which on crystallization from ethanol–water melted at 217.4–217.6°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69. Found: C, 67.09; H, 7.91.

2,4-Diaminocumene Dibenzoate.—The dibenzoyl derivative was prepared by the Schotten–Baumann procedure. The white product was crystallized from ethanol, m.p. 241.2–241.5°.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.14. Found: C, 77.30; H, 6.44.

2,4-Diaminocumene Dihydrochloride.—The diaminocumene was best stored as the hydrochloride which was stable toward air oxidation. This derivative was prepared by passing dry HCl into an ether solution of the amine and filtering the resulting precipitate; m.p. about 275° dec.

Anal. Calcd. for $C_9H_{16}N_2Cl_2$: C, 48.43; H, 7.18. Found: C, 48.02; H, 7.41.

2,4-Dinitroethylbenzene.—This substance was prepared according to the procedure of Borsche[16]; yield 56%, b.p. 126° (2 mm.), n^{25}D 1.5655. On fractionation of the 2,4-dinitroethylbenzene it was found that the first fraction on cooling and standing yielded a considerable amount of a solid which after crystallization from methanol melted at 57–57.8°. Brady, Day and Allam[17] report 2,6-dinitroethylbenzene melts at 57.5°.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.08. Found: C, 48.71; H, 4.59.

2,4-Diaminoethylbenzene.—This substance was prepared according to the procedure used for diaminocumene; yield 86%, b.p. 127° (2 mm.), n^{25}D 1.6088. 2,4-Diaminoethyl benzene has been previously reported by Weisweiller,[18] but he gave no physical constants.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.59; H, 8.83. Found: C, 70.63; H, 9.29.

2,4-Diaminoethylbenzene Dibenzoate.—The dibenzoate was prepared by the Schotten–Baumann reaction. It was purified by crystallization from glacial acetic acid; m.p. 231.2–231.6°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.82. Found: C, 76.68; H, 6.24.

2,4-Diaminoethylbenzene Dihydrochloride.—The free diamine was very sensitive to air oxidation and was stored as the hydrochloride; m.p. about 270° dec.

Anal. Calcd. for $C_9H_{14}N_2Cl_2$: C, 45.93; H, 6.70. Found: C, 45.88; H, 7.03.

Acknowledgment.—This research was supported by the Office of Naval Research under contract NR-055-149. The carbon–hydrogen analyses reported in this paper were made by C. F. Geiger of Chaffey College, Ontario, California.

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[16] W. Borsche, *Ann.*, **386**, 365 (1919).

[17] O. L. Brady, J. N. E. Day and P. S. Allam, *J. Chem. Soc.*, 978 (1928).

[18] Weisweiller, *Monatsh.*, **21**, 41 (1900).

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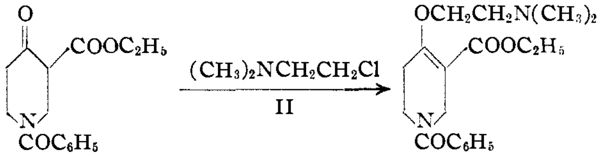
[CONTRIBUTION FROM HAVEMEYER LABORATORY, COLUMBIA UNIVERSITY]

The Alkylation of β-Ketoesters with β-Dimethylaminoethyl Chloride[1]

BY W. VON E. DOERING AND SARA JANE RHOADS[2]

β-Dimethylaminoethyl chloride reacts with sodio-1-benzoyl-3-carbethoxy-4-piperidone to give C-alkylation, with sodio- and potassio-2-carbethoxycyclohexanone to give the O- and C-alkylated products and with sodio-acetoacetic ester to give the C-alkylated product.

A hypothetical path for the synthesis of homomeroquinene[3] involves the alkylation of 1-benzoyl-3-carbethoxy-4-piperidone (I)[4] with a two carbon fragment convertible to a vinyl group.



I III

One fragment of this type, β-phenoxyethyl iodide, was found by Stork and McElvain[5] to be insufficiently reactive to alkylate I, although benzyl chloride and ethyl iodide reacted smoothly, the latter leading to a successful synthesis of cincholoipon. β-Dimethylaminoethyl chloride (II) seemed promising as a very reactive halide which is reported to give C-alkylation with acetoacetic ester[6] and with 2-carbethoxycyclohexanone[7] and is closely related to β-diethylaminoethyl chloride, a reagent that has been reported to give C-alkylation with acetoacetic ester[8] and 2-carbethoxycyclohexanone.[9]

In refluxing *t*-butyl alcohol, benzene, toluene or xylene, I reacts with II to give the product of O-alkylation, ethyl 1-benzoyl-4-(β-dimethylaminoethoxy) - 1,2,5,6 - tetrahydropyridine - 3 - carboxylate (III), instead of the expected C-alkylation product. The structural assignment depends primarily on the facts that III decolorizes bromine and potassium permanganate instantly, reacts with alcoholic hydrogen chloride to regenerate I and is hydrolyzed by aqueous hydrochloric acid to give carbon dioxide, benzoic acid, a small amount of 4-piperidone hydrochloride and β-dimethylaminoethanol (recovered as the benzoate).

Although a few examples of O-alkylation are known,[10,11,12] it is of interest to determine whether II characteristically reacts by O- rather than C-alkylation. With ethyl acetoacetate reaction is by C-alkylation (IV) as previously asserted but not proved.[6] Acid hydrolysis of the product gives 1-dimethylaminopentanone-4 (V) in good yield. On the other hand, 2-carbethoxycyclohexanone

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[1] Taken from a dissertation submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

[2] Vassie James Hill Fellow of the American Association of University Women, 1947–1948.

[3] R. B. Woodward and W. E. Doering, THIS JOURNAL, **67**, 860 (1945).

[4] S. M. McElvain and G. Stork, *ibid.*, **68**, 1049 (1946).

[5] G. Stork and S. M. McElvain, *ibid.*, **68**, 1053 (1946).

[6] English Patent 167,781 [*Chem. Centr.*, **92**, IV, 1223 (1921)].

[7] Grewe, *Ber.*, **76**, 1072 (1943).

[8] English Patent 267,169 [*Chem. Centr.*, **100**, I, 1967 (1929)]. F. Giral and M. L. Cascajares, *Ciencia* (*Mex.*), **5**, 105 (1944) [*C. A.*, **41**, 4891 (1947)].

[9] J. A. Barltrop, *J. Chem. Soc.*, 399 (1947).

[10] S. Archer and M. G. Pratt, THIS JOURNAL, **66**, 1656 (1944).

[11] C. D. Hurd and K. Wilkinson, *ibid.*, **70**, 739 (1948).

[12] J. C. Sheehan and C. E. Mumaw, *ibid.*, **72**, 2127 (1950).

(VI) which is more closely allied to I reacts in *t*-butyl alcohol to give mainly O-alkylated products (72%) accompanied by some C-alkylation (19%). In toluene, Grewe[7] reported VI to react by C-alkylation but on repetition of this work it has been found that the actual course involves both O-alkylation (42%) and C-alkylation (42%). The O-alkylated product is recognized by its reconversion to VI with ethanolic hydrogen chloride and by its hydrolysis to cyclohexanone with aqueous acid. Apparently there is no uniformity in the behavior of II or in the behavior of I[5] and VI[12,13] which give both types of alkylation.

Experimental[14]

Ethyl 1-Benzoyl-4-(β-dimethylaminoethoxy)-1,2,5,6-tetrahydropyridine-3-carboxylate (III).—In this and subsequent alkylations, the reaction vessel was a 3-necked flask, equipped with mercury-sealed stirrer, condenser and dropping funnel, filled with dry nitrogen, and protected against atmospheric moisture. 1-Benzoyl-3-carbethoxy-4-piperidone (I) was prepared according to McElvain and Stork[4] in good yield (66%) as a cream-colored solid, m.p. 56–58°, which crystallized as colorless needles from ether at −10°, m.p. 60–61° (reported[4] m.p. 54–56°). β-Dimethylaminoethyl chloride (II) was prepared as the hydrochloride (90% yield) according to Slotta and Behnisch[15] and converted to the free base (60–70% yield) shortly before use by mixing a cold, aqueous solution of the hydrochloride with cold, concentrated potassium hydroxide, extracting with pentane, drying and distilling; b.p. 109–111° (reported 109°[15] and 109–110°[16]).

The addition of 6.1 g. (0.022 mole) of I in 10 cc. of anhydrous *t*-butyl alcohol to a solution of potassium *t*-butoxide (prepared from 0.87 g. (0.022 mole) of potassium and 30 cc. of anhydrous *t*-butyl alcohol) produced an immediate precipitate. To the gently refluxing mixture, 3.0 g. (0.028 mole) of II in 3 cc. of toluene was added over a period of 30 minutes, after which refluxing was continued three hours. A precipitate weighing 1.73 g. and consisting mainly of potassium chloride was filtered and washed with ether. The filtrate and ether washings were concentrated *in vacuo* to a viscous, dark red oil which was triturated with ether leaving undissolved an orange-red, polymer-like substance. An extract of the ether solution with ice-cold, 2 *N* hydrochloric acid was rapidly extracted twice with ether, chilled, made strongly alkaline with ice-cold, 20% sodium hydroxide and extracted with ether. The ether solution was washed several times with saturated salt solution, filtered through anhydrous sodium sulfate and evaporated on the steam-bath. A benzene solution of the residue was concentrated, finally being heated on a steam-bath *in vacuo* for several hours. The residual, viscous oil (III, 3.2 g., 42%) gave a negative ferric chloride test, decolorized potassium permanganate instantly and added bromine rapidly forming an insoluble, yellow bromine derivative which evolved hydrogen bromide on warming. III was purified by molecular distillation at 0.6 micron at a bath temperature of 145–147°.

Anal. Calcd. for $C_{19}H_{26}O_4N_2$: C, 65.88; H, 7.57; N, 8.09. Found: C, 65.26; H, 7.43; N, 7.93.

The **methiodide** of III formed spontaneously on mixing III and methyl iodide and could be crystallized from acetone–alcohol, m.p. 159–160°.

Anal. Calcd. for $C_{20}H_{29}O_4N_2I$: C, 49.19; H, 5.99; N, 5.74; I, 25.99. Found: C, 49.00; H, 6.32; N, 6.16; I, 25.06.

The **picrate** of III prepared from saturated, absolute ethanolic picric acid, m.p. 86–88° crude, was crystallized from absolute ethanol, m.p. 89–91°.

Anal. Calcd. for $C_{25}H_{29}O_{11}N_5$: C, 52.18; H, 5.08; N, 12.17. Found: C, 52.20; H, 5.25; N, 12.00.

Reaction of III with Ethanolic Hydrogen Chloride.—A solution of 2.00 g. of purified III in 10 cc. of absolute ethanol was saturated with dry hydrogen chloride, allowed to stand one hour at room temperature, diluted with water, cooled and extracted with ten portions of ether to give 1.42 g. (90%) of I, m.p. 60–61°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.23. Found: C, 65.64; H, 6.56.

Reaction of III with Aqueous Hydrogen Chloride.—Boiling a solution of 3.2 g. of crude III in 100 cc. of 6 *N* hydrochloric acid for two hours produced the theoretical quantity of carbon dioxide. Benzoic acid in 96% of the theoretical yield was obtained directly by crystallization and by extraction with ether. Evaporation of the aqueous acid solution to dryness *in vacuo* afforded 2.35 g. of crude, sticky hydrochlorides, of which 2.21 g. was extracted with hot acetonitrile. On cooling, very crude material (m.p. *ca.* 85–140°) separated. Repeated recrystallization from acetonitrile accompanied by treatment with Norit permitted the isolation of a small quantity of 4-piperidone hydrochloride as fine needles, m.p. 145.5–147°.

Anal. Calcd. for $C_9H_{20}ON_2Cl_2$: C, 44.45; H, 8.29; N, 11.52; Cl, 29.16. Calcd. for $C_5H_{10}ONCl$: C, 44.29; H, 7.43; N, 10.33; Cl, 26.16. Found: C, 44.24; H, 7.41; N, 9.85; Cl, 25.53.

An authentic sample of 4-piperidone hydrochloride, prepared from I under the same conditions, melted at 147.5–149° after recrystallization from acetonitrile and in admixture with the material obtained above showed no depression of m.p. Koenigs and Neumann report m.p. 147–149°.[17]

Further the dibenzal derivatives of both samples were prepared according to Ruzicka and Farnasir[18] and in admixture showed no depression of m.p. (observed 274–276°; reported[18] 275–277°).

When the methiodide of III was treated in the same way, 4-piperidone hydrochloride identified as the dibenzal derivative was also obtained.

An aqueous solution (5 cc.) of the crude hydrochlorides (0.6 g.) obtained above as the initial product of the decarboxylation of III was stirred overnight with 2.8 g. of potassium carbonate and 0.7 g. of benzoyl chloride in 4 g. of chloroform. The chloroform solution was separated, washed with ammonium hydroxide and with water, dried over anhydrous sodium sulfate and concentrated. The residual oil was evaporatively distilled at 0.5 mm. and a bath temperature of 160–170°. Treatment of 0.22 g. of the distilled oil with picric acid in benzene produced the yellow **picrate of β-dimethylaminoethyl benzoate**, m.p. 210–211° after recrystallization from water (0.07 g., 15%). Mixed with an authentic sample (*vide infra*), this picrate showed no depression in m.p.

Anal. Calcd. for $C_{17}H_{18}O_9N_4$: C, 48.35; H, 4.30. Found: C, 48.04; H, 4.49.

β-Dimethylaminoethyl Benzoate Picrate.—A solution of 1.0 g. of β-dimethylaminoethanol in 10 cc. of benzene was treated with caution and cooling with 2.0 g. of benzoyl chloride. The benzene solution was shaken vigorously with saturated potassium carbonate, separated, dried by distilling some of the benzene and added to a benzene solution of picric acid. Recrystallization from water gave yellow needles, m.p. 210.5–212°.

Anal. Calcd. for $C_{17}H_{18}O_9N_4$: C, 48.35; H, 4.30; N, 13.27. Found: C, 48.46; H, 4.41; N, 13.42.

Ethyl α-(β-Dimethylaminoethyl)-acetoacetate (IV).—To a suspension of sodio acetoacetic ester, prepared from 2.3 g. of sodium sand and 13.0 g. of ethyl acetoacetate in 100 cc. of dry benzene, a solution of 12.1 g. of II in 10 cc. of benzene was added dropwise over a period of 30 minutes. The reaction mixture was refluxed six hours, filtered from 6.3 g. of insoluble salts and concentrated *in vacuo* on the steam-bath. The dark yellow residue was dried in ether solution by passing through sodium sulfate, concentrated again and distilled. The main product weighing 10.7 g., b.p. 87–90°

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(13) A. Kötz and A. Michaels, *Ann.*, **350**, 204 (1906); R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 1012 (1933); L. Ruzicka, L. Ehmann, M. W. Goldberg and H. Hosli, *Helv. Chim. Acta*, **16**, 833 (1933); M. Tiffeneau, B. Tchoubar, Mme. Saiaslambert and Mme. Le Tellier-Despre, *Bull. soc. chim. France*, 445 (1947).

(14) Melting points are corrected. Microanalyses are by Miss Lois May, the Elek Micro Analytical Laboratories and the Clark Microanalytical Laboratories.

(15) V. H. Slotta and R. Behnisch, *Ber.*, **68**, 757 (1935).

(16) L. Knorr, *ibid.*, **37**, 3507 (1904).

(17) E. Koenigs and L. Neumann, *ibid.*, **48**, 956 (1915).

(18) L. Ruzicka and V. Farnasir, *Helv. Chim. Acta*, **3**, 806 (1920).

at 3.5 mm., gave a blue-violet color with ferric chloride when carefully acidified to the neutral point.

The picrate of **IV** prepared in ethanol could be crystallized from methanol at −10°; yellow, rhombic prisms, m.p. 69–71°.

Anal. Calcd. for $C_{16}H_{22}O_{10}N_4$: C, 44.65; H, 5.15; N, 13.02. Found: C, 45.22; H, 5.18; N, 12.86.

1-Dimethylaminopentanone-4 (V).—When 3.0 g. of IV was refluxed with 3 *N* hydrochloric acid for two hours, the characteristic ferric chloride test became negative. The resulting solution was treated with excess potassium carbonate to give 2.0 g. of crude V. Distillation produced 1.3 g. (68%) of colorless oil, b.p. 65–68° at 32 mm.

The picrate of V crystallized from benzene as stout, yellow prisms, m.p. 79.5–80°.

Anal. Calcd. for $C_{13}H_{18}O_8N_4$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.78; H, 5.19; N, 15.61.

V semicarbazone was recrystallized from benzene–hexane mixture, m.p. 105–106.5°.

Anal. Calcd. for $C_8H_{18}ON_4$: C, 51.59; H, 9.74; N, 30.07. Found: C, 51.70; H, 10.09; N, 29.86.

1-Carbethoxy-2-(β-dimethylaminoethoxy)-cyclohexene (VII).—2-Carbethoxycyclohexanone[19] (VI, 6.8 g.) was alkylated with II (5.72 g.) by the same procedure as employed for the preparation of III, the reaction being refluxed six and a half hours. The acid-soluble fraction obtained from the reaction mixture weighed 6.3 g. (65% yield), b.p. 122–126° at 1.8 mm.

VII reacted rapidly with methyl iodide to give the **methiodide**, m.p. 166–173° (crude) and m.p. 178–178.5° after recrystallization from ethyl acetate–ethanol mixture.

Anal. Calcd. for $C_{14}H_{26}O_3NI$: C, 43.87; H, 6.84; N, 3.66. Found: C, 43.88; H, 6.65; H, 3.44.

VII (1.0 g.) in 3 cc. of absolute ethanol was saturated with dry hydrogen chloride and allowed to stand overnight. The addition of water precipitated an oil which was extracted with ether and converted to the 2,4-dinitrophenylhydrazone of VI, m.p. 143–150°. Repeated recrystallization from ethanol raised the m.p. to 153–156°. No depression was shown on mixing with an authentic sample of m.p. 156–157.5°. Ruhkopf reported m.p. 156°.[20]

Refluxing 0.244 g. of VII with 5 cc. of 6 *N* hydrochloric acid evolved the theoretical amount of carbon dioxide and produced an oil which was recovered by ether extraction and converted to the 2,4-dinitrophenylhydrazone. There was obtained 0.218 g. of cyclohexanone 2,4-dinitrophenylhydrazone (78% yield), m.p. 155–159.5° crude and m.p. 158.5–160° after crystallization. There was no depression of m.p. in admixture with authentic material m.p. 162°.

2-β-Dimethylaminoethyl-2-carbethoxycyclohexanone.—(a) When the previous alkylation was repeated with 10.5 g. of VI, 8.9 g. of product, b.p. 121–124° at 1.5 mm., was obtained. Warming 8.0 g. in 30 cc. of 2 *N* hydrochloric acid produced immediate turbidity. Exhaustive extraction with ether afforded 4.04 g. of VI identified as the 2,4-dinitrophenylhydrazone and corresponding to 72% O-alkylation. From the aqueous acid solution, a basic fraction was obtained distillation of which afforded 0.40 g. of β-dimethylaminoethanol and 1.50 g. of 2-β-dimethylaminoethyl-2-carbethoxycyclohexanone, b.p. 159–161° at 16 mm., identified as the picrate, m.p. 130–131°.[7] This yield corresponds to 19% C-alkylation in the reaction.

2-β-Dimethylaminoethyl-2-carbethoxycyclohexanone methiodide was prepared in ethyl acetate with methyl iodide. Recrystallized from ethanol–ethyl acetate, it melts from 136–137° to a cloudy liquid, clearing at 139°.

(b) The alkylation was repeated using the conditions employed by Grewe.[7] A dry, toluene solution of β-dimethylaminoethyl chloride was added dropwise to a boiling suspension of sodio-2-carbethoxycyclohexanone (from 15.0 g. of VI). The reaction mixture was refluxed for six hours, diluted with water and extracted with 1.5 *N* hydrochloric acid. The aqueous extract afforded 8.66 g. (42%) of material, b.p. 114–119° at 1 mm. upon treating with alkali, extraction with ether and distillation. This material gave a picrate, m.p. 122–127° (crude) and 129–130° after recrystallization from 95% ethanol. Grewe[7] reports 130°.

Four grams of the distilled product was warmed and finally boiled in 80 cc. of water containing 10 g. of barium hydroxide. The basic solution was acidified with hydrochloric acid, evaporated to one-half the original volume, cooled, made strongly alkaline with sodium hydroxide and extracted with ether. Concentration of the ether gave 0.71 g. of crude material from which 0.43 g. (15%) of 2-β-dimethylaminoethylcyclohexanone, b.p. 105–106° at 12 mm., was obtained on distillation. The picrate melted at 119–120° in agreement with Grewe[7] (m.p. 119°).

When a solution of 4.26 g. of the crude alkylation product was warmed momentarily with 2 *N* hydrochloric acid, an oil separated almost immediately. Exhaustive extraction with ether gave 1.27 g. of 2-carbethoxycyclohexanone forming the characteristic 2,4-dinitrophenylhydrazone, m.p. 154–155°. This result corresponds to 42% of O-alkylation in the original alkylation.

The ether-extracted aqueous acid solution was saturated with potassium carbonate and extracted with ether. Concentration left 2.15 g. of material distillation of which gave 0.13 g. of β-dimethylaminoethanol (identified as the picrate m.p. 93–94°) and 1.80 g. of 2-β-dimethylaminoethyl-2-carboethoxycyclohexanone, b.p. 152–157° at 16 mm. (picrate m.p. 130–131°). This amount corresponds to 42% of C-alkylation.

Refluxing 1.74 g. of the C-alkylated product with 10 cc. of 6 *N* hydrochloric acid afforded 1.00 g. of β-dimethylaminoethylcyclohexanone.

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[19] Prepared according to "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 531.

[20] H. Ruhkopf, *Ber.*, **72**, 1978 (1939).