456. *Syntheses of Heterocyclic Compounds. Part VI.*[1] *Cyclisations of* ortho-*Substituted* N-*Phenylglycines.*

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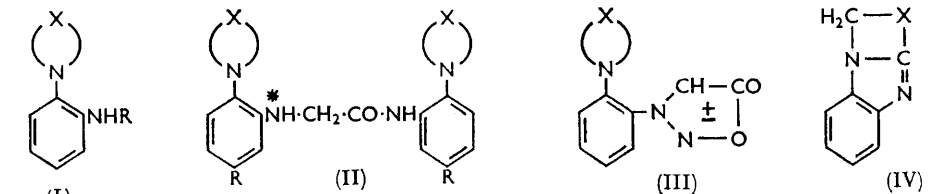
Cyclisations of the title compounds to sydnones and benzimidazoles are described.

Attempts to prepare the *N*-phenylglycines (I; R = $CH_2 \cdot CO_2H$) by condensing sodium monochloroacetate with the appropriate anilines (I; R = H) in aqueous ethanol gave non-acidic compounds in every case. These were shown to be the amides [II; R = H, X as in (I)] by hydrolysis back to the original amines and phenylglycines. It is noteworthy that aniline under similar conditions gives only *N*-phenylglycine, whereas the amide analogous to (II) is produced in the presence of sodium acetate at high temperature.[2]

The required glycines (I; R = $CH_2 \cdot CO_2H$) were eventually prepared by hydrolysis of their ethyl esters obtained from ethyl chloroacetate and the appropriate aniline (I; R = H). Their conversion into the corresponding sydnones [III] occurred smoothly, by way of the *N*-nitroso-compounds, by Eade and Earl's method.[3] In another tentative approach



to sydnones, nitrosation of the piperidino-amide (II; R = H, X = $[CH_2]_5$) with sodium nitrite produced a mixture of the nitro-compound (II; R = NO_2, X = $[CH_2]_5$) and the *N*-nitroso-compound (II; R = H, X = $[CH_2]_5$, NO group on N*) as evidenced by Liebermann's test, infrared data (cf. Experimental section), analysis, and absence of absorption above 400 mμ in the ultraviolet spectrum where *C*-nitroso-compounds show strong bands. The *N*-nitroso-compound could not, however, be cyclised. Use of nitrosyl chloride as the nitrosating agent led to a nitro-compound only, identical with the above nitrosation product. Its structure was confirmed by synthesis from monochloroacetic acid and the appropriate nitro-amine.

We recently demonstrated[4] the ease of benzimidazole formation from appropriately substituted anilines by simple oxidation. Since the amides [II; R = H, X as in (I)] appeared constitutionally suitable for such a cyclisation, they were treated with a mixture of hydrogen peroxide and formic acid on a water-bath. The observed yields of the benzimidazoles (IV) are accounted for only by participation of both ring pairs of the molecule (II) in the cyclisation. Since the strength of formic acid used in the reaction was insufficient to hydrolyse the amide, it is probable that a benzimidazole is first formed from the ring system near to the acyl group (cf. II) in accordance with a mechanism recently put forward by us.[4] This leads to liberation of the appropriate *N*-phenylglycine (I; R = $CH_2 \cdot CO_2H$) from which a further benzimidazole molecule is formed. The *N*-phenylglycines did indeed give benzimidazoles in high yield under the conditions of the reaction.

[1] Part V, Denton, Smalley, and Suschitzky, preceding Paper.
[2] Bischoff and Hausdörfer, *Ber.*, 1890, **23**, 1987.
[3] Eade and Earl, *J.*, 1946, 591.
[4] Meth-Cohn and Suschitzky, *J.*, 1963, 4666.

Experimental

Condensations with Monochloroacetic Acid.—The appropriate heterocyclic amine [4] (1 mol.), dissolved in a minimum of ethanol, was added to an aqueous solution of sodium chloroacetate (1 mol.). The mixture was refluxed for 10 hr., and ethanol and unchanged amine were removed by steam-distillation. The solid obtained by filtration of the residue was recrystallised from light petroleum (b. p. 60—80°) to give the *amide* (Table 1).

Table 1.

Substituted amides of *N*-phenylglycine (II).

			Yield *	Found (%)			Required (%)	
R	X	M. p.	(%)	C	H	Formula	C	H
H	$[CH_2]_4$	130°	57	72·2	7·7	$C_{22}H_{28}N_4O$	72·5	7·7
H	$[CH_2]_5$	148	68	73·4	8·4	$C_{24}H_{32}N_4O$	73·5	8·2
H	$[CH_2]_6$	115	75	74·2	8·6	$C_{26}H_{36}N_4O$	74·3	8·6
H	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	142	54	66·2	6·9	$C_{22}H_{28}N_4O_3$	66·7	7·1
NO_2	$[CH_2]_5$	142	61	59·5	6·2	$C_{24}H_{30}N_6O_5$	59·75	6·2

* Based on the amount of amine used.

Condensations with Ethyl Monochloroacetate.—The N-*phenylglycine esters* (Table 2) were made from the appropriate amine (0·19 mol.), ethyl chloroacetate (0·2 mol.), and sodium acetate (0·2 mol.) by refluxing for 9 hr., according to Eade and Earl's method.[3]

Table 2.

ortho-Substituted phenylglycine esters (I; R = $CH_2{\cdot}CO_2Et$).

		Yield	Found (%)		Required (%)
X	B. p.	(%)	N	Formula	N
$[CH_2]_4$	160°/0·6 mm.	52	10·8	$C_{14}H_{20}N_2O_2$	11·2
$[CH_2]_5$	160/1·5	50	10·7	$C_{15}H_{22}N_2O_2$	10·7
$[CH_2]_6$	180/2·5	57	10·0	$C_{16}H_{24}N_2O_2$	10·1
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	78 (m. p.)	55	10·9	$C_{14}H_{20}N_2O_3$	10·6

Preparation of Sydnones.—The above esters were hydrolysed with an excess of boiling ethanolic sodium hydroxide for 2 hr. The solvent was driven off and the residue adjusted with 3N-hydrochloric acid to pH 6. The precipitated *acids* were recrystallised from light petroleum in high yield (Table 3).

Table 3.

ortho-Substituted phenylglycines (I; R = CH_2CO_2H).

		Found (%)		Required (%)
X	M. p.	N	Formula	N
$[CH_2]_4$	115°	12·2	$C_{12}H_{16}N_2O_2$	12·7
$[CH_2]_5$	124	12·3	$C_{13}H_{18}N_2O_2$	11·95
$[CH_2]_6$	145	11·7	$C_{14}H_{20}N_2O_2$	11·3
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	143	12·2	$C_{12}H_{16}N_2O_3$	11·85

The *N*-nitroso-compounds (1 g.), prepared from the acids listed in Table 3 by Eade and Earl's method,[3] were dissolved in acetic anhydride (20 ml.) and the solution kept for 2 days at room temperature in the dark. Addition of aqueous ammonia (*d* 0·88) and cooling precipitated the *sydnones*, which crystallised from aqueous ethanol (Table 4).

Table 4.

Substituted sydnones (III).

		Yield	Found (%)		Required (%)
X	M. p.	(%)	N	Formula	N
$[CH_2]_4$	133°	70	18·3	$C_{12}H_{13}N_3O_2$	18·1
$[CH_2]_5$	125	70	17·0	$C_{13}H_{15}N_3O_2$	17·1
$[CH_2]_6$	115	70	16·1	$C_{14}H_{17}N_3O_2$	16·2
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	160	75	17·2	$C_{12}H_{13}N_3O_3$	17·0

The nitrosation mixture of the piperidino-amide (II; R = H, X = $[CH_2]_5$) gave, on addition of 4N-sodium hydroxide to pH 6, the dinitro-compound (II; R = NO_2, X = $[CH_2]_5$), m. p. 142° identical with an authentic specimen (cf. Table 1). On making the mixture strongly alkaline, the pale yellow N-*nitroso-compound* (II; R = H, X = $[CH_2]_5$, NO on N*) was precipitated, m. p. 130° (from aqueous acetone) (Found: C, 68·2; H, 7·6; N, 16·3. $C_{34}H_{31}N_5O_2$ requires C, 68·4; H, 7·4; N, 16·6%), $\nu_{max.}$ (in CCl_4) 770 and 757 (*ortho*-disubstitution), 1451 $cm.^{-1}$ (N·NO).[5] Nitrosation of the amide with nitrosyl chloride in acetic acid gave the dinitro-derivative only.

Benzimidazole Formation.—A mixture of 1 g. of the *N*-phenylglycine (I; R = CH_2·CO_2H) or of the amide [II; R = H, X as in (I)], 90% formic acid (6 ml.), and 30% hydrogen peroxide (3 ml.) was heated on a water-bath for 10—15 min. A vigorous reaction ensued. Dilution and neutralisation of the mixture with aqueous ammonia precipitated the corresponding benzimidazoles (IV) in 80—90% yield. Their m. p.s were undepressed on admixture with specimens previously prepared.[4]

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[5] Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1960.