# The Synthesis of Derivatives of Methionic Acid*

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**The marked hypnotic activity of numerous aliphatic derivatives of methionic acid suggested the synthesis of aromatic and heterocyclic amides of methionic acid as compounds of possible medicinal value. The occurrences of the pyridine, pyrimidine, and thiazole nuclei in active antibacterial compounds, the use of quinoline derivatives as antimalarials, and the bacteriostatic property of compounds such as *p*-aminoacetophenone and *p*-aminobenzophenone have had a direct bearing on the choice of some of the compounds synthesized. Twenty-two new such derivatives of methionic acid have been prepared and sufficient quantities have been prepared for bacteriological and pharmacological testing.**

THE marked hypnotic activity of numerous aliphatic derivatives of methionic acid and the successful use of sulfanilamide and its derivatives in chemotherapy suggested the synthesis of aromatic and heterocyclic amides of methionic acid as compounds of possible medicinal value. The occurrences of the pyridine, pyrimidine, and thiazole nuclei in active antibacterial compounds, the use of quinoline derivatives as antimalarial agents, and the bacteriostatic property of compounds such as *p*-aminoacetophenone and *p*-aminobenzophenone have had direct bearing on the choice of some of the compounds synthesized. In order that aromatic and heterocyclic derivatives of methionic acid may be tested for pharmacological activity, several compounds containing the methionamide nucleus have been prepared.

The synthesis of N,N′-bis(2-pyridyl) methionamide, N,N′-bis (2-pyrimidyl) methionamide, N,N′-bis (4-methyl-2-pyrimidyl) methionamide, N,N′-bis (4,6-dimethyl-2-pyrimidyl) methionamide, and N,N′-bis (2-thiazolyl) methionamide was accomplished by the condensation of the respective heterocyclic amines with methionyl chloride in the presence of copper-bronze catalyst.

Numerous ring-substituted derivatives of phenyl- and naphthylamines were condensed with methionyl chloride to yield a diversified group of aromatic amides of methionic acid.

From *p*-aminobenzophenone, prepared by the action of benzoyl chloride on aniline in the presence of zinc chloride, and the subsequent saponification of the resulting benzoyl *p*-aminobenzophenone, N,N′-bis(*p*-benzophenoyl) methionamide was synthesized.

The synthesis of N,N′-bis(8-chloro-5-quinolyl) methionamide was accomplished by the following reactions. The Skraup synthesis on *o*-chloroaniline produced 8-chloroquinoline, which was nitrated to yield 5-nitro-8-chloroquinoline. Reduction of the latter compound with iron and acetic acid produced the amine which was condensed with methionyl chloride to form N,N′-bis(8-chloro-5-quinolyl) methionamide.

## EXPERIMENTAL[1]

**Preparations of Methionyl Chloride, Phenyl Methionate, and Methionamide.**—The procedures used were essentially those of Bauer (1), Schroeter (2), and Backer (3). The methionyl chloride was collected as a colorless oil, but when cooled it formed a snow-white crystalline mass which melted at about 60°. Bauer (1) and Schroeter (2) reported the existence of the chloride in both the liquid and crystalline form. A small amount of the phenyl methionate was recrystallized from carbon tetrachloride to form white needles which melted at 82–83° (uncorr.); Bauer (1) reported a m. p. of 82–83° (uncorr.). Recrystallization of the methionamide from water yielded white plate-like crystals which melted at 233° (uncorr.); Bauer (1) reported a m. p. of 232–233° (uncorr.). A 61.1% yield of the chloride was obtained.

**Preparation of Methionamide Derivatives (Table I) General Procedure.**—A solution of 5.32 Gm. (0.025 mole) of methionyl chloride in 25 cc. of anhydrous benzene was slowly added through a dropping funnel to 300 cc. of a hot anhydrous benzene solution of 0.1 mole, unless otherwise stated, of the reacting amino-compound to which was added a small amount of copper-bronze catalyst.[2] The reaction was carried out in a round-bottomed, 3-necked, 500-cc. flask equipped with a mechanical stirrer and heated on a water bath. The reaction mixture was refluxed for a period of from one-half to three hours in every instance and the mixture cooled. The solid product which formed was washed with water and recrystallized from alcohol using decolorizing charcoal unless otherwise stated.

**Preparation of 8-Chloroquinoline and 5-Nitro-8-chloroquinoline.**—The procedures used were essentially those of Fourneau, *et al.* (7), Urist and Jen-

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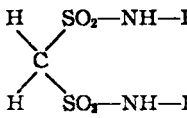
[1] All melting points are corrected unless otherwise stated.
[2] Copper-bronze powder used is the same as that used for painting copper-bronze colored radiators.

TABLE I.—METHIONAMIDE DERIVATIVES



| R | M. P., °C.[a] | Yield, % | Formula | N Analysis, % Calcd. | Found |
|---|---|---|---|---|---|
| 2-Pyridyl[c, d, e] | 277 | 58.7 | $C_{11}H_{13}O_4N_4S_2$ | 17.05 | 16.90 |
| 2-Pyrimidyl[e, f] | 306 | 75.4 | $C_9H_{10}O_4N_6S_2$ | 25.43 | 25.66 |
| 4-Methyl-2-pyrimidyl[e, f] | 282 | 54.8 | $C_{11}H_{14}O_4N_6S_2$ | 23.46 | 23.64 |
| 4,6-Dimethyl-2-pyrimidyl[c, e, g] | 278 | 25.1 | $C_{13}H_{18}O_4N_6S_2$ | 21.76 | 22.23 |
| 2-Thiazolyl[e, h] | 259 | 50.6 | $C_7H_8O_4N_4S_4$ | 16.47 | 16.58 |
| *p*-Acetanilido[i] | 282 | 77.6 | $C_{17}H_{20}O_6N_4S_2$ | 12.73 | 12.70 |
| *o*-Xenyl[j] | 166 | 79.5 | $C_{28}H_{22}O_4N_2S_2$ | 5.86 | 5.90 |
| 1-Naphthyl[d] | 208 | 38.7 | $C_{21}H_{18}O_4N_2S_2$ | 6.57 | 6.51 |
| 2-Naphthyl | 233 | 56.5 | $C_{21}H_{18}O_4N_2S_2$ | 6.57 | 6.53 |
| *o*-Tolyl | 196 | 56.6 | $C_{15}H_{18}O_4N_2S_2$ | 7.91 | 7.88 |
| *m*-Tolyl | 201 | 57.8 | $C_{15}H_{18}O_4N_2S_2$ | 7.91 | 7.81 |
| *p*-Tolyl | 215.5 | 56.6 | $C_{15}H_{18}O_4N_2S_2$ | 7.91 | 7.85 |
| *o*-Chlorophenyl | 146 | 60.8 | $C_{13}H_{12}O_4N_2S_2Cl_2$ | 7.08 | 7.04 |
| *m*-Chlorophenyl | 240 | 69.8 | $C_{13}H_{12}O_4N_2S_2Cl_2$ | 7.08 | 7.07 |
| *p*-Chlorophenyl | 250 | 59.8 | $C_{13}H_{12}O_4N_2S_2Cl_2$ | 7.08 | 7.08 |
| *o*-Anisyl | 161 | 46.8 | $C_{15}H_{18}O_6N_2S_2$ | 7.25 | 7.10 |
| *p*-Anisyl | 191.5 | 61.3 | $C_{15}H_{18}O_6N_2S_2$ | 7.25 | 7.21 |
| *o*-Nitrophenyl | 183.5 | 45.3 | $C_{13}H_{12}O_8N_4S_2$ | 13.46 | 13.43 |
| *m*-Nitrophenyl | 195 | 47.1 | $C_{13}H_{12}O_8N_4S_2$ | 13.46 | 13.49 |
| *α*-Trifluoro-*m*-tolyl | 218 | 60.6 | $C_{15}H_{12}O_4N_2S_2F_6$ | 6.06 | 6.06 |
| *p*-Benzophenonyl | 193 | 21.1 | $C_{27}H_{22}O_6N_2S_2$ | 5.24 | 5.31 |
| 1-Phenyl-1-hydroxy-2-propyl | 201–246[b] | 65.2 | $C_{19}H_{26}O_6N_2S_2$ | 6.33 | 5.92 |

[a] Corrected melting points [micro m. p. (*k*)], with decomposition.
[b] Begins to decompose at 201°, liquefies at 246°.
[c] Product washed with hot alcohol.
[d] Dissolved in 5% NaOH and precipitated with 10% HCl before recrystallizing.
[e] Recrystallized from water using decolorizing charcoal.
[f] Washed with alcohol.
[g] Refluxed seven hours.
[h] Washed with hot water.
[i] 0.0047 Mole of methionyl chloride and 0.0187 mole of *p*-aminoacetanilide used.
[j] *o*-Aminobiphenyl·HCl obtained on cooling benzene; product obtained on concentrating and cooling benzene filtrate.

kins (8), and Christian (9). A small amount of the 5-nitro-8-chloroquinoline recrystallized from alcohol melted at 145° (uncorr.), previously reported as 144° (9) and 145° (8). A 64% yield of 8-chloroquinoline was obtained. A 52.7% yield of the nitrated compound was obtained.

**Preparation of 5-Amino-8-chloroquinoline.**—The method used was that described by Christian (9) and Dikshoorn (10) with modifications. To 25 Gm. of crude 5-nitro-8-chloroquinoline dissolved in 375 cc. of 50% acetic acid was added 37.5 Gm. of iron (20 mesh) over a period of two hours, during which time the suspension was heated to boiling and the stirring was continuous. The stirring and heating were continued for one hour longer after which the mixture was diluted to twice its volume with water, brought to boiling, made alkaline with 20% NaOH, filtered, and the filtrate placed in the cold. The precipitate was recrystallized from water to yield 7.1 Gm. (33.2%) of product; m. p. 153° (uncorr.) previously reported as 152° (11) and 153–154° (9).

**Preparation of N,N′-Bis(8-chloro-5-quinolyl) Methionamide.**—One and one-half grams (0.007 mole) of methionyl chloride was slowly added through a dropping funnel to 300 cc. of an anhydrous benzene solution containing 5 Gm. (0.028 mole) of 5-amino-8-chloroquinoline in a round-bottomed 3-necked flask equipped with a mechanical stirrer. A small amount of copper-bronze catalyst was added. A deep blood-red product was formed, and the mixture was refluxed gently for one-half hour on a water bath. After cooling, the mixture was filtered, and the dark red powder obtained was washed with several 50-cc. portions of warm water. The remaining product was recrystallized from alcohol, using decolorizing charcoal; pink crystals, m. p. 345° (dec.) yield 2.1 Gm. (60%).

*Anal.*—Calcd. for $C_{19}H_{14}O_4N_4S_2Cl_2$: N, 11.29%. Found: N, 11.44%.

## SUMMARY

Twenty-three new derivatives of methionic acid possessing possible medicinal value have been synthesized. They are as follows:

1. N,N′-Bis(2-pyridyl) methionamide
2. N,N′-Bis(2-pyrimidyl) methionamide
3. N,N′-Bis(4-methyl-2-pyrimidyl) methionamide
4. N,N′-Bis(4,6-dimethyl-2-pyrimidyl) methionamide
5. N,N′-Bis(2-thiazolyl) methionamide
6. N,N′-Bis(*p*-acetanilido) methionamide
7. N,N′-Bis(*o*-xenyl) methionamide
8. N,N′-Bis(1-naphthyl)methionamide
9. N,N′-Bis(2-naphthyl) methionamide
10. N,N′-Bis(*o*-tolyl) methionamide
11. N,N′-Bis(*m*-tolyl)methionamide
12. N,N′-Bis(*p*-tolyl) methionamide
13. N,N′-Bis(*o*-chlorophenyl) methionamide
14. N,N′-Bis(*m*-chlorophenyl) methionamide
15. N,N′-Bis(*p*-chlorophenyl) methionamide
16. N,N′-Bis-(*o*-anisyl) methionamide

17. N,N′-Bis(*p*-anisyl) methionamide
18. N,N′-Bis(*o*-nitrophenyl) methionamide
19. N,N′-Bis(*m*-nitrophenyl) methionamide
20. N,N′-Bis(α-trifluoro-*m*-tolyl) methionamide
21. N,N′-Bis(*p*-benzophenonyl) methionamide
22. N,N′-Bis(8-chloro-5-quinolyl) methionamide
23. N,N′-Bis(1-phenyl-1-hydroxy-2-propyl) methionamide

Sufficient quantities of these compounds have been prepared for bacteriological and pharmacological testing.

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# The Relationship between Estrogenic Action and Chemical Constitution in a Group of Azomethine Derivatives*,†,‡

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**The relation between chemical constitution and estrogenic action has been investigated in a group of azomethine derivatives comprising all 4,4′ substitution combinations of four groups—H, $CH_3$, $CH_3O$, OH. 4,4′-Dihydroxy benzylidene aniline produced an estrogenic response in 12.5 mg. doses subcutaneously and 25 γ doses intravaginally. Absorption spectra were determined for all derivatives.**

IN RECENT years it has been indicated that the development of pharmacologic agents is receiving new impetus through applications derived from considerations of the relation between pharmacologic action and chemical constitution (1–9).

The present work has received its basis in the working hypothesis that estrogenic compounds may consist of rather large, rigid, relatively inert and lipoid-soluble, molecular structures with two active hydrogen-bond forming groups located at an optimum distance of 14.5 Å.[1] units from one another (8).

Table I illustrates the application of this hypothesis to some known estrogenic compounds. It is to be noted that as the distance between active hydrogen bond forming groups is either increased or decreased from the optimum of 14.5 Å. the potency is also decreased. 4,4′-Dihydroxyazobenzene and 4,4′-dihydroxystilbene are particularly interesting in view of the similarity between the ethylenic and azo ring linkages. It is probable that the discrepancy in subcutaneous potency between these two derivatives is due to deactivation of the azo linkage *in vivo* before the compound reaches its site of action (10), especially since the azo derivative shows estrogenic action in doses of 40 γ when applied intravaginally (11).

As a logical follow-up of these two types of ring linkage it was thought to be of interest to investigate the intermediate type as represented in the azomethines.

| —CH=CH— | —CH=N— | —N=N— |
|---|---|---|
| Ethylenic | Azomethine | Azo |

As a class, the diphenyl azomethines fulfill quite closely the requirements of the working hypothesis, when the benzene rings are in the *trans* position. That the *trans* configuration actually exists is indicated by analogy to stilbene

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§ Fellow, American Foundation for Pharmaceutical Education.
[1] Distances in Å. units throughout this paper are measured on Fisher-Hirschfelder-Taylor Atomic Models.