ir (neat) 1715, 1735 cm^{-1}; nmr ($CDCl_3$) τ 5.94 (t, 2, OCH_2), 7.61 (m, 6, $CH_2C{=}O$), 8.0–8.65 (m, 18); mass spectrum (10 eV) *m/e* (rel intensity) 254 ($M\cdot^+$, 72), 236 (78), 226 (18), 222 (13), 208 (30), 156 (87), 153 (10), 139 (10), 112 (28), 111 (11), 98 (34), 97 (30), 86 (57), 85 (100).

The semicarbazone (79%) had mp 156.5–158°. *Anal.* Calcd for $C_{16}H_{29}N_3O_3$: C, 61.71; H, 9.39; N, 13.49. Found: C, 61.71; H, 9.43; N, 13.66.

Registry No.—**1**, 38223-26-6; **2**, 38223-27-7; **2** semicarbazone, 38223-28-8; **3**, 38223-29-9; **3** semicarbazone, 38223-30-2; **4**, 4017-56-5; **5**, 4017-57-6; **6**, 4753-59-7; **7**, 38223-49-3; **8**, 38223-50-6; **9**, 38223-51-7; **10**, 38223-52-8; **12**, 32539-82-5; **13**, 32539-83-6; **15**, 38223-55-1; 2-(2′-carbethoxyethyl)cyclododecanone dinitrophenylhydrazone, 38223-56-2; cyclonoanone, 3350-30-9; 1,6-dioxacyclopentadeca-1,15-dione, 38223-57-3; 1,7-dioxacyclopentadeca-2,8-dione, 38223-58-4.

Acknowledgment.—We are indebted to Dr. Gary Koppel for experimental assistance.

Selective C-Alkylation of Phenylacetylureas through 1,3,5-Trialkali Salt Intermediates[1]

Jack D. Taylor,[2] George B. Trimitsis,
Tomas Hudlicky,[3] and James F. Wolfe*

*Department of Chemistry,
Virginia Polytechnic Institute and State University,
Blacksburg, Virginia 24061*

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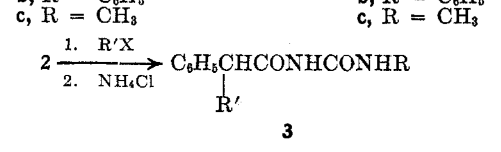
Recently,[4–6] we have found that 1,3,5 trianions derived from certain imides and β-keto imides can serve as useful synthetic intermediates by virtue of the high degree of regioselectivity accompanying their reactions with electrophilic reagents. During the course of these studies it occurred to us that arrangement of potential anion-stabilizing groups in phenylacetylurea (**1a**) might permit conversion of this compound into the 1,3,5-trialkali salt **2a**, which would represent the first example of a ureide trianion. It was anticipated that alkylation might then be directed selectively to the carbanion site of **2a** to afford *C*-alkyl derivatives **3**, a class of compounds which continue to attract considerable attention as anticonvulsant agents.[7] Moreover, such a direct new synthesis involving a single precursor, **2a**, could offer a more expedient method for certain structural variations than the multistep procedures[8] currently used for the preparation of compounds **3**.



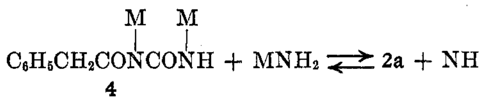
$$C_6H_5CH_2CONHCONHR \xrightarrow[NH_3]{4.5MNH_2} C_6H_5\overset{M}{\overset{|}{C}}HCO\overset{M}{\overset{|}{N}}CO\overset{M}{\overset{|}{N}}R$$

1a, R = H; **b**, R = C_6H_5; **c**, R = CH_3 — **2a**, R = H; **b**, R = C_6H_5; **c**, R = CH_3

$$2 \xrightarrow[2.\ NH_4Cl]{1.\ R'X} C_6H_5\underset{R'}{\underset{|}{C}}HCONHCONHR$$

3

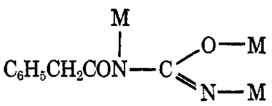
Treatment of **1a** with 2 mol equiv of potassium amide in liquid ammonia resulted in essentially complete consumption of the base as evidenced by the absence of stilbene formation upon addition of benzyl chloride.[9] Removal of the ammonia, followed by quenching with excess deuterium oxide, gave a good recovery of **1a** containing only N-bonded deuterium, indicating that 2 equiv of base produced the weakly nucleophilic dianion **4**, which failed to undergo appreciable alkylation at −33°.[10] Reaction of **1a** with 3 mol equiv of potassium amide in liquid ammonia followed by benzyl chloride afforded a mixture of *C*-benzyl derivative **3a**, unreacted **1a**, and stilbene. Since these results appeared to be consistent with an unfavorable equilibrium involving abstraction of a benzylic proton from dianion **4** to form trianion **2a** (eq 1), attempts were made to increase the concentration of **2a** by replacing the ammonia with ether. This proved to be unsatisfactory because of extensive ammonolysis of the trianion during solvent exchange.[11] However, treatment of **1a** with 4.5 mol equiv of potassium amide in liquid ammonia, followed by a series of representative halides, afforded C-alkylation derivatives **3a–e** in good yields (Table I). Similarly, reaction of *N′*-phenyl- and *N′*-methylureides **1b** and **1c** with excess potassium amide in liquid ammonia followed by benzyl chloride afforded *C*-alkyl products **3f** and **3i** in good yields, while attempted benzylations in the presence of stoichiometric amounts of base gave mixtures consisting of **3f** and **3i**, unreacted starting materials, and stilbene.



$$C_6H_5CH_2CO\overset{M}{\overset{|}{N}}CO\overset{M}{\overset{|}{N}}H + MNH_2 \rightleftarrows \mathbf{2a} + NH_3 \qquad (1)$$

4

It is conceivable that reaction of dianion **4** with a third equivalent of potassium amide could lead to a mixture of intermediates more complex than that illustrated in eq 1, possibly consisting of **2a** and the isomeric trianion **5**.[12] The excess amide necessary for



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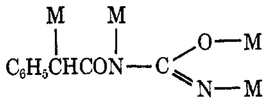

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[1] This investigation was supported by the National Institutes of Health, Grants GM-14340 and NS-10197.

[2] Abstracted from the Ph.D. dissertation of J. D. T., Virginia Polytechnic Institute and State University, July 1971.

[3] NSF undergraduate research participant, summer 1971.

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[9] C. R. Hauser, W. R. Barsen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

[10] D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

[11] W. S. Murphy and C. R. Hauser, *Chem. Ind. (London)*, 832 (1969).

[12] For examples of related trianions, see E. M. Kaiser, R. L. Vaux, and C. R. Hauser, *J. Org. Chem.*, **33**, 3640 (1967).

TABLE I

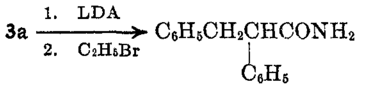
ALKYLATIONS OF TRIALKALI SALTS 2

Trialkali salt (M)	Halide R′X (registry no.)	Product	Mp, °C	Yield, %
2a (K)	$PhCH_2Cl$ (100-44-7)	**3a**	209–210	66
2a (Na)	$PhCH_2Cl$	**3a**	209–210	52
2a (Li)	$PhCH_2Cl$	**3a**	209–210	47
2a (K)	CH_3I (74-88-4)	**3b**	156–157[a,b]	73
2a (K)	C_2H_5Br (74-96-4)	**3c**	148–149[c,d]	76
2a (K)	$CH_2{=}CHCH_2Br$ (106-95-6)	**3d**	139–141[c,e]	76
2a (K)	$ClCH_2CO_2Na$ (3926-62-3)	**3e**	210–202[f,g]	60
2b (K)	$PhCH_2Cl$	**3f**	158–160[f,h]	73
2b (K)	CH_3I	**3g**	180–181[f,i]	52
2b (Li)	C_2H_5Br	**3h**	144–146[j,k]	57
2c (K)	$PhCH_2Cl$	**3i**	125–127[l,m]	57

[a] Recrystallized from aqueous ethanol. [b] Lit.[8b] mp 158–159°. [c] Recrystallized from acetone–heptane. [d] Lit.[8a] mp 137°. [e] Lit.[8a] mp 133–134°. [f] Recrystallized from absolute ethanol. [g] *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.93; H, 5.22; N, 11.91. [h] *Anal.* Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.59; H, 5.94; N, 8.17. [i] *Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.65; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.19. [j] Recrystallized from aqueous methanol. [k] Lit.[8d] mp 143–144°. [l] Purified by chromatography on silica gel and recrystallized from heptane. [m] *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.61; H, 6.38; N, 9.96. Found: C, 72.61; H, 6.39; N, 9.68.

successful alkylation might then be utilized in conversion of both trianions into a common 1,1,3,5 tetraanion (**6**), which reacts with halide to afford products **3**. Alternatively, the use of excess base might result in kinetically favored formation of trianion **2a** at the expense of trianion intermediate **5**. However, the absence of N-substituted derivatives in alkylations of **1a** and the requirement for excess amide in alkylations of **1b–c**, neither of which can form trianions such as **5** or tetraanions like **6**, appear to rule out both of the foregoing possibilities. Thus, excess potassium amide apparently exerts a simple mass law effect as shown in eq 1, and the appropriate 1,3,5-trialkali salts are the actual reactive intermediates in the observed C-alkylations.

In a brief study of the scope and limitations of the present reactions it was found that they were subject to a metallic cation effect, with tripotassio **2a** being more reactive toward benzyl chloride than the corresponding sodio or lithio salts (Table I). Trilithio **2b** could be generated in concentrations suitable for alkylation by means of 4 mol equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF)–hexane, but formation of **2a** (M = Li) under similar conditions was less satisfactory as evidenced by incomplete alkylation with several halides. Therefore LDA, which is often superior to alkali amides for multiple anion formation,[13] appears to offer no advantage in these alkylations. Attempts to effect alkylation of trianion **1a** (M = K) with secondary halides were unsuccessful. Finally, it should be mentioned that, although N′-aryl and N′-alkyl substituents appear to be generally compatible with the present trianion approach to C-alkylation, such was not the case with phenylacetyl ureides possessing an alkyl substituent at the benzylic position. For example, reaction of **3a** with excess potassium amide in liquid ammonia followed by ethyl bromide afforded a mixture of products in which starting material predominated. Attempted C-alkylation of **3a** with ethyl bromide in the presence of excess LDA gave none of the desired dialkyl derivative; instead **3a** underwent extensive decarboxamidation to yield 2,3-diphenylpropionamide (**7**) (eq 2). Although elucidation of the mechanism and



$$\mathbf{3a}\xrightarrow[\text{2. } C_2H_5Br]{\text{1. LDA}} C_6H_5CH_2\underset{\substack{|\\ C_6H_5}}{C}HCONH_2 \qquad (2)$$

7

generality of this reaction must await further study, preliminary results indicate that it may proceed in a manner similar to that described by Smith and Hauser[14] for the butyllithium-catalyzed decarboxamidation of certain primary amides.

Experimental Section[15]

Formation and Alkylations of Trialkali Salts 2a–c with Excess Alkali Amide.—The following synthesis of 2,3-diphenylpropionylurea (**3a**) is typical of the procedure used for the preparation of compounds **3a–g** and **3i** (Table I).

To a stirred solution of 0.09 mol of potassium amide, prepared from 3.52 g (0.09 g-atom) of potassium in 300 ml of anhydrous liquid ammonia, was added 3.57 g (0.02 mol) of solid phenylacetylurea (**1a**). The resulting green–yellow reaction mixture was allowed to stir for 20 min to ensure complete formation of trianion **2a** (M = K). A solution of 6.58 g (0.052 mol) of benzyl chloride in 40 ml of anhydrous ether was added and the reaction mixture was stirred for 1 hr. During the addition of the halide the bright purple color associated with stilbene formation was evident. The reaction mixture was neutralized with excess solid ammonium chloride and the liquid ammonia was removed (steam bath) as an equal volume of ether was added. Addition of 200 ml of water to the resulting ethereal suspension resulted in separation of a considerable amount of solid material between the layers. This was collected by suction filtration and combined with a second portion of crude product obtained by concentration of the

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(13) See T. M. Harris and G. P. Murphy, *J. Amer. Chem. Soc.*, **91**, 517 (1969), and references cited therein.

(14) H. A. Smith and C. R. Hauser, *ibid.*, **91**, 7774 (1969).

(15) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed in this laboratory by Miss Q. H. Tan using a Perkin-Elmer Model 240 C, H, and N analyzer. Thin layer chromatography (tlc) analyses were carried out with Eastman chromagram sheets, Type 6060 (silica gel), with fluorescent indicator. Spots were detected with ultraviolet light. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer using potassium bromide pellets and chloroform solutions. Proton magnetic resonance (pmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to tetramethylsilane, were measured to the center of a singlet or multiplet. Unless specified otherwise, chemicals were commercial reagent grade, and were used without further purification. *n*-Butyllithium was obtained from Foote Mineral Co., New Johnsonville, Tenn., as a solution in hexane and was standardized prior to use. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves. Phenylacetylurea (**1a**), mp 211–213° (lit.[16] mp 209°), was prepared by heating an equimolar mixture of phenylacetyl chloride and urea at 160° for 20 min and then recrystallizing the resulting crude solid from absolute ethanol. Similarly, 1-phenyl-3-(phenylacetyl)urea (**1b**), mp 170.5–171° (lit.[8d] mp 164–166°), and 1-methyl-3-(phenylacetyl)urea (**1c**), mp 188.5–190° (lit.[17] mp 190°), were prepared from the appropriately substituted urea and phenylacetyl chloride.

(16) S. Basterfield and M. E. Greig, *Can. J. Res.*, **8**, 450 (1933).

(17) J. Lehreau and P. Poignant, French Addn., 83,764; *Chem. Abstr.*, **64**, 644*h* (1966).

original ethereal layer and two 100-ml ethereal extracts of the aqueous layer. The total crude product was recrystallized from absolute ethanol to afford 3.55 g of **3a**: pmr (DMSO-d_6) δ 10.68 (s, 1, NH), 7.56 (m, 12, NH_2 and Ph), 4.28 (m, 1, CHCO), and 3.28 ppm (m, 2, CH_2Ph); ir (KBr) 2.93 (NH_2), 3.07 (NH), 5.95 (imide C=O), and 6.31 μ (amide C=O).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.79; H, 6.10; N, 10.27.

Alkylations of **1a** with benzyl chloride in the presence of 4.5 equiv of sodium amide or lithium amide were carried out in a similar manner.

Alkylation of tripotassio salt **2a** with sodium chloroacetate to afford 3-carboxy-2-phenylpropionylurea (**3e**) was conducted as described above except that the reaction time was extended to 2 hr and the product was isolated by acidification of the basic aqueous phase.

Attempted alkylation of 2,3-diphenylpropionylurea (**3a**) with ethyl bromide in the presence of excess potassium amide as described above afforded a mixture of products. Analysis of this mixture by tlc (THF–heptane) revealed the presence of unreacted **3a** along with traces of 2,3-diphenylpropionamide.

Although the observed melting points of alkyl derivatives **3c** and **3d** were somewhat higher than previously reported values (Table I), both of these compounds had analytical and spectral properties consistent with the assigned structures.

Formation and Attempted Benzylation of Dianion 4.—To a stirred suspension of 0.02 mol of potassium amide in 150 ml of liquid ammonia was added 1.78 g (0.01 mol) of **1a**. The resulting mixture was allowed to stir for 1 hr, and 1.26 g (0.01 mol) of benzyl chloride in 20 ml of ether was added; there was no evidence of stilbene formation. After 1 hr the ammonia was replaced by 200 ml of anhydrous ether and the resulting suspension treated with 10 ml of deuterium oxide. Filtration of the ethereal suspension and recrystallization of the residue from acetone–heptane afforded 1.36 g (76%) of recovered **1a**, the pmr (DMSO-d_6) spectrum of which had no absorption for imide or amide protons, but still retained a singlet (2 H) at 3.68 ppm for benzylic hydrogens. Analysis of the ethereal layer by tlc (ether–heptane) revealed traces of **1a** but no stilbene. Concentration of the ethereal layer afforded a nearly quantitative recovery of benzyl chloride.

Attempted Formation and Benzylation of Trialkali Salts 2a–c with 3 Equiv of Potassium Amide.—Each of the ureides **1a–c** (0.01 mol) was treated with 0.03 mol of potassium amide in liquid ammonia for 1 hr. Benzyl chloride (0.011 mol) was added, stirring was continued for 1 hr, and the reaction mixture was neutralized with ammonium chloride and processed in the usual fashion. In all cases addition of the halide resulted in appearance of the purple color accompanying stilbene formation. Each of the crude product mixtures was analyzed by tlc (THF–heptane), which revealed the presence of unreacted starting material, the appropriate *C*-benzyl derivative, and stilbene.

Formation and Alkylation of 1b (M = Li) Using LDA.—To a solution of 12.14 g (0.12 mol) of diisopropylamine in 200 ml of THF, maintained at 0° under a nitrogen atmosphere, was added 0.12 mol of *n*-butyllithium in hexane. The reaction mixture was allowed to stir for 15 min to form LDA and 7.62 g (0.03 mol) of solid **1b** was added. The resulting yellow solution was allowed to stir for 20 min, and 6.87 g (0.063 mol) of ethyl bromide in 50 ml of THF was added. The reaction mixture was stirred for 1 hr at 25° and then poured into a slurry of 200 g of ice and 15 ml of 12 *N* HCl. The THF layer was separated and combined with three 100-ml ethereal extracts of the aqueous solution. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized to give 4.8 g of **3h** (Table I).

In a similar experiment **1a** (0.015 mol) was treated with 0.07 mol of lithium diisopropylamide and 0.03 mol of ethyl bromide to afford a mixture (tlc) of ethyl derivative **3c** and unreacted **1a**.

Attempted Ethylation of 3a by Means of LDA.—To a solution of 0.07 mol of LDA in 160 ml of THF–hexane, maintained at 0° under nitrogen, was added 4.02 g (0.015 mol) of **3a**. After 20 min, 3.43 g (0.03 mol) of ethyl bromide was added, the reaction mixture was allowed to warm to 25°, and stirring was continued for 1 hr. The reaction was processed as described above and the solid residue remaining after concentration of the organic extracts was analyzed by tlc (benzene–acetone) to reveal the presence of traces of **3a** and one other product. The crude product mixture was chromatographed on silica gel (benzene–acetone) to afford, after one recrystallization from aqueous ethanol, 2.3 g (66%) of 2,3-diphenylpropionamide, mp 131–132° (lit.[18] mp 133–134°). The ir spectrum of this material was identical with that of an authentic sample of 2,3-diphenylpropionamide. The aqueous layer was freeze-dried. The ir spectrum of the resulting solid has an intense band at 4.48 μ attributable to cyanate.[14]

Registry No.—**2a** (K), 37991-57-4; **2a** (Na), 37991-58-5; **2a** (Li), 37991-59-6; **2b** (K), 37991-75-6; **2b** (Li), 37991-76-7; **2c** (K), 37991-77-8; **3a**, 37991-66-5; **3b**, 37991-67-6; **3c**, 90-49-3; **3d**, 37991-69-8; **3e**, 37991-70-1; **3f**, 37991-71-2; **3g**, 37991-72-3; **3h**, 4287-43-8; **3i**, 37991-74-5.

[18] A. Meyer, *Chem. Ber.*, **21**, 1306 (1888).

Studies on Lactams. XXII.[1]
An Unusual Reaction of Some 6-Azidopenams

M. S. Manhas,* J. S. Chib, and Ajay K. Bose

Department of Chemistry and Chemical Engineering,
Stevens Institute of Technology, Hoboken, New Jersey 07030

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As a continuation of our work on the synthesis of penicillin analogs *via* α-azido-β-lactams,[2] we prepared the 6-azidopenams **3** and **4** by the reaction of azidoacetyl chloride and triethylamine on the appropriate thiazolines (**1** and **2**). Catalytic reduction of **3** led to the disappearance of the ir band characteristic of the azido group and gave a material which was used without further purification for reaction with phenoxyacetyl chloride and triethylamine. We had expected to obtain the penicillin V analog **5**, but, to our surprise, the crystalline product formed in high yield was found to be **6**, a penam that is readily synthesized from the thiazoline **1**, phenoxyacetyl chloride, and triethylamine. Similarly, **4** was transformed into **7** in about 80% yield by catalytic reduction followed by treatment with phenoxyacetyl chloride and triethylamine.

In a recent communication Bell and coworkers[3] have described the degradation of penicillin G methyl ester (**8**) and penillonic acid methyl ester (**11**) in refluxing trifluoroacetic acid to the thiazoline D-5,5-dimethyl-2-thiazoline-4-carboxylic acid methyl ester (**12**). This cleavage of the β-lactam in **8** is reminiscent of the fragmentation of 6-aminopenicillanic acid (**9**) under photolytic conditions. Gotfredsen and coworkers[4] observed that photolysis of an aqueous solution of the potassium salt of **9** resulted in a new penicillin, **10**. They proposed that the β-lactam ring was cleaved with the generation of the thiazoline **13** and amino ketene or its equivalent which reacted with 6-APA (**9**) to give **10**.

Our own observations on the formation of **6** and **7** from **3** and **4** can be easily accounted for if by analogy with 6-aminopenicillanic acid fragmentation we assume

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[1] For part XXI, see A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Lett.*, 4091 (1972).

[2] (a) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967), and subsequent papers in this series.

[3] M. R. Bell, J. C. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, **92**, 2177 (1970).

[4] W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experientia*, **23**, 280 (1967).