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Reaction of O-Methyl-N,N'-diisopropylisourea with Amino Acids and Amines

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The reaction of O-methyl-N,N'-diisopropylisourea with amino acids and amines, as their hydrochlorides, has been examined, and exhaustive methylation has been found to be the reaction pattern. Thus conversion of L-proline, L-N-methylproline, L-4-hydroxyproline, and DL-2-aminobutyric acid to the corresponding betaines was effected in good yield. Also, the hydrochlorides of benzylamine and codeine gave the quaternary derivatives, benzyltrimethylammonium chloride and codeine methochloride. Clean conversion of morphine to codeine could be realized without N-methylation; however, reaction of this aminophenol was solvent sensitive and in methanol and acetonitrile α-codeimethine was formed as a minor side product. In each case, the more nucleophilic site in the molecule was selectively alkylated.

The utility of O,N,N'-trialkylisoureas in the conversion of carboxylic acids to esters,[1,2] phenols to arylalkyl ethers,[3,4] thiophenols to arylalkyl sulfides,[5,6] and thiols to dialkyl sulfides,[7] and in the alkylation of β-diketones[6] and thymidine and uridine,[8] has been demonstrated. Much less is known about the reactivity of these reagents toward compounds containing more than a single nucleophilic site, and such reactions have received only cursory attention.[5-7]

We now report our findings on the reaction of O-methyl-N,N'-diisopropylisourea (1) with amino acids, amine hydrochlorides, and an aminophenol. These reactions and results appear to be applicable to a variety of other amines and O,N,N'-trialkylisoureas.

Conversion of Amino Acids to Betaines. When the amino acids, L-proline (2), L-N-methylproline (4), L-4-hydroxyproline (5), and DL-2-aminobutyric acid (7), were allowed to react with excess isourea 1 in methanol at room temperature for several days, the corresponding betaines 3, 6, and 8 were isolated in moderate to high yield (Table I). In no case was esterification observed, and no etherification of the hydroxyl group of 5 was detected.

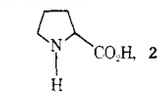
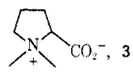
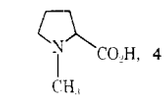
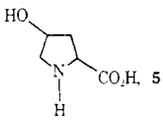
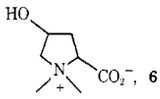
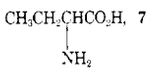
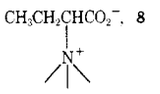
The rationalization for betaine formation lies in the relative nucleophilicities of the amino and carboxyl functionalities present in the reaction. Following protonation of 1, the amino acid species is present as the carboxylate anion. N-Methylation leading to betaine formation is attributed to the amino group being a more powerful nucleophile than the carboxylate anion in the ensuing SN2 reaction.

An interesting solvent dependence was observed in the reaction of L-proline (2) with isourea 1. Whereas betaine formation was the sole process occurring at room temperature in methanol or water, both formation of betaine 3 and L-proline methyl ester were detected in *tert*-butyl alcohol or methoxyacetonitrile under reflux. O-Alkylation leading to methyl ester formation can be attributed to the decreased solvation, and, hence, greater availability as a nucleophile, of the more electronegative carboxylate oxygen in *tert*-butyl alcohol and methoxyacetonitrile relative to the more polar and protic methanol and water.

Use of isourea 1 to prepare betaines directly from amino acids affords a mild and effective alternative to the more classical procedures of treating an amino acid with silver oxide and methyl iodide,[9-11] an alkali metal hydroxide and a methylating agent,[9,12,13] or diazomethane[9,14,15] that have been employed to prepare some of these, as well as other betaines. Further, optical activity measurements show the recrystallized product obtained by the isourea method to be optically pure.

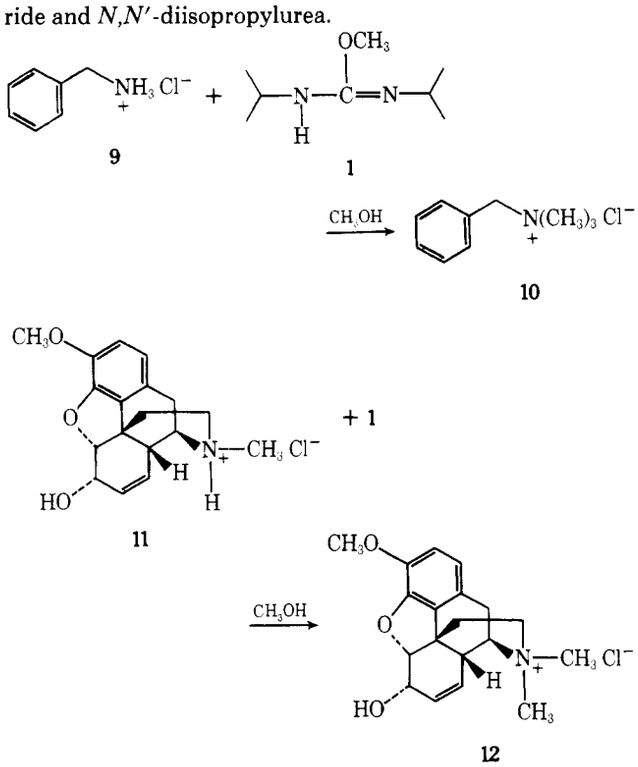
Exhaustive Methylation of Amine Hydrochlorides. The mechanism for alkylation with O,N,N'-trialkylisoureas requires a proton source and a sufficiently powerful nucleophile.[1,2,16] In view of the ease of betaine formation from amino acids, it was postulated that an amine hydrohalide could serve as both proton source and nucleophile and react with excess O-methyl-N,N'-diisopropylisourea (1) to yield the corresponding quaternary ammonium halide. In agreement with the prediction, treatment of benzylamine hydrochloride (9) and codeine hydrochloride (11) with excess isourea 1 in methanol at room temperature for several days resulted in the formation of benzyltrimethylammonium chloride (10) and codeine methochloride (12), respectively. The low isolated yields of 10 and 12, 17 and 25%, were attributed to incomplete

Table I. Reaction of *O*-Methyl-*N,N'*-diisopropylisourea (1) with Amino Acids to Form Betaines

Amino acid	Betaine	Yield, %[a]
 2	 3	86 (68)
 4	3	87 (60)
 5	 6	100 (74)
 7	 8	63 (44)

[a] Chromatographed yield (recrystallized yield).

reaction under the conditions used. No attempt was made to determine the extent to which 1 decomposes to methyl chloride and *N,N'*-diisopropylurea.



Conversion of Morphine (13) to Codeine (14). It is known that phenols can be etherified with isoureas in good yield.[3,4] Furthermore, it has been shown that thiophenols are alkylated by these reagents and that the resultant thioether formation is not affected by the presence of phenolic, amino, or carboxyl groups.[5,6] It was of interest to treat morphine (13), an aminophenol, with *O*-methyl-*N,N'*-diisopropylisourea (1) to determine if selective O-alkylation to codeine could be realized.

Treatment of morphine (13) with excess isourea 1 in methanol under reflux resulted in moderate yields of codeine (14) and formation of α-codeimethine (15) as a minor product (see Table II). Comparison of GC peak areas indicated the extent of conversion of 13 to methine 15 to be about 5–10% that of 13 to codeine. The formation of 15 to about the same extent was also observed when the reaction was performed in methanol at room temperature.

Table II. Reaction of *O*-Methyl-*N,N'*-diisopropylisourea (1) with Morphine (13) to Form Codeine (14)

Mol %			% isolated yield		
13	1	Conditions[a]	14	13	15
100	112	CH_3OH, Δx, 24 h	47	34	Not detd
100	307	CH_3OH, Δx, 100 h	71	Not detd	5
100	501	THF, Δx, 48 h	56	46	None
100	200	THF, Δx, 24 h	10	87	None
100	200[b]	THF, Δx, 24 h	21	40	None
100	502	CH_3CN, Δx, 48 h	73	12	<4
100	499	Neat, 100 °C, 7 h	89	5	<1
100	501	Neat, 100 °C, 20 h	83	5	<1

[a] All reactions in which solvent was employed were done at morphine (13) concentration of 0.25 M; Δx = reflux. [b] Reaction performed in the presence of added *N,N'*-diisopropylurea (16) (200 mol %).

When morphine was allowed to react with excess isourea 1 in acetonitrile under reflux, moderate yields of codeine were again realized. Since the extent of α-codeimethine formation was decreased (relative GC peak areas of **14:15** ~ 18.5:1), a clean conversion to codeine appeared possible in a less polar solvent. Accordingly, treatment of **13** with excess **1** in THF under reflux resulted in good yields of **14** without concomitant formation of **15**; isolated codeine and recovered morphine accounted for greater than 90% of starting morphine.

In neither acetonitrile nor THF could total reaction of **13** be achieved. While the heterogeneity of the reaction mixture and the relatively nonpolar nature of the solvent can be blamed for retardation of the reaction rate, these factors cannot explain the failure to achieve complete reaction. Interference in the desired reaction by an increasing concentration of *N,N'*-diisopropylurea (**16**) as the reaction progresses was considered a possible explanation. However, in a reaction in THF in which a twofold excess of **16** was added, neither the rate of reaction nor the yield of codeine was adversely affected.

The preparation of codeine (**14**) from morphine (**13**) without solvent was effected in high yield by stirring a suspension of **13** in excess isourea **1** for several hours at 100 °C. With this procedure, yields of **14** of 90% were attained and contamination by **15** was less than 1%.

The formation of α-codeimethine (**15**) arises from N-methylation of codeine and subsequent Hofmann elimination of the resulting ammonium salt. In proceeding from protic, polar methanol to acetonitrile and THF, it appears that the lessened solvation, and, hence, increased nucleophilicity, of the more electronegative phenoxide oxygen would increase the extent of O-alkylation at the expense of N-alkylation. While a decrease in the extent of N-alkylation, ultimately leading to **15**, was observed in acetonitrile, it was in THF that this effect was fully realized.

Although reaction conditions were not optimized, our results show that the use of THF as solvent affords a clean conversion of morphine (**13**) to codeine (**14**) with a high recovery of unreacted **13**, and that performing the reaction in the absence of solvent affords a high-yield conversion of **13** to **14**. Since the strongly alkaline conditions and high temperatures required by more traditional procedures[17,18] are avoided, this method offers a mild, effective alternative for the preparation of codeine. Unlike the Rodionov procedure,[17,18] in which methine **15** is also a side product, there is no contamination by codeine methyl ether.[19] Also, it appears that this method will be applicable to the synthesis of a variety of *O*-3-ethers of morphine.

This investigation of the reactions of isourea **1** with compounds containing more than a single nucleophilic site indicates that selective alkylation of the more nucleophilic func-

tion can be achieved. It is also reasonable to expect the reactions discussed to be general for a variety of isoureas.

Experimental Section

General. O-Methyl-N,N'-diisopropylisourea (1) was prepared as described.[20] All melting points are uncorrected. Microanalyses were performed by the Analytical Laboratory, University of California, Berkeley. NMR spectra were recorded on a Varian T-60 spectrophotometer. Mass spectra were obtained on an MS12 instrument. Optical rotations were recorded on a Bendix Ericsson ETL-NPL automatic polarimeter, Type 143A. Thin layer chromatography was done on Camag silica gel and column chromatography was done with Merck silica gel (0.063–0.2 mm), unless otherwise specified. Conversion of morphine (13) to codeine (14) was followed analytically by GC using an Aerograph HY-FI Model 600-D with a 6 ft × 0.125 in. glass column packed with 3% OV-17 on Aeropak 30; column temperature, 235 °C; He flow rate, 67 ml/min. Retention times relative to morphine (1.00) follow: codeine (14), 0.78; α-codeimethine (15), 0.70.

L-Proline Betaine (Stachydrine) (3). A solution of 346 mg (3.0 mmol) of L-proline (2) and 1.59 g (10.0 mmol) of 1 in 6 ml of absolute methanol was stirred at room temperature for 48 h, the mixture was diluted with 5 ml of H_2O and filtered to remove precipitated urea 16, and the filtrate was evaporated to give 593 mg of an oily white solid. Chromatography on 50 g of silica gel with CH_3OH/concentrated NH_3/$CHCl_3$ (10:1.5:13.5) as eluent gave 370 mg (86%) of betaine 3 as a white solid, R_f 0.32. Recrystallization from absolute C_2H_5OH/Et_2O gave 290 mg (67.5%) of 3, mp 220–230 °C dec (lit.[21] mp 235 °C dec). The product was identical by TLC and NMR with an authentic sample.[10]

L-Proline Betaine (3) from L-N-Methylproline (4). A solution of 107 mg (0.83 mmol) of L-N-methylproline[22] (4) and 269 mg (1.64 mmol) of 1 in 2 ml of absolute CH_3OH was stirred at room temperature for 48 h. Isolation as described above gave 104 mg (87%) of 3 after chromatography and 71 mg (60%) after recrystallization, mp 227–235 °C dec (lit.[21] mp 235 °C dec).

L-4-Hydroxyproline Betaine (Betonicine) (6). A solution of 302 mg (2.30 mmol) of L-4-hydroxyproline (5) and 1.455 g (9.19 mmol) of 1 in 6 ml of absolute CH_3OH was stirred at room temperature for 72 h. Isolation as described above gave 368 mg (100%) of 6 after chromatography as a white solid, R_f 0.10. Recrystallization from absolute C_2H_5OH/acetone gave 270 mg (74%) of 6: mp 244–245 °C dec (lit. mp 252–253,[11] 243–244 °C[23]); $[\alpha]^{24}D$ −36.1° (c 0.956, H_2O) [lit. $[\alpha]^{20}D$ −34.2° (c 1.0, H_2O),[11] $[\alpha]^{15}D$ −36.6° (c 4.88, H_2O)[23]]. The product was identical by TLC and NMR with an authentic sample.[11]

DL-2-Aminobutyric Acid Betaine (8). A solution of 310 mg (3.01 mmol) of DL-2-aminobutyric acid (7) and 1.91 g (12.1 mmol) of 1 in 10 ml of absolute CH_3OH was stirred at room temperature for 5 days. Isolation as described above gave 274 mg (62.7%) of 8 as a solid, R_f 0.25. Recrystallization from absolute C_2H_5OH/Et_2O gave 193 mg (44.1%): mp 218–220 °C dec; NMR [D_2O, internal $(CH_3)_3Si(CH_2)_3SO_3Na$] δ 0.97 (t, 3 H, J = 8 Hz), 1.90–2.23 (m, 2 H), 3.20 (s, 9 H), 3.40–3.70 (AB q, 1 H); mass spectrum m/e 144 ($M^+ - 1$, 1.0%), 86 ($M^+ - CO_2CH_3$, $M^+ - C_3H_9N$, 81.5%), 59 (C_3H_9N, 73.6%), 58 (C_3H_8N, 100%).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.9; H, 10.4; N, 9.6. Found: C, 57.5; H, 10.5; N, 9.6.

Benzyltrimethylammonium Chloride (10). A solution of 144 mg (1.00 mmol) of benzylamine hydrochloride (9) and 640 mg (4.05 mmol) of 1 in 4 ml of absolute CH_3OH was stirred at room temperature for 5 days and evaporation of the solvent gave 632 mg of a residue which was filtered through 30 g of silica gel using ethyl acetate/methanol/acetic acid (16:4:1) as eluent, to remove 16 and unreacted 1 and 9. A CH_3OH wash of the column gave 57 mg (31%) of 10 which was recrystallized from acetone to give 31 mg (17%), mp 220–235 °C (lit.[24] mp 243 °C).

Codeine Methochloride (12). A solution of 334 mg (1.00 mmol) of codeine hydrochloride (11) and 319 mg (2.01 mmol) of 1 in 2 ml of absolute CH_3OH was stirred at room temperature for 11 days, solvent was evaporated, and the residue of 591 mg was filtered through 10 g of silica gel with $CHCl_3$/15% CH_3OH as eluent, removing 16 and unreacted 11. A CH_3OH wash of the column gave 122 mg of methochloride 12 which was recrystallized from absolute C_2H_5OH to give 87 mg (25%) of 12, mp 258–265 °C dec (lit.[25] mp 260–265 °C dec).

Reaction of Morphine (13) with O-Methyl-N,N'-diisopropylisourea (1) to Yield Codeine (14). In CH_3OH. A solution of 285 mg (1.00 mmol) of morphine (13) and 485 mg (3.07 mmol) of 1 in 4 ml of absolute CH_3OH was heated under reflux in a nitrogen atmosphere for 100 h. Evaporation of the solvent and chromatography of the residue on 30 g of silica gel with $CHCl_3$/15% CH_3OH as the eluent gave 211 mg (71%) of codeine (14), and 61 mg of a yellow oil containing 14, R_f 0.40, α-codeimethine (15), R_f 0.27, and 13, R_f 0.14. Sublimation of the codeine (14) fraction at 130 °C (0.05 mm) gave 14, mp 151–154 °C, identical by GC, TLC, NMR, and MS with an authentic sample.

The mixture of 13, 14, and 15 was partitioned between 10 ml of $CHCl_3$ and 5 ml of 2 N NaOH, the $CHCl_3$ was removed, and the aqueous portion was extracted with an additional 10 ml of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to give 29 mg of an oil containing 14 and 15. Chromatography on silica gel with $CHCl_3$/15% CH_3OH as the eluent gave 14.0 mg (4.5%) of 15, mp 113–117 °C (lit.[26] mp 118.5 °C) after recrystallization from ether, identical with an authentic sample[26] by GC, TLC, NMR, and MS.

In THF. A suspension of 286 mg (1.00 mmol) of 13 in a solution of 793 mg (5.01 mmol) of 1 in 4 ml of THF was heated under reflux in a nitrogen atmosphere for 48 h. The solvent was removed, the residue of 684 mg was partitioned between 15 ml of $CHCl_3$ and 5 ml of 2 N NaOH, the $CHCl_3$ was removed, and the aqueous portion was extracted with an additional 15-ml portion of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to give 362 mg of an oil which was chromatographed on 40 g of silica gel with $CHCl_3$/15% CH_3OH as the eluent to give 166 mg (56%) of 14 as a yellow solid. Sublimation at 130 °C (0.03 mm) gave 136 mg (45%) of pure codeine.

The alkaline aqueous portion was brought to pH 8.5 with 2 N HCl and extracted with 3 × 15 ml of $CHCl_3$/25% 2-propanol; the combined organic extracts were evaporated to give 131 mg (46%) of recovered morphine.

In Acetonitrile. A suspension of 283 mg (0.99 mmol) of 13 in a solution of 795 mg (5.02 mmol) of 1 with 4 ml of CH_3CN was heated under reflux in a nitrogen atmosphere for 48 h. Isolation as described above gave 216 mg (73%) of codeine (14). From the alkaline aqueous portion was recovered 33 mg (12%) of morphine (13).

Neat. A suspension of 285 mg (1.00 mmol) of 13 in 790 mg (4.99 mmol) of 1 was stirred in a 100 °C bath in a nitrogen atmosphere for 7 h. Isolation as described above gave 267 mg (89%) of codeine (14). From the alkaline aqueous portion was recovered 14.3 mg (5%) of morphine (14).

Registry No.—1, 54648-79-2; 2, 147-85-3; 4, 475-11-6; 5, 51-35-4; 7, 2835-81-6; 8, 60526-21-8; 9, 3287-99-8; 11, 1422-07-7; 13, 57-27-2.

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