From o-$O_2NC_6H_4N_2HSO_4$: 10 ml., 100°, 1 d., 99, 2; 50 ml., R., 7 d., 94, 2.

From p-$CH_3OC_6H_4N_2HSO_4$: 20 ml., 65° (O_2), 7 d., 13, 79; 10 ml., 65°, 7 d., 14, 79; 20 ml., 65°, 7 d., 21, 69; 20 ml., 65°, 7 d., 26, 70; 30 ml., 65°, 7 d., 24, 66; 40 ml., 65°, 7 d., 25, 68; 50 ml., 65°, 7 d., 29, 64; 50 ml. (100 μmoles), 65°, 7 d., 28, 65; 10 ml., 100°, 20 h., 12, 84; 10 ml., 150°, 20 h., 10, 85; 20 ml., 65° (N_2), 7 d., 96, 4; 50 ml., R., 5 d., 94, 4, 50 ml., R., 3 d., 92, 5; 50 ml., R., 7 d., 99, 1; 50 ml., R., 7 d., 89, 12; 50 ml., R., 7 d., 93, 8; 50 ml., R–O_2, 7 d., 64, 32; 50 ml. (0.5 ml. of formalin), R., 7 d., 76, 18; 50 ml. (3 ml. of formalin), R., 7 d., 80, 14; 50 ml. (85 mg. of HCOOH), R., 7 d., 97, 6; 50 ml. (400 μmoles), R., 7 d., 60, 38; 50 ml., R., 7 d., 83, 13.

From m-$CH_3OC_6H_4N_2HSO_4$: 10 ml., 100°, 1 d., 2, 94; 50 ml., R., 2 d., 2, 94.

COLUMBIA, S. C.

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE[1]]

Aminoketones. I. The Preparation of α-Aminoketones from Di-t-butyl Acetamidomalonate[2]

BY ANTHONY W. SCHRECKER AND MARY M. TRAIL

RECEIVED JUNE 13, 1958

Benzoylation of diethyl sodioacetamidomalonate yields the C-acyl derivative (II), and not an O-acyl compound as had been postulated. Acid-catalyzed cleavage of di-t-butyl acylacetamidomalonates provides acetamidoketones, which can be hydrolyzed to 1-amino-2-alkanone hydrochlorides.

As part of a program dealing with the preparation of amino acid antimetabolites to be tested for potential effect against experimental tumors, the synthesis of certain α-aminoketone derivatives of the general structure $RCOCH_2NHR'$ appeared of interest. Some compounds of this type, such as δ-aminolevulinic acid,[3] have been shown to be involved in biochemical pathways, while others have been employed in the synthesis of antibiotics.[4]

In a search for improved methods of preparing such compounds, the acylation and subsequent decarbalkoxylation of N-acylaminomalonic esters has been investigated. The only known acyl derivative of this type, namely, diethyl benzoylacetamidomalonate, was prepared several years ago[5,6] by treating the sodio derivative of diethyl acetamidomalonate (I) with benzoyl chloride. The product could not, however, be made to undergo ketone cleavage. Treatment with bicarbonate led to reversal of the acylation reaction,[6] catalytic hydrogenation yielded I and benzaldehyde,[5] and no carbonyl derivatives could be obtained.[5] This led the previous investigators to believe that the compound was not the C-acyl derivative II, but an O-acyl derivative. Dalgliesh[5] favored structure III, while Viscontini and Adank[6] suggested formula IV.

$$C_6H_5COCl + CH(CO_2R)_2NHCOCH_3 \xrightarrow{NaH}$$

I, R = C_2H_5; VI, R = $C(CH_3)_3$

$C_6H_5COC(CO_2R)_2NHCOCH_3$

II, R = C_2H_5; VII, R = $C(CH_3)_3$

$C(OC_2H_5)(OCOC_6H_5)=C(NHCOCH_3)CO_2C_2H_5$ (III)

$CH(CO_2C_2H_5)_2N=C(CH_3)OCOC_6H_5$ (IV)

$C_6H_5COCH_2NHCOCH_3$ (VIII)

An attempt to degrade this benzoyl derivative to α-aminoacetophenone by heating with 6 N hydrochloric acid was unsuccessful: benzoic acid and glycine hydrochloride were obtained instead. However, this does not prove that the compound was an O-acyl derivative. Indeed, as Bowman[7] has shown, only unsubstituted diethyl acylmalonates can be hydrolyzed and decarboxylated to ketones. With compounds of the type $R'COCR''(CO_2R)_2$ (V) (R = Et, R′ = alkyl or aryl, R″ = alkyl), cleavage of the acyl-carbon bond occurs preferentially.[7]

Methods have been developed in recent years which do permit converting esters of this type to ketones. Bowman has shown that the dibenzyl esters (V, R = $C_6H_5CH_2$) can be hydrogenolyzed and decarboxylated,[8] and that the bis-tetrahydropyranyl esters (V, R = $\overline{OCH_2CH_2CH_2CH_2CH}$–) can be pyrolyzed,[9] while Fonken and Johnson,[10] and also Puterbaugh, Swamer and Hauser,[11] have made use of the facile acid-catalyzed cleavage of the di-t-butyl esters (V, R = CMe_3). Application of such a procedure to the preparation and degradation of an appropriate ester of benzoylacetamidomalonic acid appeared desirable not only in order to prove whether C- or O-benzoylation had taken place, but also for the development of a general method of synthesizing aminoketones of the type shown in the introductory paragraph.

The present report deals with the application of the t-butyl ester method.[12] Commercially available[13] diethyl acetamidomalonate (I) was saponified to the free acid, which was converted to the di-t-butyl ester VI by the method of McCloskey.[10,14]

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) Presented in part before the Medicinal Chemistry Division of the American Chemical Society in San Francisco, Calif., April 14, 1958; *cf.* Abstracts of Papers, **133**, 7M (1958).

(3) (a) A. Neuberger and J. J. Scott, *Nature*, **172**, 1093 (1953); (b) *J. Chem. Soc.*, 1820 (1954); (c) D. Shemin and C. S. Russell, THIS JOURNAL, **75**, 4873 (1953).

(4) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469, 2473 (1949).

(5) C. E. Dalgliesh, *J. Chem. Soc.*, 90 (1949).

(6) M. Viscontini and K. Adank, *Helv. Chim. Acta*, **35**, 1342 (1952).

(7) R. E. Bowman, *J. Chem. Soc.*, 322 (1950); *cf.* H. G. Walker and C. R. Hauser, THIS JOURNAL, **68**, 1386 (1946).

(8) R. E. Bowman, *J. Chem. Soc.*, 325 (1950).

(9) R. E. Bowman and W. D. Fordham, *ibid.*, 3945 (1952).

(10) G. S. Fonken and W. S. Johnson, THIS JOURNAL, **74**, 831 (1952).

(11) W. H. Puterbaugh, F. W. Swamer and C. R. Hauser, *ibid.*, **74**, 3438 (1952).

(12) Hydrogenolysis of dibenzyl benzoylacetamidomalonate failed to yield α-acetamidoacetophenone (see Experimental). Attempts to prepare bis-(tetrahydropyranyl) acetamidomalonate by Bowman's method[9] failed.

(13) Matheson, Coleman and Bell, Norwood (Cincinnati), Ohio.

(14) A. L. McCloskey, G. S. Fonken, R. W. Kluiber and W. S. Johnson, *Org. Syntheses*, **34**, 26 (1954).

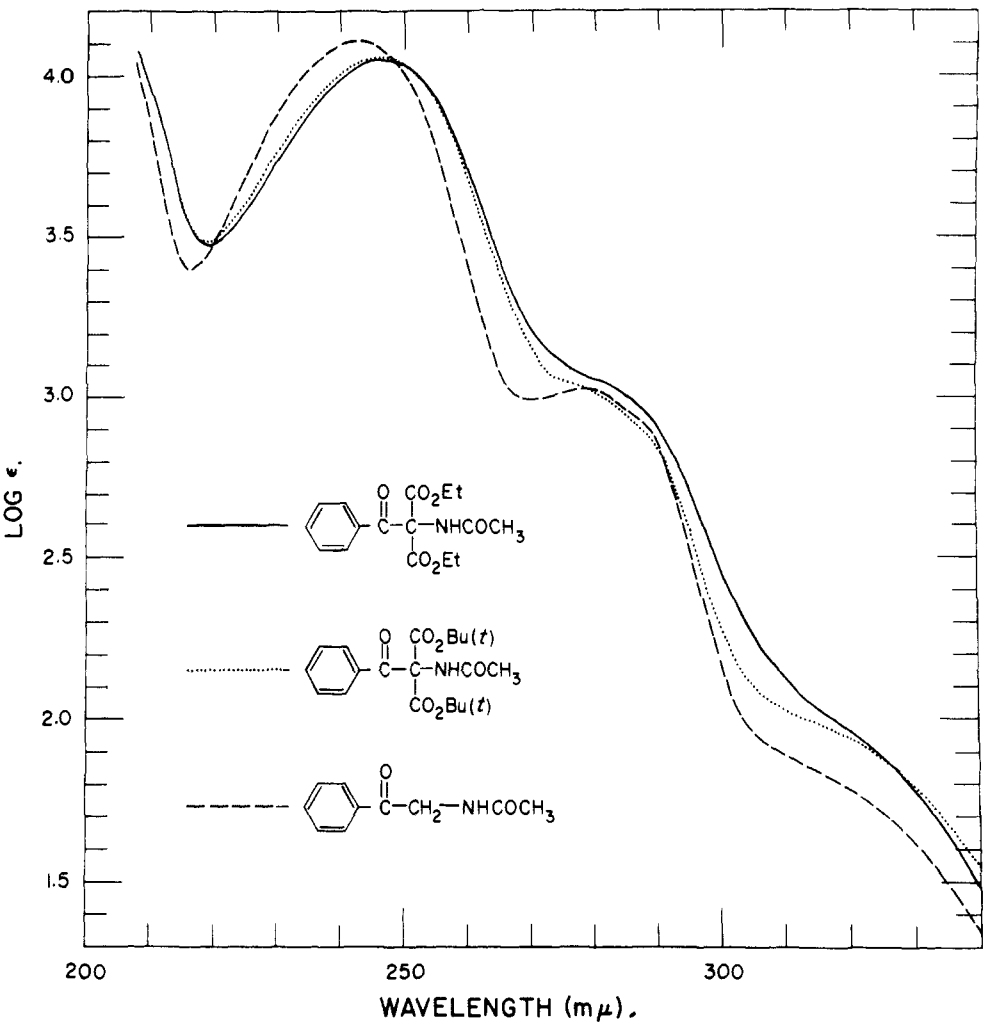


Fig. 1.—Ultraviolet absorption spectra in absolute ethanol of: ———, diethyl benzoylacetamidomalonate (II); ....., di-*t*-butyl benzoylacetamidomalonate (VII); – – – –, α-acetamidoacetophenone (VIII).

The sodio derivative of VI, when treated with benzoyl chloride, afforded di-*t*-butyl benzoylacetamidomalonate (VII), which was cleaved to α-acetamidoacetophenone (VIII) by refluxing with *p*-toluenesulfonic acid in 1,1,2-trichloroethane. Formation of VIII proves the C-acyl structure VII. The ultraviolet absorption spectrum of VII (Fig. 1) was found to be almost identical with that of diethyl benzoylacetamidomalonate; therefore, the latter has also the C-acyl structure II, and not one of the O-acyl structures III[5] or IV[6]. The absorption maximum at 245.5 and 246.5 mμ, respectively, is characteristic of the C_6H_5COC system: the corresponding maximum is present at 240–242 mμ in acetophenone,[15] at 242.5 mμ in ethyl benzoylacetate,[16] at 242.5 mμ in VIII, but is shifted to 228 mμ in alkyl benzoates.[17]

By the same procedure, *p*-nitro- and *p*-chloro-α-acetamidoacetophenone were prepared readily from VI and the appropriate acid chlorides. In the aliphatic series, 1-acetamido-2-heptanone and 1-acetamido-2-tridecanone were obtained without isolation of the intermediary malonic esters; they were hydrolyzed in good yields to the corresponding aminoketone hydrochlorides. This procedure appears more direct than the previously reported[18] preparations of the homologous 1-amino-2-alkanone hydrochlorides. Acylation of VI with β-carbomethoxypropionyl chloride, followed by decarbalkoxylation and saponification, gave δ-acetamidolevulinic acid,[19] $CH_3CONHCH_2COCH_2CH_2CO_2H$ (IX), in 10% yield. Thus, acylation of di-*t*-butyl acetamidomalonate (VI) would seem to afford a convenient method for the preparation of a number of α-aminoketone derivatives.

Experimental[20]

Acetamidomalonic Acid.—A suspension of 63 g. of diethyl acetamidomalonate (I)[13] in 120 ml. of an ice–water

(15) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934); T. W. Campbell, S. Linden, S. Godshalk and W. G. Young, THIS JOURNAL, **69**, 880 (1947); R. P. Mariella and R. R. Raube, *ibid.*, **74**, 521 (1952).

(16) R. A. Morton, A. Hassan and T. C. Calloway, *J. Chem. Soc.*, 883 (1934).

(17) H. E. Ungnade and R. W. Lamb, THIS JOURNAL, **74**, 3789 (1952).

(18) (a) M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and S. Archer, *ibid.*, **70**, 2884 (1948); (b) J. P. Vila and B. Massó, *Anales real soc. espan. fis. y quim.*, **48B**, 155 (1952) [*C. A.*, **47**, 6871*a* (1953)].

(19) A. Neuberger, J. J. Scott and L. Shuster, *Biochem. J.*, **66**, 137 (1956).

(20) Melting points are corrected and were determined with the

slurry was treated with 120 ml. of 5 *N* sodium hydroxide, stirred magnetically until a clear solution was obtained, and kept at room temperature for 1 hr. The solution, after dilution to about 600 ml., was passed through a column containing 250 g. of Amberlite CG-120,[21] previously converted to the hydrogen form, which was then washed with about 800 ml. of water. The eluate, after freeze-drying, yielded 46.8 g. (100%) of colorless crystalline acid, m.p. 120° (foaming). A sample, recrystallized from acetone–pentane, formed small needles which melted with foaming at 122°, resolidified, and remelted with darkening at 206°. The compound was very soluble in water and alcohol, soluble in hot acetone, and difficultly soluble in benzene, chloroform and ether.

Anal. Calcd. for $C_5H_7O_5N$: C, 37.27; H, 4.38; N, 8.69. Found: C, 37.07; H, 4.47; N, 8.75.

Di-*t*-butyl Acetamidomalonate (VI).—A chilled suspension of 15 g. of acetamidomalonic acid in 100 ml. of dry ether and 75 ml. of liquid isobutylene was treated with 3.8 ml. of concd. sulfuric acid and shaken in a 500-ml. pressure bottle[14] for 18 hr. The mixture, which consisted of two liquid layers, became homogeneous upon addition of benzene. It was treated with 20 g. of solid potassium carbonate, then with ice and water. The organic layer was washed with aqueous potassium carbonate, dried over potassium carbonate, and evaporated *in vacuo*. The pale solid (14.9 g., 58.5%) was recrystallized from hexane to yield 13.4 g. of colorless elongated prisms, m.p. 89–90.5°. A sample, once more recrystallized, melted at 90.1–90.4°.

Anal. Calcd. for $C_{13}H_{23}O_5N$: C, 57.12; H, 8.48; N, 5.13. Found: C, 57.25; H, 8.54; N, 4.97.

Di-*t*-butyl Benzoylacetamidomalonate (VII).—A mixture of 4.35 g. of VI, 0.573 g. of sodium hydride, 32 ml. of dry benzene and 0.032 ml. of *t*-butyl alcohol was stirred and refluxed with exclusion of moisture during 4 hr. It then was treated dropwise with 2.04 ml. (2.47 g., 10% excess) of benzoyl chloride in 15 ml. of benzene, stirred and refluxed for 1 more hr., cooled, and treated (stirring) with a few chips of Dry Ice, then with 15 ml. of water. The aqueous phase was extracted with additional benzene, and the benzene layers were washed thrice with sodium chloride solution, dried and evaporated *in vacuo*. The residue, after digestion with hot hexane and cooling, yielded 3.37 g. (56%) of colorless elongated leaflets, m.p. 158–159° dec., unchanged after recrystallization from benzene-hexane, λ_{max}^{EtOH} 245.5 mμ (log ε 4.05).

Anal. Calcd. for $C_{20}H_{27}O_6N$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.58; H, 7.11; N, 3.77.

Diethyl benzoylacetamidomalonate (II) was similarly prepared from 10.86 g. of I and 1.21 g. of sodium hydride in 20 ml. of benzene and 0.06 ml. of absolute ethanol with 5.95 ml. of benzoyl chloride in 10 ml. of benzene. The crude product was recrystallized once from benzene–hexane (11.87 g., 74%, m.p. 111–122°), then from 30% methanol to yield 9.93 g. (62%) of colorless needles, m.p. 124.6–125.5° (lit. 125°,[5] 122–123°[6]), λ_{max}^{EtOH} 246.5 mμ (log ε 4.05).

Refluxing II with 6 *N* hydrochloric acid for 17 hr. gave a reaction mixture from which benzoic acid and glycine hydrochloride were isolated in 65 and 100% yields, respectively.

Di-*t*-butyl (*p*-nitrobenzoyl)-acetamidomalonate was prepared from 2.86 g. of VI, 0.377 g. of sodium hydride and 2.13 g. of *p*-nitrobenzoyl chloride. The crude product was crystallized from benzene–hexane to yield 1.83 g. of colorless prismatic needles, m.p. 136.5–137.5° dec. Another 0.91 g., m.p. 131–134°, was isolated from the mother liquor; total yield 62%. Recrystallization from benzene–hexane gave material, m.p. 137.5–138.2° dec., λ_{max}^{EtOH} 265 mμ (log ε 4.15).

Anal. Calcd. for $C_{20}H_{26}O_8N_2$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.00; H, 6.10; N, 6.48.

Di-*t*-butyl (*p*-chlorobenzoyl)-acetamidomalonate was obtained from 2.86 g. of VI and 1.5 ml. (2.04 g.) of *p*-chlorobenzoyl chloride. The crude product crystallized upon digestion with hot hexane; yield 2.89 g. (67%), m.p. 129–131° dec. Repeated recrystallizations from 60% methanol, then from 1:10 benzene–hexane provided colorless needles, m.p. 143.1–143.8° dec.

Anal. Calcd. for $C_{20}H_{26}O_6NCl$: C, 58.32; H, 6.36; Cl, 8.61. Found: C, 58.37; H, 6.07; Cl, 8.57.

α-Acetamidoacetophenone (VIII).—Di-*t*-butyl benzoylacetamidomalonate (VII) (1.133 g.) was refluxed with 0.05 g. of anhydrous *p*-toluenesulfonic acid in 10 ml. of 1,1,2-trichloroethane for 10 hr. The mixture was cooled, shaken with sodium carbonate solution and extracted with chloroform in a continuous extractor. The extract was evaporated and the residue recrystallized from benzene–hexane to yield 0.434 g. (81.5%)[22] of long colorless needles, m.p. 81.5–86.5°. Another recrystallization raised the m.p. to 86.8–88.2° (lit.[4] 86–87°), no mixed melting point depression and identical infrared spectrum with a sample, m.p. 87.1–88.4°, prepared by Wolfheim's[23] method; λ_{max}^{EtOH} 242.5 mμ (log ε 4.11), 279.5 mμ (log ε 3.02).

***p*-Nitro-α-acetamidoacetophenone** was obtained analogously in 69% yield after recrystallizing the evaporation residue from a small amount of ethyl acetate; m.p. 155–159°. Chromatography on neutral alumina, elution with chloroform and recrystallization from ethyl acetate furnished pale yellow needles, m.p. 158.5–161.5° (lit.[4] 161–163°), λ_{max}^{EtOH} 263 mμ (log ε 4.15).

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.23; H, 4.69; N, 12.66.

***p*-Chloro-α-acetamidoacetophenone**, prepared similarly from crude di-*t*-butyl (*p*-chlorobenzoyl)-acetamidomalonate in 75% yield, crystallized from ethyl acetate in colorless leaflets, m.p. 173–176° (lit.[24] 174–177°).

Anal. Calcd. for $C_{10}H_{10}O_2NCl$: C, 56.75; H, 4.76; Cl, 16.75. Found: C, 57.02; H, 4.94; Cl, 16.68.

1-Acetamido-2-heptanone.—Reaction of 2.95 g. of VI with 0.389 g. of sodium hydride and 1.65 ml. (1.60 g.) of caproyl chloride furnished 3.92 g. of yellow oil, which could not be obtained crystalline. This oil was refluxed with 0.175 g. of *p*-toluenesulfonic acid in 35 ml. of 1,1,2-trichloroethane for 6 hr., and the mixture was worked up as in the preparation of VIII. The evaporation residue, after chromatography on neutral alumina, elution with chloroform and crystallization from hexane, yielded 0.771 g. (42%) of pale tan scales, m.p. 85–89°. Further recrystallizations afforded colorless scales, m.p. 88.1–88.8°.

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.42; H, 10.07; N, 8.24.

Refluxing 411 mg. of this compound with 2 ml. of 10% hydrochloric acid for 7 hr., evaporating the solution on the steam-bath, reevaporating twice with addition of ethanol and recrystallizing from ethanol–ether gave 325 mg. (82%) of **1-amino-2-heptanone hydrochloride**, colorless scales, m.p. 166.5–168° dec. (lit.[18a] m.p. 159–162°).

Anal. Calcd. for $C_7H_{15}ON\cdot HCl$: Cl, 21.41. Found: Cl, 21.46.

1-Acetamido-2-tridecanone was prepared analogously from 3.075 g. of VI, 0.405 g. of sodium hydride and 2.71 g. of lauroyl chloride. The partly solid evaporation residue, obtained after the treatment with *p*-toluenesulfonic acid, was crystallized from chloroform–hexane; yield 1.575 g. (55%), m.p. 105.5–107.5°. Chromatography and repeated recrystallization provided tiny colorless soapy scales, which were strongly electrified, m.p. 107.8–108.3°.

Anal. Calcd. for $C_{15}H_{29}O_2N$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.77; H, 11.14; N, 5.54.

1-Amino-2-tridecanone hydrochloride was obtained in 97% yield by refluxing 1.06 g. of the acetamido derivative with 5 ml. of 10% hydrochloric acid for 10 hr. It crystallized from ethanol–pentane in colorless glistening electrified scales, m.p. 160–161° dec.

Anal. Calcd. for $C_{13}H_{27}ON\cdot HCl$: Cl, 14.19. Found: Cl, 14.21.

δ-Acetamidolevulinic Acid (IX).—Reaction of 4.12 g. of VI with 0.543 g. of sodium hydride and 2.76 ml. (3.4 g., 50% excess) of β-carbomethoxypropionyl chloride[3b] gave a pale yellow oil, which was refluxed with 0.2 g. of *p*-toluenesulfonic acid in 20 ml. of 1,1,2-trichloroethane for 4 hr. The

Hershberg apparatus. Ultraviolet spectra were recorded with the Cary spectrophotometer. Microanalyses were performed by Dr. W. C. Alford and collaborators.

(21) A strongly acidic cation exchange resin produced by Rohm and Haas Co., Philadelphia, Pa.

(22) Refluxing 2.5 g. of VII with 0.1 g. of *p*-toluenesulfonic acid, 0.5 ml. of acetic anhydride and 25 ml. of glacial acetic acid[10] for 2 hr., adding excess alkali and extracting with benzene yielded 60% of product, m.p. 81–85°.

(23) F. Wolfheim, *Ber.*, **47**, 1440 (1914).

(24) L. L. Bambas, H. D. Troutman and L. M. Long, THIS JOURNAL, **72**, 4445 (1950).

dark yellow oil (1.65 g.), obtained after treatment with sodium carbonate solution, extraction with chloroform and evaporation, was shaken with 6.5 ml. of 2 *N* sodium hydroxide for 4 hr. The aqueous solution was extracted with chloroform, passed through a column of Amberlite CG-120[21] in the hydrogen form, decolorized with Norit and freeze-dried. The tan solid (1.61 g.) was crystallized from ethyl acetate to yield 276 mg. (10.5%) of product, m.p. 91–94°. Another recrystallization afforded small colorless prisms, m.p. 95.5–96.5° (lit.[19] 97°), no depression with an authentic sample.[19]

Dibenzyl Acetamidomalonate. (a) By Acetylation of Dibenzyl Aminomalonate.—Dibenzyl aminomalonate (7.14 g.), prepared by Kissman and Witkop's[25] procedure, was treated with 5 ml. of acetic anhydride. The mixture rapidly solidified to a magma, which after 3 hr. at room temperature was boiled with 15 ml. of ethanol for a few moments. The solution, when treated with water to incipient turbidity, deposited 7.39 g. (91%) of colorless needle-shaped prisms, m.p. 111–113°. Recrystallization from ethyl acetate–hexane yielded 6.89 g. of colorless prismatic needles, m.p. 112.6–113.3°. A sample, recrystallized from methylene chloride–pentane, had m.p. 112.8–113.3°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.55; H, 5.67; N, 3.99.

(25) H. M. Kissman and B. Witkop, THIS JOURNAL, **75**, 1967 (1953).

(b) By **Transesterification.**—Following essentially Bowman's technique,[8] a magnetically stirred suspension of 2.40 g. of sodium hydride in 50 ml. of dry benzene was treated dropwise with 5 ml. of absolute ethanol, then with 21.71 g. of I and 21.65 g. of benzyl alcohol, which were rinsed in with 100 ml. of dry benzene. The mixture was stirred for 15 min., then slowly distilled (with continued stirring) through a Fenske column until the temperature at the head reached 79°. The residue was cooled and treated with 7 ml. of glacial acetic acid, then with water. The organic layer was washed with sodium chloride solution, dried over sodium sulfate, evaporated, and the residue crystallized from ethyl acetate–hexane to yield 17.23 g. (50%) of colorless crystalline solid, m.p. 108.5–110°. Recrystallization from 50% methanol provided colorless needles, m.p. 112.6–113.7°, which did not depress the melting point of material prepared by method (a).

An attempt to obtain the benzoyl derivative of this ester by the procedure used in the preparation of II and VII resulted in a crystalline product, m.p. 75–86°, the melting point of which was raised to 86–91° by recrystallization from 75%, then from absolute methanol, but which could not be obtained pure. Hydrogenolysis of this material with palladium-on-strontium carbonate[8] or with palladium-on-carbon,[25] followed by heating failed to yield any α-acetamidoacetophenone (VIII).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Formation of Homopiperazine Rings by the Lithium Aluminum Hydride Catalyzed Rearrangement of Some Piperidone Oximes in the Phenothiazine Series

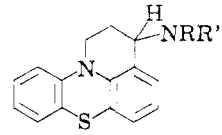
BY M. HARFENIST AND E. MAGNIEN

RECEIVED JUNE 6, 1958

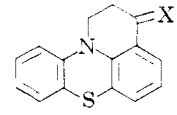
Lithium aluminum hydride reduction of the 4-piperidone oxime (II) gave only the homopiperazine IIIa, with ring enlargement. Similarly, lithium aluminum hydride reduction of the piperidinedione monoxime IVa and of 2-acetylphenothiazine oxime gave the homopiperazine IIIc and 2-ethylaminophenothiazine, respectively, as the only detectable bases. The compound Ia was prepared by two different methods for comparison of its pK'a value with those of the compounds III. Aqueous dimethyl sulfoxide was found to be a most satisfactory solvent for the titrations which were required. The pK'_a of N-*n*-propylaniline hydrochloride in this solvent mixture and in water were nearly identical.

A recent publication[1] gave the details of the preparation in excellent yield of what was quite reasonably presumed to be the tetracyclic amine Ia, made by lithium aluminum hydride reduction of the oxime IIA. Since compound I might be looked on as a "tied-back" 3-(10-phenothiazinyl)-propylamine and therefore would be related to a number of useful and interesting drugs, we wished to prepare some dialkylamino analogs of this substance.

Our reduction of the oxime IIa by means of lithium aluminum hydride gave the presumed Ia in 85% yield. This was monoacetylated readily, presumably to Ib. The monoacetyl compound was reduced by lithium aluminum hydride to a monoethyl compound, presumed to be Ic. However, an attempt to acetylate the presumed Ic gave no acetyl compound.



Ia, R = R' = H
Ib, R = CH_3CO, R' = H
Ic, R = C_2H_5, R' = H
Id, R = R' = CH_3



IIa, X = NOH
IIb, X = O

Since no obvious reason for this failure could be found in the chemical properties which would be anticipated for the structure Ic, it seemed likely that Beckmann-like rearrangement[2a] of the oxime II had occurred during the reduction procedure, leading to ring expansion to an intermediate having a 7-membered ring. The latter then must have been reduced to the homopiperazine IIIa.

The structure of the product III could best be corroborated by comparison of the pK'_a values for any of the compounds IIIa-c with pK'_a values for compounds known to be of type I.

The corresponding compound I with its six-membered ring still intact was prepared for comparison purposes, both by the Bouveault–Blanc re-

(1) E. F. Godefroi and E. L. Wittle, *J. Org. Chem.*, **21**, 1163 (1956). Since this work was written up for publication, summaries of two pertinent Japanese papers have become available. In one [H. Kano, Y. Makizumi and K. Ozata, *C. A.*, **51**, 6644 (1957)] procedures similar to those of Godefroi and Wittle have been reported, and the structures Ia and 10-(or 4-)chloro Ia (from 2-chlorophenothiazine) have been ascribed to the products. In another publication [K. Fujii, *C. A.*, **52**, 5417 (1958)] the compounds Ia and 10-chloro-Ia were reported as made by a formamide procedure similar to that reported below. The corresponding compounds by the two methods are reported to have similar melting points, well within the reproducibility which we have found for these high-melting salts, and no mention is made of the fact that different products are obtained by the different methods.

(2) (a) R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.*, **20**, 1757 (1955); E. Larsson, *C. A.*, **44**, 1898 (1950). (b) D. R. Smith, M. Maienthal and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).