[CONTRIBUTION FROM THE OHARA INSTITUTE FOR AGRICULTURAL BIOLOGY, OKAYAMA UNIVERSITY]

Synthesis of Ring-Substituted *N*-Phenylglycines, Their Nitriles and Amides

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Received August 26, 1955

Fourteen new 2,4-di-, 3,4-di- and 2,4,5-trisubstituted *N*-phenylglycines were synthesized *via* the sequence: arylamine, sodium *N*-arylaminomethanesulfonate, *N*-arylglycinonitrile, *N*-arylglycinamide and *N*-arylglycine. Preliminary biological testing of these compounds indicated that all the glycines and the amides were active as plant growth substances.

The high activities of *N*-(2,4-dichlorophenyl) glycine[1] and N-(2,4-dibromophenyl)glycine[2] as well as of N-(3,4-dichlorophenyl)glycine[3] as plant growth regulators, comparable with those of *O*-(2,4-dichlorophenyl)glycolic and α-naphthylacetic acids stimulated the attempt to prepare new

TABLE I

RING-SUBSTITUTED *N*-PHENYLGLYCINES

Substituted[a] Glycine	*p*H[b]	M.P. (Decomposition), °C.	Yield, % Method A[c]	Yield, % Method B[d]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Activity[e] in Pea Test
N-(2,4-Dichlorophenyl)-	5.2–5.4	151–152	72 (33)	87	$C_8H_7Cl_2NO_2$	6.36	6.4	1.90
Diethylamine salt		88–90			$C_{12}H_{18}Cl_2N_2O_2$	9.55	9.5	
N-(3,4-Dichlorophenyl)-	5.2–5.4	128–129	83 (25)	82 (7)	$C_8H_7Cl_2NO_2$	6.36	6.4	0.23
Diethylamine salt		137–138			$C_{12}H_{18}Cl_2N_2O_2$	9.55	9.5	
N-(3-Chloro-4-methylphenyl)-	4.2–4.4	125–126	60 (18)	86 (8)	$C_9H_{10}ClNO_2$	7.01	7.1	6.02
Diethylamine salt		120–121			$C_{13}H_{21}ClN_2O_2$	10.26	10.2	
N-(3-Methyl-4-chlorophenyl)-	4.2–4.4	115–117		69 (6)	$C_9H_{10}ClNO_2$	7.01	6.9	3.22
Diethylamine salt		134–134.5			$C_{13}H_{21}ClN_2O_2$	10.26	10.3	
N-(2-Bromo-4-methylphenyl)-	5.6–5.8	169–170	54 (66)	78 (8)	$C_9H_{10}BrNO_2$	5.74	5.7	6.30
Diethylamine salt		123–124			$C_{13}H_{21}BrN_2O_2$	8.83	8.9	
N-(2-Methyl-4-bromophenyl)-	4.8–5.0	142–145		82 (6)	$C_9H_{10}BrNO_2$	5.74	5.7	10.70
Diethylamine salt		109–111			$C_{13}H_{21}BrN_2O_2$	8.83	8.8	
N-(2-Chloro-4-methylphenyl)-	4.2–4.6	161–164	31 (71)	91	$C_9H_{10}ClNO_2$	7.01	7.2	20.20
Diethylamine salt		110–111			$C_{13}H_{21}ClN_2O_2$	10.26	10.3	
N-(2-Methyl-4-chlorophenyl)-	4.2–4.4	143–144	57 (52)	83 (5)	$C_9H_{10}ClNO_2$	7.01	7.1	7.30
Diethylamine salt		109–110			$C_{13}H_{21}ClN_2O_2$	10.26	10.2	
N-(2-Chloro-4-bromophenyl)-	5.6–5.8	156–157		90 (3)	$C_8H_7BrClNO_2$	5.29	5.4	4.20
Diethylamine salt		107–108			$C_{12}H_{18}BrClN_2O_2$	8.29	8.3	
N-(2-Bromo-4-chlorophenyl)-	5.6–5.8	163–164		87 (6)	$C_8H_7BrClNO_2$	5.29	5.4	5.02
Diethylamine salt		118–118.5			$C_{12}H_{18}BrClN_2O_2$	8.29	8.3	
N-(2,4,5-Trichlorophenyl)-	4.0–4.2	185–186	89 (54)	62 (8)	$C_8H_6Cl_3NO_2$	5.50	5.6	0.35
Diethylamine salt		174–175			$C_{12}H_{17}Cl_3N_2O_2$	8.55	8.6	
N-(2,5-Dichloro-4-methylphenyl)-	4.6–4.8	173–175		83 (4)	$C_9H_9Cl_2NO_2$	5.96	5.9	14.50
Diethylamine salt		141–143			$C_{13}H_{20}Cl_2N_2O_2$	9.11	9.2	
N-(2-Bromo-4-methyl-5-chlorophenyl)-	6.2–6.4	195–196		85 (4)	$C_9H_9BrClNO_2$	5.03	5.1	14.70
Diethylamine salt		170–174			$C_{13}H_{20}BrClN_2O_2$	7.96	8.1	
N-(3-Nitro-4-methylphenyl)-	3.8–4.2	147–149		82 (6)[f]	$C_9H_{10}N_2O_4$	13.32	13.1	4.52
Diethylamine salt		149–150			$C_{13}H_{21}N_3O_4$	14.82	14.8	
N-(3-Nitro-4-chlorophenyl)-	3.8–4.0	174.5–175		67 (17)[f]	$C_8H_7ClN_2O_4$	12.14	12.2	0.79
Diethylamine salt		128–129			$C_{12}H_{18}ClN_3O_4$	13.83	13.9	

[a] These compounds are new with the exception of *N*-(2,4-dichlorophenyl)glycine, whose melting point was recorded as 127° (ref. 6). Since the so-called *N*-(2,4-dichlorophenyl)glycine recorded in the literature, however, has been prepared from *p*-chloronitrobenzene *via* dichloronitrobenzene and dichloroaniline, it is suspected to be *N*-(3,4-dichlorophenyl)glycine. Starting from appropriate dichloroanilines, *N*-(3,4-dichlorophenyl)glycine melting at 128–129° (decomposition) and *N*-(2,4-dichlorophenyl)glycine melting at 151–152° (decomposition) have now been prepared and the surmise mentioned above has been proved correct. Since writing this paper, Dr. Henri Pachéco has kindly sent me his thesis (University of Lyon, 1952) describing the preparation of *N*-(2-methyl-4-bromophenyl)glycine by the method of Schwalbe *et al.*, but there the melting point of this new compound could not be found. [b] Approximate values of *p*H at which glycines were precipitated. They were observed colorimetrically with solutions of methyl red, bromocresol green and bromophenol blue. Enough dilute hydrochloric acid (1:1) was added to bring *p*H of the solution to values lower than these figures by 0.4–0.6. [c] Yields based on the consumed anilines. Parenthesized figures indicate their recoveries. [d] Yields based on the used nitriles. Parenthesized figures are those of accompanying amides. [e] Diethylamine salts of the acids were employed for the experiment. Figures indicate the threshold minimum concentrations to exhibit activity, mg./l. [f] A 2% aqueous solution of sodium hydroxide was used for saponification.

TABLE II

SODIUM *N*-PHENYLAMINOMETHANESULFONATES[a]

Substituted[b] Aminomethanesulfonate	Reaction Time, Min.	Yield,[c,d] %	Formula	Nitrogen, %[e] Calcd.	Found
N-(2,4-Dichlorophenyl)-	120	87[d] (23)	$C_7H_6Cl_2NNaO_3S$	5.03	5.0
N-(3,4-Dichlorophenyl)-	25	94 (0)	$C_7H_6Cl_2NNaO_3S$	5.03	4.8
N-(3-Chloro-4-methylphenyl)-	25	91 (1)	$C_8H_9ClNNaO_3S$	5.43	5.3
N-(3-Methyl-4-chlorophenyl)-	25	90 (0)	$C_8H_9ClNNaO_3S$	5.43	5.3
N-(2-Bromo-4-methylphenyl)-	60	88[d] (7)	$C_8H_9BrNNaO_3S$	4.63	4.4
N-(2-Methyl-4-bromophenyl)-	40	99.5 (0)	$C_8H_9BrNNaO_3S$	4.63	4.5
N-(2-Chloro-4-methylphenyl)-	120	84[d] (8)	$C_8H_9ClNNaO_3S$	5.43	5.2
N-(2-Methyl-4-chlorophenyl)-	120	90[d] (16)	$C_8H_9ClNNaO_3S$	5.43	5.1
N-(2-Chloro-4-bromophenyl)-	120	86[d] (44)	$C_7H_6BrClNNaO_3S$	4.34	4.2
N-(2-Bromo-4-chlorophenyl)-	120	69[d] (51)	$C_7H_6BrClNNaO_3S$	4.34	4.1
N-(2,4,5-Trichlorophenyl)-	180[f]	38[d] (84)	$C_7H_5Cl_3NNaO_3S$	4.48	4.6
N-(2,5-Dichloro-4-methylphenyl)-	180[f]	42[d] (71)	$C_8H_8Cl_2NNaO_3S$	4.79	4.6
N(-2-Bromo-4-methyl-5-chlorophenyl)-	180[f]	82[d] (83)	$C_8H_8BrClNNaO_3S$	4.16	3.9
N-(3-Nitro-4-methylphenyl)-	20	84 (0)	$C_8H_9N_2NaO_5S$	10.44	10.2
N-(3-Nitro-4-chlorophenyl)-	20	87 (0)	$C_7H_6ClN_2NaO_5S$	9.70	9.6

[a] In repeating the *N*-sulfomethylation of monochloro-, mononitro- and monomethylanilines it was experienced that the reaction occurred readily and resulted in almost the theoretical yield except in cases of *o*-nitroaniline and *o*-chloroaniline where 75% and 4%, respectively, of the starting materials were recovered. Sulfomethylation of 2-nitro-4-chloroaniline, 2,4-dichloro-6-bromoaniline, 2,4,6-trichloroaniline, 2-methyl-4,6-dichloroaniline was unsuccessful even with a prolonged heating. [b] These substances appear as glossy white scales which do not melt below 300°. All the compounds listed here are new. The biological tests were all negative. [c] Yield based on the consumed amine. The figures in parentheses indicate the recovery of unchanged amines (%) which had been collected by steam-distillation. [d] Formaldehyde-sodium bisulfite solution was used in great excess (1:2) for the preparation of compounds. [e] Samples were dried for 24 hours at 60–70° after two recrystallizations from water and washing twice with absolute alcohol. [f] Heatings for more than 3 hr. were generally ineffective.

derivatives in the 2,4-di-, 3,4-di- and 2,4,5-trisubstituted *N*-phenylglycine series. This is of interest in order to make clear how the activities of these compounds are changed by the structure modification, since it is not as yet established definitely whether the imino as a linking group in the side chain may be as effective as the oxygen linkage of the ring-substituted *O*-phenylglycolic acids in bringing about the enhanced biological activity.[4]

Fourteen new compounds of the general types mentioned above, along with their intermediates, have been synthesized *via* two routes as formulated in Scheme I, where R_1, R_2 and R_3 are hydrogen, chlorine, bromine, nitro and/or methyl groups, respectively. The properties and yields of the glycines as well as of the intermediates are summarized in Tables I, II, III, and IV, where their responses to the Went pea test[5] are also recorded.

In general, the treatment of arylamines (I) with formaldehyde and potassium cyanide according to the method of Schwalbe *et al.*[6] (Method A) failed to afford satisfactory yields of the desired *N*-arylglycines (V), a large amount of the amine being recovered unchanged as shown in Table I. The glycines herein described were mostly prepared by way of the hydrolysis of the corresponding nitriles (III) synthesized *via* *N*-arylaminomethanesulfonates (II) according to Knoevenagel's method[7] with some modifications which enabled the higher conversion of amines, Method B.

The *N*-sulfomethylation of the amines was carried out by the action of a 3*M* solution of formaldehyde-sodium bisulfite in excess (1:1.5) instead of in an equimolar ratio. This helped to shorten the reaction time without the formation of *N,N*-disulfomethylated compound as a by-product. The yield of *N*-sulfomethylation calculated on the starting material, as shown in Table II, varied widely with regard to the position and number of substituents.

These results, with a certain exception, suggest that one *ortho* substituent reduces the reactivity of of the aniline markedly and a second *ortho* substituent reduces the reactivity still further. It must be noted here that the effect of a nitro group is so great that the sulfomethylation of 2-nitro-4-chloroaniline, a mono-*ortho*-substituted compound, also failed. Also Long and Burger[8] reported the failure of the attempt to prepare *N*-(2,4,6-triiodophenyl)glycine according to the method of Schwalbe *et al.*

Sodium *N*-arylaminomethanesulfonates thus pro-

(1) Veldstra and Booij, *Biochim. Biophys. Acta*, **3**, 278 (1949).
(2) Pachéco, *Chem. Abstr.*, **44**, 10993 (1950).
(3) Takeda and Senda, *Rept. Ohara Inst. Agr. Biol.*, **42**, 19 (1954).
(4) Audus, *Plant Growth Substances*, Leonard Hill Ltd., London, 1953, p. 63.
(5) Went, *Proc. Kon. Akad. Wet., Amst.*, **37**, 547 (1934).
(6) Schwalbe, Schulz, and Jochheim, *Ber.*, **41**, 3792 (1908).
(7) Knoevenagel, *Ber.*, **37**, 4080 (1904).
(8) Long and Burger, *J. Am. Chem. Soc.*, **63**, 1586 (1941).

TABLE III

N-PHENYLGLYCINONITRILES

Substituted[a] Glycinonitrile	M.P., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
N-(2,4-Dichlorophenyl)-	76–78	87	$C_8H_6Cl_2N_2$	13.92	14.0
N-(3,4-Dichlorophenyl)-	101–102	95	$C_8H_6Cl_2N_2$	13.92	14.0
N-(3-Chloro-4-methylphenyl)-	62–63	91	$C_9H_9ClN_2$	15.50	15.5
N-(3-Methyl-4-chlorophenyl)-	86–87	93	$C_9H_9ClN_2$	15.50	15.6
N-(2-Bromo-4-methylphenyl)-	62–63	89	$C_9H_9BrN_2$	12.44	12.5
N-(2-Methyl-4-bromophenyl)-	104.5–105.5	89	$C_9H_9BrN_2$	12.44	12.5
N-(2-Chloro-4-methylphenyl)-	47–48	83	$C_9H_9ClN_2$	15.50	15.6
N-(2-Methyl-4-chlorophenyl)-	101–101.5	86	$C_9H_9ClN_2$	15.50	15 5
N-(2-Chloro-4-bromophenyl)-	81–82	90	$C_8H_6BrClN_2$	11.40	11.4
N-(2-Bromo-4-chlorophenyl)-	104–105	94	$C_8H_6BrClN_2$	11.40	11.4
N-(2,4,5-Trichlorophenyl)-	122–123	91	$C_8H_5Cl_3N_2$	11.89	11.9
N-(2,5-Dichloro-4-methylphenyl)-	110–112	91	$C_9H_8Cl_2N_2$	12.96	13.0
N-(2-Bromo-4-methyl-5-chlorophenyl)-	121–122	74	$C_9H_8BrClN_2$	10.79	10.8
N-(3-Nitro-4-methylphenyl)-	101–102	99	$C_9H_9N_3O_2$	21.97	21.9
N-(3-Nitro-4-chlorophenyl)-	90.5–91.5	92	$C_8H_6ClN_3O_2$	19.85	20.0

[a] All the compounds listed here are new with the exception of *N*-(2,4-dichlorophenyl)glycinonitrile. Since the contribution of this paper, the author found that this compound had been reported before by Marxer, the reported m.p. 73–75° (uncorrected), *Helv. Chim. Acta*, **37**, 166 (1954); *Chem. Abstr.*, **49**, 13938 (1955).

TABLE IV

N-PHENYLGLYCINAMIDES

Substituted[a] Glycinamide	M.P. (Decomposition) °C.	Yield,[b] %	Formula	Nitrogen, % Calcd.	Found	Activity in Pea Test
N-(2,4-Dichlorophenyl)-	141–142	27 (50)	$C_8H_8Cl_2N_2O$	12.78	12.8	1.36
N-(3,4-Dichlorophenyl)-	139–139.5	49 (37)	$C_8H_8Cl_2N_2O$	12.78	12.8	0.25
N-(3-Chloro-4-methylphenyl)-	152–153	66 (20)	$C_9H_{11}ClN_2O$	14.09	14.1	4.55
N-(3-Methyl-4-chlorophenyl)-	122–123	38 (36)	$C_9H_{11}ClN_2O$	14.09	14.0	6.40
N-(2-Bromo-4-methylphenyl)-	149.5–150.5	38 (45)	$C_9H_{11}BrN_2O$	11.52	11.6	10.80
N-(2-Methyl-4-bromophenyl)-	156–157	40 (39)	$C_9H_{11}BrN_2O$	11.52	11.5	20.20
N-(2-Chloro-4-methylphenyl)-	134–135	18 (55)[c]	$C_9H_{11}ClN_2O$	14.09	14.1	45.25
N-(2-Methyl-4-chlorophenyl)-	152.5–154	37 (48)	$C_9H_{11}ClN_2O$	14.09	14.1	3.86
N-(2-Chloro-4-bromophenyl)-	150–151	46 (45)	$C_8H_8BrClN_2O$	10.62	10.6	4.43
N-(2-Bromo-4-chlorophenyl)-	144–146	44 (51)	$C_8H_8BrClN_2O$	10.62	10.7	2.85
N-(2,4,5-Trichlorophenyl)-	152–153	47 (31)	$C_8H_7Cl_3N_2O$	11.04	11.0	0.27
N-(2,5-Dichloro-4-methylphenyl)-	156–157	55 (24)	$C_9H_{10}Cl_2N_2O$	12.01	11.9	10.10
N-(2-Bromo-4-methyl-5-chlorophenyl)-	167–168	44 (40)	$C_9H_{10}BrClN_2O$	10.09	10.3	—[d]
N-(3-Nitro-4-methylphenyl)-	143.5–144	48 (36)	$C_9H_{11}N_3O_3$	20.07	20.0	5.18
N-(3-Nitro-4-chlorophenyl)-	141–142	48 (33)	$C_8H_8ClN_3O_3$	18.29	18.4	1.05

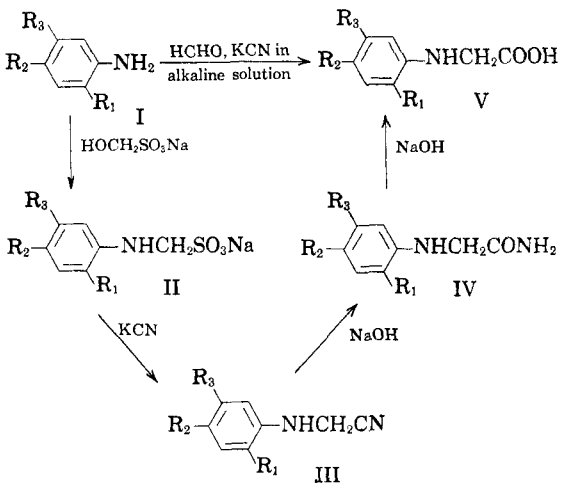
[a] All the compounds listed here are new. [b] The produced amide is partly hydrolyzed to the corresponding glycine. Figures in parentheses are the per cent of nitriles which have been converted to the glycines. [c] Hydrolysis was continued for 1 hr. [d] The biological activity of this compound could not be determined by this method because of its low solubility in water, the saturated aqueous solution containing 15.60 mg. of solute per liter exhibiting no response in the test.

duced were treated with hot potassium cyanide solution to give the corresponding nitriles in about 90% yield (Table III).

Hydrolysis of the nitriles with a 5% sodium hydroxide solution afforded the corresponding glycines together with a small quantity of amides, while saponification of the nitriles with a 1% sodium hydroxide solution gave the amides in better yields as shown in Table IV.

The diethylamine salts of the glycines were prepared. Since these salts are easily soluble both in water and in organic solvents such as ethanol or benzene, they are convenient for use in the biological tests.

The glycines and the amides exhibited reasonable responses in accordance with the nature of the substituted benzene nucleus, whereas the tests of the corresponding nitriles and sodium *N*-arylaminomethanesulfonates were negative.[4] The biological data indicate that neither of the chlorine atoms in *N*-(3,4-dichlorophenyl)glycine which possesses the highest activity in this series can be replaced by a methyl group without the loss of activity, while the chlorine atom in the *ortho* position on *N*-(2,4-dichlorophenyl)glycine can be replaced. *N*-(2,4,5-Trichlorophenyl)glycine is as active as *N*-(3,4-dichlorophenyl)glycine and the replacement of the chlorine atom in the *para*



SCHEME I

position of the former compound is also accompanied by a considerable decrease in the activity. The details of the biological assay which was carried out by Miss Nobuko Yamaji and Mr. Jiro Senda of our laboratory using the Went pea test,[5] the *Avena* cylinder test[9] and the Aduki bean curvature test[3] will be reported elsewhere.

EXPERIMENTAL

Materials. A 3*M* solution of formaldehyde-sodium bisulfite was prepared in the following way. To a solution of 375 g. of sodium bisulfite in 600 ml. of water, 243 g. (3 moles) of commercial formalin (37%) was added gradually with stirring. The mixture was then refluxed for about 10 min. and the filtrate was made up to 1000 ml. by adding water.

2-Bromo-4-methyl-5-chloroaniline. This new compound was prepared *via* the acetanilide as follows: To a stirred solution of 36.6 g. (0.2 mole) of 3-chloro-4-methylacetanilide in 100 ml. of acetic acid, 32 g. (0.2 mole) of bromine was added slowly. During the course of the addition, which required about 10 min., the temperature reached 60°. The mixture was stirred at 50–60° for an additional 40 min. and then poured slowly with efficient stirring into 2000 ml. of cold water containing 6 g. of sodium bisulfite. Needles melting at 139–149° (all m.p. are uncorrected) were separated; yield 47 g. (90% based on 3-chloro-4-methylacetanilide), m.p. 153–154° after two recrystallizations from alcohol.

Anal. Calcd. for $C_9H_9BrClNO$: N, 5.33. Found: N,[10] 5.4.

Saponification of 26 g. of this acetanilide with a 20% sodium hydroxide solution gave 19 g. of the crude amine, m.p. 79–82°. Several recrystallizations from ethyl alcohol gave a pure sample melting at 91–92°.

Anal. Calcd. for C_7H_7BrClN: N, 6.35. Found: N, 6.4.

Deamination of 10.5 g. of this amine[11] yielded 5.5 g. of colorless, non-nitrogenous material, b.p. 116–119°/40 mm. Oxidation of 1.5 g. of this substance with excess potassium permanganate in alkaline solution gave 0.55 g. of 2-chloro-5-bromobenzoic acid (m.p. 157–158°) which did not depress the melting point of an authentic sample.[12]

Sodium N-(3-chloro-4-methylphenyl)aminomethanesulfonate. Since all the compounds given in the accompanying tables were synthesized by essentially the same procedures, only some examples are presented in detail. The following experiments will serve to illustrate the manner in which they were obtained.

A mixture of 28.2 g. of 3-chloro-4-methylaniline (0.2 mole) and 100 ml. of the 3*M* solution of formaldehyde-sodium bisulfite was refluxed in a 300 ml. flask. A clear solution was obtained after about 15 min. and heating was continued for an additional 10 min. The mixture was steam-distilled in order to drive off any unreacted amine. On cooling, the white crystals which precipitated were collected on a filter, washed twice with 50 ml. portions of alcohol, and dried for 24 hr. at 60–70°. The total yield of the crude product, including a small amount obtained from the filtrate after it was concentrated to 80 ml., weighed 47 g. (91% based on the used 3-chloro-4-methylaniline). Further purification was not necessary for use in the next step. For the analysis, it was recrystallized twice from aqueous alcohol, washed twice with alcohol, and dried as above. There were obtained snow-white crystals which did not melt below 300°.

N-(3-Chloro-4-methylphenyl)glycinonitrile. A solution of 7.2 g. (0.11 mole) of potassium cyanide in 20 ml. of water was added to a hot solution of 25.7 g. (0.1 mole) of sodium *N*-(3-chloro-4-methylphenyl)aminomethanesulfonate in 50 ml. of water. The mixed solution was then refluxed for about 40 min. The crude product which separated as an oil at first and solidified on cooling, was filtered off, m.p. 54–58°, yield 16.4 g. (91%) after drying for several days at room temperature *in vacuo* and one day at 40°. Two recrystallizations from alcohol gave pure, fine needles, m.p. 62–63°.

N-(3-Chloro-4-methylphenyl)glycine. Method A. To a vigorously stirred solution of 28.2 g. (0.2 mole) of 3-chloro-4-methylaniline in 40 ml. of alcohol a solution of 13.5 g. (0.2 mole) of potassium cyanide in 35 ml. of water was added together with 1 g. of a 30% aqueous solution of potassium hydroxide. Then 16.2 g. (0.2 mole) of commercial formalin was added to the mixture. After the reaction mixture was refluxed for 6 hr. with stirring, it was steam-distilled until no oil came over. Recovery of 3-chloro-4-methylaniline amounted to 5.1 g. (18% of the used amine). The residual solution was concentrated to 50 ml. on a water bath treated with active carbon and filtered. After cooling, the filtrate was adjusted to a *p*H slightly below 4.0 with dilute hydrochloric acid (1:1) in order to complete the precipitation of the glycine. The oily product solidified on standing for several hours; the crude product, which was freed from moisture with efficient suction and by drying for 12 hr. at 60°, weighed 19.5 g. (60% based on the consumed amine), m.p. 122–123°. Recrystallization from aqueous alcohol afforded white needles melting at 125–126° with decomposition.

Method B. Purified *N*-(3-chloro-4-methylphenyl)glycinonitrile (3.6 g., 0.02 mole) was refluxed with 60 ml. of a 5% aqueous solution of sodium hydroxide for 3 hr. From the alkaline hydrolysate on cooling there separated 0.3 g. of white needles melting at 144–147°; after two recrystallizations from hot water the melting point was 152–153° with decomposition. This substance was shown to be identical with *N*-(3-chloro-4-methylphenyl)glycinamide by analysis and by mixed m.p.

Anal. Calcd. for $C_9H_{11}ClN_2O$: N, 14.09. Found: N, 14.1.

The glycine was precipitated from the filtrate in the manner described in the foregoing experiment. The crude product melted at 124–126°, yield 3.4 g. (86%). Recrystallization from aqueous alcohol gave needles melting at 125–127° (decomposition).

Anal. Calcd. for $C_9H_{10}ClNO_2$: N, 7.01. Found: N, 7.1.

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N-(3-Chloro-4-methylphenyl)glycinamide. A mixture of 3.6 g. (0.02 mole) of *N*-(3-chloro-4-methylphenyl)glycinonitrile and 60 ml. of a 1% aqueous solution of sodium hydroxide was heated at 94–95° for several minutes under vigorous stirring until ammonia began to be generated as detected by means of litmus paper. Heating was continued for an additional 20 min. The product separated from the cooled reaction mixture was contaminated with the unchanged nitrile. Repeated extraction with 20 ml. of hot water gave 2.6 g. (66%) of white needles melting at 142–145° (decomposition). Two recrystallizations from aqueous alcohol afforded a pure sample, m.p. 152–153° (decomposition). From the filtrate *N*-(3-chloro-4-methylphenyl)glycine was precipitated in the usual manner, yield 0.8 g. (20%).

The diethylamine salts of glycines were prepared by cautious addition of a little excess of the base to a solution of the purified acid in a small amount of alcohol. Products of high purity were obtained in one step. For analysis, they were recrystallized from a mixture of alcohol and diethylamine (1:1).

Acknowledgments. The author wishes to thank Dr. Keiiti Sisido (at present: Ben May Laboratory, University of Chicago) and Dr. Hitosi Nozaki, both of Kyoto University, for their kind guidance. He also thanks Miss Kei Utida and Mr. Jiro Senda of our laboratory for the analyses.

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[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VII.[1] Azabicyclo[3.2.0]heptane Derivatives[2]

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March 1, 1957

Series of *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptane-2,4-dione have been prepared from the reaction of the appropriate primary amines and *cis*-1,2-cyclobutane dicarboxylic anhydride and cyclization of the resulting amic acids. The *N*-alkyl and *N*-dialkylaminoalkyl imides thus obtained were reduced to the corresponding *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptanes with lithium aluminum hydride. These bases were characterized as hydrochlorides, mono- and bis-methiodides and picrates. The bis-quaternary salts derived from the 3-azabicyclo[3.2.0]heptane nucleus with a dialkylaminoalkyl side chain possessed hypotensive activity in cannulated dogs. The most favorable structure was one in which the number of methylene carbon atoms between the onium centers was 2 or 3 and the introduced quaternary group was a short chain alkyl group such as methyl or ethyl.

In a study of optimum ganglionic blockage in a series of *alpha, omega* symmetrically substituted bis-trimethylammonium compounds, Paton and Zaimis[5] have shown that for this type of compound the most desirable structure is one that contains 5 to 6 methylene carbon atoms between the positive centers. That this is not necessarily the case when the *alpha, omega* symmetrically substituted polymethylene chain bears bis-quaternary groups, part of which consists of a heterocyclic ring attached at the secondary amine ring nitrogen, has been shown by a comparison of several ring variations of the basic isoindole nucleus.[6] In the case of unsymmetrical bis-quaternary salts containing a large group at one of the quaternary centers and a trimethylammonium group on the other, it has turned out in most cases that a chain of 2 or 3 methylene carbon atoms between the nitrogen atoms gives the most favorable configuration when judged by the criteria of therapeutic index, minimum toxicity, and blood pressure lowering.

In continuation of our work in the synthesis of bis-quaternary salts containing a heterocyclic amine as one of the ammonium centers we have synthesized a series of compounds in which the azabicyclo[3.2.0] heptane nucleus is thus employed. The key starting material in our present investigations was *cis*-1,2-cyclobutane dicarboxylic anhydride. This anhydride was found to be readily accessible through the procedure of Buckman *et al.*[7] The bases prepared in these studise were obtained through the reaction of primary alkyl or dialkylaminoalkyl amines with the anhydride and proceeded through the amic acid, I, and imide, II, to the bases, III, as shown in Figure 1. The only example of any compound of this type previously re-

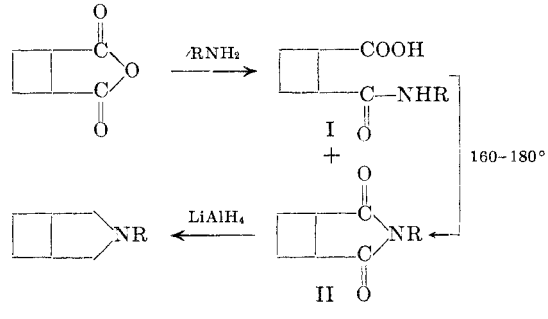

FIG. 1

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(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

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