TABLE II

$RR'C_6H_5OCH_2CH_2COOH$

RR'	Yield, %		M. p., °C.	Analyses, %			
	Phenol[g]	Sodium phenoxide[a]		Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H	14.8	18.1[b]	94–95	65.06	65.13	6.07	6.14
o-CHO	..	32.0	113–114	61.85	61.87	5.19	5.27
p-CHO	..	54.8	127–128	61.85	61.84	5.19	5.24
o-NO_2[c]	0.2	32.2	117–118	51.19	51.36	4.29	4.37
m-NO_2[c]	3.7	45.1	111–112	51.19	51.33	4.29	4.38
p-NO_2[c]	0.2	51.2	114–115	51.19	51.28	4.29	4.36
o-Cl[d]	0.4	49.9	112–113	53.87	53.99	4.52	4.55
m-C[d]	1.5	36.2	82–83	53.87	53.95	4.52	4.55
p-Cl[d]	4.5	28.9	134–135	53.87	54.00	4.52	4.53
2,4-di-Cl	..	51.4	91–92	45.98	46.11	3.43	3.45
o-Br[e]	..	52.2	109–110	44.10	44.15	3.70	3.72
p-Br[e]	..	29.9	142–143	44.10	44.17	3.70	3.76
o-OCH_3	0.8	20.2	127–128	61.21	61.38	6.17	6.18
m-OCH_3	3.9	24.0	81–82	61.21	61.22	6.17	6.13
p-OCH_3	11.6	11.5	106–107	61.21	61.35	6.17	6.16
o-C_6H_5	..	12.5	93–94	74.36	74.47	5.83	5.95
m-C_6H_5	..	19.0	136–137	74.36	74.42	5.83	5.89
p-C_6H_5	..	3.0	168–169	74.36	74.46	5.83	5.89
o-CH_3[f]	3.3	12.9	91–92	66.65	66.69	6.71	6.73
m-CH_3[f]	4.4	16.8	104–105	66.65	66.72	6.71	6.76
p-CH_3[f]	14.4	14.7	144–145	66.65	66.64	6.71	6.74
3,5-di-CH_3	..	16.2	86–87	68.02	68.06	7.27	7.25
o-C_6H_{11}	..	3.4	89–90	72.55	72.59	8.12	8.16
p-C_6H_{11}	..	11.6	115–116	72.55	72.67	8.12	8.12
p-*t*-C_4H_9	..	12.9	93–94	70.24	70.26	8.16	8.14
p-$CH_2C_6H_5$	..	14.4	133–134	74.98	75.07	6.29	6.31
p-$OCH_2C_6H_5$	..	13.1	147–148	70.57	70.52	5.92	5.89
2-OCH_3-4-C_3H_3	..	20.8	97–98	66.08	66.08	6.83	6.79
2-*i*-C_3H_7-5-CH_3	..	4.4	93–94	70.24	70.28	8.16	8.15

[a] % yields are for purified products. [b] Less than 1 g. of β-phenoxypropionic acid was lost due to water solubility when it was carried through the work-up procedure. Other reaction conditions and results were: The yield was not changed with increased time. The yield was lower (7.8%) at 50° in one hour and with less time it was still lower. Greater dilution (300 ml. water) gave decreased yield (16.9%). Increase in the ratio of sodium phenoxide to lactone (2:1) did not change the yield. [c] *Anal.* Calcd. for $C_9H_9O_5N$: N, 6.63. Found: N, *o*-, 6.62; *m*-, 6.57; *p*-, 6.59. [d] *Anal.* Calcd. for $C_9H_9O_3Cl$: Cl, 17.67. Found: Cl, *o*-, 17.60; *m*-, 17.67; *p*-, 17.59. [e] *Anal.* Calcd. for $C_9H_9O_3Br$: Br, 32.61. Found: Br, *o*-, 32.58; *p*-, 32.73. [f] Sodium phenoxide reactions at lower temperatures (30°) for one hour gave the following % yields with the cresols: *o*-, 5.0%; *m*-, 7.0%; *p*-, 5.8%. Although the yields of β-cresoxypropionic acids are lower, the ratio of yields is similar to that at 100°. [g] A above; six hours, 100°.

for an additional hour. The crystals which separated after acidification with 100 ml. of concentrated hydrochloric acid were filtered, washed with water, dried and recrystallized from ether–petroleum ether, m.p. 57–58°; yield, 166 g. (91%). The mixture melting point with the above sample was not depressed.

Summary

β-Propiolactone reacts with phenol to give β-phenoxypropionic acid. In the presence of acid catalysts phenyl hydracrylate is formed. It reacts with sodium phenoxide to give sodium β-phenoxypropionate. The effects of nuclear substituents on these reactions are described. Thiophenol and its sodium salt react more rapidly but give similar products in higher yields.

BRECKSVILLE, OHIO RECEIVED JULY 10, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Carbon Alkylations with 1-Methylgramine and its Methiodide[1]

BY H. R. SNYDER AND ERNEST L. ELIEL[2]

In previous papers,[3] alkylations of sodium cyanide and acetamidocyanoacetic ester with the methiodide (I) of 1-methylgramine (II) have been described. These alkylations, which proceed much more readily than corresponding reactions of quaternary salts of benzyldimethylamine,[4,5] undoubtedly occur by a substitution mechanism. However, their existence does not constitute proof that the Mannich base itself (II), as well as the quaternary ammonium salt (I), is capable of reacting by any mechanism other than the elimination-addition scheme[3a] proposed for gramine.

Further experiments have now been undertaken to elucidate this point. The alkylation reactions of the methiodide (I) have been extended to ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate, and tricarbethoxymethane, all of which were alkylated in the form of the sodium salts. The intermediate esters were not isolated but were hydrolyzed to the substituted malonic acid (III). Decarboxylation of this acid, either thermally or in refluxing pyridine,[6] yielded 1-methylindole-3(β)-propionic acid (IV). In view of the allylic rearrangement observed in the alkylation of sodium cyanide with the salt (I),[3b] an unequivocal proof of the structure of IV was considered necessary. The structure was proved by a Curtius degradation *via* the methyl ester, hydrazide, and azide of IV; the azide was subjected to rearrangement in dry xylene, and the resulting isocyanate was converted directly into N-phthalyl-1-methyltryptamine by baking it with phthalic anhydride. The phthalimide thus obtained was identical with an authentic specimen. The possibility still exists that in

---

(1) Presented in part before the Organic Division of the American Chemical Society at the Chicago meeting in April, 1948.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) (a) Snyder and Eliel, THIS JOURNAL, **70**, 1703 (1948); (b) **70**, 1857 (1948); (c) **70**, 3855 (1948).

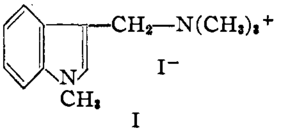
(4) von Meyer, *Abhandl. math.-phys. Klasse sächs. Akad. Wiss.*, **31**, 179 (1908); *Chem. Zentr.*, **80**, II, 1800 (1909).

(5) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

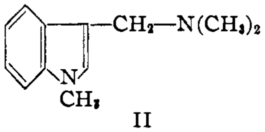
(6) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2609 (1942).

the alkylations with ethyl malonate and ethyl cyanoacetate small amounts of rearrangement products accompanying the major product (III) may have escaped detection, but in the other two alkylations the crude product (III) had essentially the same melting point as an analytically pure specimen, indicating that it was quite homogeneous.

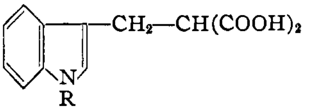
Alkylations by 1-methylgramine (II) itself were found to proceed with ethyl cyanoacetate, ethyl acetamidomalonate, and tricarbethoxymethane. From an attempted alkylation of sodium cyanide in refluxing aqueous alcohol no neutral products could be obtained; 92% of the base (II) was recovered. Gramine under the same conditions yields indole-3-acetamide and indole-3-acetic acid.[7] The alkylation products from ethyl cyanoacetate and tricarbethoxymethane were identified by hydrolysis to the malonic acid (III). The product from ethyl acetamidomalonate was identified by hydrolysis and decarboxylation to N-acetyl-1-methyltryptophan.[3c] Some of the alkylation reactions were carried out in the presence of a trace of the sodium salt of the active methylene compound, and some without any added base. In one case (cyanoacetic ester) in which the reaction was carried out both with and without the sodium salt, it was noted that the presence of the sodium salt retards the speed of the reaction considerably and seems to have no appreciable effect on the yield of the alkylation product. Thus there seems to be some indication that the alkylation reaction is acid-base catalyzed.



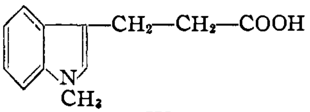
I



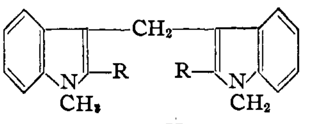
II



III R = CH$_3$
V R = H



IV



VI R = H
VII R = —COOH

Even with tricarbethoxymethane, which gave the highest yield of alkylation product, the overall yield of IV was only about 25%, while in a comparison experiment with gramine, skatylmalonic acid (V) was obtained in a yield of 67%. The yields from the other two alkylations were of the order of 15% and compare very unfavorably with the yields of the corresponding alkylation products from gramine.[5,8] Any explanation of the mechanism of the alkylation reaction must take this difference into account, but the fact that 1-methylgramine does act as an alkylating agent suggests that the elimination-addition mechanism[3a] is not *necessarily* the path of alkylations with Mannich bases of the gramine type.

The reactions of ethyl cyanoacetate and ethyl acetamidomalonate with II produced as a by-product (12–15% yield) a crystalline substance, the analysis of which indicated that it might be 1,1′-dimethyl-3,3′-diindolylmethane (VI). That the by-product is VI was proved by an unequivocal synthesis from α,α'-diketopimelic acid and *unsym*-methylphenylhydrazine; treatment of the dihydrazone of the diketo acid with hydrochloric acid (Fischer synthesis) yielded the dicarboxylic acid (VII) which was decarboxylated to VI in refluxing quinoline. A simpler, but less unequivocal synthesis of VI consists in the condensation of methylindole and formalin in the presence of acetic acid, which yields over 90% of VI.[9] The formation of VI from 1-methylgramine (II) involves a reversal of the Mannich reaction. Similar reactions are known in the case of phenolic Mannich bases, which undergo self-alkylation when treated with boiling dilute sodium hydroxide.[10] The self-alkylation of 1-methylgramine, however, does not seem to be brought about by base alone. The base II was recovered to the extent of 70% or more after prolonged heating at 225° in the presence of sodium methoxide and metallic sodium with or without the addition of an equal weight of 1-methylindole, and none of the condensation product VI could be isolated from these reactions. However, methylgramine *acetate* yielded 66% of the coupling product (VI) when refluxed in aqueous solution for one hour. Thus the self-condensation of 1-methylgramine appears to be acid-base catalyzed. Similar self-alkylations of other indole derivatives of the Mannich base type have been reported in the literature.[11]

Methylgramine methiodide (I) also underwent self-alkylation to VI when refluxed with aqueous sodium hydroxide or sodium acetate. In this case the formation of formaldehyde was demonstrated by its odor and by conversion to its methone derivative. Two experiments were devised to obtain evidence as to whether self-alkylation consists in a reverse Mannich reaction of part of the methiodide

---

[7] Snyder and Pilgrim, *ibid.*, **70**, 3770 (1948); Salzer, "Verfahren zur Darstellung substitutierter Essigsaueren," Department of Commerce. U. S. Publication Board PB 706.

[8] Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

[9] 1-Methylindole reacts with benzaldehyde at 100° in the presence of catalytic amounts of zinc chloride; the product is assumed to be 1,1′-dimethyl-3,3′-diindolylphenylmethane, but its structure has not been proved [Fischer, *Ber.*, **19**, 2988 (1886); *Ann.*, **242**, 372 (1887)].

[10] Auwers and Dombrowski, *Ann.*, **344**, 280 (1906).

[11] Passerini, *et al.*, *Gazz. chim. ital.*, **63**, 138 (1933); **65**, 933 (1935); Neri, *ibid.*, **64**, 420 (1934).

(I) followed by alkylation of the methylindole so formed by more of the quaternary salt (I), or whether two molecules of the methiodide couple and subsequently lose the elements of formaldehyde and trimethylamine. In one experiment a mixture of the quaternary salt (I), water, and sodium hydroxide was steam distilled in the hope of removing methylindole before it had an opportunity to react. However, no methylindole was found in the steam distillate. In another experiment, the methiodide (I), methylindole, and sodium hydroxide were refluxed in aqueous alcohol. The high yield of the product VI (98% of practically pure material if calculated on the basis of the methiodide alone) and the low recovery of methylindole make it almost certain that part of the methylindole was alkylated, but the evidence is not quite conclusive.

When the methiodide or the hydrochloride of 1-methylgramine was refluxed with water alone, an oily product soon separated and solidified on cooling; the solution contained free formaldehyde, as shown by the methone test. However, no homogeneous indole derivative could be isolated from this reaction.

Experimental[12,13]

Reaction of Methylgramine Methiodide (I) with Sodiomalonic Ester.—Sodium (0.23 g., 0.01 atom) was dissolved in 8 g. of ethyl malonate at 80° in a two-necked flask equipped with a stirrer and an air-cooled condenser protected by a soda-lime tube. Three and three-tenths grams of I (0.01 mole) was added, the temperature was raised to 130–140°, and the mixture was stirred for ten hours. Trimethylamine was given off. At the end of the reaction period gas evolution had practically ceased. Stirring was continued for two hours at 140–150°. A solution of 10 g. of potassium hydroxide in 100 ml. of 80% ethanol was then added and the solution was refluxed for four and one-half hours. Fifty milliliters of water was added and most of the alcohol was distilled. The residual solution was decanted from some resin, boiled with Norite, filtered, and acidified with hydrochloric acid. An oily precipitate, which solidified on standing in the ice box overnight, was obtained. It was collected and dissolved in sodium bicarbonate solution and the solution was boiled with Norite, filtered with suction, acidified, and chilled as before. The brown solid (III) was collected, washed with water and dried; wt. 0.55 g. (22%), m. p. 165.5–167.5° (dec.). Repeated washings with chloroform and recrystallization from ethyl acetate-petroleum ether (b. p. 30–60°) raised the melting point to 172.5–173° (dec.).

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.14; H, 5.30. Found: C, 63.29, 63.55; H, ——, 5.48.

When absolute ethanol was employed as a solvent in the alkylation, the yield of III was essentially the same but the product was less pure.

Reaction of Methylgramine Methiodide (I) with Sodiocyanoacetic Ester.—Sodium (0.34 g., 0.015 atom) was dissolved in 8.4 g. (0.075 mole) of ethyl cyanoacetate. Five grams (0.015 mole) of I was added and the suspension was stirred at 125° for twelve hours. A solution of 15 g. of potassium hydroxide in 75 ml. of 80% ethanol was added and the mixture was refluxed for eleven hours. It was worked up as described for the reaction with sodiomalonic ester. The product was partly crystalline and partly resinous. The crystals weighed 0.65 g. (17.5%) and melted at 159–160° (dec.); two recrystallizations raised the melting point to 170–171° (dec.) and the mixed melting point with the product from malonic ester was 172–172.5° (dec.). The resinous part crystallized after several weeks and melted at 135–145° (dec.), weight 1.7 g.

Reaction of Methylgramine Methiodide (I) with Ethyl Cyanomalonate Sodium Salt.—A solution of 3.3 g. of I (0.01 mole) and 2.1 g. (0.01 mole) of ethyl cyanomalonate sodium salt[14] in 20 ml. of water was refluxed for one hour. There was a vigorous evolution of trimethylamine, and a viscous oil separated. The aqueous layer was decanted, filtered from a little solid material, and extracted with ether. The ether extract, the solid collected and the oily residue were combined and the ether was removed in a current of air. The residue was refluxed for six hours with 25 ml. of 10% aqueous sodium hydroxide solution. The solution was cooled, decanted from some resinous material, boiled with Norite, filtered with suction and acidified with hydrochloric acid. A crystalline precipitate appeared. The solution was chilled, and the precipitate was collected, washed with ice water and dried. There was obtained 1.25 g. (51%) of a light pink powder of m. p. 172–173° (dec.); the mixed melting point with III was 172–173° (dec.).

The use of absolute alcohol as a solvent in this alkylation did not affect the yield and quality of the product.

Reaction of Methylgramine Methiodide (I) with Tricarbethoxymethane Sodium Salt.—To a solution of 0.23 g. (0.01 atom) of sodium in 30 ml. of absolute alcohol were added 4.65 g. (0.02 mole) of tricarbethoxymethane[15] and 3.3 g. (0.01 mole) of I. The mixture was refluxed for one and one-half hours while a current of nitrogen was passed over it. There was a vigorous evolution of trimethylamine. Ten milliliters of 40% aqueous sodium hydroxide was added, followed, after ten minutes, by 10 ml. of water, while refluxing was continued. Trimethylamine evolution resumed for a short time. After two and one-fourth hours heating was discontinued, and the solution was concentrated *in vacuo*, extracted twice with ether, acidified with concentrated hydrochloric acid and chilled. Brown crystals separated. They were collected and dissolved in 15 ml. of a saturated solution of sodium carbonate and 25 ml. of water. The solution was boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid, and chilled. After having been thoroughly washed with ice water and dried, the light pink crystals (III) weighed 1.55 g. (62.5%), m. p. and mixed m. p. 171–172° (dec.).

When the alkylation was carried out in aqueous medium, the yield was only 34.5%.

Decarboxylation of III.—(a) Thermal: Fairly pure III of m. p. 165.5–167.5 (0.550 g.) was heated in an oil-bath at 180–190° until gas evolution ceased (about five minutes). The product was distilled in a short-path apparatus at 0.4 mm., bath temperature 150°. The yield of IV was 0.300–0.325 g. (67–72%), m. p. 123–125°. Recrystallization from benzene gave white platelets, m. p. 125.5–126°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.28; H, 6.65; N, 6.95.

When impure III (melting point around 140°) was decarboxylated, pure IV was obtained by sublimation, but the yield dropped to 38%.

(b) In Pyridine: Two grams of pure III was refluxed for twenty minutes in 20 ml. of pyridine. The pyridine was distilled *in vacuo*, and 20 ml. of 1:4 hydrochloric acid was added to the residue, which then crystallized promptly. The crystals were collected, washed with water, and dried; weight 1.47–1.56 g. (89.5–94.5%), m. p. 120.5–123.5°. Recrystallization from benzene raised the melting point to 124–126°.

Curtius Degradation of IV.—(a) Methyl Ester of IV: To 0.624 g. of IV dissolved in 30 ml. of ether was added an

---

[12] All melting points are corrected.

[13] Microanalyses by Miss Emily Davis, Mrs. Jane Wood and Mr. Howard Clark.

[14] Haller, *Ann. chim.*, [6] **16**, 426 (1889). The authors are indebted to Mr. George Segre of the division of chemical engineering for a sample of this compound.

[15] Lund and Voigt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 594.

ethereal solution of diazomethane prepared from 2 g. of nitrosomethylurea.[16] There was an immediate evolution of nitrogen. The solution was allowed to stand for two hours, then a solution of glacial acetic acid in ether was added dropwise until the excess diazomethane was destroyed, as shown by decolorization of the solution. The ethereal solution was extracted twice with small portions of 10% sodium carbonate solution, which were then extracted with about 50 ml. of ether in a second separatory funnel. The ethereal solutions were washed with water, combined, dried over sodium sulfate and distilled. A viscous oil resulted which would not crystallize. It was distilled in a two-bulb microdistillation apparatus at 0.25 mm., bath temperature 180–190°, to yield 0.58 g. (83.5%) of a light yellow oil.

The picrate crystallized in dark red needles from methanol, melting point 98–99°.

Anal. Calcd. for $C_{19}H_{18}O_9N_4$: C, 51.12; H, 4.06. Found: C, 51.25; H, 4.33.

(b) Hydrazide of IV: A solution of 0.40 g. of the above ester in 4 ml. of methanol was refluxed for twenty hours with 0.75 ml. of 85% hydrazine. On concentration of the solution the hydrazide crystallized. It was collected, washed with aqueous methanol and dried. The yield was 0.32 g. (80%), m. p. 135.5–136.5°. Recrystallization of a sample from benzene containing a little absolute ethanol yielded fine white needles of melting point 136.5–137.5°.

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.32; H, 6.97. Found: C, 66.28; H, 6.81.

(c) **N-Phthalyl-1-methyltryptamine.**—Two milliliters of a solution of 0.6 ml. of concentrated hydrochloric acid in 10 ml. of water was cooled to 10° and there was added to it, in succession, 0.175 g. of the above hydrazide, 2 ml. of ether, and 0.2 ml. of a 37.5% solution of sodium nitrite in water. After thorough shaking, the layers were separated, and the aqueous layer was twice more extracted with small portions of ether. The ether layers were washed with sodium bicarbonate solution followed by water; they were then combined and dried over calcium chloride. Five milliliters of xylene was added and the ether and part of the xylene were distilled *in vacuo*. The xylene solution was then refluxed for a short time, 0.2 g. of phthalic anhydride was added, and refluxing was continued for a total of two hours. The xylene was distilled and the residue was heated to 240°. It was then allowed to cool somewhat and 3 ml. of ethanol was added. The tan crystals which appeared when the solution was cooled weighed 0.050 g. After one recrystallization the derivative melted at 172–175°. Two further recrystallizations from the same solvent raised the melting point to 174.5–176.5°. The mixed melting point with an authentic sample of the phthalimide[3a] of melting point 176.5–177° was 176–176.5°. The two samples were indistinguishable under the microscope and their infrared spectra were essentially identical.[17]

Reaction of 1-Methylgramine (II) with Cyanoacetic Ester.—In the presence of sodium: To a solution of 3.8 g. (0.02 mole) of 1-methylgramine in 6.8 g. (0.06 mole) of ethyl cyanoacetate 25 mg. of sodium was added and the mixture was heated at 150° for twenty-four hours in a flask equipped with a short air condenser. Additional 25-mg. portions of sodium were added at the end of five and eighteen hours. A basic gas was evolved. When the gas evolution had ceased at the end of twenty-four hours, the reaction mixture was cooled and 50 ml. of 1 *N* hydrochloric acid was added. The mixture was extracted twice with 70-ml. portions of ether. No unchanged methylgramine was recovered when the aqueous layer was made alkaline. The ether layers were washed twice with water, combined, dried over sodium sulfate, and the solvent was distilled. The residue was hydrolyzed by refluxing overnight with a solution of 10 g. of potassium hydroxide in 50 ml. of 80% ethanol. Forty milliliters of water was then added and most of the ethanol was distilled. The residue was extracted with ether, boiled with Norite, filtered with suction, acidified with hydrochloric acid and chilled. The acid was partly resinous and partly crystalline. The crystals were collected, washed, and dried; weight 0.2 g., m. p. 164.5–165.5° (dec.). Three recrystallizations raised the melting point to 171.5–172° (dec.); the mixed melting point with III was 172–172.5 (dec.). Decarboxylation of the acid yielded IV, identified by melting point and mixed melting point. The resinous part crystallized after standing in the ice box for several weeks; weight 1.3 g., m. p. 139.5–147.5° (dec.). The over-all yield of very impure material was 1.5 g. (30%), which corresponds to about 15% of pure material, as shown by the fact that the low-melting material gave a 38% yield of IV upon decarboxylation.

The ether solution containing the unsaponifiable reaction products was distilled to give a brown residue, which recrystallized on standing. Recrystallization from 95% ethanol yielded 0.3 g. of crystals of melting point 92–96°. Four more recrystallizations from 95% ethanol (Norite was used in the second) gave pure 1,1′-dimethyl-3,3′-diindolylmethane (VI) melting at 109.5–111.5°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.16; H, 6.61; N, 10.21. Found: C, 83.06, 83.06; H, 6.60, 6.75; N, 10.31, 10.19.

The dipicrate was obtained by dissolving the parent substance in benzene, adding an excess of a saturated solution of picric acid in benzene, allowing the solution to evaporate, and digesting the residue with absolute ethanol to remove excess picric acid. The material was recrystallized from benzene–petroleum ether (b. p. 30–60) as dark red crystals melting at 112–113°.

Anal. Calcd. for $C_{31}H_{24}N_8O_{14}$: C, 50.81; H, 3.30. Found: C, 51.05; H, 3.43.

Without sodium: A solution of 3.8 g. (0.02 mole) of II and 3 g. (0.03 mole) of methyl cyanoacetate was heated at 135–150° for two hours. There was a very vigorous evolution of a basic gas, which practically ceased at the end of one and one-half hours. The reaction product was hydrolyzed by refluxing it overnight with a solution of 6 g. of potassium hydroxide in 50 ml. of water. The solution was cooled, decanted from undissolved material, extracted with ether, boiled with Norite, filtered with suction and acidified. A dark oil separated which solidified on standing in the ice box for several days. It was collected, washed with water and dissolved in acetone (there was no acetone-insoluble material). The acetone was distilled and the residue was decarboxylated by heating it at 180–190° until no more gas was given off. The decarboxylated acid was evaporatively distilled at 0.1 mm., bath temperature 135–205°. There was obtained 1.24 g. of crystals of m. p. 101–115°. Recrystallization from benzene yielded 0.71 g. (17.5%) of IV, m. p. and mixed m. p. 124.5–126°. No further amount of pure material could be recovered from the mother liquors.

The neutral residue of the saponification was taken up in ethyl acetate and added to the ether extract of the alkaline saponification mixture. The combined solutions were dried over sodium sulfate and concentrated. The addition of alcohol to the concentrate yielded 0.225 g. of crystals (VI); m. p. 106.5–110.5°; there was no depression in melting point when the crystals were mixed with the analytical sample obtained as described above. The mother liquors yielded a second crop weighing 0.035 g. of m. p. 105.5–109°; total yield 0.260 g. (9.5%).

Reaction of 1-Methylgramine (II) with Acetamidomalonic Ester.—A solution of 3.8 g. (0.02 mole) of II, 8.7 g. (0.04 mole) of ethyl acetamidomalonate and *ca.* 25 mg. of sodium was heated under nitrogen for twenty-four hours at 115–120° and for fifteen hours at 140–145° in a flask equipped with a short air condenser. A basic gas was evolved. The solution was cooled and the resulting syrup was taken up in 60 ml. of ether and extracted with 1 *N* hydrochloric acid. When the aqueous extract was made alkaline, no methylgramine was liberated. The

---

[16] Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166.

[17] The authors are indebted to Mrs. Agatha Johnson for the absorption studies.

ether solution was washed with water, dried over sodium sulfate, and concentrated. The residual amber sirup could not be crystallized. It was hydrolyzed by refluxing for three hours with 7 g. of potassium hydroxide in 7 ml. of water and 63 ml. of 95% ethanol. Thirty-five milliliters of water was added and most of the ethanol was distilled. The aqueous solution was extracted twice with 50-ml. portions of ether, boiled with Norite, filtered with suction, acidified with hydrochloric acid and chilled. A partly crystalline and partly resinous precipitate resulted. The crystalline material (presumably the alkylated acetamidomalonic acid) was collected, washed, and dried; it weighed 0.23 g. (3.8%). It was recrystallized once from absolute ethanol–acetone–benzene–petroleum ether and melted at 110.5–111.5° (dec.); it was not further purified.

When 40 mg. of this material was refluxed with *ca.* 3 ml. of water for four hours, white crystals of melting point 171–172° separated on cooling. The mixed melting point with N-acetyl-1-methyltryptophan[30] was 171–172.5°.

The resinous part of the malonic acid was collected by decantation and washed with water. It was refluxed with water for three and one-half hours and filtered to remove some resin. On cooling, the filtrate deposited tan crystals which were collected and dried; weight 0.40 g. (7.7%), m. p. 166.5°. Recrystallization from acetone–benzene (Norite) raised the melting point to 169–171°; the mixed melting point with N-acetyl-1-methylptryptophan was 169.5–171°.

The ether solution containing the unsaponifiable reaction products was concentrated and the residue was crystallized from 95% ethanol (Norite) to yield 0.25 g. of crystals (VI) of melting point 107.5–111° and 0.15 g. of impure material. Recrystallization from petroleum ether (b. p. 60–90°) raised the melting point to 108.5–111°. The mixed melting point with the neutral material obtained from the ethyl cyanoacetate reaction was 108.5–111°.

An attempt was made to condense II with acetamidomalonic ester in boiling xylene in the presence of sodium hydroxide,[8] but no crystalline materials could be obtained from the condensation under these conditions.

Reaction of 1-Methylgramine (II) with Tricarbethoxymethane.—A solution of 3.8 g. (0.02 mole) of II in 10.8 g. (0.05 mole) of tricarbethoxymethane[14] was heated under nitrogen at 160–170° for three hours. A basic gas was evolved. A solution of 20 g. of potassium hydroxide in 20 ml. of water and 160 ml. of 95% ethanol was added and the mixture was refluxed for six hours. One hundred and sixty milliliters of water was added and most of the ethanol was distilled. The solution was cooled, extracted with ether, boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid, and allowed to stand in the ice box for five days. The precipitate was partly crystalline and partly resinous. The crystals were collected, washed and dried; weight 0.51 g., m. p. and mixed m. p. (with III) 165.5–168° (dec.). Much of the non-crystalline portion dissolved in acetone, leaving 0.30 g. of crystals, apparently the mono-potassium salt, which melted around 250° after darkening around 200°. The crystals were dissolved in water (in which they were readily soluble) and hydrochloric acid was added to the solution. There was obtained 0.22 g. of crystals of melting point 173–175° (dec.); mixed m. p. with III 171–172° (dec.). The total yield of III was 0.73 g. (15%).

The acetone wash was concentrated, and the resinous residue was decarboxylated at 180–190° and sublimed at 0.1 mm. The sublimate was dissolved in sodium carbonate solution; the solution was extracted twice with ether, boiled with Norite, filtered, acidified, and chilled. It yielded 0.34 g. (8.5%) of crystals of IV; melting point and mixed melting point 122.5–124.5°.

Attempted Reaction of 1-Methylgramine (II) with Sodium Cyanide.—A solution of 3.8 g. of II and 5 g. of sodium cyanide in 10 ml. of water and 40 ml. of 95% ethanol was refluxed for eighty-four hours. Part of the ethanol was distilled, 50 ml. of water was added, and the emulsion was twice extracted with 100-ml. portions of ether.

The aqueous portion was boiled with Norite, filtered, and acidified with concentrated hydrochloric acid (hood!). There was no separation of organic material.

The ether layers were washed once with water, extracted with three 25-ml. portions of 1 *N* hydrochloric acid, washed with water, dried, and distilled. The residue weighed less than 0.1 g.

The acid layer was made alkaline with 10% sodium hydroxide, and extracted twice with 50-ml. portions of ether. After having been dried, the ether was distilled from 3.5 g. of 1-methylgramine (92% recovery) identified by its picrate (melting point 145.5–146°, mixed melting point 145.5–146.5°).

Reaction of Gramine with Tricarbethoxymethane.—A solution of 3.5 g. (0.02 mole) of gramine in 10.8 g. (0.05 mole) of tricarbethoxymethane[14] was heated under nitrogen at 115–120° for an hour and at 125–130° for an hour. There was a vigorous evolution of a basic gas, which ceased at the end of the heating period. Hydrolysis was effected by refluxing the product for six hours with a solution of 20 g. of potassium hydroxide in 20 ml. of water and 160 ml. of 95% ethanol. One hundred and forty milliliters of water was added and most of the ethanol was distilled. The solution was filtered, extracted with ether, boiled with Norite, filtered with suction and acidified with concentrated hydrochloric acid. After one week in the ice box the solution had deposited crystals which were collected, washed with ice water and dried; weight 1.26 g., m. p. 165.5–167.5° (dec.). Concentration of the mother liquors in a current of air led to the separation of a second crop; weight 1.79 g., m. p. 160–163° (dec.). The total yield was 3.05 g. (67%). Recrystallization from water (Norite) raised the melting point to 175.5–177° (dec.) [(lit.[5] 178° (dec.); lit.[18] 188–189° (dec.)].

Decarboxylation in Pyridine: The above acid (V) (0.60 g.) was decarboxylated in exactly the same manner as described for the acid III. There was obtained 0.38 g. (78%) of indole-3(β)-propionic acid, m. p. 129.5–132.5°. Recrystallization from water raised the melting point to 133–134° (lit.[5] 132–133°, lit.[18,19] 134°).

1,1′-Dimethyl-2,2′-dicarboxy-3,3′-diindolylmethane (VII).—Methylenebisoxalacetic ester was obtained from oxalacetic ester and formaldehyde by the method of Blaise and Gault.[20] To convert it into α,α'-diketopimelic acid, 28 g. of the hydrate of methylenebisoxalacetic ester, 28 ml. of water and 12 ml. of concentrated hydrochloric acid were refluxed until the solution had become homogeneous (one hour). The solution was neutralized with 10% aqueous sodium hydroxide and then acidified slightly with a few drops of glacial acetic acid. The addition of 6 ml. of *unsym*-methylphenylhydrazine in 25 ml. of water containing sufficient glacial acetic acid to make a homogeneous solution caused the separation of a dark oil. The mixture was allowed to stand for two hours, the aqueous phase was decanted, and the residue was washed once with water by decantation. The water layers were extracted with ether, and the ether layer was combined with the water-insoluble oil. The ether was removed in a current of air, and the residue was swirled on the steam-bath with 45 ml. of water and 15 ml. of concentrated hydrochloric acid until it had solidified and then for five minutes longer. The suspension was chilled and the solid was collected. It was then dissolved in a slight excess of 5% aqueous sodium hydroxide. The aqueous solution was extracted with ether, boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid and chilled. Slightly tan crystals separated. They were collected, washed with ice-water and dried; weight 2.5 g. (40%), m. p. 202–203.5° (dec.). Four recrystallizations from acetone–alcohol raised the melting point to 227–228° (dec.).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.58; H, 5.01; N, 7.73. Found: C, 69.71; H, 5.30; N, 7.92.

1,1′-Dimethyl-3,3′-diindolylmethane (VI).—From VII: A solution of 0.250 g. of VII (m. p. 226–227°) in 2.5

---

[18] Maurer and Moser, *Z. physiol. Chem.*, **161**, 131 (1926).

[19] Ellinger, *Ber.*, **38**, 2884 (1915).

[20] Blaise and Gault, *Bull. soc. chim.*, [4] **1**, 78 (1907).

ml. of distilled quinoline was refluxed for ten minutes. It was cooled and taken up in *ca.* 25 ml. of ether. The ether solution was washed five times with 10-ml. portions of 1 *N* hydrochloric acid, five times with 5-ml. portions of 2.5% sodium hydroxide and twice with water. It was dried over sodium sulfate, the solvent was distilled, and the residue was crystallized from 95% ethanol. There was obtained 0.045 g. (20%) of white crystals; melting point 107.5–110°. Recrystallization from 95% ethanol raised the melting point to 109.5–111.5°. The mixed melting point with the material obtained in the alkylation reactions (described above) was the same, and the two samples had the same crystalline aspect under the microscope.

1,1′-Dimethyl-3,3′-diindolylmethane is very sensitive to both air and acids. When exposed to the atmosphere it turns pink. Ordinary Darco could not be used to decolorize solutions of VI, as it turns them bright red. Ammonia washed Darco was found satisfactory for decolorization purposes.

From Methylindole.—To 1 ml. (1.07 g.) of methylindole dissolved in 2 ml. of glacial acetic acid, 1 ml. of 40% aqueous formalin was added, and the reagents were mixed by shaking. The mixture warmed up and after a few minutes became heterogeneous and crystallized in part. The crystals were collected, and the non-crystalline, viscous portion was treated with a mixture of 95% ethanol and ethyl acetate, whereupon it also crystallized. The combined crystals were washed with 95% ethanol and dried. By reworking the mother liquors a total yield of 1.05 g. (94%) of VI of melting point 100.5–108.5° was obtained. Two recrystallizations from 95% ethanol (with ammonia-washed Darco in the first) raised the melting point to 108.5–110.5°. The mixed melting point with samples obtained by other methods (see above) was the same.

From I.—(a) A solution of 3.3 g. of I and 5 g. of the trihydrate of sodium acetate in 25 ml. of water was refluxed for three hours. Trimethylamine was evolved. The emulsion was cooled and extracted with ether. The ether layer was dried and concentrated and the residual oil was crystallized from 95% ethanol containing a little ethyl acetate. The crystals were collected, washed with 95% ethanol and dried; weight 1.19 g. (87%), m. p. 93–105.5°. Recrystallization from ether–petroleum ether (b. p. 30–60°) followed by two recrystallizations from 95% ethanol raised the melting point to 108.5–111.5°. There was no depression of melting point on admixture with samples of VI obtained by other methods.

Formaldehyde was identified in the aqueous layer by its odor and by the melting point of its methone derivative obtained by adding an alcoholic solution of methone to the aqueous layer; melting point and mixed melting point 190.5–191.5°.

(b) A solution of 3.3 g. of I and 1.5 ml. of 40% aqueous sodium hydroxide in 18.5 ml. of water was steam distilled for one hour. The distillate did not have the odor of methylindole. It was extracted with ether, and the ether was dried over sodium sulfate and distilled. There was a small amount of viscous residue which had none of the properties of 1-methylindole.

The residue, which contained a water-insoluble oil, was extracted with ethyl acetate. The ethyl acetate solution was concentrated by evaporation until crystals began to form; 95% ethanol was then added, and the mixture was chilled. The crystals were collected, washed with cold 95% ethanol, and dried; weight 0.87 g. (63.5%), m. p. 107.5–110°.

(c) A solution of 3.30 g. (0.01 mole) of I, 1.31 g. (0.01 mole) of 1-methylindole and 1.5 ml. of 40% aqueous sodium hydroxide in 7.5 ml. of water and 17.5 ml. of 95% ethanol was refluxed for six hours. The mixture was then steam distilled until the odor of methylindole in the residue was very faint. The distillate was extracted with ether and the ether was dried and distilled. The residue, after brief drying at 100° and 15 mm. pressure, weighed 0.64 g. It was distilled at 15 mm., air-bath 140–160°. The distillate was somewhat impure 1-methylindole (n^{20}_D 1.6029, melting point of crude picrate[21] 135.5–138.5°) and weighed 0.53 g. (40.5% recovery). There was a distillation residue of 0.06 g.

The residue of the steam distillation was extracted with ethyl acetate and worked up as described before; yield 1.34 g. of VI (98% if based on I alone), m. p. 107–110°. When the experiment was repeated, the yield was 1.28 g. of material of melting point 108.5–110.5° and 0.08 g. of melting point 102.5–107.5°.

When the alcoholic mother liquor was evaporated to dryness, and the residue was dried *in vacuo* (15 mm.) at 100°, 0.81 g. of a viscous oil remained. This oil was only very slightly soluble in cold 95% ethanol and could therefore not have contained much 1-methylindole.

(d) A solution of 1.12 g. (0.005 mole) of methylgramine hydrochloride[22] and 0.68 g. (0.005 mole) of sodium acetate trihydrate in 10 ml. of water was refluxed for one hour. The resulting mixture had a strong formaldehyde odor and contained an oil which crystallized on cooling. The solid was extracted with ethyl acetate, and the ethyl acetate extract was dried over sodium sulfate and evaporated in a current of nitrogen. The concentrate crystallized. Ethanol was added to it and the crystals were collected, washed with 95% ethanol and dried; weight 0.45 g. (66%), melting point and mixed melting point with samples obtained by other routes, 110–112°.

When the aqueous layer of the reaction mixture was made alkaline, some unchanged methylgramine separated and a basic gas (presumably dimethylamine) was liberated.

When a solution of 0.6 g. of methylgramine and 0.44 g. of sodium acetate trihydrate in 10 ml. of 50% ethanol was refluxed for one hour, there was no noticeable evolution of formaldehyde or dimethylamine, and no neutral material was formed. Methylgramine (77%, isolated as the hydrochloride) was recovered.

Behavior of Methylgramine Methiodide and of Methylgramine Hydrochloride in Boiling Water.—One gram of I was refluxed for one hour with 10 ml. of water. An oil separated and solidified on cooling. It was collected and dried; weight 0.35 g., m. p. 77–99°. Attempts to obtain a homogeneous substance from this material failed. The water solution contained formaldehyde, identified by its methone derivative, melting point and mixed melting point 188.5–190.5°.

The hydrochloride of II under the same conditions yielded an intractable white solid of melting point 50–90°. The water solution contained formaldehyde, identified by its odor and methone derivative. When it was made alkaline, a basic gas of ammoniacal odor (presumably dimethylamine) was given off.

Thermal Stability of Gramine and of 1-Methylgramine. When gramine was heated above its melting point, dimethylamine was evolved copiously and a brown resin resulted.

Heating of 1-methylgramine (1 g.) in the presence of small amounts of sodium methoxide and metallic sodium at 150–155° for four hours, then at 215–225° for nine hours, and finally at 160° for twelve hours, yielded an oil which was almost entirely soluble in 1 *N* hydrochloric acid. Extraction of the acid solution with ether yielded only a trace of neutral material. When the acid solution was made alkaline and extracted with ether, there was recovered 0.7 g. (70%) of 1-methylgramine, identified by its picrate, melting point 138.5–143.5° and after recrystallization 144–145.5°.

Attempted Reaction of 1-Methylgramine (II) with 1-Methylindole.—One gram of II, 1 g. of 1-methylindole and a trace of sodium methoxide were heated for four hours at 150–155°, for nine hours at 215–225° and then for twelve hours at 160°. The oil was cooled and dissolved in ether. The ether solution was exhaustively ex-

---

[21] The melting point of the picrate of 1-methylindole recorded in the literature is 150°, but we have never obtained specimens melting higher than 143.5–144.5° from pure 1-methylindole.

[22] For details of the preparation of this hydrochloride see Snyder and Eliel, THIS JOURNAL, **70**, 4233 (1948).

tracted with 1 *N* hydrochloric acid. The neutral products, obtained by distillation of the ether, weighed 0.77 g., were entirely soluble in cold petroleum ether, and yielded a picrate of melting point 141.5–143.5°, indicating that the material was practically pure 1-methylindole. The alkaline fraction, recovered by making the acid extract alkaline and extracting with ether, weighed 0.90 g. (90% recovery) and yielded a picrate of melting point 135.5–137.5°. Two recrystallizations from 95% ethanol raised the melting point to 140–141.5°; mixed melting point with the picrate of II, 144–145.5°.

Summary

The sodium salts of ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate and tricarbethoxymethane have been alkylated with 1-methylgramine methiodide. The highest yield (62.5%) of the substituted malonic acid was obtained by saponifying the alkylation product of tricarbethoxymethane. Decarboxylation of the substituted malonic acid in refluxing pyridine gave a 90% yield of 1-methylindole-3(β)-propionic acid, whose structure was proved by a Curtius degradation.

Ethyl cyanoacetate, ethyl acetamidomalonate, and tricarbethoxymethane have been alkylated with 1-methylgramine. The yields of alkylation products are consistently lower than in the case of corresponding alkylations with gramine.

As a by-product in the alkylations with 1-methylgramine, 1,1′-dimethyl-3,3′-diindolylmethane was obtained. The structure of this product has been proved by unequivocal synthesis. The same product was obtained from methylindole and formaldehyde in the presence of acetic acid, from 1-methylgramine methiodide and aqueous sodium hydroxide or sodium acetate, and from 1-methylgramine hydrochloride and aqueous sodium acetate.

1-Methylgramine was found to be much more stable to heat than gramine.

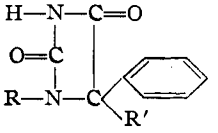
URBANA, ILLINOIS RECEIVED AUGUST 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO., DETROIT, MICHIGAN]

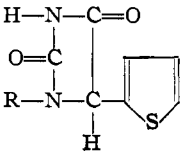
The Preparation of 1-R-5-(2-Thienyl)-hydantoins

BY LOREN M. LONG, C. A. MILLER AND GRAHAM CHEN

We have reported the synthesis and pharmacological activity of a series of 1-R-5-R′-5-phenylhydantoins[1] which may be represented by formula I. As reported in that paper, the more effective compounds in regard to protection against electrically induced convulsions are those in which R represents a short chain hydrocarbon group while R′ represents hydrogen.



I



II

Although our evidence to date does not indicate that the mere substitution of the 2-thienyl group for the phenyl group in physiologically active compounds is likely to lead to derivatives of greatly increased activity, the comparison of such related series is of interest and is sometimes necessary for patent purposes. For these reasons we decided to prepare the 2-thienyl derivatives represented by formula II in which R represents an alkyl, alkenyl, cycloalkyl or aralkyl group.

The only series of thiophene-containing hydantoins previously reported was prepared by Spurlock.[2] This series consists of 5-R-5-(2-thienyl)-hydantoins where R may be an alkyl or a phenyl group. Careful studies[3] recently made employing the electroshock method with cats have indicated that at best these derivatives are equal in activity to the corresponding phenyl compounds and that as a rule they are inferior. Final proof of relative therapeutic effectiveness, however, must await clinical studies.

The compounds summarized in Table I were prepared by the general method outlined in the earlier paper.[1] 2-Thiophenealdehyde was treated with an amine and the resulting thenylidene R-amine was converted to the corresponding aminonitrile by the addition of hydrogen cyanide. Treatment with cyanic acid yields the desired hydantoin. The various intermediates were not isolated. As indicated in Table I, in most instances the yields were inferior to those obtained with benzaldehyde. No attempt was made to improve the method, as sufficient material for testing was obtained in each case.

Pharmacology.—Most of the compounds herein reported have been tested both for inhibition of electrically induced convulsions in cats and metrazol-induced convulsions in rats. The activities listed in Table I indicate that the lower members of the series are the more effective anticonvulsants. This is in accord with the results obtained with the corresponding phenyl derivatives reported in the earlier publication.[1]

In each case, those compounds exhibiting an activity of 4+ when administered to cats in doses of 100 mg./kg. showed a lower activity at 50 mg./kg. Thus, no member of the series is as active as Dilantin.[4]

---

[1] Long, Miller and Troutman, THIS JOURNAL, **70**, 900 (1948).

[2] Spurlock, U. S. Patent 2,366,221.

[3] Chen and Ensor, unpublished data.

[4] Dilantin, registered trade-mark of Parke, Davis & Co. for 5,5-diphenylhydantoin.