

Studies in the Alicyclic Series. Part I. 1-Benzoylcycloalkenes as Acceptors in the Michael Condensation.

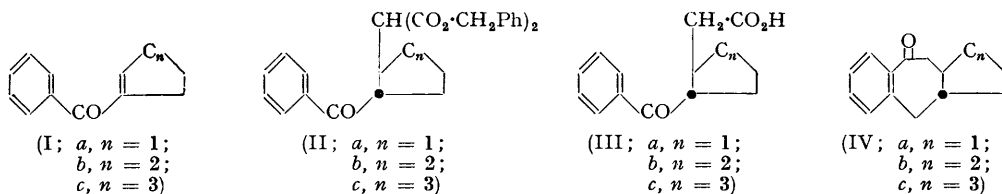
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[Reprint Order No. 5177.]

Michael condensation of 1-benzoylcycloalkenes with benzyl malonate affords products which can be transformed into 2-benzoylcycloalkylacetic acids. The latter can be cyclised to give linear tricyclic substances containing a central seven-membered ring.

THE Michael condensation has been employed extensively for the synthesis of alicyclic systems. (A review on "The Michael Condensation" will appear shortly: Bergmann, Ginsburg, and Pappo, "Organic Reactions," Wiley, New York.) In view of our interest in alicyclic systems containing seven-membered rings (cf. Ginsburg and Pappo, *J. Amer. Chem. Soc.*, 1953, 75, 1094) it seemed that tricyclic compounds containing a central seven-membered ring would be readily accessible through Michael condensation of 1-benzoylcycloalkenes with suitable hydrogen donors.

This expectation was realised when three acceptors of this type (I) were treated with benzyl malonate in the presence of potassium *tert.*-butoxide. The corresponding dibenzyl ester adducts (II) were obtained and then hydrogenolysed to give the malonic acids (Ginsburg and Pappo, *loc. cit.*; cf. *J.*, 1953, 1524). Decarboxylation of the latter led to the corresponding 2-benzoylcycloalkylacetic acids (III).



Reduction of the keto-acids by Huang-Minlon's procedure (*J. Amer. Chem. Soc.*, 1946, 68, 2487) led to the corresponding 2-benzoylcycloalkylacetic acids and their respective acid chlorides were treated with aluminium chloride, yielding the tricyclic ketones (IV). In (IVc), for example, one has a linear condensed system containing an aromatic ring and two seven-membered rings, isomeric with the angular system and more analogous with that present in colchicine. Certain derivatives of both systems are being prepared for pharmacological evaluation and will be described in a future communication.

The 2-benzoylcyclohexylacetic acid obtained had m. p. 74°. Colonge and Sibeud (*Compt. rend.*, 1952, 234, 530) described the synthesis of this compound from 2-benzoylcyclohexanone and ethyl chloroacetate, with hydrolysis, dehydration, and Raney-nickel reduction of the unsaturated acid thus obtained; their product had m. p. 58.5°. It has been shown that these are polymorphic forms of the substance and that their infra-red spectra in solution are identical. It appears therefore that in the Raney-nickel reduction the more stable stereochemical possibility is obtained. The semicarbazone of their product

of cyclisation had m. p. 202° upon recrystallisation from ethanol; the similar derivative prepared in this investigation had m. p. 205°. A mixture showed m. p. 204—205°.

Since the 2-benzoylcycloalkylacetic acids are obtained by means of several reactions involving strongly alkaline conditions, it seems reasonable to assign to them the *trans*-configuration. The *trans*-isomer would be diequatorial. The *cis*-isomer would have one substituent in the equatorial, the other in the axial conformation (cf. Barton, *J.*, 1953, 1028). Similar results have been obtained in a study of the Michael condensation of 2-arylcyclohex-2-enones (Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, 1, No. 3, 121) and of 2-phenylcyclohept-2-enone (Ginsburg and Pappo, *loc. cit.*). Presumably, therefore, the two alicyclic rings in the ketones (IV) are fused in the *trans*-manner.

1-Benzoylcycloheptene was prepared from benzoyl chloride and cycloheptene in the presence of aluminium chloride. The product was dehydrochlorinated by heating it in dimethylaniline. As this ketone was not previously known, it was necessary to prove that no rearrangement to a cyclohexane derivative had taken place during its preparation by this method. It has been shown that the similar Friedel-Crafts reaction with acetyl chloride must be carried out at low temperature in order to avoid such rearrangement (Fries and Pinson, jun., *J. Amer. Chem. Soc.*, 1951, 73, 3512; Taub and Szmuszkowicz, *ibid.*, 1952, 74, 2117). The benzylation reaction was therefore carried out at -30° to -40° and the resulting product gave a single 2:4-dinitrophenylhydrazone, m. p. 132—133°, in high yield, indicating that a mixture of ketones was not present. Furthermore, 1-benzoylcycloheptene was prepared through the reaction of cycloheptenyl-lithium with benzonitrile, in which the possibility of ring contraction is ruled out. The product was identical in infra-red spectrum and in its 2:4-dinitrophenylhydrazone with the ketone and its corresponding derivative prepared by the benzylation procedure. We learned subsequently (Dr. E. A. Braude, personal communication) that 1-benzoylcycloheptene has also been prepared by oxidation of the alcohol which results from the reaction of cycloheptenyl-lithium and benzaldehyde. The 2:4-dinitrophenylhydrazone of the ketone so prepared had m. p. 133—134° (Braude and Forbes, *J.*, 1953, 2208).

EXPERIMENTAL

1-Benzoylcyclopentene.—This ketone was prepared according to Fuson, Johnson, and Cole (*J. Amer. Chem. Soc.*, 1938, 60, 1594).

1-Benzoylcyclohexene.—The product was obtained by Christ and Fuson's method (*ibid.*, 1937, 59, 893).

1-Benzoylcycloheptene.—(a) To a mixture of cycloheptene (113 g.), benzoyl chloride (172 g.), and carbon disulphide (400 ml.), small portions of aluminium chloride (176 g.) were added during 3 hr., the temperature being kept at -30° to -40°. Stirring was continued for 2 hr., and the temperature allowed to rise to -10°. No hydrogen chloride was evolved. The mixture was poured into dilute hydrochloric acid containing ice shavings, and the carbon disulphide layer was separated. The solvent was removed under reduced pressure and the residue was refluxed with dimethylaniline for 3 hr. The mixture was cooled, poured into dilute acid, and extracted with chloroform. Fractionation afforded 1-benzoylcycloheptene (130 g.), b. p. 155°/8 mm. (Found: C, 83.5; H, 8.1. C₁₄H₁₆O requires C, 84.0; H, 8.1%). Infra-red absorption: 6.01 μ (C=O). A higher-boiling chlorine-containing fraction (30—40 g.), presumably 1-benzoyl-2-chlorocycloheptane, was also obtained.

The 2:4-dinitrophenylhydrazone formed red prismatic needles, m. p. 132—133° (from ethanol-ethyl acetate). Braude and Forbes (*loc. cit.*) report m. p. 133—134°.

(b) Preparation from cycloheptenyl-lithium and benzonitrile. cycloHeptenyl-lithium was prepared from 1-bromocycloheptene (8.25 g.) and lithium wire (0.69 g.) in dry ether (100 ml.). To the solution was added benzonitrile (10.3 g.) in dry ether (30 ml.). After refluxing for 4 hr. the mixture was poured into dilute hydrochloric acid. The resulting imine was extracted by the acid, and its solution was refluxed for 3 hr. The solution soon became turbid and drops of ketone were formed in the refluxing solution. After cooling, the ketone was taken up in ether and subsequently purified by distillation. It gave a 2:4-dinitrophenylhydrazone, m. p. 132—133°, identical with the one reported above.

Michael Condensations.—The conditions and working-up followed the procedure of Ginsburg and Pappo (*loc. cit.*).

From 1-benzoylcyclopentene (44.5 g.), benzyl malonate (113 g.), and potassium *tert.*-butoxide (prepared from 3.3 g. of potassium and 50 ml. of *tert.*-butanol), 2-benzoylcyclopentylmalonic acid (34 g.), m. p. 144—145° (decomp.) (from carbon tetrachloride), was obtained (Found : C, 65.4; H, 5.6. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%).

2-Benzoylcyclohexylmalonic acid (25 g.) was similarly obtained from 1-benzoylcyclohexene (37.2 g.), benzyl malonate (63.9 g.), and the alkoxide prepared from potassium (1.6 g.) and *tert.*-butanol (24 ml.). The acid had m. p. 190—191° (decomp.) (from carbon tetrachloride) (Found : C, 66.4; H, 6.1. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.25%).

2-Benzoylcycloheptylmalonic acid (10.5 g.) was obtained from 1-benzoylcycloheptene (15 g.), benzyl malonate (42.6 g.), and alkoxide solution prepared from potassium (1 g.) and *tert.*-butanol (15 ml.). It had m. p. 169—170° (decomp.) (from carbon tetrachloride) (Found : C, 67.0; H, 6.4. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%).

Since all of the 1-benzoylcycloalkenes were prepared by a Friedel-Crafts reaction in carbon disulphide solution, it is necessary to remove traces of sulphur-containing impurities from the Michael condensation mixtures before hydrogenolysis with palladium-charcoal. This purification is easily effected by refluxing the ethyl acetate solution of the reaction mixture with Raney nickel for 3—4 hr., followed by separation of the Raney nickel.

2-Benzoylcycloalkylacetic Acids.—These acids were obtained through decarboxylation of the corresponding malonic acids at 180—190° for 15—30 min. 2-Benzoylcyclopentylacetic acid was obtained as an oil and purified by evaporative distillation (Found : equiv., 224. $C_{14}H_{16}O_3$ requires equiv., 232.3). Infra-red absorption : 5.78 μ (weak) and 5.89 μ (strong) (monomeric and dimeric CO_2H); 5.97 μ ($C=O$). 2-Benzoylcyclohexylacetic acid formed prisms, m. p. 103—104° (from carbon tetrachloride) (Found : C, 73.3; H, 7.35. $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.4%). Infra-red absorption : 5.89 μ (CO_2H); 5.97 μ ($C=O$). 2-Benzoylcycloheptylacetic acid was obtained as an oil (Found : equiv., 254. $C_{16}H_{20}O_3$ requires equiv., 260.3). Infra-red absorption : 5.88 μ (CO_2H); 5.97 μ ($C=O$).

2-Benzoylcycloalkylacetic Acids.—These acids were obtained according to Huang-Minlon's method (*loc. cit.*) : 2-Benzylcyclopentylacetic acid, m. p. 53—54° (from light petroleum) [Duff and Ingold (*J.*, 1934, 93) report m. p. 53—54°] (Found : C, 76.8; H, 8.2. Calc. for $C_{14}H_{18}O_2$: C, 77.0; H, 8.3%). 2-Benzylcyclohexylacetic acid, m. p. 74—75° (from light petroleum). Colonge and Sibeud (*loc. cit.*) report m. p. 58.5°. The infra-red spectra of the polymorphic modifications in carbon tetrachloride solution are identical between 2 and 14 μ . When equal amounts of each form are melted together and allowed to solidify, the m. p. obtained is that of the higher-melting form (Found : C, 77.8; H, 8.5. Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.7%). 2-Benzylcycloheptylacetic acid was obtained as an oil which did not crystallise (Found : equiv., 238. $C_{16}H_{22}O_2$ requires equiv., 246.3).

Cyclisation of 2-Benzoylcycloalkylacetic Acids.—The acid (0.01 mole) was dissolved in dry benzene (20 ml.) and thionyl chloride (5 ml.) was added. After 2 hours' refluxing evolution of gas was complete. The excess of solvents was removed under reduced pressure. To the residual acid chloride were added carbon disulphide (20 ml.) and aluminium chloride (0.01 mole) in one portion. The mixture was refluxed for 3 hr. and stored overnight. After decomposition with dilute hydrochloric acid and chloroform extraction, the combined organic extracts were distilled under reduced pressure.

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-Octahydro-7-oxo-5 : 6-benzazulene (IVa), m. p. 56° (from light petroleum), was obtained from 2-benzylcyclopentylacetic acid (Found : C, 84.1; H, 8.0. Calc. for $C_{14}H_{16}O$: C, 84.0; H, 8.05%). Infra-red absorption : 6.01 μ ($C=O$). The orange 2 : 4-dinitrophenylhydrazine had m. p. 184—185° (from ethanol-ethyl acetate) (Found : C, 63.4; H, 5.2; N, 15.0. Calc. for $C_{20}H_{20}O_4N_4$: C, 63.15; H, 5.3; N, 14.7%). Cook, McGinnis, and Mitchell (*J.*, 1944, 286) report m. p.s 56° and 169—170°, respectively, for these two compounds.

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-Octahydro-7-hydroxy-5 : 6-benzazulene, m. p. 128° (from light petroleum), was obtained by reduction of the above ketone with sodium borohydride in methanol (Found : C, 83.0; H, 9.1. Calc. for $C_{14}H_{18}O$: C, 83.1; H, 9.0%). Cook *et al.* (*loc. cit.*) report m. p. 128—129°

2 : 3 : 12 : 13 : 14 : 15-Hexahydrodibenzosuber-5-one (IVb) was obtained as an oil from 2-benzylcyclohexylacetic acid. Infra-red absorption : 6.03 μ ($C=O$). The ketone was characterised through its semicarbazone, m. p. 205° (from ethanol) (Found : C, 70.5; H, 7.6; N, 15.6. Calc. for $C_{16}H_{21}ON_3$: C, 70.8; H, 7.8; N, 15.5%). A sample of this compound kindly furnished by Professor J. Colonge had m. p. 202° (from ethanol); mixed m. p., 204—205°.

1 : 4 : 5 : 6 : 7 : 8 : 9 : 10 : 11 : 12-Decahydro-5-oxo-2 : 3-benzoheptalene (IVc) was obtained as an oil from 2-benzylcycloheptylacetic acid. Infra-red absorption 6.03 μ ($C=O$). It was charac-

terised through its orange 2 : 4-*dinitrophenylhydrazone*, m. p. 227—228° (decomp.) (from ethanol), raised to 229—230° (from ethanol-ethyl acetate) (Found : C, 64.4; H, 6.0; N, 13.5. $C_{22}H_{24}O_4N_4$ requires C, 64.7; H, 5.9; N, 13.7%).

We are grateful to Professor J. Colonge for samples of his specimens. This work was carried out while the author was on leave of absence from the Weizmann Institute of Science during the tenure of a United States Public Health Service post-doctoral fellowship, 1952—1953.

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[Received, March 3rd, 1954.]
