

Synthesis and Herbicidal Properties of Some New Substituted 2-(*m*-Tolyl)-acetamides and Related Compounds

H. C. GODT, Jr., P. C. HAMM,
and R. E. WANN

Organic Chemicals Division,
Monsanto Co., St. Louis, Mo.

The synthesis, physical characteristics, and herbicidal properties of *N,N*-dimethyl-2-(*m*-tolyl)acetamide, its 2-chloro, 2-methoxy, and 2-dimethylamino analogs, and related intermediates are described.

THE pre-emergent herbicidal activity of 2-phenylacetamides and 2-chloroacetamides has been known for several years (4, 8). Also, *dl*-methoxyphenylacetic acid (MOPA) has systemic herbicidal properties (6, 10)—i.e., it is absorbed by plant tissue and translocated to all parts of the plant.

Since *N,N*-dimethyl-2-(*m*-tolyl)acetamide (I) was found in this laboratory to be active as a pre-emergent herbicide, the synthesis and screening of its 2-chloro (II), 2-methoxy (III), and 2-dimethylamino (IV) analogs were of interest.

Chemical Studies

The various substituted 2-(*m*-tolyl)-acetamides and related intermediates which were prepared during this investigation are shown in Table I.

N,N-Dimethyl-2-(*m*-tolyl)acetamide (I) was prepared from α -bromo-*m*-xylene through the known nitrile (13), acid (V) (7, 9, 17), and acid chloride (VI) (3).

In preparing the desired compounds (II, III, and IV) several synthetic routes were investigated for structure proof purposes. The basic intermediate compound for these studies was the known *dl*-*m*-methylmandelic acid (VII) (2, 7).

To prepare the key compound (VII), α -bromo-*m*-xylene was converted to *m*-tolualdehyde via the Sommelet reaction (12). The crude aldehyde was converted to its bisulfite addition product, which was made to react with hydrogen cyanide (generated in situ) to form the cyanohydrin. Acid hydrolysis of this material yielded VII.

Esterification of VII with methanol produced VIII, which was made to react with thionyl chloride to give the chloro ester (IX). Hydrolysis of IX yielded the chloro acid (X). Treatment of X with thionyl chloride gave the chloro acid chloride (XI). Compound XI was also obtained directly by reaction of the hydroxy acid (VII) with thionyl chloride. Reaction of XI with two equivalents of dimethylamine in the cold gave the desired chloro dimethylamide (II). Treatment of II with sodium methylate yielded the methoxy dimethylamide (III) in 62% yield. The methoxy acid (XII) was also ob-

tained in 22% yield. The desired dimethylamino dimethylamide (IV) was achieved by reaction of the chloro dimethylamide (II) with excess dimethylamine.

A second route for the synthesis of the methoxy dimethylamide (III) involved the reaction of the chloro ester (IX) with sodium methylate, which gave the methoxy ester (XIII) in 64% yield. Also, the methoxy acid (XII) was obtained in 36% yield. Compound XII was likewise obtained in high yield when the methoxy ester (XIII) reacted with an aqueous solution of dimethylamine in an attempt to form the methoxy dimethylamide (III). Because of the failure of the latter reaction, the methoxy acid (XII) was converted to the methoxy acid chloride (XIV) with thionyl chloride. XIV then reacted with anhydrous dimethylamine to form the methoxy dimethylamide (III), which was identical with III produced from the chloro dimethylamide (II) with respect to boiling point, refractive index, and infrared analysis.

Infrared data were obtained on all of the final products and related intermediates. The shifts of the carbonyl stretching band to progressively lower wave lengths in the case of the dimethylamides, acids, methyl esters, and acid

chlorides, respectively, are consistent with published work.

Synthesis Procedures

***m*-Tolylacetic Acid(V).** The method of Mayer and English (5) was adapted to prepare this material. The crude yield was 94% (m.p. 61°) from petroleum ether (30° to 60°), which agrees closely with values reported when the material was prepared by other methods (7, 9, 17). Infrared (melt, capillary film, 0.01 mm.): broad absorption centered at 3.35 microns (COOH), sharp band at 5.88 microns (CO).

***m*-Tolylacetyl Chloride(VI)** was prepared according to the literature (3). Infrared (capillary film, 0.01 mm.): sharp band at 5.57 microns (CO).

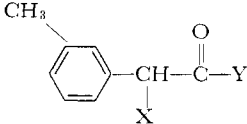
***N,N*-Dimethyl-2-(*m*-tolyl)acetamide (I).** The acid chloride(VI) (18.0 grams, 0.11 mole) was added dropwise to a stirred, chilled solution of dimethylamine (18.0 grams, 0.4 mole) in 200 ml. of ether at such a rate that the temperature of the reaction mixture did not exceed 10°. After addition was complete, the mixture was stirred 16 hours. Water (100 ml.) was then added to dissolve the precipitated salt. The ether layer was then separated, washed twice with 100 ml. of water, and dried over magnesium sulfate. After removal of the ether, the product was distilled [b.p. 102.5–5° (0.55 mm.); n_D^{25} , 1.5363]. The yield was 11.7 grams (61.6%).

Analysis. Calculated for $C_{11}H_{15}NO$: N, 7.91. Found: N, 8.01.

Infrared (capillary film, 0.01 mm.): sharp band at 6.08 microns (CO).

***dl*-*m*-Methylmandelic Acid(VII).** The sodium bisulfite addition product of *m*-tolualdehyde (134.4 grams, 0.6 mole) and sodium bisulfite (65 grams, 0.6 mole) were slurried in 500 ml. of water and cooled to 0°. A solution of 78.1 grams (1.2 moles) of potassium cyanide in 200 ml. of water was added over a 30-minute period with rapid stirring and cooling. Ether (300 ml.) was then introduced and the mixture stirred for 2 hours. The ether layer was separated and the aqueous layer extracted again with ether. The combined ether extracts were washed with 10% sodium bisulfite. Upon removal of the ether, the crude cyanohydrin remained (88.2

Table I. Substituted 2-(*m*-Tolyl)-acetamides and Intermediates

Compound No.		
	X	Y
I	H	N(CH ₃) ₂
II	Cl	N(CH ₃) ₂
III	OCH ₃	N(CH ₃) ₂
IV	N(CH ₃) ₂	N(CH ₃) ₂
V	H	OH
VI	H	Cl
VII	OH	OH
VIII	OH	OCH ₃
IX	Cl	OCH ₃
X	Cl	OH
XI	Cl	Cl
XII	OCH ₃	OH
XIII	OCH ₃	OCH ₃
XIV	OCH ₃	Cl

grams). This material was added dropwise to 100 ml. of concentrated hydrochloric acid with stirring. The reaction was faintly exothermic and was allowed to proceed at 25° for 12 hours and then heated at 70° for 6 hours. After evaporation of the reaction mixture to dryness on a steam bath, the residue was extracted three times with 200 ml. of boiling benzene. The combined hot benzene extract was then filtered and cooled, whereupon VII crystallized and was filtered. Yield, 68.5 grams (47%). The melting point (92–93°) agreed closely with product made by other methods (2, 7).

Analysis. Calculated for $C_9H_{10}O_3$: C, 65.05; H, 6.07; neutralization equivalent, 166.2. Found: C, 65.03; H, 6.15; neutralization equivalent, 166.9. Infrared (40% Nujol mull): broad band with maxima at 2.87 and 3.43 microns (alcoholic and carboxylic OH groups), two sharp bands at 5.85 and 5.97 microns (CO).

dl - Methyl *m* - Methylmandelate (VIII). The acid (VII) (41.5 grams, 0.25 mole) and 75 ml. of methanol containing 2.5 grams of hydrogen chloride were refluxed for 5 hours and then poured into 250 ml. of ice water. The mixture was made basic with 200 ml. of saturated sodium bicarbonate solution and extracted twice with 100 ml. of ether. The ether extract was dried over sodium sulfate and the ether evaporated, whereupon the product solidified. Yield, 42.0 grams (93.1%) [m.p., 52° (from hexane)].

Analysis. Calculated for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.59; H, 6.89. Infrared (40% Nujol mull): band centered at 2.87 microns (OH), sharp band at 5.76 microns (CO).

dl - Methyl Chloro - *m* - tolylacetate (IX). The hydroxy ester (VIII) (37 grams, 0.206 mole) was dissolved in 27.4 grams (0.23 mole) of thionyl chloride. After stirring for 16 hours at 25°, the mixture was refluxed for 30 minutes and poured into 250 ml. of ice water. The mixture was extracted twice with 150 ml. of ether. After the ether extracts had been dried with sodium sulfate, the ether was evaporated and the product distilled [b.p. 123° (5.1 mm.); n_D^{25} , 1.5228]. The yield was 33.6 grams (82.2%).

Analysis. Calculated for $C_{10}H_{11}ClO_2$: Cl, 17.85. Found: Cl, 17.88. Infrared (capillary film, 0.01 mm.): a sharp band at 5.70 microns (CO), a broad band centered at 13.68 microns (CCl grouping).

dl-Chloro-*m*-tolylacetic Acid (X). The chloro ester (IX) (20.1 grams, 0.1 mole), glacial acetic acid (40 ml.), and concentrated hydrochloric acid (20 ml.) were refluxed for 2 hours. After distilling the reaction mixture to a pot temperature of 90° at 25 mm., the residue was cooled, poured into cold water (150 ml.), and made slightly basic with sodium bicarbonate. The mixture was extracted with 50 ml. of ether, made distinctly acid to Congo Red paper with 50% sulfuric acid, and then extracted twice with 50 ml. of ether. The latter ether extract was washed twice with 25 ml. of ice water, and dried over sodium

sulfate, and the ether was evaporated. The residue was heated with 85 ml. of concentrated hydrochloric acid at 50° to 60° and then cooled in ice, whereupon the chloro acid (X) crystallized. The product was filtered and dried in a vacuum desiccator over potassium hydroxide [yield, 14.2 grams (76.3%); m.p. 58–9°].

Analysis. Calculated for $C_9H_9ClO_2$: Cl, 19.21; neutralization equivalent, 184.6. Found: Cl, 19.28; neutralization equivalent, 184.4. Infrared (40% Nujol mull): broad absorption centered at 3.41 microns (COOH); two sharp bands at 5.70 and 5.79 microns (CO); a band centered at 14.02 microns (CCl grouping).

dl - Chloro - *m* - tolylacetyl Chloride (XI). The chloro acid (X) (9.2 grams, 0.05 mole) and thionyl chloride (16.6 grams, 0.14 mole) were stirred and refluxed (79°) for 3 hours. Fractionation yielded 8.7 grams (85.7%) of XI [b.p. 96° (3.0 mm.); n_D^{25} , 1.5413].

Analysis. Calculated for $C_9H_9Cl_2O$: Cl, 34.92. Found: Cl, 34.51. Infrared (capillary film, 0.01 mm.): two sharp bands at 5.55 and 5.65 microns (CO); a broad band centered at 13.8 microns (CCl grouping).

XI was also obtained by stirring the hydroxy acid (VII) (49.9 grams, 0.3 mole) with 178.5 grams (1.5 moles) of thionyl chloride at 25° for 16 hours, and then at 70° for 3 hours. Fractionation gave 34.1 grams (56%) of the product. The boiling point, refractive index, and infrared spectrum were identical with the material prepared from X. There remained a viscous residue (10.5 grams) of undetermined structure.

dl - 2 - Chloro - *N,N* - dimethyl - 2 - (*m*-tolyl)acetamide (II). The chloro acid chloride (XI) (31.3 grams, 0.154 mole), in 100 ml. of ether, was stirred and maintained at –25° while a cold solution of 14.8 grams (0.328 mole) of dimethylamine in 150 ml. of ether was added dropwise over a 30-minute period. After stirring an additional 30 minutes, water (100 ml.) was added to dissolve the amine salt and the ether layer was separated. The aqueous layer was extracted with 50 ml. of ether. The combined ether extracts were dried and the solvent was removed by evaporation. The solid product (30.5 grams, 93.6%) was recrystallized from diisopropyl ether (m.p. 51.5°).

Analysis. Calculated for $C_{11}H_{14}ClNO$: Cl, 16.75; N, 6.62. Found: Cl, 16.84; N, 6.31. Infrared (3% in $CHCl_3$): sharp band at 6.03 microns (CO).

dl - *N,N* - Dimethyl - 2 - dimethylamino - 2 - (*m* - tolyl)acetamide (IV). The chloro amide (II) (12.7 grams, 0.06 mole) and dimethylamine (8.1 grams, 0.18 mole) in 75 ml. of toluene were heated at 80° for 3 hours in a pressure bottle. After cooling the reaction mixture to 0° and extracting with 50 ml. of ice water, the toluene layer was dried over magnesium sulfate, and stripped of solvent and the product distilled [b.p. 103° (0.18 mm.); n_D^{25} , 1.5295; yield, 9.9 (75.0%)].

Analysis. Calculated for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.0; H, 9.11; N, 12.26. Infrared (capillary film, 0.01 mm.): sharp band at 6.03 microns (CO).

Hydrochloride Salt was prepared in 2-propanol in the usual manner (m.p. 233–4° after washing with acetone).

Analysis. Calculated for $C_{13}H_{21}ClN_2O$: Cl, 13.81; N, 10.91. Found: Cl, 13.99; N, 10.56.

dl - *m,N,N,O* - Tetramethylmandelamide (III) and dl-*m,O*-Dimethylmandelic Acid (XII) from the Chloro Amide (II). Sodium chips (1.5 grams, 0.065 gram atom) were dissolved in 50 ml. of dry methanol. II (11.6 grams, 0.055 mole) in 25 ml. of dry methanol was then added to the sodium methoxide solution at 25° in 15 minutes with stirring. The reaction mixture was refluxed for 2 hours and then stirred at 25° for 16 hours, filtered to remove the sodium chloride, and stripped of methanol under vacuum (water aspirator). The residual yellow oil was poured into 100 ml. of ice water and the mixture extracted with ether. The ether extract was dried over magnesium sulfate, the solvent removed, and the methoxy amide (III) distilled [b.p. 103–4° (0.22 mm.); n_D^{25} , 1.5272; yield 7.1 grams (62.3%)].

Analysis. Calculated for $C_{12}H_{17}NO_2$: C, 69.89; H, 8.31; N, 6.76. Found: C, 68.9; H, 8.01; N, 6.95. Infrared (capillary film, 0.01 mm.): a broad band centered at 9.1 microns (COC), sharp band at 6.05 microns (CO).

The aqueous basic solution, after extraction with ether, was acidified with concentrated hydrochloric acid and heated to boiling. After cooling, the mixture was extracted with ether. The ether extract was dried over magnesium sulfate and the solvent evaporated, yielding 2.2 grams (22.2%) of the methoxy acid (XII), as determined by infrared comparison with sample of XII prepared from its methyl ester (XIII).

dl - Methyl *m,O* - Dimethylmandelate (XIII) and dl-*m,O*-Dimethylmandelic Acid (XII). Sodium chips (5.8 grams, 0.255 gram atom) were dissolved in 175 ml. of dry methanol. The chloro ester (IX) (133.8 grams, 0.17 mole) reacted with the sodium methoxide solution and the resulting mixture was worked up in the same manner as for the methoxy amide (III) from the chloro amide (II). The yield of XIII was 21.0 grams (63.6%) [b.p. 112–3° (2.4 mm.); n_D^{25} , 1.5026].

Analysis. Calculated for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.43; H, 7.19. Infrared (capillary film, 0.01 mm.): broad band centered at 9.07 microns (COC); sharp band at 5.76 microns (CO).

On acidifying the aqueous basic solution, after extraction with ether, and working up the mixture in the same manner as indicated for reaction of II with sodium methoxide, there was obtained 11.0 grams (33.9%) of the methoxy acid (XII) (identified by infrared spectra comparison).

dl-*m,O*-Dimethylmandelic Acid (XII) from Methyl Ester (XIII). In an attempt to form the methoxy amide (III),

the methoxy ester (XIII) (13.6 grams, 0.07 mole) and 126.4 grams of a 25% aqueous solution of dimethylamine (0.7 mole) were stirred for 12 hours in a sealed flask at 25°. The water and dimethylamine were then removed under vacuum. The residual yellow oil was dissolved in chloroform and dried over magnesium sulfate. Removal of solvent and distillation gave 10.3 gram (81.7%) of XII [b.p. 129–30.5° (0.5 mm.); n_D^{25} , 1.5243].

Analysis. Calculated for $C_{10}H_{15}O_3$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.88. Infrared (capillary film, 0.01 mm.): broad bands centered at 3.42 microns (COOH) and 9.05 microns (COC), sharp band at 5.80 microns (CO).

dl-*m*,*O*-Dimethylmandeloyl Chloride (XIV). Thionyl chloride (13.8 grams, 0.12 mole) was added to XII (15.4 grams, 0.09 mole) at 0° with stirring. The temperature of the reaction mixture was then raised to 25° and it was stirred for 12 hours. The excess thionyl chloride was stripped under vacuum and the product distilled [b.p. 89–90° (0.95 mm.); n_D^{25} , 1.5180; yield, 13.6 grams (76%)].

Analysis. Calculated for $C_{10}H_{11}ClO_2$: Cl, 17.85. Found: Cl, 17.99. Infrared (capillary film, 0.01 mm.): bands at 9.03 microns (COC) and 5.58 microns (CO).

dl-*m*,*N*,*N*,*O*-Tetramethylmandelamide (III) from the Methoxy Acid Chloride (XIV). To a solution of anhydrous dimethylamine (11.4 grams, 0.252 mole) in 100 ml. of ether, the methoxy acid chloride (XIV) (12.6 grams, 0.063 mole) was added dropwise with stirring and cooling at 0°. The mixture was stirred for an additional hour and then washed with 40 ml. of salt water. The ether portion was separated and dried over magnesium sulfate.

After evaporation of the solvent, the product was distilled [b.p. 108° (0.4 mm.); n_D^{25} , 1.5270; yield, 8.1 grams (61.8%)]. The infrared spectrum (capillary film, 0.01 mm.) was identical with that of a sample of III prepared from the chloro amide (II).

Herbicide Screening Results. The final products (I to IV) and all of the related intermediates except the relatively unstable cyanohydrin and the acid chlorides were evaluated for pre-emergence (seed germination inhibition) and postemergence (foliage spray) herbicidal activity. Representatives of six species of grasses (monocotyledons) and seven species of broadleaf plants (dicotyledons) were employed. The pre-emergent test procedure used has been reported (4). Postemergent application was made to 2-week-old foliage of the same group of plant species at desired solution concentrations. Volumes were controlled to give precise rates per acre.

Action of any significance was confined to four of the compounds tested. *N*,*N*-Dimethyl-2-(*m*-tolyl) acetamide (I) was the most effective pre-emergent herbicide, exhibiting severe inhibition of germination of four grass species and one broadleaf species at rates as low as 5 pounds per acre. The chloro dimethylamide (II) showed activity against several grass and broadleaf species at the rate of 25 pounds per acre.

The methoxy methyl ester (XIII) and the methoxy acid (XII) exhibited pre-emergent activity at 25 pounds per acre with a change in plant specificity. Seeds from representatives of the Cruciferae (mustards) and Chenopodeaceae (lambsquarter) failed to germinate with these two compounds.

Compounds XII and XIII also showed postemergence activity on broadleaf plants, the visual injury being charac-

terized by formative changes of the leaves. Radishes (Cruciferae) were severely injured at rates as low as 4 pounds per acre.

The methoxy dimethylamine (III) and the dimethylamino dimethylamide (IV) were essentially inactive in all tests.

Acknowledgment

The authors thank B. Katalfsky, O. E. Kinast, J. L. O'Sullivan, and O. S. Kring for their assistance with the numerous infrared and elemental analyses.

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Received for review May 18, 1966. Accepted August 12, 1966.

LABELED CARBAMATES

Synthesis of C¹⁴-Labeled 2-Methyl-2-(methylthio)propionaldehyde O-(Methylcarbamoyl)oxime

W. J. BARTLEY, D. L. HEYWOOD, T. E. N. STEELE, and W. J. SKRABA

Union Carbide Corp.,
South Charleston, W. Va.

DURING THE PAST THREE YEARS, extensive field tests on 2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime—Union Carbide 21149, formulated as a 10% granular under the proposed trademark Temik—have shown this compound to be a very promising broad spectrum systemic insecticide, nematocide, and acaricide (1,2,7,8). Its potential use on cotton, tobacco, potatoes, and other crops required a study of its metabolism in both plants and animals. To implement these metabolic studies (4,7,8), technical Temik was synthesized labeled with C¹⁴ at three different sites of the molecule. In addition, the correspond-

ing sulfoxide was prepared by oxidation of C¹⁴-labeled Temik.

To facilitate discussion, the carbamate insecticide [2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime] will be referred to as Temik, the corresponding sulfoxide [2-methyl-2-(methylsulfinyl)propionaldehyde O-(methylcarbamoyl)oxime] as Temik sulfoxide and the parent oxime [2-methyl-2-(methylthio)propionaldehyde oxime] as Temik oxime.

Discussion

tert-C¹⁴ Temik (III) was prepared by the sequence of reactions summarized in Figure 1. The transformations, which

are detailed in the experimental section, generally proceeded smoothly as anticipated from preliminary syntheses. However, for unknown reasons, abnormally low yields were obtained in the syntheses of 2-methyl-2-propanol-2-C¹⁴ and 2-chloro-2-methyl-2-C¹⁴-1-nitrosopropane dimer (I) resulting in the loss of considerable radioactivity in these steps. The over-all yield of Temik from barium carbonate-C¹⁴ was about 4%.

The *S*-methyl-C¹⁴ Temik (IV) was prepared by reaction of sodium methyl-C¹⁴-mercaptide with 2-chloro-2-methyl-1-nitrosopropane dimer (I) followed by reaction with methyl isocyanate. The over-all yield from dimer was 64%.