Tetrahedron, 1963, Vol. 19, pp. 85 to 89. Pergamon Press Ltd. Printed in Northern Ireland

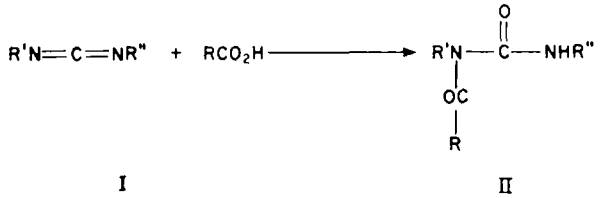
A NEW SYNTHESIS OF SUBSTITUTED BARBITURIC ACIDS[1]

A. K. BOSE and S. GARRATT
Department of Chemistry and Chemical Engineering, Stevens Institute of Technology
Hoboken, N.J., U.S.A.

(*Received* 5 *July* 1962; *revised* 8 *August*)

Abstract—Malonic acid and substituted malonic acids react under mild conditions with N,N′-disubstituted carbodiimides to give barbiturates. The reaction of malonic acid and ethylmalonic acid with N,N′-di-*p*-tolylcarbodiimide, however, follows a different course.

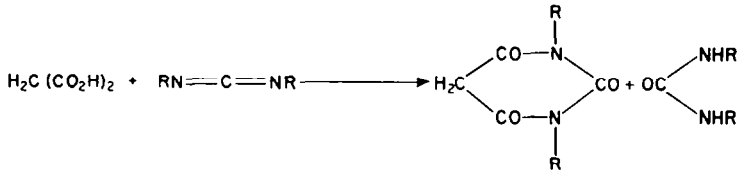
IT IS well known[2] that N,N′-disubstituted carbodiimides (I) react with carboxylic acids to form N-acyl derivatives (II). Dicarboxylic acids of type III, $n > 1$ have been reported to form the corresponding anhydride (IV). However, the reaction between N,N′-disubstituted carbodiimides and malonic acid or substituted malonic acids has not been well defined.



I II

III IV
n > 1

We have found that a solution of two moles of N,N′-dicyclohexyl carbodiimide (V) in tetrahydrofuran reacted exothermally with one mole of malonic acid with the immediate separation of N,N′-dicyclohexylurea. Evaporation of the filtrate gave a colorless compound VI which analyzed for $C_{16}H_{24}O_3N_2$. From its NMR and IR



V R = C_6H_{11}
VII R = i-Pr

VI R = C_6H_{11}
VIII R = i-Pr

$H_2C(COCl)_2$ + $OC(NHR)_2$

[1] Preliminary report: K. Bose and S. Garratt, *J. Amer. Chem. Soc.* **84**, 1318 (1962).
[2] H. G. Khorana, *Chem. Rev.* **53**, 145 (1953).

spectra, the barbituric acid structure VI was deduced for it. An alternative synthesis of VI was carried out in very low yield by the condensation of malonyl chloride with N,N'-dicyclohexylurea. The samples of VI prepared by the two different methods were found to be identical on the bases of their m.p., mixed m.p., IR and NMR spectra.

The reaction of N,N'-diisopropyl carbodiimide (VII) with malonic acid gave a compound VIII which was also obtained from malonyl chloride and diisopropyl urea. Elemental analyses and spectral data too were consistent with the barbiturate structure assigned to VIII. This reaction therefore constitutes a one step synthesis of 1,3-disubstituted barbiturates. Previously[3] the most general methods of preparation were the direct alkylation of the unsubstituted or monosubstituted barbiturate, or the condensation of malonyl chloride with the disubstituted urea. Both methods require several steps involving fairly drastic conditions and often result in low yields. In our hands the acid chloride method gave only 5% of 1,3-dicyclohexyl and 1,3-diisopropyl barbiturates, whereas the carbodiimide method gave over 60% yield. As symmetrical and unsymmetrical disubstituted carbodiimides are readily obtainable,[1] the synthesis of many new barbiturates should be facilitated.

It was found that this new synthesis of barbituric acid could be extended to substituted malonic acids. Thus, ethyl-, diethyl- and benzylmalonic acids gave the corresponding barbiturates with V. When ethylmalonic acid was reacted with N,N'-diisopropylcarbodiimide, an exothermic reaction with precipitation of diisopropylurea took place but evaporation of the filtrate gave an oil which failed to crystallize. A similar result was obtained from the reaction between N,N'-diisopropylcarbodiimide and diethylmalonic acid. Neither of these oily products has been investigated further.

Malonic acid and di-*p*-dimethylaminophenylcarbodiimide have been reported to reach in pyridine medium to give a diacylurea but the fate of malonic acid on reaction with di-*p*-tolylcarbodiimide has not been established.[4] We found that the reaction of malonic acid with N,N'-di-*p*-tolylcarbodiimide in tetrahydrofuran solution afforded N,N'-di-*p*-tolylurea and a compound that melted at 141–142°, solidified at about 150° and remelted at 225–230°; only limited di-*p*-tolylurea was formed in this reaction. Pyrolysis of this compound at 150° gave the di-*p*-toluidide of malonic acid (IX) identified by comparison with an authentic sample. On the basis of the method of preparation and the structure of the pyrolysis product, the alternative structures X and XI can be assigned to the compound, 141–142°. The IR spectrum of this compound shows a strong absorption peak at 5·76 μ and weak absorption peaks at 5·95 μ and 6·00 μ. The acylurea structure XI can be expected to show the carbonyl peaks near 6 μ rather than at 5·76 μ. On the other hand, the structure X is consistent with the observed IR spectrum. A clear-cut choice between X and XI does not seem to be possible on the basis of the NMR spectrum.

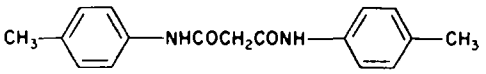
Authentic 1,3-di-*p*-tolylbarbituric acid, m.p. 213–214°, was prepared by the reaction of malonyl chloride with N,N'-di-*p*-tolylurea.

The reaction of ethylmalonic acid with N,N'-di-*p*-tolylcarbodiimide did not produce any di-*p*-tolylurea; the product that was isolated (in 67% yield) has been assigned the structure XII by analogy with X.

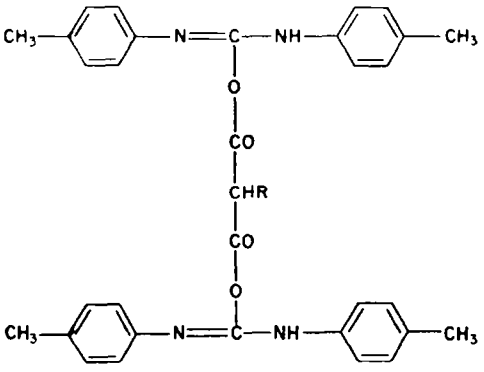
The reaction of diethylmalonic acid with N,N'-di-*p*-tolylcarbodiimide led to the

[3] D. J. Doran, *Medicinal Chemistry* (Edited by F. F. Blicke and R. H. Cox) Vol. IV; Wiley, New York (1959).

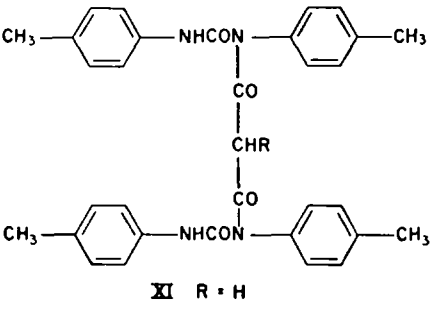
[4] F. Zetzsche and H. Lindlar, *Ber. Dtsch. Chem. Ges.* **71**, 2095 (1938).



IX



X R = H
XII R = Et



XI R = H

separation of nearly one mole of N,N′-di-*p*-tolylurea; the other product of the reaction was 1,3-di-*p*-tolyl-5,5-diethylbarbituric acid.

The difference between aromatic and aliphatic carbodiimides in the reaction with malonic acid is striking. It is also remarkable that diethylmalonic acid yields a barbiturate on reaction with di-*p*-tolylcarbodiimide but ethylmalonic and malonic acids do not. The role of steric and electronic factors in these reactions is under investigation.

EXPERIMENTAL[5]

1,3 *Dicyclohexylbarbituric acid* (VI)

(a) *From malonic acid and* N,N′-*di-cyclohexylcarbodiimide.* Dicyclohexylcarbodiimide (3·88 g, 0·019 mole) dissolved in tetrahydrofuran (10 ml) was added to a cooled solution of malonic acid (0·979 g, 0·009 mole) in tetrahydrofuran (10 ml). Immediate reaction occurred and N,N′-dicyclohexylurea was precipitated. After standing at room temp 1 hr the urea was filtered, washed with tetrahydrofuran and dried (2·24 g, 0·01 mole), m.p. 229–230°. The combined filtrates were evaporated under red. press. leaving a crystalline residue (2·7 g) which on recrystallization from absolute ethanol gave 1,3-dicyclohexylbarbituric acid as white needles (0·10 g; 65%) m.p. 200–201°. λ_{max}^{nujol}: 5·86 μ (strong), 5·92 μ (strong). NMR peaks: 8·26 (center of multiple peak, 2H). (Found: C, 66.00; H, 8·19; N, 9·39; $C_{16}H_{24}N_2O_3$ requires: C, 65·72; H, 8·27; N, 9·58%).

(b) *From malonyl chloride and* N,N′-*dicyclohexylurea.* N,N′-dicyclohexylurea (2 g, 0·009 mole) was carefully added to malonyl chloride (1·2 g, 0·009 mole) in chloroform and the reaction mixture heated under reflux. After 4 hr the chloroform was removed under red. press. The brown gummy residue was dissolved in dil sodium carbonate solution, the solution filtered, and the filtrate acidified with dil hydrochloric acid. The precipitated barbituric acid was extracted with chloroform. Evaporation of the chloroform extracts gave a crystalline product (0·31 g) which recrystallized from ethanol to give 1,3-dicyclohexylbarbituric acid (0·14 g, 5·5%) m.p. 199–200° unchanged when mixed with product from (a). IR and NMR spectra were identical with those of the barbituric acid obtained by method (a).

[5] All NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard; peaks are reported in τ values. All m.p. are uncorrected. Dicarboxylic acids which were not commercially available were prepared by the hydrolysis of the corresponding diethyl ester. Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim (Ruhr), West Germany.

1,3-*Dicyclohexyl*-5,5-*ethylbarbituric acid*

Ethyl malonic acid (0·997 g, 0·075 mole) and N,N′-dicyclohexylcarbodiimide (3·14 g, 0·015 mole) in tetrahydrofuran gave N,N′-dicyclohexylurea (2·26 g, 0·01 mole) and 1,3-dicyclohexyl-5,5-ethylbarbituric acid (2·05 g) which recrystallized from absolute ethanol as needles (1·99 g, 62·5%) m.p. 110°. λ_{max}^{nujol}: 5·72 μ (weak), 5·90 μ (strong) (Found: C, 67·63; H, 8·78; N, 8·55; $C_{18}H_{28}O_3N_2$ requires: C, 67·48; H, 8·81; N, 8·75%).

1,3-*Dicyclohexyl*-5,5-*diethylbarbituric acid*

Diethylmalonic acid (1·09 g, 0·0062 mole) and N,N′-dicyclohexylcarbodiimide (2·6 g, 0·013 mole) in tetrahydrofuran gave N,N′-dicyclohexylurea (1·42 g, 0·006 mole) and a crude product (2·15 g). Recrystallization of the latter from absolute ethanol gave 1,3-dicyclohexyl-5,5-diethylbrabituric acid as prisms (1·09 g, 50%) m.p. 160–161°. λ_{max}^{nujol}: 5·72 μ (weak, 5·92 μ (strong). (Found: C, 69·24; H, 9·19; N, 8·10; $C_{20}H_{32}N_2O_3$ requires: C, 68·93; H, 9·26; N, 8·04%).

1,3-*Dicyclohexyl*-5-*benzylbarbituric acid*

Benzylmalonic acid (4 g, 0·02 mole) and N,N′-dicyclohexylcarbodiimide (8·48 g, 0·04 mole) in tetrahydrofuran gave N,N′-dicyclohexylurea (6·81 g, 0·03 mole) and a crude product (6·21 g) which on recrystallization from absolute ethanol gave 1,3-dicyclohexyl-5,5-benzylbarbituric acid (2·5 g, 31·5%) m.p. 121°. λ_{max}^{nujol}: 5·72 μ (weak), 5·9 μ (strong). NMR peaks: 8·50 (center of multiple peak, 20H), 7·40 (center of multiple peak, 3H), 5·5 (center of multiple peak, 2H), 2·90 (center of multiple peak, 5H). (Found: C, 72·92; H, 8·30; N, 7·43; $C_{23}H_{30}O_3N_2$ requires: C, 72·22; H, 7·91; N, 7·32%).

1,3-*Di*-p-*tolyl*-5,5-*diethylbarbituric acid*

Diethylmalonic acid (1·8 g, 0·01 mole) and N,N′-ditolylcarbodiimide (5·0 g, 0·022 mole) in tetrahydrofuran gave N,N′-ditolylurea (2·07 g, 0·008 mole) m.p. 266–267° and a crude product. Recrystallization of the latter from absolute ethanol gave 1,3-di-*p*-tolyl-5,5-diethylbarbituric acid (1·28 g, 32%) m.p. 168–168·5°. (NMR peaks: 8·93 (center of triplet 6H), 7·81 (center of quartet 4H), 7·59 (6H), 2·97 (center of multiple peak 8H). (Found: C, 72·14; H, 6·10; N, 7·89; $C_{23}H_{24}O_3N_2$ requires: C, 72·50; H, 6·64; N, 7·69%).

1,3-*Diisopropylbarbituric acid* (VIII)

(a) *From malonic acid and* N,N′-*diisopropylcarbodiimide.* Malonic acid (2 g, 0·02 mole) and N,N′-diisopropylcarbodiimide (4·8 g, 0·04 mole) in tetrahydrofuran gave N,N′-diisopropylurea (2·15 g, 0·015 mole) and a crystalline product (4·4 g). Recrystallization of the latter from absolute ethanol afforded 1,3-diisopropylbarbituric acid as needles (2.4 g, 60%) m.p. 128–129°. (Found: C, 56·69; H, 7·68; N, 13·23; $C_{10}H_{16}O_3N_2$ requires: C, 56·58; H, 7·59; N, 13·20%).

(b) *From malonyl chloride and* N,N′-*diisopropylurea.* Malonyl chloride (2·43 g, 0·017 mole) and N,N′-diisopropylurea (2·48 g, 0·017 mole) were kept at room temp for 12 hr. After removal of the solvent the crude product was recrystallized from absolute ethanol (0·21 g, 4%) m.p. 126–127° unchanged when mixed with a sample of the product obtained by method (a).

Reaction of malonic acid with N,N′-*di*-p-*tolylcarbodiimide*

N,N′-di-*p*-tolycarbodiimide (8·8 g, 0·04 mole) in tetrahydrofuran (30 ml) was added slowly to a stirred solution of malonic acid (2 g, 0·02 mole) in tetrahydrofuran (10 ml) at room temp. N,N′-di-*p*-tolylurea slowly precipitated and after standing at room temp overnight the urea was filtered and washed with tetrahydrofuran (2·23 g, 0·009 mole) m.p. 265°. Evaporation of the filtrate gave a gummy product (9·00 g). Crystallization from absolute ethanol gave compound X (4·08 g, 30%) m.p. 141–142° (solidified at 153°, remelt 225–230°). λ_{max}^{nujol}: 3·05–3·20 μ (weak), 5·76 μ (strong), 5·95 μ (weak), 6·00 μ (weak). NMR peaks: 7·68 (6H), 7·58 (6H), 6·77 (2H), 2·78 (center of multiple peak, 16H), −0·87 (2H). (Found: C, 72·63; H, 5·68; N, 9·93; Mol. wt., 570; Calcd. for $C_{33}H_{32}O_4N_4$: C, 72·24; H, 5·88; N, 10·21%; Mol. wt., 548·6).

Pyrolysis of compound X. The foregoing compound (1 g, 0·0017 moles) was heated at 150° for 10 min. Recrystallization of the pyrolysis product from absolute ethanol gave the di-*p*-toluidide of

malonic acid (0·41 g, 85%) m.p. 249–250° unchanged when mixed with an authentic sample. (Found: C, 72·19; H, 6·36; N, 10·01; $C_{17}H_{18}O_3N_2$ requires: C, 72·32; H, 6·43; N, 9·92%).

Reaction of ethylmalonic acid with N,N′-*di*-p-*tolylcarbodiimide*

Di-*p*-tolylcarbodiimide (6·8 g, 0·03 mole) in tetrahydrofuran (20 ml) was added to a solution of ethylmalonic acid (2 g, 0·015 mole) in tetrahydrofuran (20 ml). The reaction solution was stirred at room temp for 16 hr and no urea precipitated during this period. The solution was evaporated to dryness and the crude product was recrystallized from absolute ethanol affording XII (5·0 g, 66·5%) m.p. 140–141°. λ_{max}^{nujol}: 3·05 μ (weak), 5·76 μ (strong), 5·95 μ (weak), 6·00 μ (weak). MNR peaks: 9·33 (center of triplet 3H), 8·05 (center of multiple peak 2H), 7·61 (6H), 7·47 (6H), 6·42 (center of triplet 1H), 2·70 (center of multiple peak 16H). (Found: C, 72·46; H, 6·46; N, 9·83. $C_{33}H_{36}O_4N_4$ requires: C, 72·89; H, 6·29; N, 9·72%).

1,3-*Di*-p-*tolylbarbituric acid*

A solution of malonyl chloride (1·22 g, 0·008 mole) and N,N′-di-*p*-tolylurea (2·0 g, 0·008 mole) in chloroform was kept at room temp for 48 hr. The reaction mixture was extracted 3 times with dil sodium carbonate solution. The combined extracts were acidified with dil hydrochloric acid and re-extracted three times with chloroform. After drying over anhydrous magnesium sulfate the chloroform was removed under red. press. The residue was recrystallized from ethanol giving 1,3-di-*p*-tolylbarbituric acid (0·336 g, 14%) m.p. 213–214°. (Found: C, 70·53; H, 5·23; N, 9·41, $C_{18}H_{16}N_2O_3$ requires: C, 70·11; H, 5·23; N, 9·09%).

Acknowledgement—We are thankful to J. Zuclich[6] and J. Pelosi[6] for valuable technical assistance and to Dr. E. R. Malinowski and R. S. Magee[6] for the NMR spectra and their interpretation. This investigation was supported in part by a research grant (MY-3930) from the National Institute of Mental Health, U.S. Public Health Service, for which grateful acknowledgement is made.

[6] National Science Foundation undergraduate research participant.