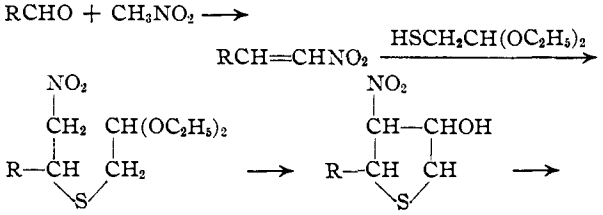
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

β-Nitrosulfides and β-Aminosulfides

BY WILLIAM E. PARHAM AND FLOYD L. RAMP[1]

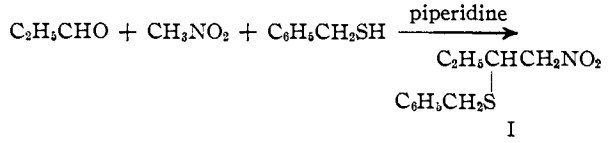
This paper reports a new and convenient synthesis of β-nitrosulfides. The method consists in allowing a mixture of carbonyl compound, nitroparaffin and mercaptan to react in the presence of piperidine and in the absence of solvent. The reaction has been extended to include aliphatic and aromatic aldehydes, ketones, and a variety of mercaptans. The β-nitrosulfides can be reduced in good yield to β-aminosulfides with lithium aluminum hydride. A proposed synthesis for thiophane derivatives related to biotin is included.

The fact that nitroölefins give 1,4-adducts with mercaptans[2] suggested a new synthetic approach for the preparation of thiophane derivatives related to biotin.



Each of the three steps normally employed[3] for the preparation of aliphatic nitroölefins (condensation, acylation and decomposition of the acetate) is reported to occur in good yield; however, several distillations are required for their synthesis and subsequent conversion to β-nitrosulfides by the method outlined and preliminary experiments with model compounds revealed that the over-all yield of product is not high. Since addition reactions of this type involving conjugated systems are base-catalyzed, it seemed reasonable to expect that the aldol reaction and subsequent conjugate addition for the synthesis of nitroalkanes having a substituent in the β-position could be effected in one step. The preparation of β-nitrosulfides by the direct condensation of nitroparaffins, carbonyl compounds and mercaptans was investigated and is the subject of this report.

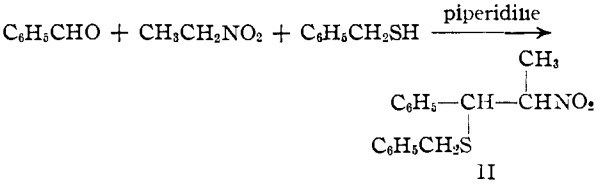
In our experiments the nitroparaffin, carbonyl compound and mercaptan were mixed in the absence of solvent and a catalytic amount of piperidine was added to catalyze the reaction. In this manner propionaldehyde, nitromethane and benzyl mercaptan were found to react exothermically to give 2-benzylthio-1-nitrobutane (I) in nearly quantitative yield.



I

Since this method has not been previously reported for the preparation of β-nitrosulfides, various carbonyl compounds and mercaptans were employed in order to explore the generality of the reaction. It was observed that ketones, such as acetone and cyclohexanone, and aromatic aldehydes can be successfully substituted for propionaldehyde. β-Nitrosulfides were prepared in good yield using benzyl, butyl and ethyl mercaptan. In most cases the products were oils which distilled with some decomposition. 2 - Benzylthio - 2 - phenylnitroethane was isolated as a crystalline solid in 63% yield from the reaction product obtained from benzaldehyde, nitromethane and benzylmercaptan. Attempts to distil the products obtained from aromatic aldehydes resulted in low yields of product due to thermal decomposition.

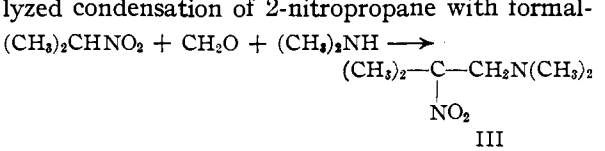
The use of nitroparaffins other than nitromethane leads to a mixture of racemates which are difficult to separate because of their thermal instability. The condensation of benzaldehyde, nitroethane and benzyl mercaptan in the presence of piperidine resulted in an oil which did not crystallize and which underwent extensive decomposition upon distillation at 2 mm. We believe, however, that the yield in this step is good and that the crude product, without further purification, can be used directly as an important intermediate in further synthesis. Product II, on oxidation, gave a sulfone (m.p. 113–126°)



II

having the correct analysis but consisting of a mixture of racemates.

The condensation reaction just described bears a formal similarity in appearance to the Mannich reaction and several alternate mechanisms can be formulated to account for the formation of the β-nitrosulfides. Since it is known[4] that 2-nitropropane will react with formaldehyde and dimethylamine to give III (Mannich reaction), the base-catalyzed condensation of 2-nitropropane with formaldehyde and butyl mercaptan was considered of interest relative to the mechanism of β-nitrosulfide formation.



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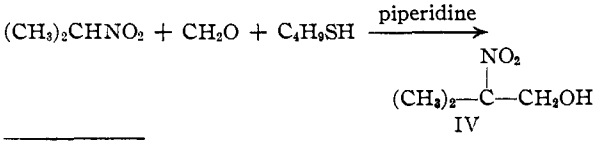


IV

(1) From the Ph.D. Thesis of Floyd L. Ramp, 1950.

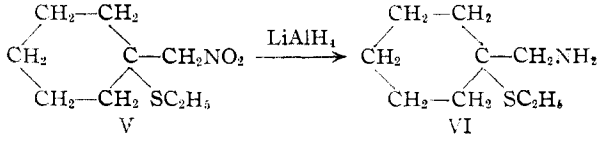
(2) R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947).

(3) *Cf.* D. Nightingale and J. R. Janes, THIS JOURNAL, **66**, 352 (1944), for the general procedure used for the preparation of aliphatic α-nitroölefins.

(4) H. Johnson, *ibid.*, **68**, 12, 14 (1946); *cf.* M. Senkus, *ibid.*, **68**, 10 (1946), for the reaction of 2-nitropropane with N-hydroxymethylalkylamines.

The product of this reaction was found to be 2-nitro-2-methylpropanol-1 (IV). The failure to isolate a β-nitrosulfide in this case suggests that the condensation reaction previously described proceeds *via* the addition of a mercaptan to a nitroolefin formed as an intermediate in the reaction.

The reduction of the β-nitrosulfides with iron and acid or better with lithium aluminum hydride resulted in the formation of β-aminosulfides. The reduction of 1-nitromethyl-1-ethylthiocyclohexane (V) with lithium aluminum hydride resulted in the formation of 1-aminomethyl-1-ethylthiocyclohexane (VI) in 60% yield (isolated as the hydrochloride). A 56% yield of the corresponding amine was



V VI

obtained by a similar reduction of 2-benzylthio-2-phenylnitroethane.

Experimental

2-Benzylthio-1-nitrobutane (I).—Propionaldehyde (19.3 g., 0.33 mole) was added to a mixture of benzyl mercaptan (37.2 g., 0.3 mole), nitromethane (20.3 g., 0.33 mole) and piperidine (3 ml.). The solution was warmed on a steam-cone for one-half hour and then taken up in 100 ml. of ether. The ethereal solution was washed with dilute acid and then with water, dried, and the ether removed by distillation. The residue (69.5 g., $n^{20}D$ 1.5400) distilled at 2 mm. with slight decomposition to give 51 g. (75%) of 2-benzylthio-1-nitrobutane, b.p. 125–140° (2 mm.), $n^{20}D$ 1.5428. A sample, b.p. 129–131° (2 mm.), $n^{25}D$ 1.5453, was submitted for analysis.

Anal. Calcd. for $C_{11}H_{15}O_2NS$: C, 58.64; H, 6.71. Found: C, 59.01; H, 6.92.

The observed effect of reaction time, temperature, and amount of catalyst is:

Reacn. time, hr.	Temp., °C.	Catalyst (piperidine ml./mole)	Yield of distillate, %
1.5	25	10	28
0.5	90	10	75
5.0	90	18	67

2-Benzylthio-2-phenylnitroethane.—Benzaldehyde (13.2 g., 0.125 mole) was added to a solution of nitromethane (7.6 g., 0.125 mole), benzyl mercaptan (12.4 g., 0.1 mole) and piperidine (1 ml.). An exothermic reaction took place. The reaction mixture was allowed to stand at room temperature for 20 days and was then treated with 30 ml. of glacial acetic acid and 5 ml. of water. The mixture was cooled and 17.4 g. (63%) of white solid, m.p. 43–44.5°, was collected. A sample recrystallized from an acetic acid–water mixture melted at 43.5–44.5°.

Anal. Calcd. for $C_{15}H_{15}O_2NS$: C, 65.91; H, 5.53. Found: C, 65.66; H, 5.50.

The reaction was carried out more conveniently by heating the reaction mixture for 4 hours at 100°. The yield obtained by this method was somewhat lower (53%).

β-Nitrosulfides Derived from Ketones.—The procedure used was essentially that described for I. The mixture in each case was heated at the reflux temperature for 24 hours. 1-Nitromethyl-1-ethylthiocyclohexane (V) was obtained from cyclohexanone, nitromethane and ethylmercaptan as a yellow oil (50%), b.p. 70–110° (2 mm.), $n^{18.5}D$ 1.5072. A sample, b.p. 98–99° (1.5 mm.), $n^{18.5}D$ 1.5080 was submitted for analysis.

Anal. Calcd. for $C_9H_{17}O_2NS$: C, 53.17; H, 8.43. Found: C, 53.32; H, 8.51.

2-Butylthio-1-nitroisobutane was obtained from acetone, nitromethane and *n*-butylmercaptan as a colorless oil (58%), b.p. 65–69° (2 mm.), $n^{25}D$ 1.4752 (reported[2] b.p. 124° (11 mm.)).

Anal. Calcd. for $C_8H_{17}O_2NS$: C, 50.23; H, 8.96. Found: C, 50.07; H, 8.94.

DERIVATIVES OF β-NITROSULFIDES

Compound	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzyl-1-(1-ethyl-2-nitroethyl) sulfone[a]	84.5–85.5	51.33	51.47	5.88	6.14
Benzyl-1-(1-phenyl-2-nitroethyl) sulfone[a]	143.5–145	59.10	59.04	4.96	5.17
1-Aminomethyl-1-ethylthiocyclohexane hydrochloride[b]	200–201	51.55	51.33	9.55	9.38
1-Aminomethyl-1-ethylthiocyclohexane picrate[c]	161–163	44.76	45.05	5.52	5.62
2-Benzylthio-2-phenylethylamine hydrochloride[d]	165–166.5	64.38	64.30	6.48	6.63
2-Benzylthiobutylamine hydrochloride[e]	110–110.5	57.00	57.08	7.83	7.97

[a] The sulfones were prepared from the corresponding sulfides by oxidation with excess H_2O_2 in hot glacial acetic acid. Recrystallized from ethanol. [b] Obtained in 60% yield by reduction of V with $LiAlH_4$. Recrystallized from absolute ethanol–ether. Nitrogen anal. calcd.: N, 6.69. Found: N, 6.86. [c] The picrate was easily obtained by the addition of alcoholic picric acid to an alcoholic solution of the amine. Recrystallized from ethanol. Nitrogen anal. Calcd.: N, 13.90. Found: N, 13.93. [d] Procedure and yield described in experimental section. [e] Prepared (37%) by reduction with Fe–HCl as described for 2-benzylthio-2-phenylethylamine. The reduction mixture was distilled with steam to separate the amine and unreduced nitro compound from the mixture. Recrystallized from absolute ethanol–ether.

2-Benzylthio-2-phenylethylamine Hydrochloride. A. Reduction with Lithium Aluminum Hydride.[5]—2-Benzylthio-2-phenylnitroethane (5 g.) in 40 ml. of absolute ether was added dropwise to an ethereal solution of lithium aluminum hydride (2 g.). The reaction mixture was heated at reflux temperature for 1 hour after the addition was complete. Water was added dropwise until excess lithium aluminum hydride was decomposed, the solution was made alkaline, and the amine was distilled with steam. The distillate was made strongly alkaline and extracted with absolute ether. The aluminum hydroxide was collected on a filter and washed with absolute ether. The ethereal solutions were combined and dried. Dry ethereal hydrogen chloride was added to the ethereal solution containing the amine. The amine hydrochloride (2.85 g., 56%), m.p. 164–166°, was collected as a white solid and purified by precipitation from absolute alcohol by addition of absolute ether. The analytical sample melted at 165.5–166.5°.

B. Reduction with Iron and Hydrochloric Acid.—Iron filings (7.5 g.) and ferric chloride (0.5 g.) were placed in a flask fitted with a condenser and stirrer. Dilute hydrochloric acid (25 ml. of water and 3 ml. of concentrated hydrochloride acid) was added and the mixture was stirred until the evolution of hydrogen was complete. 2-Benzylthio-2-phenylnitroethane (7.2 g.) was added and the reaction mixture was stirred and heated at the reflux temperature for 8 hours. Fifty ml. of 10% potassium hydroxide was added and the solution was extracted with six portions (300 ml. total) of ether. The ethereal solution was extracted with 5% hydrochloric acid and the acidic solution was made alkaline by the addition of solid potassium hydroxide. The free amine was extracted with ether and the ethereal solution was dried over magnesium sulfate. Ethereal hydrogen chloride was added to the dry ether solution containing the amine and the solid amine hydrochloride (0.8 g., 11%) was collected, m.p. 162–166°. The amine hydrochloride was recrystallized from absolute ethanol, m.p. and mixed melting point with the product obtained in A was 165.5–166.5°.

Benzyl-1-(1-phenyl-2-nitropropyl) Sulfone (II).—To a flask containing benzyl mercaptan (24.8 g., 0.2 mole), nitroethane (18.7 g., 0.25 mole) and piperidine (2 ml.) was added benzaldehyde (26.5 g., 0.25 mole). The mixture was

(5) *Cf.* R. F. Nystrom and W. C. Brown, THIS JOURNAL, **70**, 3738 (1948), for the reduction of 2-nitrobutane with $LiAlH_4$.

heated on a steam-cone for 1.5 hours and worked up as described for 2-benzylthio-1-nitrobutane (I). An attempt to distil the crude product at 0.2 mm. resulted in extensive decomposition. Three fractions were collected during the decomposition: (1) 2.5 g., b.p. 60–87°, $n^{23}D$ 1.5768; (2) 1.0 g., b.p. 88–130°, $n^{23}D$ 1.5779; (3) 2.5 g., b.p. 130–155°, $n^{23}D$ 1.5874.

A one-gram sample of each fraction was oxidized in hot glacial acetic acid with excess hydrogen peroxide. Fraction 1 yielded 0.5 g. of sulfone, m.p. 110–126°; fraction 2 yielded 0.5 g. of sulfone, m.p. 115–122°; fraction 3 yielded 0.6 g. of sulfone, m.p. 113–122°. Each sample of sulfone was recrystallized three times from ethanol. The melting points remained essentially unchanged and mixed melting points of the three samples showed no depression.

Anal. Calcd. for $C_{16}H_{12}O_4NS$: C, 60.17; H, 5.46. Found: C, 60.18; H, 5.37.

Attempted Preparation of 1-Butylthio-2-nitroisobutane.—A 40% solution of formaldehyde (26.2 g., 0.35 mole of formaldehyde) was added to a solution of 2-nitropropane (31.2 g., 0.35 mole), butyl mercaptan (27.0 g., 0.30 mole) and piperidine (3 ml.). An exothermic reaction occurred. The mixture was heated on a steam-cone for 24 hours. The solution smelled strongly of mercaptan. Glacial acetic acid (0.5 ml.) was added and the reaction mixture heated for an additional 24 hours. The odor of mercaptan was still present. The solution was cooled and dissolved in 100 ml. of ether. The ethereal solution was washed with 50 ml. of 5% hydrochloric acid and then with water. The ethereal solution was dried and then distilled. All material boiling below 120° (b.p. of 2-nitropropane) was discarded. The residue boiled at 62–75° (3 mm.) and readily solidified. The solid was washed with a small amount of petroleum ether. There was obtained 16.4 g. of white solid melting at 80–83°. Recrystallization of the solid from carbon tetrachloride raised the melting point to 89.5–90.5°.

Anal. Calcd. for $C_4H_9O_3N$: C, 40.32; H, 7.61. Found: C, 40.03; H, 7.63.

The melting point of 2-nitro-2-methylpropanol (IV) is reported to be 82°.[6] Its *p*-toluenesulfonyl ester, prepared according to the procedure of Riebsomer,[7] melted at 73–74°. The reported melting point for the *p*-toluenesulfonate of 2-nitro-2-methylpropanol is 73–74°.

(6) L. Henry, *Bull. soc. chim.*, [33] **18**, 1002 (1895).
(7) J. L. Riebsomer, *J. Org. Chem.*, **11**, 182 (1946).

MINNEAPOLIS 14, MINN. RECEIVED OCTOBER 2, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ARKANSAS]

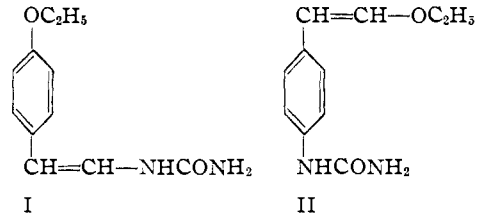
Vinylogy in Sweetening Agents. I. A Vinylog of Dulcin[1]

BY WILLIAM K. NOYCE, CHARLES H. COLEMAN AND JOHN T. BARR

In order to study the principle of vinylogy in connection with the effects of functional groups on a physiological property such as taste, a vinylog of dulcin has been prepared. This involved the synthesis of several new compounds. The final product, *p*-ethoxystyrylurea, and two of the four intermediates have been isolated. This vinylog of dulcin was found to be sweet, but an intermediate, *p*-ethoxy-β-nitrostyrene, was not sweet although it is the vinylog of a sweet compound.

Although a great many individual facts are known and a considerable number of empirical rules have been formulated,[2] no basic underlying principle is known which relates the structure of an organic compound to its taste. For example, in the case of the sweetening agent, dulcin (*p*-ethoxyphenylurea), the substitution of a methoxy group for the ethoxy group does not destroy the sweetness,[3] nor does the substitution of a methyl group on the α-nitrogen of the urea.[4] However, neither the meta nor the ortho isomer of dulcin is sweet, nor is the resulting compound sweet when a methylene group is interposed between the phenyl group and the urea residue.[5] The purpose of this investigation is to study the functional relationship between groups in connection with the principle of vinylogy.[6] Since δ-ethoxybutylurea is not sweet,[7] it appears that more than merely the number of connecting carbon atoms is involved.

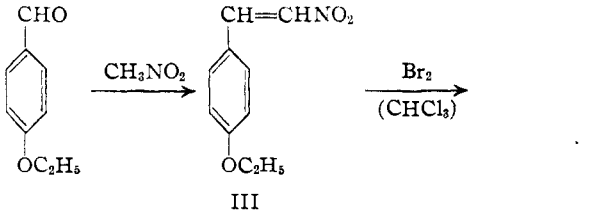
Assuming that the ethoxy group and the urea group are the functions whose relationships are involved, then the two simplest "vinylogs" of dulcin are *p*-ethoxystyrylurea (I) and *p*-ureidostyryl ethyl ether (II).



I II

The vinylogs of the ortho isomer of dulcin are also of interest because of their structural similarities to dulcin itself.

Progress has been made toward the preparation of *o*-ethoxystyrylurea and *p*-ethoxystyrylurea has been synthesized by means of the steps



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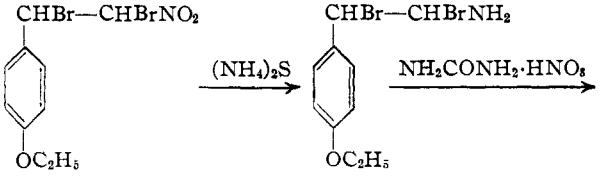

IV V

(1) Presented before the Division of Organic Chemistry at the 118th Meeting of the American Chemical Society, Chicago, September 6, 1950.
(2) Moncrieff, "The Chemical Senses," John Wiley and Sons, Inc., New York, N. Y., p. 274 (1944).
(3) Lorang, *Rec. trav. chim.*, **47**, 179 (1928).
(4) Bergmann, Camacho and Dreyer, *Ber. deut. pharm. Ges.*, **32**, 249 (1922).
(5) Wertheim, THIS JOURNAL, **57**, 545 (1935).
(6) Fuson, *Chem. Revs.*, **16**, 1 (1935).
(7) Wertheim, THIS JOURNAL, **56**, 735 (1934).