

Antimalaria Agents II. Synthesis and Reactions of 3-([*p*-(4-Nitrophenyl)sulfonyl]phenyl)sydnone

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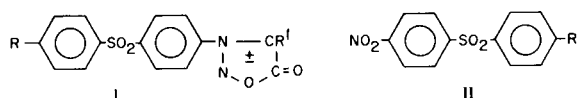
The synthesis and several reactions of a sydnone substituted with strongly electron-withdrawing substituents are described. Infrared evidence for labile open chain iminoanhydride is presented.

DISCUSSION

3-([*p*-(4-Nitrophenyl)sulfonyl]phenyl)sydnone (Ia) was a precursor for the synthesis of 3-([*p*-(4-aminophenyl)sulfonyl]phenyl)sydnone (2) (Ib) which was of interest to our program on antimalarials. One of the common methods for the synthesis of sydnones is hydrolysis of *N*-substituted glycine esters followed by nitrosation and dehydration of the glycine. The most widely used method for the preparation of the *N*-substituted glycine esters is the reaction of an amine and ethyl haloacetate (3,4). For the synthesis of the title compound Ia the starting amine, namely 4-amino-4'-nitrodiphenyl sulfone (IIa), was prepared by the hydrolysis of 4-acetamido-4'-nitrodiphenyl sulfone (IIb) (5). 4-Amino-4'-nitrodiphenyl sulfone (IIa) proved to be very resistant to carbethoxymethylation and was recovered almost quantitatively after 5 hours refluxing with ethyl bromoacetate and sodium acetate. An 11% conversion of IIa to ethyl *N*-([4-(*p*-nitrophenyl)sulfonyl]phenyl)glycinate (IIc) could be obtained under more drastic conditions but the isolation of the pure product from the reaction mixture was quite difficult.

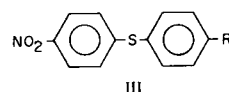
Because of the combined electron withdrawing effects of the nitro and the sulfone groups, 4-amino-4'-nitrodiphenyl sulfone is not basic enough for carbethoxymethylation with ethyl bromoacetate. It was thought that if 4-amino-4'-nitrodiphenyl sulfide (IIIa) was used as the starting amine the cumulative electron withdrawing effect of the two groups will be avoided and the sulfide would react easily with ethyl bromoacetate. This was verified when a 70-80% conversion to the corresponding glycine ethyl ester IIIb was obtained by 2.5 hours refluxing of a mixture of the sulfide IIIa, ethyl bromoacetate and sodium acetate. 4-(Carbethoxymethyl)amino-4'-nitrodiphenyl sulfide (IIIb) could be acetylated to the *N*-acetylglycine ester IIIc in 70% conversion. The latter could be oxidized to the sulfone IIb in 95% conversion; alternatively, a 90% conversion of IIIb to IIb could be obtained without the isolation of the acetylated intermediate IIIc.

The *N*-acetyl group of IIb could be cleaved off with aqueous hydrochloric acid to give ethyl *N*-([4-(*p*-nitrophenyl)sulfonyl]phenyl)glycinate (IIc) in 59% conversion. The melting point of a mixture of this compound with a sample of IIc prepared directly by carbethoxymethylation of 4-amino-4'-nitrodiphenyl sulfone (IIa) was undepressed. On saponification with 5% aqueous sodium hydroxide the ester IIc gave the corresponding glycine IIe.

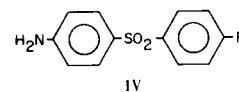


Ia, R = NO₂, R¹ = H
 Ib, R = NH₂, R¹ = H
 Ic, R = NO₂, R¹ = Br

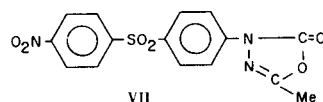
IIa, R = NH₂
 IIb, R = NHAc
 IIc, R = NHCH₂CO₂Et
 IId, R = N(Ac)CH₂CO₂Et
 IIe, R = NHCH₂CO₂H
 IIe, R = N(NO)CH₂CO₂H
 IIg, R = N(NO)CH₂C(O)N(C₆H₁₁)C(O)NHC₆H₁₁
 IIh, R = N(NO)CH₂C(O)OC(=NC₆H₁₁)NHC₆H₁₁
 Iii, R = NHNH₂



IIIa, R = NH₂
 IIIb, R = NHCH₂CO₂Et
 IIIc, R = N(Ac)CH₂CO₂Et



IVa, R = NHNH₂
 IVb, R = NH₂
 IVc, R = N(NO)CH₂C(O)NHC₆H₁₁

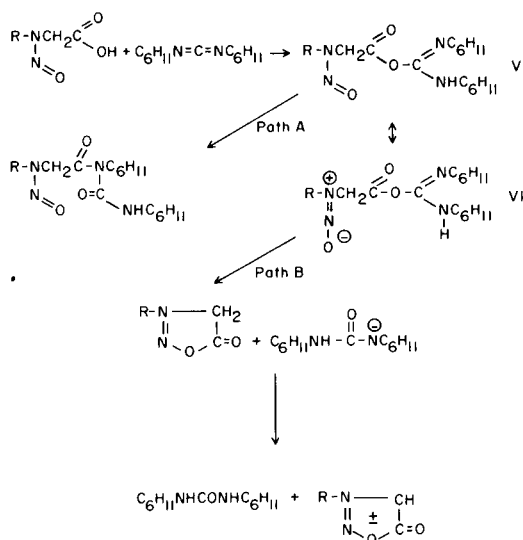


An attempt to cleave both the *N*-acetyl and the ester groups of the ethyl *N*-acetylglycinate (IId) in one step by refluxing briefly with Claisen's alkali was not successful. Within a few minutes the mixture developed an odor of oil of bitter almonds and a good yield of *p*-nitroanisole

was isolated from the mixture after it was refluxed for 15 minutes. The simultaneous cleavage of both groups was attained by refluxing the ethyl *N*-acetylglycinate (II_d) with hydrochloric acid and acetic acid; 89% conversion to the glycine II_e was obtained. The nitrosation of the glycine II_e with sodium nitrite gave a 93% conversion to the nitrosoglycine (II_f). Alternatively, the nitrosoglycine (II_f) could be obtained from ethyl *N*-acetylglycinate in 91% conversion without the isolation of the intermediate glycine (II_e).

When the nitrosoglycine (II_f) was heated with acetic anhydride the desired sydnone (I_a) was obtained in 44% conversion. In order to improve the yield of sydnone (I_a) the dehydration of the nitrosoglycine (II_f) with dicyclohexylcarbodiimide (6) was attempted. The sydnone (I_a) could be isolated in 33% conversion while *N,N'*-dicyclohexylurea was obtained in 57% conversion. The mother liquor of these two compounds seemed to contain a mixture of the sydnone (I_a) and acylurea (II_g); the latter was purified by fractional recrystallization of the residue obtained by evaporation of the mother liquor. This anomalous behavior in the synthesis of this sydnone by the use of dicyclohexylcarbodiimide can be explained on the basis of electronic effects. By analogy of the reaction of carboxylic acids with carbodiimide (7) the initial reaction of nitrosoglycines with dicyclohexylcarbodiimide gives iminoanhydrides (V), a resonance form of which is represented by VI in the Diagram A.

DIAGRAM A



Form VI will be stabilized by electron donating groups in R. The iminoanhydrides (V) can rearrange immediately (Path A) to give the acylated urea. The polarized form VI

can undergo the cyclization resulting in the formation of sydnone and dicyclohexylurea. The significant amount of resonance energy gained by going to an aromatic system facilitates the cyclization. This accounts for the exclusive formation of sydnones in the experiments described by Nyberg and Cheng (6) where the R of V and VI represents electron donating groups favoring VI. In our case R is an exceptionally strong electron withdrawing moiety. Consequently the reaction proceeded by both Path A and Path B to give the sydnone (I_a), the acylated dicyclohexylurea (II_g) and dicyclohexylurea. It is surprising that such a significant amount (57%) of *N,N'*-dicyclohexylurea was formed, since it appears that the Path A is strongly favored. It is interesting to note that the iminoanhydride (V) has been postulated (7) for non-cyclic systems but its physical presence has not been unequivocally demonstrated until recently (8b). We were able to isolate the labile intermediate II_h, which corresponds to V, by carrying out the reaction of the nitrosoglycine (II_f) with dicyclohexylcarbodiimide at 0° for a short period of time. An infrared spectrum of the isolated solid showed a doublet at 5.42 μ and 5.65 μ , i. e. $\Delta\mu = 0.23$. This split has been attributed to iminoanhydride (8a, b) moiety in cyclic iminoanhydrides. The nitrosydnone (I_a) shows a doublet at 5.6 μ and 5.75 μ , the nitrosoacylurea (II_g) shows a strong peak at 5.95 μ with a shoulder at 5.90 μ . The diacylimides [i. e. the system-C(O)N(R)-C(O)] have been known (8a, 9, 10) to show a split band characterized by small separation $\Delta\mu = 0.05 \mu$.

It was found that trifluoroacetic anhydride dehydrates nitrosoglycine (II_f) almost quantitatively to the sydnone (I_a).

The nitrosydnone (I_a) gave all the usual reactions of sydnone. Thus upon treatment with concentrated hydrochloric acid it gave 4-hydrazino-4'-nitrodiphenyl sulfone (II_i) which could be reduced with stannous chloride and hydrochloric acid to 4-amino-4'-hydrazinodiphenyl sulfone (IV_a). A small sample of hydrazinonitrosulfone (II_i) could also be reduced with 2% acetic acid and iron powder to aminohydrazino sulfone (IV_a); on a larger scale, however, the experiment failed and gave only bis-(*p*-aminophenyl)sulfone (IV_b). Bromination in the absence of sodium acetate resulted in 2-methyl-4-([*p*-4(nitrophenyl)sulfonyl]phenyl)-5-oxo- Δ^2 , 1,3,4-oxadiazoline (VII). 3-([*p*-4-Aminophenyl)sulfonyl]phenyl)sydnone (I_b) obtained by the reduction of the nitrosydnone (I_a) reacted with benzylamine to give *N*-([4(*p*-aminophenyl)sulfonyl]phenyl)-*N'*-benzyl-*N*-nitrosoglycylamide (IV_c).

EXPERIMENTAL

Ethyl *N*-([4(*p*-Nitrophenyl)thio]phenyl)glycinate (III_b).

A stirred mixture of 123 g. of 4-amino-4'-nitrodiphenyl sulfide (III_a), 85 g. of ethyl bromoacetate, 70 g. of sodium

acetate and 20 ml. of ethanol was heated at 128-133° for 3 hours and allowed to cool to room temperature. The resulting solid was crushed well, treated with 1.5 l. of 5% of aqueous sodium bicarbonate solution, filtered, washed well with water and recrystallized from 95% ethanol to yield 126 g. (76% conversion) of the product IIIb, m.p. 133-134°; 15 g. of starting sulfide IIIa was recovered from the filtrate.

Anal. Calcd. for C₁₆H₁₆N₂O₄S (IIIb): C, 57.84; H, 4.81; N, 8.40. Found: C, 58.21; H, 5.40; N, 8.31.

Ethyl *N*-Acetyl-*N*-([4-(*p*-nitrophenyl)thio]phenyl)glycinate (IIIc).

A stirred mixture of 20 g. of glycinate (IIIb), 40 ml. of acetic anhydride and 200 ml. of acetic acid was refluxed for 2 hours; 160 ml. of solvents were distilled off from the mixture and the residue was poured into 800 ml. of ice-water. The resulting solid was collected, washed well with water and recrystallized from acetone-petroleum ether to give 16.1 g. (71% conversion) of light yellow needles, m.p. 118-119°.

Anal. Calcd. for C₁₈H₁₈N₂O₅S (IIIc): N, 7.49. Found: N, 7.49.

Ethyl *N*-Acetyl-*N*-([4-(*p*-nitrophenyl)sulfonyl]phenyl)glycinate (IIId).

(A).

To a stirred solution of 11.2 g. of *N*-acetylated glycinate (IIIc) in 80 ml. of acetic acid was added in portions a solution of 8 g. of potassium permanganate in 100 ml. of water. It was stirred for 20 minutes, treated with 15 g. of sodium bisulfite and diluted with 700 ml. of ice water. The resulting solid was collected, washed with water and dried. Recrystallization from acetone-petroleum ether gave 11.5 g. (95% conversion) of white solid, m.p. 166-167°.

Anal. Calcd. for C₁₈H₁₈N₂O₇S (IIId): C, 53.21; H, 4.43; N, 6.90. Found: C, 53.05; H, 4.63; N, 6.88.

B. Preparation of IIId Without Isolating IIIc.

A mixture of 99.6 g. glycinate (IIIb), 60 ml. of acetic anhydride and 100 ml. of acetic acid was refluxed for 1.5 hours. The mixture was diluted with 750 ml. of acetic acid and oxidized with a solution of 100 g. of potassium permanganate in 1.5 l. of water as described above; 110.5 g. (91% conversion), of IIId was obtained.

Ethyl *N*-([4-(*p*-Nitrophenyl)sulfonyl]phenyl)glycinate (IIc).

(A) -By Hydrolysis of the *N*-Acetylated Glycinate (IIId).

A stirred mixture of 12.1 g. of IIId, 25 ml. of concentrated hydrochloric acid and 100 ml. of 1:1 aqueous ethanol was refluxed for 3 hours. The starting solid did not dissolve but turned deep yellow. The mixture was chilled in ice and made just basic with 10% aqueous sodium hydroxide. The solid was collected, washed well with water, dried and recrystallized from ethanol-petroleum ether to give 6.4 g. (59% conversion) of the product, m.p. 180-181°.

Anal. Calcd. for C₁₆H₁₆N₂O₆S (IIc): C, 52.75; H, 4.40; N, 7.69. Found: C, 52.88; H, 4.68; N, 7.43.

(B). From 4-Amino-4'-nitrodiphenyl Sulfone (IIa).

A stirred mixture of 55.6 g. of 4-amino-4'-nitrodiphenyl sulfone (IIa), 33.5 g. of ethyl bromoacetate, 27.5 g. of sodium acetate and 10 ml. of ethanol was heated in an oil bath at 135-140° for 20 hours. After cooling the mixture was taken up in 500 ml. of methylene chloride, washed with 200 ml. of water, 200 ml. of 5% aqueous sodium bicarbonate, again with 200 ml. of water, dried over sodium sulfate and filtered. Methylene chloride was removed from the filtrate under reduced pressure and the residue was extracted with ether (4 x 150 ml.) followed by 150 ml. of hot ethanol. The solid left after

extraction with ethanol was recrystallized from THF-petroleum ether to give 8 g. (11% conversion) of a yellow solid, m.p. 179-181°. The melting point of a mixture of this product with a sample prepared above was undepressed.

N-([4-(*p*-Nitrophenyl)sulfonyl]phenyl)glycine (IIe).

(A) By Hydrolysis of the Ethyl Glycinate (IIc).

A stirred mixture of 3.64 g. of the ethyl glycinate (IIc), 650 ml. of water, 35 ml. of ethanol and 20 ml. of 50% aqueous sodium hydroxide was heated to reflux during 45 minutes, whereupon a clear solution was obtained. The solution was filtered, cooled in ice and acidified with concentrated hydrochloric acid to pH 3-4. The resulting solid was collected, washed with ice water, dissolved in 850 ml. of 95% ethanol and chilled in ice. A small amount of solid which separated was filtered off. The filtrate was concentrated to 300 ml. and cooled in ice again. There was obtained 25 g. (74% conversion) of deep yellow solid, m.p. 228-230° dec.

Anal. Calcd. for C₁₄H₁₂N₂O₆S (IIe): C, 50.00; H, 3.57; N, 8.34. Found: C, 49.99; H, 3.95; N, 8.34.

(B). By Hydrolysis of the *N*-Acetylated Ethyl Glycinate (IIId) with Hydrochloric Acid- Acetic Acid.

A mixture of 8.2 g. of IIId, 75 ml. of acetic acid and 25 ml. of concentrated hydrochloric acid was refluxed with stirring for 4 hours. The clear solution was chilled in ice and diluted with 300 ml. of ice water. The resulting solid was washed well with water, dried and recrystallized from acetone-petroleum ether to give 5.9 g. (89% conversion) of IIe, m.p. 228-230° dec.

N-([4-(*p*-Nitrophenyl)sulfonyl]phenyl)-*N*-nitrosoglycine (IIIf).

(A). By Nitrosation of Purified Glycine (IIe).

To a stirred solution of 10.1 g. of IIe in 170 ml. of concentrated sulfuric acid at 5-10° was added 2.5 g. of sodium nitrite. The mixture was stirred at 5-10° for 1 hour, then at room temperature for 1.5 hours and was poured onto 1 kg. of crushed ice. The resulting solid was collected, washed well with water and dried to give 10.2 g. (93% conversion) of a solid, m.p. 180-182° dec. A recrystallization from acetone-ether raised the m.p. to 182-183° dec.

Anal. Calcd. for C₁₄H₁₁N₃O₇S (IIIf): C, 46.02; H, 3.01; N, 11.48. N.E. 365. Found: C, 46.13; H, 2.93; N, 11.19; N.E. 365.

(B). From *N*-Acetylated Ethyl Glycinate (IIId) without Isolation of the Glycine (IIe).

A stirred mixture of 16.2 g. of IIId, 50 ml. of concentrated hydrochloric acid and 150 ml. of acetic acid was refluxed for 4 hours and cooled to 40°. To the stirred mixture was added all at once, at 40°, a solution of 3.1 g. of sodium nitrite in 70 ml. of water and simultaneously cooled with ice. Within a few minutes, a product precipitated. After stirring and cooling in an ice bath for 45 minutes the solid was collected, washed well with water and recrystallized from 95% ethanol to give 13.1 g. (91% conversion) of the nitrosoglycine (IIIf), m.p. 182-183° dec. It was identical with the sample of IIIf prepared above.

3-([*p*-(4-Nitrophenyl)sulfonyl]phenyl)syndnone (Ia).

(A). By Dehydration of IIIf with Acetic Anhydride.

A mixture of 21 g. of IIIf and 70 ml. of acetic anhydride was heated to 90°. A clear solution resulted; it was allowed to stand 3 days in the dark, heated at 80° for 2 hours and evaporated to dryness under vacuum. The residual solid was triturated with 200 ml. of ether, filtered and washed with ether. Recrystallization from DMF-water (Darco) gave 8.8 g. (44% conversion) of a light yellow solid, m.p. 214-216° dec. An analytical sample obtained by additional recrystallization had a melting point of 218-220° dec.

Anal. Calcd. for $C_{14}H_9N_3O_6S$ (Ia): C, 48.42; H, 2.59; N, 12.10; S, 9.22. Found: C, 48.72; H, 2.70; N, 11.93; S, 9.12.

The infrared spectrum showed characteristic bands at 3.2μ (sydnone C-H), 5.6μ and 5.75μ (sydnone carbonyl), 6.45μ and 7.5μ (NO_2), and 7.7μ and 8.6μ (SO_2).

(B). By Dehydration of IIf with Dicyclohexylcarbodiimide. Formation of 1,3-Dicyclohexyl-1-(*N*-nitroso-*N*'-[4-(*p*-nitrophenyl)sulfonyl]phenyl)glycylurea (IIg).

To a stirred solution of 14.6 g. of IIf in 200 ml. of THF was added a solution of 8.3 g. of dicyclohexylcarbodiimide in 50 ml. of THF. Within approximately 2 minutes a solid precipitated out. The mixture was chilled in ice and stirred for a total of 7 minutes and the solid was collected.

An infrared spectrum of the solid showed characteristic bands at 5.42μ and 5.65μ [attributed to $-C(O)O-C(=N)-$ of IIh]. Attempts to purify this solid were not successful; even on standing at room temperature it changed as evidenced by the infrared spectrum. The solid was transferred to its filtrate and the mixture was refluxed for 3 hours. The solid was slowly replaced by another crystalline compound. The mixture was chilled in ice and the product was filtered off and washed with THF (2 x 75 ml.) to give 9 g. (57% conversion) of *N,N*'-dicyclohexylurea, m.p. $232-233^\circ$; its identity was established by infrared spectrum and a mixture melting point with an authentic sample. The filtrate was allowed to stand for 4 days during which time it had deposited a solid; it was collected and washed with ether to obtain 8.1 g. (33% conversion), m.p. $218-220^\circ$ dec.; its infrared spectrum was superimposable with that of the analytical sample of sydnone (Ia) obtained above. The melting point of the mixture of the two samples was undepressed. The filtrate was concentrated to dryness, the residual solid was dissolved in 750 ml. of boiling toluene and filtered hot to remove 1.1 g. of insoluble material. The toluene solution was concentrated to 50 ml. under reduced pressure and diluted with 250 ml. of ether. The resulting solid was collected, washed with ether and dried to give 20 g. of a solid, m.p. $172-175^\circ$ dec. It seemed to be a mixture of sydnone and acylurea as evidenced by infrared spectrum which showed characteristic bands at 5.6μ and 5.75μ (sydnone CO) and 5.95μ with a shoulder at 5.90μ [$-C(O)NC(O)-$]. A 5 g. sample of this solid was repeatedly recrystallized from benzene (filtering off the insoluble material) and acetone-petroleum ether to give 2 g. of the glycinated dicyclohexylurea (IIg), m.p. $187-188^\circ$. It gave a positive Liebermann reaction for the nitroso group.

Anal. Calcd. for $C_{27}H_{33}N_5O_7S$ (IIg): C, 56.74; H, 5.78; S, 5.60. Found: C, 56.84; H, 6.49; S, 5.54.

The infrared spectrum of this material had a strong band at 5.95μ with a shoulder at 5.90μ . There were no other bands between 5μ and 5.9μ .

(C). By Dehydration of IIf with Trifluoroacetic Anhydride.

To a suspension of 11 g. of the finely powdered nitrosoglycine (IIf) in 250 ml. of ether was added 10 ml. of trifluoroacetic anhydride and the mixture was stirred at room temperature for 1.5 hours. The solid was collected, washed with ether (3 x 50 ml.) and recrystallized from DMF-water (Darco) to give 9.5 g. (91% conversion) of the sydnone (Ia), m.p. $218-219^\circ$ dec. Its identity was established by comparing its infrared spectrum and melting point with those of the sydnone (Ia) obtained above.

4-Hydrazino-4'-nitrodiphenylsulfone (III).

A stirred mixture of 7 g. of the sydnone (Ia) and 150 ml. of concentrated hydrochloric acid was slowly heated to $90-100^\circ$ and

held at this temperature for 3.5 hours. There was a brisk evolution of carbon dioxide. The mixture was allowed to stand overnight and diluted with 150 ml. of water. The resulting solid was collected, suspended in excess of 10% aqueous sodium carbonate, filtered, washed well with water and dried. Two recrystallizations from THF-petroleum ether gave 4.3 g. (73% conversion) of yellow solid, m.p. 192° dec.

Anal. Calcd. for $C_{12}H_{11}N_3O_4S$ (III): C, 49.18; H, 3.76; N, 14.33; S, 10.92. Found: C, 49.17; H, 4.10; N, 14.33; S, 10.98.

4-Amino-4'-hydrazinodiphenyl Sulfone (IVa).

A stirred mixture of 5 g. of the sydnone (Ia) and 110 ml. of concentrated hydrochloric acid was heated at $90-95^\circ$ for 3 hours and chilled. To it was added a solution of 30 g. of stannous chloride in 35 ml. of concentrated hydrochloric acid and the mixture was stirred at 45° for 30 minutes. The clear solution was poured slowly into 1 l. of 10% aqueous sodium hydroxide keeping the temperature below 20° . The resulting solid was collected, washed well with water and recrystallized twice from ethanol-petroleum ether to give 3 g. (79% conversion) of the product, m.p. $157-158^\circ$ with softening at 142° .

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$ (IVa): C, 54.74; H, 4.94; N, 15.96. Found: C, 54.67; H, 5.32; N, 16.20.

4-Bromo-3([*p*-(4-nitrophenyl)sulfonyl]phenyl)sydnone (Ic).

A mixture of 3.47 g. of the sydnone (Ia), 50 ml. of acetic anhydride, 10 g. freshly fused sodium acetate and 2 ml. of bromine was heated at 90° for 30 minutes, chilled with ice and filtered. The solid was washed with ice water, (2 x 50 ml.), 95% ethanol (2 x 50 ml.) and ether (2 x 20 ml.), and was recrystallized twice from acetone-petroleum ether to give 2.1 g. (50% conversion) of the product (Ic), m.p. $161-163^\circ$ dec.

Anal. Calcd. for $C_{14}H_8BrN_3O_6S$ (Ic): Br, 18.78; N, 9.86. Found: Br, 18.58; N, 9.59.

2-Methyl-4-([*p*-(4-nitrophenyl)sulfonyl]phenyl)-5-oxo- Δ^2 , 1,3,4-oxadiazoline (VII).

To a stirred suspension of 3.47 g. of the sydnone (Ia) and 60 ml. of acetic anhydride was added 2 ml. of bromine and the mixture was heated at $80-85^\circ$ for 2 hours. The solvents were removed from the clear solution under vacuum. The residue was taken up in 50 ml. of ether, filtered, washed with ether and recrystallized from acetone-petroleum ether (Darco) to give 2.25 g. (62% conversion) of the product VII, m.p. $221-222.5^\circ$.

Anal. Calcd. for $C_{15}H_{11}N_3O_6S$ (VII): C, 49.87; H, 3.05; N, 11.63. Found: C, 50.01; H, 3.49; N, 11.47.

N-([4-(*p*-Aminophenyl)sulfonyl]phenyl)-*N*'-benzyl-*N*-nitrosoglycylamide (IVc).

A mixture of 3.2 g. of aminosydnone (Ib), obtained by the reduction (1) of the nitrosydnone (Ia) with iron, and 15 ml. of benzylamine was stirred at $110-115^\circ$. At 100° the sydnone dissolved and then a product slowly precipitated out from the clear solution. The mixture was allowed to cool to room temperature and 25 ml. of ethanol was added. The solid was collected, washed with a small amount of ether and recrystallized from DMF-ether to give 2.5 g. (57% conversion) of the product, m.p. $198-199^\circ$.

Anal. Calcd. for $C_{21}H_{20}N_4O_4S$ (IVc): C, 59.43; H, 4.72; N, 13.21. Found: C, 59.33; H, 5.15; N, 13.10.

Cleavage of Ethyl *N*-Acetyl-*N*'-[4-(*p*-nitrophenyl)sulfonyl]phenyl-glycinate (IIc) with Claisen's Alkali.

A mixture of 32.5 ml. of Claisen's alkali and 12.2 g. of the

N-acetylated ethyl glycinate (II_d) was heated with stirring on a steam bath for 15 minutes. An odor of bitter almonds was apparent. It was diluted with 50 ml. of water and heated for an additional 30 minutes. The mixture was chilled in ice, diluted with 150 ml. of ice water and extracted with ether (3 x 100 ml.). The ether extract was washed with water (2 x 100 ml.), dried over sodium sulfate and evaporated to dryness. The residual solid was recrystallized from petroleum ether to give 2.7 g. (59% conversion) of *p*-nitroanisole, m.p. 53-54°. The melting point of a mixture of this solid with authentic *p*-nitroanisole was undepressed.

Acknowledgment.

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REFERENCES

- (1) To whom inquiries should be directed. For previous paper see ref. 2.
- (2) I. C. Popoff and Gopal H. Singhal, *J. Med. Chem.*, in press.
- (3) R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 591 (1946).
- (4) P. L. Southwick, H. L. Dimond and R. E. Stansfield,

J. Am. Chem. Soc., 78, 1608 (1956).

(5) C. W. Ferry, J. S. Buck and R. Baltzly, "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 239.

(6) W. H. Nyberg and C. C. Cheng, *J. Med. Chem.*, 8, 532 (1965).

(7) H. G. Khorama, *Chem. Rev.*, 53, 145 (1953).

(8a) C. L. Stevens and M. E. Munk, *J. Am. Chem. Soc.*, 80, 4065 (1958). (8b) D. Y. Curtin and L. L. Miller, *ibid.*, 89, 637 (1967), have recently reported the preparation of iminoanhydrides carrying two nitro groups, e.g., *N*-(2,4-dinitrophenyl)benzimidoyl benzoate in 3% conversion, by working at temperatures below 25°. The infrared spectrum of these compounds show a doublet at 5.71 μ and 5.95 μ ($\Delta \mu = 0.24$); they rearrange to diaroyl imides simply on warming.

This publication appeared a year after we had made our infrared observations.

(9) B. Witkop and J. B. Patrick, *ibid.*, 74, 3861 (1952).

(10) J. C. Sheehan and E. J. Corey, *ibid.*, 74, 360 (1952).

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King of Prussia, Pa. 19406