrine Type[1]

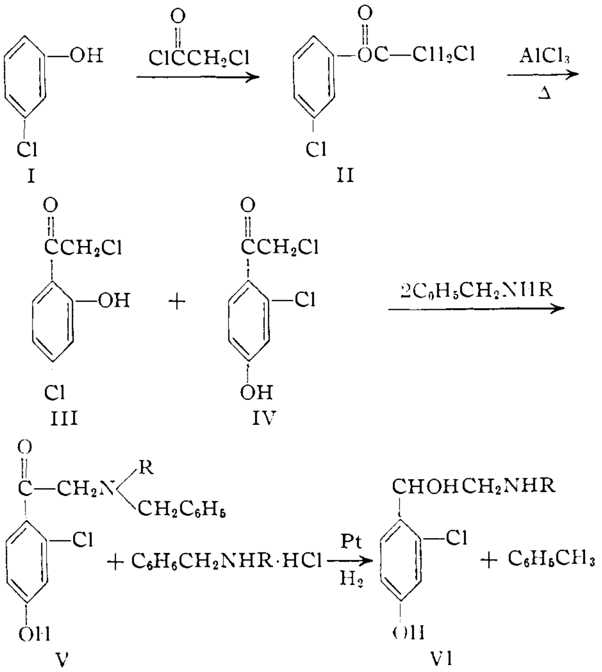
By J. A. Carbon and L. S. Fosdick

Received May 25, 1955

2-Chloro-4-hydroxy-α-(methylaminomethyl)-benzyl alcohol hydrochloride and the corresponding N-ethyl compound have been prepared and their physical properties described. Pharmacological testing of these compounds has shown that the halogen atom in the 2-position greatly reduces vasopressor activity.

Even though epinephrine has long been used in conjunction with local anesthetics as a vaso-constricting agent, other compounds which would possess high vaso-constrictor properties, but which would be free from the undesirable side effects of epinephrine have been sought. Many substituents have been introduced into the aromatic nucleus of epinephrine, but the introduction of halogen atoms has received comparatively little attention.

This work is an extension of the early work of Hansen,[2a] and later of Fosdick, Fancher and Urbach,[2b] on the preparation of halogen-substituted synephrine derivatives. These workers prepared some 3-chloro- and 3-fluoro-4-hydroxy-α-(alkylaminomethyl)-benzyl alcohol hydrochlorides and showed that the halogen atom in the 3-position reduced the pressor activity to $^1/_{400}$ that of epinephrine. The effect of fluorine in the aromatic ring of a pressor amine compared favorably with chlorine in the same position, but both were inferior to a hydroxyl group in this respect. The reaction scheme used was



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[1] This paper is derived from part of the thesis submitted for partial fulfillment of the Ph.D. degree.

[2] (a) H. L. Hansen, This Journal, **59**, 280 (1937); (b) L. S. Fosdick, O. E. Fancher and K. F. Urbach, *ibid.*, **68**, 840 (1946)