464. *Further Studies on the Sydnones.*

By Ronald A. Eade and J. Campbell Earl.

Weakly alkaline salts decompose *N*-phenylsydnone giving products different from those obtained with sodium hydroxide. *C*-Bromo-*N*-phenylsydnone on alkaline decomposition gives principally aniline, sodium nitrite, and sodium oxalate. The optical activity of (—)-*N*-nitroso-α-anilinophenylacetic acid disappears during its conversion into *CN*-diphenylsydnone. Several new sydnones have been prepared.

N-Phenylsydnone (I) (Earl and Mackney, *J.*, 1935, 899; Eade and Earl, *J.*, 1946, 591; Earl, *Nature*, 1946, **158**, 909) is completely soluble in boiling water and can be recrystallised from it without decomposition. In the presence of some salts, however, rapid decomposition occurs with evolution of carbon dioxide and deposition of tarry products (*Nature*, 1946, **158**, 909). Among the salts which bring about this decomposition are sodium carbonate, acetate, and oxalate, potassium chromate, and lead acetate. Other salts such as sodium chloride, sulphate, iodate, and thiosulphate have no apparent effect. The obvious conclusion is that salts of weak acids which undergo slight hydrolysis in aqueous solution are those which are effective. In other words, a slight increase in pH causes decomposition of *N*-phenylsydnone in boiling aqueous solution. The decomposition reaction is self-inhibiting. After the first vigorous reaction, evolution of gas soon ceases and if the resinous product is removed by filtration most of the *N*-phenylsydnone is recovered unchanged. This is easily understandable if acid by-products are formed. By boiling solutions of *N*-phenylsydnone in mixtures of N/20-sodium oxalate and N/20-sodium hydrogen oxalate it has been determined that the critical pH above which decomposition occurs is about 5·0. Under mildly alkaline conditions, therefore, *N*-phenylsydnone gives a product which is readily decarboxylated and forms resins, while under more strongly alkaline conditions *N*-nitrosophenylglycine is formed almost quantitatively (*J.*, 1935, 899). *N*-Phenyl-*C*-methylsydnone is much more stable in aqueous solution and decomposition under the influence of added salts was not observed. Most of the other sydnones hitherto described are too little soluble in water for this type of decomposition to occur.

The bromination of *N*-phenylsydnone was recorded by Kenner and Mackay (*Nature*, 1946, **158**, 909). *C*-Bromo-*N*-phenylsydnone is a white crystalline substance, m. p. 134°, becoming red on prolonged exposure to light. It is easily decomposed by hot aqueous alkalis, giving a strong odour of phenyl *iso*cyanide. A roughly quantitative experiment with boiling 5% sodium hydroxide solution showed the principal products to be aniline (90% of theory), sodium nitrite (60%), and sodium oxalate (45%). Once the aniline had been steam-distilled from the reaction mixture, the latter did not give a red colour on being acidified and added to alkaline β-naphthol, so that sodium benzenediazoate is not a decomposition product as stated by Kenner and Mackay. The sodium oxalate probably results from the oxidation of sodium glyoxylate, first formed.

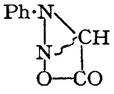
CN-*Diphenylsydnone* has been prepared by a modification of the usual procedure from both racemic and optically active *N*-nitroso-α-anilinophenylacetic acids. The products were identical and inactive showing that the asymmetry of the carbon responsible for the activity disappears during sydnone formation.

Other *sydnones* which have been prepared in addition to those previously described are the *N*-benzyl-, *N*-*cyclo*hexyl-, *N*-*m*-bromophenyl-, *N*-*p*-bromophenyl-, *N*-*o*-carboxyphenyl-, *N*-*p*-carboxyphenyl-, *C*-phenyl-*N*-methyl-, and *C*-chloro-*N*-phenyl derivatives.

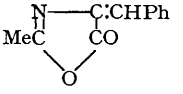
The molecular structure of the sydnones has been the subject of comments by Baker and Ollis (*Nature*, 1946, **158**, 703) and Kenner and Mackay (*ibid.*, p. 909).

It is pointed out that the difficulty in formulating them can be overcome by assuming a single dipolar structure or a hybrid of two or more dipolar structures. The determination of the dipole moments of several members of the series gave a range of values from 6·09 to 6·92 D. (Earl, Leake, and Le Fèvre, *Nature*, 1947, **160**, 366). It is improbable that any single dipolar structure would have a dipole moment as low as this, but the existence of mesomerism would be quite consistent with values of the observed magnitude and range.

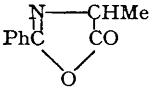
The formation of the sydnones has some counterpart in other dehydration reactions involving the carbonyl instead of the nitroso-group. Erlenmeyer and Früstück (*Annalen*, 1895, **284**, 47) observed such a reaction with a mixture of glycine, benzaldehyde, sodium acetate, and acetic anhydride. The compound formed was eventually assigned the structure (II) (Erlenmeyer, *ibid.*, 1904, **337**, 265). Benzoylalanine and other similar compounds were dehydrated to give a series of anhydrides designated lactimones (III) (Mohr and Stroschein, *Ber.*, 1909, **42**, 252; *J. pr. Chem.*, 1910, **81**, 478). In none of these cases, however, is there any difficulty in assigning a classical type of structure.



(I.)*



(II.)



(III.)

EXPERIMENTAL.

Decomposition of N-*Phenylsydnone by Boiling Sodium Acetate Solution.*—To a boiling solution of *N*-phenylsydnone (0·200 g.) in water (50 ml.) a 10% solution of crystallised sodium acetate (5 ml.) was added, and the gas evolved passed through calcium chloride into a weighed soda–lime tube. The increases in weight in two experiments were 0·0100 and 0·0112 g., corresponding to 18 and 20% of the amount of carbon dioxide which would be derived from complete decarboxylation. With 10 ml. of sodium acetate solution, the weight of carbon dioxide collected was 0·0130 g. or 24%, but with 20 ml. of the solution no apparent decomposition occurred during 15 mins.' boiling. With the more concentrated solution the critical pH is presumably not reached under the conditions of the experiment.

Determination of Critical pH *for the Decomposition of* N-*Phenylsydnone.*—Powdered *N*-phenylsydnone (1 g.) was added to boiling N/20-sodium oxalate solution (20 ml.). Decomposition with the evolution of gas and deposition of tarry material took place almost immediately. Under similar conditions

* For the meaning of the wavy line see Earl, *Nature*, 1946, **158**, 909.

N/20-sodium hydrogen oxalate caused no decomposition. Experiments with mixtures of the two standard solutions gave the following results :

N/20-$NaHC_2O_4$, ml.	N/20-$Na_2C_2O_4$, ml.	Decomposition observed.	pH of mixed solns. at 15°.*
2	18	None	4·87
1·5	18·5	After 2·5 mins.	4·98
1	19	After 1·25 mins.	5·17
0	20	Immediate	7·30

* Kindly determined by Mr. J. N. Phillips.

Decomposition of C-*Bromo*-N-*phenylsydnone by Sodium Hydroxide.*—*C*-Bromo-*N*-phenylsydnone (1 g.) was mixed with a solution of sodium hydroxide (5 g.) in water (100 ml.) and distilled until the distillate gave no colour with a solution of bleaching powder. The distillate (50 ml.) was made acid with hydrochloric acid and extracted with benzene. After separation, the aqueous layer was cooled and diazotised with a concentrated solution of sodium nitrite (0·4 g.) and was then poured into an alkaline solution of β-naphthol (0·7 g.). The precipitated benzeneazo-β-naphthol was filtered off, washed, and dried in a desiccator at room temperature to constant weight (0·9334 g.; corresponding to 0·346 g. of aniline or 90% of the maximum amount obtainable by quantitative decomposition). The residue in the distillation flask, after cooling, was filtered from a small dark coloured precipitate and made up to 100 ml.; 25 ml. of this solution were made acid with acetic acid and heated nearly to boiling, and excess of calcium chloride solution was added. After standing for some time, the precipitate was filtered off through a weighed Gooch and dried to constant weight at 100° (0·0686 g.). Calculated as CaC_2O_4,H_2O, this corresponds to 45% of that obtainable if the two carbons of the sydnone ring were completely converted into oxalic acid. To another 25 ml. of the alkaline solution, aniline (0·2 g.) was added, and the mixture made acid with acetic acid. After standing, the precipitated diazoaminobenzene was filtered off, washed well, and dried to constant weight at room temperature (0·1266 g.), corresponding to 62% of the amount of sodium nitrite theoretically obtainable.

CN-*Diphenylsydnone.*—Powdered α-anilinophenylacetic acid (5 g.) was stirred with a mixture of 100 ml. of glacial acetic acid and 100 ml. of water and cooled to 3—5°. During 10 mins. a solution of sodium nitrite (1·75 g.) in water (5 ml.) was added in small portions, and stirring at 3—5° continued for 90 mins. After removal of a small amount of undissolved material the filtrate was extracted with benzene (80 ml. in 4 portions). The benzene solution was dried (Na_2SO_4), mixed with an equal volume of acetic anhydride, and kept for 23 hours. The solution was shaken well with water, then with dilute sodium carbonate and again with water. On spontaneous evaporation of the dried benzene solution, a dark, partly crystalline *product* was obtained. After being washed with ligroin and recrystallised once from methanol it gave 1·24 g. of pale sandy crystals, m. p. 183—184° (Found : C, 70·2; H, 4·25; N, 11·7. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·8%).

Conversion of (—)-α-*Anilinophenylacetic Acid into Sydnone.*—Some (±)-α-anilinophenylacetic acid was resolved by the method of Mackenzie and Bate (*J.*, 1915, **107**, 1683). By carrying out the conversion into sydnone as described above, 1·5 g. of (—)-acid ($[\alpha]_D^{20°}$ in alcohol, — 110°) gave 0·64 g. of optically inactive sydnone, m. p. 184—185°. In another experiment, 0·233 g. of the (—)-acid was nitrosated in the usual way and the rotation of the dried benzene solution observed. It remained constant at — 0·62° during 2 hours. Some of the benzene solution was then mixed with half its volume of acetic anhydride and the change in rotation observed :

Time, mins.	4	8	17	36	65	83	1080
$\alpha_D^{29°}$	—0·52°	0·44°	0·38°	0·31°	0·16°	0·11°	0·0°

N-*Benzylsydnone.*—Benzylglycine ethyl ester (98 g.), prepared by the method of Mason and Winder (*J.*, 1894, **65**, 188), was hydrolysed by boiling with a solution of sodium hydroxide (40 g.) in water (250 ml.) for ¾ hour. After extraction with ether and removal of residual ether by boiling, the alkaline solution was neutralised to Congo-red with hydrochloric acid and nitrosated at 0° by adding a solution of sodium nitrite (34·5 g.) in water (100 ml.) during ½ hour. After a further 2 hours' stirring at 0°, the clear solution was acidified, whereupon the *nitroso*-compound separated as a colourless viscous oil which solidified after keeping in the refrigerator; yield, 58·0 g.; m. p. 128—130° (decomp.). Purification was effected by dissolving in 2N-ammonia, filtering, precipitating with acid, and subsequently recrystallising from hot water; 40·1 g.; m. p. 140—140·5°, raised by further recrystallisation to 140·5—141° (Found : C, 55·4; H, 5·2; N, 14·5. $C_9H_{10}O_3N_2$ requires C, 55·65; H, 5·2; N, 14·4%). The nitroso-compound (19·4 g.) was dissolved in acetic anhydride (90 ml.) and kept at 75—80° for 6 hours. The mixture was poured into water, and the product filtered off and washed; 14·7 g. (83%); m. p. 67—68°. Recrystallisation from aqueous alcohol raised the m. p. of the *sydnone* to 68—69° (Found : C, 61·5; H, 4·6; N, 16·0. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%).

N-cyclo*Hexylsydnone* (with S. KRUGER).—*N*-*cyclo*Hexylglycine hydrochloride (6·3 g.) was dissolved in water, and a solution of the calculated quantity of sodium nitrite added at 0—5°. The nitroso-compound which separated was recrystallised from hot water; 4·1 g. (55%); m. p. 112—114° (decomp.). The pure compound has m. p. 117—118° (decomp.) (Zelinsky and Arzybaschew, *Ber.*, 1907, **40**, 3055). The nitroso-compound (3·7 g.) was mixed with acetic anhydride and kept in the dark at room temperature for 24 hours. Water (100 ml.) was then added, and the mixture shaken for 90 mins. To the clear solution ammonia was cautiously added, with cooling, until it was faintly alkaline. A white oil separated and soon solidified; 1·75 g. (52%), m. p. 48—51°, raised by repeated recrystallisation from hot water to 64·5° (Found : N, 16·3. $C_8H_{12}O_2N_2$ requires N, 16·6%).

N-m-*Bromophenylsydnone.*—m-*Bromophenylglycine ester* was prepared by heating an alcoholic solution (25 ml.) of equimolecular proportions (0·2 g.-mol.) of *m*-bromoaniline, ethyl bromoacetate, and crystalline sodium acetate in an oil-bath at 120° under reflux for 4 hours. The crude ester (49·7 g.; m. p. 104—108°), precipitated on pouring the reaction mixture into water, was recrystallised from alcohol, 37·5 g., m. p. 118·5—119°, being obtained (Found: C, 46·45; H, 4·7; N, 5·5. $C_{10}H_{12}O_2NBr$ requires C, 46·6; H, 4·7; N, 5·4%). Hydrolysis of the ester was carried out in the usual way, affording an almost quantitative yield of the *glycine*, m. p. 102·5—103·5° (Found: C, 41·5; H, 3·5; N, 6·1. $C_8H_8O_2NBr$ requires C, 41·7; H, 3·5; N, 6·1%). Nitrosation of the glycine (25·5 g.) suspended in water (100 ml.) at 0—5° with a slight excess of sodium nitrite, followed after 3½ hours by acidification, gave the crude *nitroso*-compound [27·0 g., m. p. 116·5—117·5° (decomp.)]. Recrystallisation from aqueous alcohol raised the m. p. to 119—120° (decomp.) (Found: C, 36·4; H, 2·7; N, 10·9. $C_8H_7O_3N_2Br$ requires C, 37·1; H, 2·7; N, 10·8%). The nitroso-compound (13·0 g.) was mixed with acetic anhydride (45 ml.) and kept at room temperature for 6 days. Part of the *sydnone* was filtered off directly from the reaction mixture, and part was recovered from the filtrate on mixing with water. A combined yield of 9·0 g. (75%), m. p. 151—152° (decomp.), was obtained. Recrystallisation from alcohol raised the m. p. to 152—153° (decomp.) (Found: C, 39·4; H, 2·0; N, 11·6. $C_8H_5O_2N_2Br$ requires C, 39·9; H, 2·1; N, 11·6%).

N-p-*Bromophenylsydnone.*—*p*-Bromophenylglycine has been described by Dennstedt (*Ber.*, 1880, **13**, 238) and by Schwalbe, Schulz, and Jochheim (*Ber.*, 1908, **41**, 3795). Our preparation (m. p. 150°) was identical with that of the latter authors and differed from Dennstedt's (m. p. 98°). It was nitrosated similarly to the *m*-bromo-compound, except that the glycine (57·5 g.) was suspended in a mixture of alcohol (50 ml.) and water (200 ml.). The yield of crude product was 62·0 g. (95%), m. p. 126° (decomp.). Recrystallisation from aqueous alcohol raised the m. p. only slightly (Found: C, 36·8; H, 2·8; N, 10·8. $C_8H_7O_3N_2Br$ requires C, 37·1; H, 2·7; N, 10·8%). The *nitroso*-compound (52·0 g.) was dissolved in acetic anhydride (180 ml.), the solution being filtered after 1 day and then kept at room temperature for 13 days. The white crystalline precipitate which had separated was then triturated with dilute alcohol and dried in a vacuum; 15·3 g., m. p. 137·5—138·5° (decomp.). A further 17·0 g. of less pure product, m. p. 130—132° (decomp.), was recovered by decomposing the acetic anhydride in the mother-liquor. On attempting to recrystallise the well-crystallised *sydnone* of m. p. 137·5—138·5° it decomposed. It was, therefore, analysed without further treatment (Found: C, 39·7; H, 2·1; N, 11·7%).

N-o-*Carboxyphenylsydnone.*—*o*-Carboxyphenylglycine (39 g.) was dissolved in a hot solution of sodium hydroxide (8 g.) in water (300 ml.). On cooling quickly to 0—5°, the sodium salt separated. To the suspension, sodium nitrite (15 g.) in water (50 ml.) was added with stirring during 30 mins. After another 3½ hours' stirring at 5° a clear solution was obtained, from which on acidification, the nitroso-compound separated slowly as a cream powder; 35·1 g., m. p. 112—113° (decomp.). It was readily soluble in warm water and recrystallised on cooling without change of m. p. Van Ekenstein and Blanksma (*Rec. Trav. chim.*, 1905, **24**, 36) record m.p. 120° (decomp.) (Found: equiv., 114·2. Calc. for $C_9H_8O_5N_2$: equiv., 112·1). The nitroso-compound (22·4 g.) was dissolved in acetic anhydride (90 ml.) and kept for 3 weeks. The crude *product* obtained after decomposing the acetic anhydride was recrystallised once from alcohol (charcoal); yield, 9·7 g., m. p. 204—205° (decomp.), raised by recrystallisation to 205—206° (Found: C, 51·9; H, 2·9; N, 13·0. $C_9H_6O_4N_2$ requires C, 52·4; H, 2·9; N, 13·6%). On account of rapid decomposition during combustion, it was difficult to obtain consistent analytical figures.

N-p-*Carboxyphenylsydnone.*—The following procedure gave purer *p*-carboxyphenylglycine than that obtained by Mauthner and Suida (*Monatsh.*, 1890, **11**, 380). Sodium hydrogen carbonate (33·6 g.) was added to a mixture of bromoacetic acid (27·8 g.), *p*-aminobenzoic acid (27·2 g.), and water (250 ml.), and the solution boiled under reflux for 4 hours. On cooling, the monosodium salt of *p*-carboxyphenylglycine separated and was filtered off. It was dissolved in sodium hydroxide solution, and the crude glycine [26·1 g.; m. p. 241—243° (decomp.)] precipitated by acidification to pH 1—2. On digestion with hot glacial acetic acid (400 ml.), part of the glycine [11·1 g.; m. p. 255° (decomp.)] remained undissolved, and more [7·0 g.; m. p. 255° (decomp.)] was recovered on cooling the acetic acid solution; total yield, 18·1 g. (46%). The nitroso-derivative was prepared similarly to that of the *o*-carboxy-compound, rather more water (525 ml.) and a longer reaction time (9 hours) being required. Conversion into the *sydnone* was brought about by heating the nitroso-compound (22·4 g.) with acetic anhydride (90 ml.) at 80°. After isolation in the usual way, 14·4 g.(70%) of crude product, m. p. 242—243° (decomp.), were obtained. Recrystallisation from *cyclo*hexanone raised the m. p. to 248—249° (decomp.) (Found: C, 52·2; H, 2·9; N, 13·5%).

C-*Phenyl*-N-*methylsydnone.*—Phenylsarcosine (1·91 g.) was dissolved in a mixture of glacial acetic acid (20 ml.) and water (20 ml.) and cooled to 2°; a solution of sodium nitrite (0·82 g.) in water (10 ml.) was added, and the mixture kept at 0—5° for 70 mins. It was then extracted rapidly with two successive mixtures of benzene (15 ml.) and acetic anhydride (10 ml.), the extract being allowed to stand in the dark for three days. It was then shaken well with water, and the benzene layer separated and dried (Na_2SO_4). On evaporation, first on the water-bath and later at room temperature, a semicrystalline residue was obtained which was washed thoroughly with cold water and dried in a desiccator; 0·42 g., m. p. 115—120°. One recrystallisation from hot water gave 0·22 g. of pure white crystalline *sydnone*, m. p. 131—132° (Found: C, 60·8; H, 4·5; N, 15·65. $C_9H_8O_2N_2$ requires C, 61·3; H, 4·6; N, 15·9%).

C-*Chloro*-N-*phenylsydnone.*—*N*-Phenylsydnone (1 g.) and crystalline sodium acetate (1 g.) were dissolved in glacial acetic acid (20 ml.), and chlorine bubbled in until no more was absorbed (0·5 g.). The solution was mixed with water, and the precipitated *product* filtered off, recrystallised from aqueous alcohol, and dried in air; 0·45 g., m. p. 127° (decomp.) (Found: Cl, 17·8; N, 13·8. $C_8H_5O_2N_2Cl$ requires Cl, 18·0; N, 14·25%).

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